IARC MONOGRAPHS

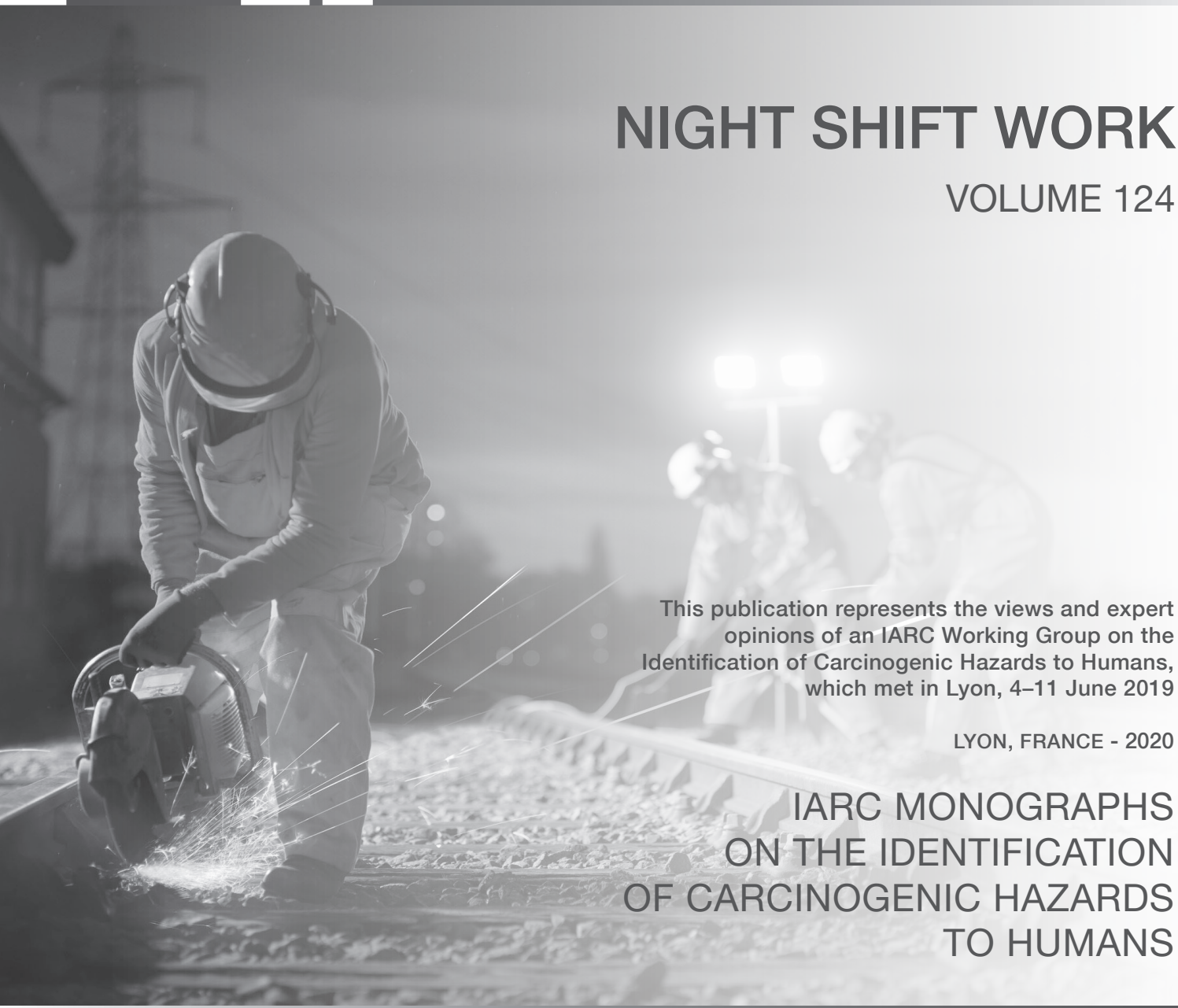
NIGHT SHIFT WORK

VOLUME 124

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS



NIGHT SHIFT WORK

VOLUME 124

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, 4–11 June 2019

LYON, FRANCE - 2020

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic hazard of chemicals to humans, involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic hazards associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of cancer hazard to humans with the help of international working groups of experts in carcinogenesis and related fields; and to identify gaps in evidence. The lists of IARC evaluations are regularly updated and are available on the internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (2014–2020) (for further information please consult: http://ec.europa.eu/social/easi). Support has also been provided since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

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The *IARC Monographs* Working Group alone is responsible for the views expressed in this publication.

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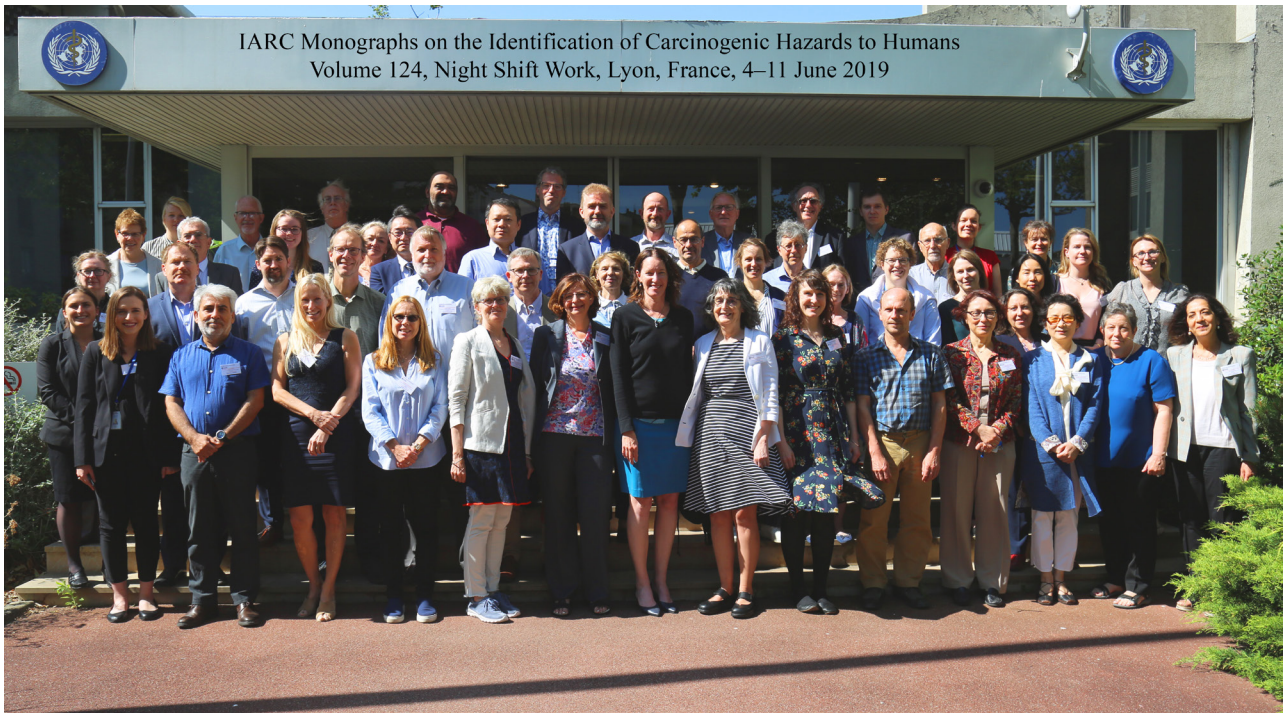

"Night shift work" involves work, including transmeridian travel, that occurs during the regular sleeping hours of the general population. This alters exposure to the natural light–dark schedule and disrupts circadian rhythms.

About the cover: the image depicts night shift workers performing maintenance on a railway track.

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NOTE TO THE READER

The evaluations of carcinogenic hazard in the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* series are made by international working groups of independent scientists. The *IARC Monographs* classifications do not indicate the level of risk associated with a given level or circumstance of exposure. The *IARC Monographs* do not make recommendations for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic hazard of an agent to humans is encouraged to make this information available to the *IARC Monographs* Group, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, or via email at imo@iarc.fr, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the *IARC Monographs* Group. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: http://publications.iarc.fr/).

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Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$ 1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[2] Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft any part of a Monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.
[3] Alex Forrest is employed by the United Fire Fighters of Winnipeg, who paid for travel costs.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, general principles and procedures, and scientific review and evaluations. The *IARC Monographs* embody principles of scientific rigour, impartial evaluation, transparency, and consistency. The Preamble should be consulted when reading a *Monograph* or a summary of a *Monograph*'s evaluations. Separate Instructions for Authors describe the operational procedures for the preparation and publication of a volume of the *Monographs*.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after the International Agency for Research on Cancer (IARC) was established in 1965, it started to receive frequent requests for advice on the carcinogenicity of chemicals, including requests for lists of established and suspected human carcinogens. In 1970, an IARC Advisory Committee on Environmental Carcinogenesis recommended "that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented." The next year, the IARC Governing Council adopted a resolution that IARC should prepare "monographs on the evaluation of carcinogenic risk of chemicals to man", which became the initial title of the series.

In succeeding years, the scope of the programme broadened as *Monographs* were developed for complex mixtures, occupational exposures, physical agents, biological organisms, pharmaceuticals, and other exposures. In 1988, "of chemicals" was dropped from the title, and in 2019, "evaluation of carcinogenic risks" became "identification of carcinogenic hazards", in line with the objective of the programme.

Identifying the causes of human cancer is the first step in cancer prevention. The identification of a cancer hazard may have broad and profound implications. National and international authorities and organizations can and do use information on causes of cancer in support of actions to reduce exposure to carcinogens in the workplace, in the environment, and elsewhere. Cancer prevention is needed as much today as it was when IARC was established, because the global burden of cancer is high and continues to increase as a result of population growth and ageing and upward trends in some exposures, especially in low- and middle-income countries (http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports).

IARC's process for developing *Monographs*, which has evolved over several decades, involves

the engagement of international, interdisciplinary Working Groups of expert scientists, the transparent synthesis of different streams of evidence (exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis), and the integration of these streams of evidence into an overall evaluation and classification according to criteria developed and refined by IARC. Since the *Monographs* programme was established, the understanding of carcinogenesis has greatly deepened. Scientific advances are incorporated into the evaluation methodology. In particular, strong mechanistic evidence has had an increasing role in the overall evaluations since 1991.

The Preamble is primarily a statement of the general principles and procedures used in developing a *Monograph*, to promote transparency and consistency across *Monographs* evaluations. In addition, IARC provides Instructions for Authors (https://monographs.iarc.fr/preamble-instructions-for-authors/), which specify more detailed working procedures. IARC routinely updates these Instructions for Authors to reflect advances in methods for cancer hazard identification and accumulated experience, including input from experts.

2. Objective and scope

The objective of the programme is to prepare, with the engagement of international, interdisciplinary Working Groups of experts, scientific reviews and evaluations of evidence on the carcinogenicity of a wide range of agents.

The *Monographs* assess the strength of the available evidence that an agent can cause cancer in humans, based on three streams of evidence: on cancer in humans (see Part B, Section 2), on cancer in experimental animals (see Part B, Section 3), and on mechanistic evidence (see Part B, Section 4). In addition, the exposure to each agent is characterized (see Part B, Section 1). In this Preamble, the term "agent" refers to any chemical, physical, or biological entity or exposure circumstance (e.g. occupation as a painter) for which evidence on the carcinogenicity is evaluated.

A cancer *hazard* is an agent that is capable of causing cancer, whereas a cancer *risk* is an estimate of the probability that cancer will occur given some level of exposure to a cancer hazard. The *Monographs* assess the strength of evidence that an agent is a cancer hazard. The distinction between hazard and risk is fundamental. The *Monographs* identify cancer hazards even when risks appear to be low in some exposure scenarios. This is because the exposure may be widespread at low levels, and because exposure levels in many populations are not known or documented.

Although the *Monographs* programme has focused on hazard identification, some epidemiological studies used to identify a cancer hazard are also used to estimate an exposure–response relationship within the range of the available data. However, extrapolating exposure–response relationships beyond the available data (e.g. to lower exposures, or from experimental animals to humans) is outside the scope of *Monographs* Working Groups (IARC, 2014). In addition, the *Monographs* programme does not review quantitative risk characterizations developed by other health agencies.

The identification of a cancer hazard should trigger some action to protect public health, either directly as a result of the hazard identification or through the conduct of a risk assessment. Although such actions are outside the scope of the programme, the *Monographs* are used by national and international authorities and organizations to inform risk assessments, formulate decisions about preventive measures, motivate effective cancer control programmes, and choose among options for public health decisions. *Monographs* evaluations are only one part of the body of information on which decisions to

control exposure to carcinogens may be based. Options to prevent cancer vary from one situation to another and across geographical regions and take many factors into account, including different national priorities. Therefore, no recommendations are given in the *Monographs* with regard to regulation, legislation, or other policy approaches, which are the responsibility of individual governments or organizations. The *Monographs* programme also does not make research recommendations. However, it is important to note that *Monographs* contribute significantly to the science of carcinogenesis by synthesizing and integrating streams of evidence about carcinogenicity and pointing to critical gaps in knowledge.

3. Selection of agents for review

Since 1984, about every five years IARC convenes an international, interdisciplinary Advisory Group to recommend agents for review by the *Monographs* programme. IARC selects Advisory Group members who are knowledgeable about current research on carcinogens and public health priorities. Before an Advisory Group meets, IARC solicits nominations of agents from scientists and government agencies worldwide. Since 2003, IARC also invites nominations from the public. IARC charges each Advisory Group with reviewing nominations, evaluating exposure and hazard potential, and preparing a report that documents the Advisory Group's process for these activities and its rationale for the recommendations.

For each new volume of the *Monographs*, IARC selects the agents for review from those recommended by the most recent Advisory Group, considering the availability of pertinent research studies and current public health priorities. On occasion, IARC may select other agents if there is a need to rapidly evaluate an emerging carcinogenic hazard or an urgent need to re-evaluate a previous classification. All evaluations consider the full body of available evidence, not just information published after a previous review.

A *Monograph* may review:

(a) An agent not reviewed in a previous *Monograph*, if there is potential human exposure and there is evidence for assessing its carcinogenicity. A group of related agents (e.g. metal compounds) may be reviewed together if there is evidence for assessing carcinogenicity for one or more members of the group.

(b) An agent reviewed in a previous *Monograph*, if there is new evidence of cancer in humans or in experimental animals, or mechanistic evidence to warrant re-evaluation of the classification. In the interests of efficiency, the literature searches may build on previous comprehensive searches.

(c) An agent that has been established to be carcinogenic to humans and has been reviewed in a previous *Monograph*, if there is new evidence of cancer in humans that indicates new tumour sites where there might be a causal association. In the interests of efficiency, the review may focus on these new tumour sites.

4. The Working Group and other meeting participants

Five categories of participants can be present at *Monographs* meetings:

(i) *Working Group* members are responsible for all scientific reviews and evaluations developed in the volume of the *Monographs*. The Working Group is interdisciplinary and comprises subgroups of experts in the fields of (a) exposure characterization, (b) cancer in humans, (c) cancer in experimental animals, and (d) mechanistic evidence. IARC selects Working Group members on the basis of

expertise related to the subject matter and relevant methodologies, and absence of conflicts of interest. Consideration is also given to diversity in scientific approaches and views, as well as demographic composition. Working Group members generally have published research related to the exposure or carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Since 2006, IARC also has encouraged public nominations through its Call for Experts. IARC's reliance on experts with knowledge of the subject matter and/or expertise in methodological assessment is confirmed by decades of experience documenting that there is value in specialized expertise and that the overwhelming majority of Working Group members are committed to the objective evaluation of scientific evidence and not to the narrow advancement of their own research results or a pre-determined outcome (Wild & Cogliano, 2011). Working Group members are expected to serve the public health mission of IARC, and should refrain from consulting and other activities for financial gain that are related to the agents under review, or the use of inside information from the meeting, until the full volume of the *Monographs* is published.

IARC identifies, from among Working Group members, individuals to serve as Meeting Chair and Subgroup Chairs. At the opening of the meeting, the Working Group is asked to endorse the selection of the Meeting Chair, with the opportunity to propose alternatives. The Meeting Chair and Subgroup Chairs take a leading role at all stages of the review process (see Part A, Section 7), promote open scientific discussions that involve all Working Group members in accordance with normal committee procedures, and ensure adherence to the Preamble.

(ii) *Invited Specialists* are experts who have critical knowledge and experience but who also have a conflict of interest that warrants exclusion from developing or influencing the evaluations of carcinogenicity. Invited Specialists do not draft any section of the *Monograph* that pertains to the description or interpretation of cancer data, and they do not participate in the evaluations. These experts are invited in limited numbers when necessary to assist the Working Group by contributing their unique knowledge and experience to the discussions.

(iii) *Representatives of national and international health agencies* may attend because their agencies are interested in the subject of the meeting. They do not draft any section of the *Monograph* or participate in the evaluations.

(iv) *Observers* with relevant scientific credentials may be admitted in limited numbers. Attention is given to the balance of Observers from constituencies with differing perspectives. Observers are invited to observe the meeting and should not attempt to influence it, and they agree to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers do not draft any section of the *Monograph* or participate in the evaluations.

(v) The *IARC Secretariat* consists of scientists who are designated by IARC and who have relevant expertise. The IARC Secretariat coordinates and facilitates all aspects of the evaluation and ensures adherence to the Preamble throughout development of the scientific reviews and classifications (see Part A, Sections 5 and 6). The IARC Secretariat organizes and announces the meeting, identifies and recruits the Working Group members, and assesses the declared interests of all meeting participants. The IARC Secretariat supports the activities of the Working Group (see Part A, Section 7) by

Table 1 Roles of participants at *IARC Monographs* meetings

Category of participant	Role			
	Prepare text, tables, and analyses	Participate in discussions	Participate in evaluations	Eligible to serve as Chair
Working Group members	✓	✓	✓	✓
Invited Specialists	✓[a]	✓		
Representatives of health agencies		✓[b]		
Observers		✓[b]		
IARC Secretariat	✓[c]	✓	✓[d]	

[a] Only for the section on exposure characterization.
[b] Only at times designated by the Meeting Chair and Subgroup Chairs.
[c] When needed or requested by the Meeting Chair and Subgroup Chairs.
[d] Only for clarifying or interpreting the Preamble.

searching the literature and performing title and abstract screening, organizing conference calls to coordinate the development of pre-meeting drafts and discuss cross-cutting issues, and reviewing drafts before and during the meeting. Members of the IARC Secretariat serve as meeting rapporteurs, assist the Meeting Chair and Subgroup Chairs in facilitating all discussions, and may draft text or tables when designated by the Meeting Chair and Subgroup Chairs. Their participation in the evaluations is restricted to the role of clarifying or interpreting the Preamble.

All participants are listed, with their principal affiliations, in the front matter of the published volume of the *Monographs*. Working Group members and Invited Specialists serve as individual scientists and not as representatives of any organization, government, or industry (Cogliano et al., 2004).

The roles of the meeting participants are summarized in Table 1.

5. Working procedures

A separate Working Group is responsible for developing each volume of the *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year before the meeting of a Working Group, a preliminary list of agents to be reviewed, together with a Call for Data and a Call for Experts, is announced on the *Monographs* programme website (https://monographs.iarc.fr/).

Before a meeting invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests form to report financial interests, employment and consulting (including remuneration for serving as an expert witness), individual and institutional research support, and non-financial interests such as public statements and positions related to the subject of the meeting. IARC assesses the declared interests to determine whether there is a conflict that warrants any limitation on participation (see Table 2).

Approximately two months before a *Monographs* meeting, IARC publishes the names and affiliations of all meeting participants together with a summary of declared interests, in the interests of transparency and to provide an opportunity for undeclared conflicts of interest to be brought to IARC's attention. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

Table 2 Public engagement during *Monographs* development

Approximate timeframe	Engagement
Every 5 years	IARC convenes an Advisory Group to recommend high-priority agents for future review
~1 year before a *Monographs* meeting	IARC selects agents for review in a new volume of the *Monographs* IARC posts on its website: Preliminary List of Agents to be reviewed Call for Data and Call for Experts Request for Observer Status WHO Declaration of Interests form
~8 months before a *Monographs* meeting	Call for Experts closes
~4 months before a *Monographs* meeting	Request for Observer Status closes
~2 months before a *Monographs* meeting	IARC posts the names of all meeting participants together with a summary of declared interests, and a statement discouraging contact of the Working Group by interested parties
~1 month before a *Monographs* meeting	Call for Data closes
~2–4 weeks after a *Monographs* meeting	IARC publishes a summary of evaluations and key supporting evidence
~9 months after a *Monographs* meeting	IARC Secretariat publishes the verified and edited master copy of plenary drafts as a *Monographs* volume

The Working Group meets at IARC for approximately eight days to discuss and finalize the scientific review and to develop summaries and evaluations. At the opening of the meeting, all participants update their Declaration of Interests forms, which are then reviewed by IARC. Declared interests related to the subject of the meeting are disclosed to the meeting participants during the meeting and in the published volume (Cogliano et al., 2004). The objectives of the meeting are peer review and consensus. During the first part of the meeting, subgroup sessions (covering exposure characterization, cancer in humans, cancer in experimental animals, and mechanistic evidence) review the pre-meeting drafts, develop a joint subgroup draft, and draft subgroup summaries. During the last part of the meeting, the Working Group meets in plenary session to review the subgroup drafts and summaries and to develop the consensus evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections. After the meeting, the master copy is verified by the IARC Secretariat and is then edited and prepared for publication. The aim is to publish the volume within approximately nine months of the Working Group meeting. A summary of the evaluations and key supporting evidence is prepared for publication in a scientific journal or is made available on the *Monographs* programme website soon after the meeting.

In the interests of transparency, IARC engages with the public throughout the process, as summarized in Table 2.

6. Overview of the scientific review and evaluation process

The Working Group considers all pertinent epidemiological studies, cancer bioassays in experimental animals, and mechanistic evidence, as well as pertinent information on exposure in humans. In general, for cancer in humans, cancer in experimental animals, and mechanistic evidence, only studies that have been published or accepted for publication in the openly available scientific literature are reviewed. Under some circumstances, materials

that are publicly available and whose content is final may be reviewed if there is sufficient information to permit an evaluation of the quality of the methods and results of the studies (see Step 1, below). Such materials may include reports and databases publicly available from government agencies, as well as doctoral theses. The reliance on published and publicly available studies promotes transparency and protects against citation of premature information.

The principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence related to cancer in humans, cancer in experimental animals, and mechanistic evidence (as described in Part B, Sections 2–4 and as detailed in the Instructions for Authors). Each *Monograph* specifies or references information on the conduct of the literature searches, including search terms and inclusion/exclusion criteria that were used for each stream of evidence.

In brief, the steps of the review process are as follows:

Step 1. Comprehensive and transparent identification of the relevant information: The IARC Secretariat identifies relevant studies through initial comprehensive searches of literature contained in authoritative biomedical databases (e.g. PubMed, PubChem) and through a Call for Data. These literature searches, designed in consultation with a librarian and other technical experts, address whether the agent causes cancer in humans, causes cancer in experimental systems, and/or exhibits key characteristics of established human carcinogens (in humans or in experimental systems). The Working Group provides input and advice to IARC to refine the search strategies, and identifies literature through other searches (e.g. from reference lists of past *Monographs*, retrieved articles, and other authoritative reviews).

For certain types of agents (e.g. regulated pesticides and pharmaceuticals), IARC also provides an opportunity to relevant regulatory authorities, and regulated parties through such authorities, to make pertinent unpublished studies publicly available by the date specified in the Call for Data. Consideration of such studies by the Working Group is dependent on the public availability of sufficient information to permit an independent evaluation of (a) whether there has been selective reporting (e.g. on outcomes, or from a larger set of conducted studies); (b) study quality (e.g. design, methodology, and reporting of results), and (c) study results.

Step 2. Screening, selection, and organization of the studies: The IARC Secretariat screens the retrieved literature for inclusion based on title and abstract review, according to pre-defined exclusion criteria. For instance, studies may be excluded if they were not about the agent (or a metabolite of the agent), or if they reported no original data on epidemiological or toxicological end-points (e.g. review articles). The Working Group reviews the title and abstract screening done by IARC, and performs full-text review. Any reasons for exclusion are recorded, and included studies are organized according to factors pertinent to the considerations described in Part B, Sections 2–4 (e.g. design, species, and end-point). Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results.

Step 3. Evaluation of study quality: The Working Group evaluates the quality of the included studies based on the considerations (e.g. design, methodology, and reporting of results) described in Part B, Sections 2–4. Based on these considerations, the Working Group may accord greater weight to some of the included studies. Interpretation of the

results and the strengths and limitations of a study are clearly outlined in square brackets at the end of study descriptions (see Part B).

Step 4: *Report characteristics of included studies, including assessment of study quality*: Pertinent characteristics and results of included studies are reviewed and succinctly described, as detailed in Part B, Sections 1–4. Tabulation of data may facilitate this reporting. This step may be iterative with Step 3.

Step 5: *Synthesis and evaluation of strength of evidence*: The Working Group summarizes the overall strengths and limitations of the evidence from the individual streams of evidence (cancer in humans, cancer in experimental animals, and mechanistic evidence; see Part B, Section 5). The Working Group then evaluates the strength of evidence from each stream of evidence by using the transparent methods and defined descriptive terms given in Part B, Sections 6a–c. The Working Group then develops, and describes the rationale for, the consensus classification of carcinogenicity that integrates the conclusions about the strength of evidence from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic evidence (see Part B, Section 6d).

7. Responsibilities of the Working Group

The Working Group is responsible for identifying and evaluating the relevant studies and developing the scientific reviews and evaluations for a volume of the *Monographs*. The IARC Secretariat supports these activities of the Working Group (see Part A, Section 4). Briefly, the Working Group's tasks in developing the evaluation are, in sequence:

(i) Before the meeting, the Working Group ascertains that all appropriate studies have been identified and selected, and assesses the methods and quality of each individual study, as outlined above (see Part A, Section 6). The Working Group members prepare pre-meeting working drafts that present accurate tabular or textual summaries of informative studies by extracting key elements of the study design and results, and highlighting notable strengths and limitations. They participate in conference calls organized by IARC to coordinate the development of working drafts and to discuss cross-cutting issues. Pre-meeting reviews of all working drafts are generally performed by two or more subgroup members who did not participate in study identification, data extraction, or study review for the draft. Each study summary is written or reviewed by someone who is not associated with the study.

(ii) At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. Subgroup Chairs ensure that someone who is not associated with the study leads the discussion of each study summary. A proposed classification of the strength of the evidence reviewed in the subgroup using the *IARC Monographs* criteria (see Part B, Sections 6a–c) is then developed from the consensus subgroup drafts of the evidence summaries (see Part B, Section 5).

(iii) During the plenary session, each subgroup presents its drafts for scientific review and discussion to the other Working Group members, who did not participate in study identification, data extraction, or study review for the drafts. Subgroup Chairs ensure that someone who is not associated with the study leads the discussion of each study summary.

After review, discussion, and revisions as needed, the subgroup drafts are adopted as a consensus Working Group product. The summaries and classifications of the strength of the evidence, developed in the subgroup in line with the *IARC Monographs* criteria (see Part B, Sections 6a–c), are considered, revised as needed, and adopted by the full Working Group. The Meeting Chair proposes an overall evaluation using the guidance provided in Part B, Section 6d.

The Working Group strives to achieve consensus evaluations. Consensus reflects broad agreement among the Working Group, but not necessarily unanimity. The Meeting Chair may poll the Working Group to determine the diversity of scientific opinion on issues where consensus is not apparent.

Only the final product of the plenary session represents the views and expert opinions of the Working Group. The entire *Monographs* volume is the joint product of the Working Group and represents an extensive and thorough peer review of the body of evidence (individual studies, synthesis, and evaluation) by an interdisciplinary expert group. Initial working papers and subsequent revisions are not released, because they would give an incomplete and possibly misleading impression of the consensus developed by the Working Group over a full week of deliberation.

B. SCIENTIFIC REVIEW AND EVALUATION

This part of the Preamble discusses the types of evidence that are considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations. In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and any key issues encountered during the meeting.

1. Exposure characterization

This section identifies the agent and describes its occurrence, main uses, and production locations and volumes, where relevant. It also summarizes the prevalence, concentrations in relevant studies, and relevant routes of exposure in humans worldwide. Methods of exposure measurement and analysis are described, and methods of exposure assessment used in key epidemiological studies reviewed by the Working Group are described and evaluated.

Over the course of the *Monographs* programme, concepts of exposure and dose have evolved substantially with deepening understanding of the interactions of agents and biological systems. The concept of exposure has broadened and become more holistic, extending beyond chemical, physical, and biological agents to stressors as construed generally, including psychosocial stressors (National Research Council, 2012; National Academies of Sciences, Engineering, and Medicine, 2017). Overall, this broader conceptualization supports greater integration between exposure characterization and other sections of the *Monographs*. Concepts of absorption, distribution, metabolism, and excretion are considered in the first subsection of mechanistic evidence (see Part B, Section 4a), whereas validated biomarkers of internal exposure or metabolites that are routinely used for exposure assessment are reported on in this section (see Part B, Section 1b).

(a) Identification of the agent

The agent being evaluated is unambiguously identified. Details will vary depending on the type of agent but will generally include physical and chemical properties relevant to the agent's identification, occurrence, and biological activity.

If the material that has been tested in experimental animals or in vitro systems is different from that to which humans are exposed, these differences are noted.

For chemical agents, the Chemical Abstracts Service Registry Number is provided, as well as the latest primary name and other names in common use, including important trade names, along with available information on the composition of common mixtures or products containing the agent, and potentially toxic and/or carcinogenic impurities. Physical properties relevant to understanding the potential for human exposure and measures of exposure used in studies in humans are summarized. These might include physical state, volatility, aqueous and fat solubility, and half-life in the environment and/or in human tissues.

For biological agents, taxonomy and structure are described. Mode of replication, life-cycle, target cells, persistence, latency, and host responses, including morbidity and mortality through pathologies other than cancer, are also presented.

For foreign bodies, fibres and particles, composition, size range, relative dimensions, and accumulation, persistence, and clearance in target organs are summarized. Physical agents that are forms of radiation are described in terms of frequency spectrum and energy transmission.

Exposures may result from, or be influenced by, a diverse range of social and environmental factors, including components of diet, sleep, and physical activity patterns. In these instances, this section will include a description of the agent, its variability across human populations, and its composition or characteristics relevant to understanding its potential carcinogenic hazard to humans and to evaluating exposure assessments in epidemiological studies.

(b) Detection and analysis

Key methods of detection and quantification of the agent are presented, with an emphasis on those used most widely in surveillance, regulation, and epidemiological studies. Measurement methods for sample matrices that are deemed important sources of human exposure (e.g. air, drinking-water, food, residential dust) and for validated exposure biomarkers (e.g. the agent or its metabolites in human blood, urine, or saliva) are described. Information on detection and quantification limits is provided when it is available and is useful for interpreting studies in humans and in experimental animals. This is not an exhaustive treatise but is meant to help readers understand the strengths and limitations of the available exposure data and of the epidemiological studies that rely on these measurements.

(c) Production and use

Historical and geographical patterns and trends in production and use are included when they are available, to help readers understand the contexts in which exposures may occur, both within key epidemiological studies reviewed by the Working Group and in human populations generally. Industries that produce, use, or dispose of the agent are described, including their global distribution, when available. National or international listing as a high-production-volume chemical or similar classification may be included. Production processes with significant potential for occupational exposure or environmental pollution are indicated. Trends in global production volumes, technologies, and other data relevant to understanding exposure potential are summarized. Minor or historical uses with significant exposure potential or with particular relevance to key epidemiological studies are included. Particular effort may be directed towards finding data on production in low- and middle-income countries, where rapid

economic development may lead to higher exposures than those in high-income countries.

(d) Exposure

A concise overview of quantitative information on sources, prevalence, and levels of exposure in humans is provided. Representative data from research studies, government reports and websites, online databases, and other citable, publicly available sources are tabulated. Data from low- and middle-income countries are sought and included to the extent feasible; information gaps for key regions are noted. Naturally occurring sources of exposure, if any, are noted. Primary exposure routes (e.g. inhalation, ingestion, skin uptake) and other considerations relevant to understanding the potential for cancer hazard from exposure to the agent are reported.

For occupational settings, information on exposure prevalence and levels (e.g. in air or human tissues) is reported by industry, occupation, region, and other characteristics (e.g. process, task) where feasible. Information on historical exposure trends, protection measures to limit exposure, and potential co-exposures to other carcinogenic agents in workplaces is provided when available.

For non-occupational settings, the occurrence of the agent is described with environmental monitoring or surveillance data. Information on exposure prevalence and levels (e.g. concentrations in human tissues) as well as exposure from and/or concentrations in food and beverages, consumer products, consumption practices, and personal microenvironments is reported by region and other relevant characteristics. Particular importance is placed on describing exposures in life stages or in states of disease or nutrition that may involve greater exposure or susceptibility.

Current exposures are of primary interest; however, information on historical exposure trends is provided when available. Historical exposures may be relevant for interpreting epidemiological studies, and when agents are persistent or have long-term effects. Information gaps for important time periods are noted. Exposure data that are not deemed to have high relevance to human exposure are generally not considered.

(e) Regulations and guidelines

Regulations or guidelines that have been established for the agent (e.g. occupational exposure limits, maximum permitted levels in foods and water, pesticide registrations) are described in brief to provide context about government efforts to limit exposure; these may be tabulated if they are informative for the interpretation of existing or historical exposure levels. Information on applicable populations, specific agents concerned, basis for regulation (e.g. human health risk, environmental considerations), and timing of implementation may be noted. National and international bans on production, use, and trade are also indicated.

This section aims to include major or illustrative regulations and may not be comprehensive, because of the complexity and range of regulatory processes worldwide. An absence of information on regulatory status should not be taken to imply that a given country or region lacks exposure to, or regulations on exposure to, the agent.

(f) Critical review of exposure assessment in key epidemiological studies

Epidemiological studies evaluate cancer hazard by comparing outcomes across differently exposed groups. Therefore, the type and quality of the exposure assessment methods used are key considerations when interpreting study findings for hazard identification. This section summarizes and critically reviews the exposure assessment methods used in the individual epidemiological studies that contribute data relevant to the *Monographs* evaluation.

Although there is no standard set of criteria for evaluating the quality of exposure assessment methods across all possible agents, some concepts are universally relevant. Regardless of the agent, all exposures have two principal dimensions: intensity (sometimes defined as concentration or dose) and time. Time considerations include duration (time from first to last exposure), pattern or frequency (whether continuous or intermittent), and windows of susceptibility. This section considers how each of the key epidemiological studies characterizes these dimensions. Interpretation of exposure information may also be informed by consideration of mechanistic evidence (e.g. as described in Part B, Section 4a), including the processes of absorption, distribution, metabolism, and excretion.

Exposure intensity and time in epidemiological studies can be characterized by using environmental or biological monitoring data, records from workplaces or other sources, expert assessments, modelled exposures, job-exposure matrices, and subject or proxy reports via questionnaires or interviews. Investigators use these data sources and methods individually or in combination to assign levels or values of an exposure metric (which may be quantitative, semi-quantitative, or qualitative) to members of the population under study.

In collaboration with the Working Group members reviewing human studies (of cancer and of mechanisms), key epidemiological studies are identified. For each selected study, the exposure assessment approach, along with its strengths and limitations, is summarized using text and tables. Working Group members identify concerns about exposure assessment methods and their impacts on overall quality for each study reviewed (see Part B, Sections 2d and 4d). In situations where the information provided in the study is inadequate to properly consider the exposure assessment, this is indicated. When adequate information is available, the likely direction of bias due to error in exposure measurement, including misclassification (overestimated effects, underestimated effects, or unknown) is discussed.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part B, Section 2b) that include cancer as an outcome. These studies encompass certain types of biomarker studies, for example, studies with biomarkers as exposure metrics (see Part B, Section 2) or those evaluating histological or tumour subtypes and molecular signatures in tumours consistent with a given exposure (Alexandrov et al., 2016). Studies that evaluate early biological effect biomarkers are reviewed in Part B, Section 4.

(a) Types of study considered

Several types of epidemiological studies contribute to the assessment of carcinogenicity in humans; they typically include cohort studies (including variants such as case–cohort and nested case–control studies), case–control studies, ecological studies, and intervention studies. Rarely, results from randomized trials may be available. Exceptionally, case reports and case series of cancer in humans may also be reviewed. In addition to these designs, innovations in epidemiology allow for many other variants that may be considered in any given *Monographs* evaluation.

Cohort and case–control studies typically have the capacity to relate individual exposures under study to the occurrence of cancer in individuals, and provide an estimate of effect (such as relative risk) as the main measure of association. Well-conducted cohort and case–control studies provide most of the evidence of cancer in humans evaluated by Working Groups. Intervention studies are much less common, but when available can provide strong evidence for making causal inferences.

In ecological studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure in the population under study. In ecological studies, data on individual exposure and outcome are not available, which renders this type of study more prone to confounding and exposure misclassification. In some circumstances, however, ecological studies may be informative, especially when the unit of exposure is most accurately measured at the population level (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

Exceptionally, case reports and case series may provide compelling evidence about the carcinogenicity of an agent. In fact, many of the early discoveries of occupational cancer hazards came about because of observations by workers and their clinicians, who noted a high frequency of cancer in workers who share a common occupation or exposure. Such observations may be the starting point for more structured investigations, but in exceptional circumstances, when the risk is high enough, the case series may in itself provide compelling evidence. This would be especially warranted in situations where the exposure circumstance is fairly unusual, as it was in the example of plants containing aristolochic acid (IARC, 2012a).

The uncertainties that surround the interpretation of case reports, case series, and ecological studies typically make them inadequate, except in rare instances as described above, to form the sole basis for inferring a causal relationship. However, when considered together with cohort and case–control studies, these types of study may support the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, pre-neoplastic lesions, malignant precursors, and other end-points are also reviewed when they relate to the agents reviewed. On occasion they can strengthen inferences drawn from studies of cancer itself. For example, benign brain tumours may share common risk factors with those that are malignant, and benign neoplasms (or those of uncertain behaviour) may be part of the causal path to malignancies (e.g. myelodysplastic syndromes, which may progress to acute myeloid leukaemia).

(b) Identification of eligible studies of cancer in humans

Relevant studies of cancer in humans are identified by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below. Eligible studies include all studies in humans of exposure to the agent of interest with cancer as an outcome. Multiple publications on the same study population are identified so that the number of independent studies is accurately represented. Multiple publications may result, for example, from successive follow-ups of a single cohort, from analyses focused on different aspects of an exposure–disease association, or from inclusion of overlapping populations. Usually in such situations, only the most recent, most comprehensive, or most informative report is reviewed in detail.

(c) Assessment of study quality and informativeness

Epidemiological studies are potentially susceptible to several different sources of error, summarized briefly below. Qualities of individual studies that address these issues are also described below.

Study quality is assessed as part of the structured expert review process undertaken by the Working Group. A key aspect of quality assessment is consideration of the possible roles of chance and bias in the interpretation of epidemiological studies. Chance, which is also called

random variation, can produce misleading study results. This variability in study results is strongly influenced by the sample size: smaller studies are more likely than larger studies to have effect estimates that are imprecise. Confidence intervals around a study's point estimate of effect are used routinely to indicate the range of values of the estimate that could easily be produced by chance alone.

Bias is the effect of factors in study design or conduct that lead an association to erroneously appear stronger or weaker than the association that really exists between the agent and the disease. Biases that require consideration are varied but are usually categorized as selection bias, information bias (e.g. error in measurement of exposure and diseases), and confounding (or confounding bias), (Rothman et al., 2008). Selection bias in an epidemiological study occurs when inclusion of participants from the eligible population or their follow-up in the study is influenced by their exposure or their outcome (usually disease occurrence). Under these conditions, the measure of association found in the study will not accurately reflect the association that would otherwise have been found in the eligible population (Hernán et al., 2004). Information bias results from inaccuracy in exposure or outcome measurement. Both can cause an association between hypothesized cause and effect to appear stronger or weaker than it really is. Confounding is a mixing of extraneous effects with the effects of interest (Rothman et al., 2008). An association between the purported causal factor and another factor that is associated with an increase or decrease in incidence of disease can lead to a spurious association or absence of a real association of the presumed causal factor with the disease. When either of these occurs, confounding is present.

In assessing study quality, the Working Group consistently considers the following aspects:

- **Study description:** Clarity in describing the study design and its implementation, and the completeness of reporting of all other key information about the study and its results.
- **Study population:** Whether the study population was appropriate for evaluating the association between the agent and cancer. Whether the study was designed and carried out to minimize selection bias. Cancer cases in the study population must have been identified in a way that was independent of the exposure of interest, and exposure assessed in a way that was not related to disease (outcome) status. In these respects, completeness of recruitment into the study from the population of interest and completeness of follow-up for the outcome are essential measures.
- **Outcome measurement:** The appropriateness of the cancer outcome measure (e.g. mortality vs incidence) for the agent and cancer type under consideration, outcome ascertainment methodology, and the extent to which outcome misclassification may have led to bias in the measure(s) of association.
- **Exposure measurement:** The adequacy of the methods used to assess exposure to the agent, and the likelihood (and direction) of bias in the measure(s) of association due to error in exposure measurement, including misclassification (as described in Part B, Section 1f).
- **Assessment of potential confounding:** To what extent the authors took into account in the study design and analysis other variables (including co-exposures, as described in Part B, Section 1d) that can influence the risk of disease and may have been related to the exposure of interest. Important sources of potential confounding by such variables should have been addressed either in the design of the study, such as by matching or restriction, or in the analysis, by statistical adjustment. In some instances, where direct information on confounders is unavailable,

use of indirect methods to evaluate the potential impact of confounding on exposure–disease associations is appropriate (e.g. Axelson & Steenland, 1988; Richardson et al., 2014).

- **Other potential sources of bias:** Each epidemiological study is unique in its study population, its design, its data collection, and, consequently, its potential biases. All possible sources of bias are considered for their possible impact on the results. The possibility of reporting bias (i.e. selective reporting of some results and the suppression of others) should be explored.
- **Statistical methodology:** Adequacy of the statistical methods used and their ability to obtain unbiased estimates of exposure–outcome associations, confidence intervals, and test statistics for the significance of measures of association. Appropriateness of methods used to investigate confounding, including adjusting for matching when necessary and avoiding treatment of probable mediating variables as confounders. Detailed analyses of cancer risks in relation to summary measures of exposure such as cumulative exposure, or temporal variables such as age at first exposure or time since first exposure, are reviewed and summarized when available.

For the sake of economy and simplicity, in this Preamble the list of possible sources of error is referred to with the phrase "chance, bias, and confounding", but it should be recognized that this phrase encompasses a comprehensive set of concerns pertaining to study quality.

These sources of error do not constitute and should not be used as a formal checklist of indicators of study quality. The judgement of experienced experts is critical in determining how much weight to assign to different issues in considering how all of these potential sources of error should be integrated and how to rate the potential for error related to each of these considerations.

The informativeness of a study is its ability to show a true association, if there is one, between the agent and cancer, and the lack of an association, if no association exists. Key determinants of informativeness include: having a study population of sufficient size to obtain precise estimates of effect; sufficient elapsed time from exposure to measurement of outcome for an effect, if present, to be observable; presence of an adequate exposure contrast (intensity, frequency, and/or duration); biologically relevant definitions of exposure; and relevant and well-defined time windows for exposure and outcome.

(d) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to inconsistent results that are difficult to interpret or reconcile. Combined analyses of data from multiple studies may be conducted as a means to address this ambiguity. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis), and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland & O'Rourke, 2008).

The strengths of combined analyses are increased precision because of increased sample size and, in the case of pooled analyses, the opportunity to better control for potential confounders and to explore in more detail interactions and modifying effects that may explain heterogeneity among studies. A disadvantage of combined analyses is the possible lack of comparability of data from various studies, because of differences in population characteristics, subject recruitment, procedures of data collection, methods of measurement, and effects of unmeasured covariates that may differ among studies. These differences in study methods and quality can influence

results of either meta-analyses or pooled analyses. If published meta-analyses are to be considered by the Working Group, their adequacy needs to be carefully evaluated, including the methods used to identify eligible studies and the accuracy of data extracted from the individual studies.

The Working Group may conduct ad hoc meta-analyses during the course of a *Monographs* meeting, when there are sufficient studies of an exposure–outcome association to contribute to the Working Group's assessment of the association. The results of such unpublished original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies, or de novo analyses.

Irrespective of the source of data for the meta-analyses and pooled analyses, the following key considerations apply: the same criteria for data quality must be applied as for individual studies; sources of heterogeneity among studies must be carefully considered; and the possibility of publication bias should be explored.

(e) Considerations in assessing the body of epidemiological evidence

The ability of the body of epidemiological evidence to inform the Working Group about the carcinogenicity of the agent is related to both the quantity and the quality of the evidence. There is no formulaic answer to the question of how many studies of cancer in humans are needed from which to draw inferences about causality, although more than a single study in a single population will almost always be needed. The number will depend on the considerations relating to evidence described below.

After the quality of individual epidemiological studies of cancer has been assessed and the informativeness of the various studies on the association between the agent and cancer has been evaluated, a judgement is made about the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several aspects of the body of evidence (e.g. Hill, 1965; Rothman et al., 2008; Vandenbroucke et al., 2016).

A strong association (e.g. a large relative risk) is more likely to indicate causality than is a weak association, because it is more difficult for confounding to falsely create a strong association. However, it is recognized that estimates of effect of small magnitude do not imply lack of causality and may have impact on public health if the disease or exposure is common. Estimates of effect of small magnitude could also contribute useful information to the assessment of causality if level of risk is commensurate with level of exposure when compared with risk estimates from populations with higher exposure (e.g. as seen in residential radon studies compared with studies of radon from uranium mining).

Associations that are consistently observed in several studies of the same design, or in studies that use different epidemiological approaches, or under different circumstances of exposure are more likely to indicate a causal relationship than are isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (e.g. differences in study informativeness because of latency, exposure levels, or assessment methods). Results of studies that are judged to be of high quality and informativeness are given more weight than those of studies judged to be methodologically less sound or less informative.

Temporality of the association is an essential consideration: that is, the exposure must precede the outcome.

An observation that cancer risk increases with increasing exposure is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship, and there are several reasons why the shape of the exposure–response

association may be non-monotonic (e.g. Stayner et al., 2003). The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Confidence in a causal interpretation of the evidence from studies of cancer in humans is enhanced if it is coherent with physiological and biological knowledge, including information about exposure to the target organ, latency and timing of the exposure, and characteristics of tumour subtypes.

The Working Group considers whether there are subpopulations with increased susceptibility to cancer from the agent. For example, molecular epidemiology studies that identify associations between genetic polymorphisms and inter-individual differences in cancer susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. Such studies may be particularly informative if polymorphisms are found to be modifiers of the exposure–response association, because evaluation of polymorphisms may increase the ability to detect an effect in susceptible subpopulations.

When, in the process of evaluating the studies of cancer in humans, the Working Group identifies several high-quality, informative epidemiological studies that clearly show either no positive association or an inverse association between an exposure and a specific type of cancer, a judgement may be made that, in the aggregate, they suggest evidence of lack of carcinogenicity for that cancer type. Such a judgement requires, first, that the studies strictly meet the standards of design and analysis described above. Specifically, the possibility that bias, confounding, or misclassification of exposure or outcome could explain the observed results should be considered and ruled out with reasonable confidence. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of relative effect of unity (or below unity) for any observed level of exposure, (b) when considered together, provide a combined estimate of relative risk that is at or below unity, and (c) have a narrow confidence interval. Moreover, neither any individual well-designed and well-conducted study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It must be noted that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the exposure levels reported and the timing and route of exposure studied, to the intervals between first exposure and disease onset observed in these studies, and to the general population(s) studied (i.e. there may be susceptible subpopulations or life stages). Experience from studies of cancer in humans indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; therefore, latency periods substantially shorter than about 30 years cannot provide evidence of lack of carcinogenicity. Furthermore, there may be critical windows of exposure, for example, as with diethylstilboestrol and clear cell adenocarcinoma of the cervix and vagina (IARC, 2012a).

3. Studies of cancer in experimental animals

Most human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species. For some agents, carcinogenicity in experimental animals was demonstrated before epidemiological studies identified their carcinogenicity in humans. Although this observation cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) present

a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, such as strong evidence that a given agent causes cancer in experimental animals through a species-specific mechanism that does not operate in humans (see Part B, Sections 4 and 6; Capen et al., 1999; IARC, 2003), these agents are considered to pose a potential carcinogenic hazard to humans. The inference of potential carcinogenic hazard to humans does not imply tumour site concordance across species (Baan et al., 2019).

(a) Types of studies considered

Relevant studies of cancer in experimental animals are identified by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below. Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (or possibly metabolites or derivatives of the agent) (see Part A, Section 7) after a thorough evaluation of the study features (see Part B, Section 3b). Those studies that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2018).

In addition to conventional long-term bioassays, alternative studies (e.g. in genetically engineered mouse models) may be considered in assessing carcinogenicity in experimental animals, also after a critical evaluation of the study features. For studies of certain exposures, such as viruses that typically only infect humans, use of such specialized experimental animal models may be particularly important; models include genetically engineered mice with targeted expression of viral genes to tissues from which human cancers arise, as well as humanized mice implanted with the human cells usually infected by the virus.

Other types of studies can provide supportive evidence. These include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies); studies in which the end-point was not cancer but a defined precancerous lesion; and studies of cancer in non-laboratory animals (e.g. companion animals) exposed to the agent.

(b) Study evaluation

Considerations of importance in the interpretation and evaluation of a particular study include: (i) whether the agent was clearly characterized, including the nature and extent of impurities and contaminants and the stability of the agent, and, in the case of mixtures, whether the sample characterization was adequately reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration and frequency of treatment, duration of observation, and route of exposure were appropriate; (iv) whether appropriate experimental animal species and strains were evaluated; (v) whether there were adequate numbers of animals per group; (vi) whether animals were allocated randomly to groups; (vii) whether the body weight, food and water consumption, and survival of treated animals were affected by any factors other than the test agent; (viii) whether the histopathology review was adequate; and (ix) whether the data were reported and analysed adequately.

(c) Outcomes and statistical analyses

An assessment of findings of carcinogenicity in experimental animals involves consideration of (i) study features such as route, doses, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age, and duration of follow-up; (ii) the spectrum of neoplastic response, from

pre-neoplastic lesions and benign tumours to malignant neoplasms; (iii) the incidence, latency, severity, and multiplicity of neoplasms and pre-neoplastic lesions; (iv) the consistency of the results for a specific target organ or organs across studies of similar design; and (v) the possible role of modifying factors (e.g. diet, infection, stress).

Key factors for statistical analysis include: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type or lesion, and (iii) duration of survival.

Benign tumours may be combined with malignant tumours in the assessment of tumour incidence when (a) they occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) they appear to represent a stage in the progression to malignancy (Huff et al., 1989). The occurrence of lesions presumed to be pre-neoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed.

Evidence of an increased incidence of neoplasms with increasing level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms. The form of the dose–response relationship can vary widely, including non-linearity, depending on the particular agent under study and the target organ. The dose–response relationship can also be affected by differences in survival among the treatment groups.

The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life and a survival-adjusted analysis would be warranted. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time that the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel–Haenszel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the poly-*k* test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other, more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

The concurrent control group is generally the most appropriate comparison group for statistical analysis; however, for uncommon tumours, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, sex, and strain, as well as other factors, such as basal diet and general laboratory environment, which may affect tumour response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003). It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls.

Meta-analyses and pooled analyses may be appropriate when the experimental protocols are sufficiently similar.

4. Mechanistic evidence

Mechanistic data may provide evidence of carcinogenicity and may also help in assessing the relevance and importance of findings of cancer in experimental animals and in humans (Guyton et al., 2009; Parkkinen et al., 2018) (see Part B, Section 6). Mechanistic studies have gained in prominence, increasing in their volume, diversity, and relevance to cancer hazard evaluation, whereas studies pertinent to other streams of evidence evaluated in the *Monographs* (i.e. studies of cancer in humans and lifetime cancer bioassays in rodents) may only be available for a fraction of agents to which humans are currently exposed (Guyton et al., 2009, 2018). Mechanistic studies and data are identified, screened, and evaluated for quality and importance to the evaluation by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below.

The Working Group's synthesis reflects the extent of available evidence, summarizing groups of included studies with an emphasis on characterizing consistencies or differences in results within and across experimental designs. Greater emphasis is given to informative mechanistic evidence from human-related studies than to that from other experimental test systems, and gaps are identified. Tabulation of data may facilitate this review. The specific topics addressed in the evidence synthesis are described below.

(a) Absorption, distribution, metabolism, and excretion

Studies of absorption, distribution, metabolism, and excretion in mammalian species are addressed in a summary fashion; exposure characterization is addressed in Part B, Section 1. The Working Group describes the metabolic fate of the agent in mammalian species, noting the metabolites that have been identified and their chemical reactivity. A metabolic schema may indicate the relevant metabolic pathways and products and whether supporting evidence is from studies in humans and/or studies in experimental animals. Evidence on other adverse effects that indirectly confirm absorption, distribution, and/or metabolism at tumour sites is briefly summarized when direct evidence is sparse.

(b) Evidence relevant to key characteristics of carcinogens

A review of Group 1 human carcinogens classified up to and including *IARC Monographs* Volume 100 revealed several issues relevant to improving the evaluation of mechanistic evidence for cancer hazard identification (Smith et al., 2016). First, it was noted that human carcinogens often share one or more characteristics that are related to the multiple mechanisms by which agents cause cancer. Second, different human carcinogens may exhibit a different spectrum of these key characteristics and operate through distinct mechanisms. Third, for many carcinogens evaluated before Volume 100, few data were available on some mechanisms of recognized importance in carcinogenesis, such as epigenetic alterations (Herceg et al., 2013). Fourth, there was no widely accepted method to search systematically for relevant mechanistic evidence, resulting in a lack of uniformity in the scope of mechanistic topics addressed across *IARC Monographs* evaluations.

To address these challenges, the key characteristics of human carcinogens were introduced to facilitate systematic consideration of mechanistic evidence in *IARC Monographs* evaluations (Smith et al., 2016; Guyton et al., 2018). The key characteristics described by Smith et al. (2016) (see Table 3), such as "is genotoxic", "is immunosuppressive", or "modulates receptor-mediated

Table 3 The key characteristics of carcinogens

Ten key characteristics of carcinogens	
1.	Is electrophilic or can be metabolically activated to an electrophile
2.	Is genotoxic
3.	Alters DNA repair or causes genomic instability
4.	Induces epigenetic alterations
5.	Induces oxidative stress
6.	Induces chronic inflammation
7.	Is immunosuppressive
8.	Modulates receptor-mediated effects
9.	Causes immortalization
10.	Alters cell proliferation, cell death, or nutrient supply

From Smith et al. (2016).

effects", are based on empirical observations of the chemical and biological properties associated with the human carcinogens identified by the *IARC Monographs* programme up to and including Volume 100. The list of key characteristics and associated end-points may evolve, based on the experience of their application and as new human carcinogens are identified. Key characteristics are distinct from the "hallmarks of cancer", which relate to the properties of cancer cells (Hanahan & Weinberg, 2000, 2011). Key characteristics are also distinct from hypothesized mechanistic pathways, which describe a sequence of biological events postulated to occur during carcinogenesis. As such, the evaluation approach based on key characteristics, outlined below, "avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence" (National Academies of Sciences, Engineering, and Medicine, 2017).

Studies in exposed humans and in human primary cells or tissues that incorporate end-points relevant to key characteristics of carcinogens are emphasized when available. For each key characteristic with adequate evidence for evaluation, studies are grouped according to whether they involve (a) humans or human primary cells or tissues or (b) experimental systems; further organization (as appropriate) is by end-point (e.g. DNA damage), duration, species, sex, strain, and target organ as well as strength of study design. Studies investigating susceptibility related to key characteristics of carcinogens (e.g. of genetic polymorphisms, or in genetically engineered animals) can be highlighted and may provide additional support for conclusions on the strength of evidence. Findings relevant to a specific tumour type may be noted.

(c) Other relevant evidence

Other informative evidence may be described when it is judged by the Working Group to be relevant to an evaluation of carcinogenicity and to be of sufficient importance to affect the overall evaluation. Quantitative structure–activity information, such as on specific chemical and/or biological features or activities (e.g. electrophilicity, molecular docking with receptors), may be informative. In addition, evidence that falls outside of the recognized key characteristics of carcinogens, reflecting emerging knowledge or important novel scientific developments on carcinogen mechanisms, may also be included. Available evidence relevant to criteria provided in authoritative publications (e.g. Capen et al., 1999; IARC, 2003) on thyroid, kidney, urinary

bladder, or other tumours in experimental animals induced by mechanisms that do not operate in humans is also described.

(d) Study quality and importance to the evaluation

Based on formal considerations of the quality of the studies (e.g. design, methodology, and reporting of results), the Working Group may give greater weight to some included studies.

For observational and other studies in humans, the quality of study design, exposure assessment, and assay accuracy and precision are considered, in collaboration with the Working Group members reviewing exposure characterization and studies of cancer in humans, as are other important factors, including those described above for evaluation of epidemiological evidence (García-Closas et al., 2006, 2011; Vermeulen et al., 2018) (Part B, Sections 1 and 2).

In general, in experimental systems, studies of repeated doses and of chronic exposures are accorded greater importance than are studies of a single dose or time-point. Consideration is also given to factors such as the suitability of the dosing range, the extent of concurrent toxicity observed, and the completeness of reporting of the study (e.g. the source and purity of the agent, the analytical methods, and the results). Route of exposure is generally considered to be a less important factor in the evaluation of experimental studies, recognizing that the exposures and target tissues may vary across experimental models and in exposed human populations. Non-mammalian studies can be synthetically summarized when they are considered to be supportive of evidence in humans or higher organisms.

In vitro test systems can provide mechanistic insights, but important considerations include the limitations of the test system (e.g. in metabolic capabilities) as well as the suitability of a particular test article (i.e. because of physical and chemical characteristics) (Hopkins et al., 2004). For studies on some end-points, such as for traditional studies of mutations in bacteria and in mammalian cells, formal guidelines, including those from the Organisation for Economic Co-operation and Development, may be informative in conducting the quality review (OECD, 1997, 2016a, b). However, existing guidelines will not generally cover all relevant assays, even for genotoxicity. Possible considerations when evaluating the quality of in vitro studies encompass the methodology and design (e.g. the end-point and test method, the number of replicate samples, the suitability of the concentration range, the inclusion of positive and negative controls, and the assessment of cytotoxicity) as well as reporting (e.g. of the source and purity of the agent, and of the analytical methods and results). High-content and high-throughput in vitro data can serve as an additional or supportive source of mechanistic evidence (Chiu et al., 2018; Guyton et al., 2018), although large-scale screening programmes measuring a variety of end-points were designed to evaluate large chemical libraries in order to prioritize chemicals for additional toxicity testing rather than to identify the hazard of a specific chemical or chemical group.

The synthesis is focused on the evidence that is most informative for the overall evaluation. In this regard, it is of note that some human carcinogens exhibit a single or primary key characteristic, evidence of which has been influential in their cancer hazard classifications. For instance, ethylene oxide is genotoxic (IARC, 1994), 2,3,7,8-tetrachlorodibenzo-*para*-dioxin modulates receptor-mediated effects (IARC, 1997), and etoposide alters DNA repair (IARC, 2012a). Similarly, oncogenic viruses cause immortalization, and certain drugs are, by design, immunosuppressive (IARC, 2012a, b). Because non-carcinogens can also induce oxidative stress, this key characteristic should be interpreted with caution unless it is found in combination

with other key characteristics (Guyton et al., 2018). Evidence for a group of key characteristics can strengthen mechanistic conclusions (e.g. "induces oxidative stress" together with "is electrophilic or can be metabolically activated to an electrophile", "induces chronic inflammation", and "is immunosuppressive"); see, for example, 1-bromopropane (IARC, 2018).

5. Summary of data reported

(a) Exposure characterization

Exposure data are summarized to identify the agent and describe its production, use, and occurrence. Information on exposure prevalence and intensity in different settings, including geographical patterns and time trends, may be included. Exposure assessment methods used in key epidemiological studies reviewed by the Working Group are described and evaluated.

(b) Cancer in humans

Results of epidemiological studies pertinent to an evaluation of carcinogenicity in humans are summarized. The overall strengths and limitations of the epidemiological evidence base are highlighted to indicate how the evaluation was reached. The target organ(s) or tissue(s) in which a positive association between the agent and cancer was observed are identified. Exposure–response and other quantitative data may be summarized when available. When the available epidemiological studies pertain to a mixed exposure, process, occupation, or industry, the Working Group seeks to identify the specific agent considered to be most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data permit.

(c) Cancer in experimental animals

Results pertinent to an evaluation of carcinogenicity in experimental animals are summarized to indicate how the evaluation was reached. For each animal species, study design, and route of administration, there is a statement about whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or pre-neoplastic lesions was observed, and the tumour sites are indicated. Special conditions resulting in tumours, such as prenatal exposure or single-dose experiments, are mentioned. Negative findings, inverse relationships, dose–response patterns, and other quantitative data are also summarized.

(d) Mechanistic evidence

Results pertinent to an evaluation of the mechanistic evidence on carcinogenicity are summarized to indicate how the evaluation was reached. The summary encompasses the informative studies on absorption, distribution, metabolism, and excretion; on the key characteristics with adequate evidence for evaluation; and on any other aspects of sufficient importance to affect the overall evaluation, including on whether the agent belongs to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans, and on criteria with respect to tumours in experimental animals induced by mechanisms that do not operate in humans. For each topic addressed, the main supporting findings are highlighted from exposed humans, human cells or tissues, experimental animals, or in vitro systems. When mechanistic studies are available in exposed humans, the tumour type or target tissue studied may be specified. Gaps in the evidence are indicated (i.e. if no studies were available in exposed humans, in in vivo systems, etc.). Consistency or differences of effects across different experimental systems are emphasized.

6. Evaluation and rationale

Consensus evaluations of the strength of the evidence of cancer in humans, the evidence of cancer in experimental animals, and the mechanistic evidence are made using transparent criteria and defined descriptive terms. The Working Group then develops a consensus overall evaluation of the strength of the evidence of carcinogenicity for each agent under review.

An evaluation of the strength of the evidence is limited to the agents under review. When multiple agents being evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single and unified evaluation of the strength of the evidence.

The framework for these evaluations, described below, may not encompass all factors relevant to a particular evaluation of carcinogenicity. After considering all relevant scientific findings, the Working Group may exceptionally assign the agent to a different category than a strict application of the framework would indicate, while providing a clear rationale for the overall evaluation.

When there are substantial differences of scientific interpretation among the Working Group members, the overall evaluation will be based on the consensus of the Working Group. A summary of the alternative interpretations may be provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

The categories of the classification refer to the strength of the evidence that an exposure is carcinogenic and not to the risk of cancer from particular exposures. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used as descriptors of different strengths of evidence of carcinogenicity in humans; *probably carcinogenic* signifies a greater strength of evidence than *possibly carcinogenic*.

(a) Carcinogenicity in humans

Based on the principles outlined in Part B, Section 2, the evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** A causal association between exposure to the agent and human cancer has been established. That is, a positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.

***Limited evidence of carcinogenicity*:** A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence regarding carcinogenicity*:** The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and cancer, or no data on cancer in humans are available. Common findings that lead to a determination of inadequate evidence of carcinogenicity include: (a) there are no data available in humans; (b) there are data available in humans, but they are of poor quality or informativeness; and (c) there are studies of sufficient quality available in humans, but their results are inconsistent or otherwise inconclusive.

***Evidence suggesting lack of carcinogenicity*:** There are several high-quality studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and the studied cancers at any

observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit below or close to the null value (e.g. a relative risk of unity). Bias and confounding were ruled out with reasonable confidence, and the studies were considered informative. A conclusion of *evidence suggesting lack of carcinogenicity* is limited to the cancer sites, populations and life stages, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

When there is *sufficient evidence*, a separate sentence identifies the target organ(s) or tissue(s) for which a causal interpretation has been established. When there is *limited evidence*, a separate sentence identifies the target organ(s) or tissue(s) for which a positive association between exposure to the agent and the cancer(s) was observed in humans. When there is *evidence suggesting lack of carcinogenicity*, a separate sentence identifies the target organ(s) or tissue(s) where evidence of lack of carcinogenicity was observed in humans. Identification of a specific target organ or tissue as having *sufficient evidence* or *limited evidence* or *evidence suggesting lack of carcinogenicity* does not preclude the possibility that the agent may cause cancer at other sites.

(b) Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity from studies in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** A causal relationship has been established between exposure to the agent and cancer in experimental animals based on an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories and/or under different protocols. An increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices (GLP), can also provide *sufficient evidence*.

Exceptionally, a single study in one species and sex may be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour, or age at onset, or when there are marked findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment and does not meet the criteria for *sufficient evidence*; (b) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; (c) the agent increases tumour multiplicity or decreases tumour latency but does not increase tumour incidence; (d) the evidence of carcinogenicity is restricted to initiation–promotion studies; (e) the evidence of carcinogenicity is restricted to observational studies in non-laboratory animals (e.g. companion animals); or (f) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.

***Inadequate evidence regarding carcinogenicity*:** The studies cannot be interpreted as showing either the presence or the absence

of a carcinogenic effect because of major qualitative or quantitative limitations, or no data are available on cancer in experimental animals.

***Evidence suggesting lack of carcinogenicity*:** Well-conducted studies (e.g. conducted under GLP) involving both sexes of at least two species are available showing that, within the limits of the tests used, the agent was not carcinogenic. The conclusion of *evidence suggesting lack of carcinogenicity* is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure covered by the available studies.

(c) Mechanistic evidence

Based on the principles outlined in Part B, Section 4, the mechanistic evidence is classified into one of the following categories:

***Strong mechanistic evidence*:** Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. Further support can be provided by studies that demonstrate experimentally that the suppression of key mechanistic processes leads to the suppression of tumour development. Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species. Quantitative structure–activity considerations, in vitro tests in non-human mammalian cells, and experiments in non-mammalian species may provide corroborating evidence but typically do not in themselves provide strong evidence. However, consistent findings across a number of different test systems in different species may provide strong evidence.

Of note, "strong" relates not to potency but to strength of evidence. The classification applies to three distinct topics:

(a) Strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans. The considerations can go beyond quantitative structure–activity relationships to incorporate similarities in biological activity relevant to common key characteristics across dissimilar chemicals (e.g. based on molecular docking, –omics data).

(b) Strong evidence that the agent exhibits key characteristics of carcinogens. In this case, three descriptors are possible:

1. The strong evidence is in exposed humans. Findings relevant to a specific tumour type may be informative in this determination.
2. The strong evidence is in human primary cells or tissues. Specifically, the strong findings are from biological specimens obtained from humans (e.g. ex vivo exposure), from human primary cells, and/or, in some cases, from other humanized systems (e.g. a human receptor or enzyme).
3. The strong evidence is in experimental systems. This may include one or a few studies in human primary cells and tissues.

(c) Strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Certain results in experimental animals (see Part B, Section 6b) would be discounted, according to relevant criteria and considerations in authoritative publications (e.g. Capen et al., 1999; IARC, 2003). Typically, this classification would not apply when there is strong mechanistic evidence that the agent exhibits key characteristics of carcinogens.

***Limited mechanistic evidence*:** The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in the studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.

***Inadequate mechanistic evidence*:** Common findings that lead to a determination of inadequate mechanistic evidence include: (a) few or no data are available; (b) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the studies; (c) the available results are negative.

(d) Overall evaluation

Finally, the bodies of evidence included within each stream of evidence are considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans. The three streams of evidence are integrated and the agent is classified into one of the following categories (see Table 4), indicating that the Working Group has established that:

The agent is carcinogenic to humans (Group 1)

This category applies whenever there is *sufficient evidence of carcinogenicity* in humans.

In addition, this category may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals.

The agent is probably carcinogenic to humans (Group 2A)

This category generally applies when the Working Group has made at least *two of the following* evaluations, *including at least one* that involves either exposed humans or human cells or tissues:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,
- *Strong evidence that the agent exhibits key characteristics of carcinogens.*

If there is *inadequate evidence regarding carcinogenicity* in humans, there should be *strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*. If there is *limited evidence of carcinogenicity in humans*, then the second individual evaluation may be from experimental systems (i.e. s*ufficient evidence of carcinogenicity* in experimental animals or *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens).*

Additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2A.

Separately, this category generally applies if there is *strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A*.

The agent is possibly carcinogenic to humans (Group 2B)

This category generally applies when only one of the following evaluations has been made by the Working Group:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,

Table 4 Integration of streams of evidence in reaching overall classifications (the evidence in *bold italic* represents the basis of the overall evaluation)

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a]	**Evidence of cancer in experimental animals**	**Mechanistic evidence**	
Sufficient	Not necessary	Not necessary	**Carcinogenic to humans (Group 1)**
Limited or Inadequate	***Sufficient***	***Strong (b)(1) (exposed humans)***	
Limited	***Sufficient***	Strong (b)(2–3), Limited, or Inadequate	**Probably carcinogenic to humans (Group 2A)**
Inadequate	***Sufficient***	***Strong (b)(2) (human cells or tissues)***	
Limited	Less than Sufficient	***Strong (b)(1–3)***	
Limited or Inadequate	Not necessary	***Strong (a) (mechanistic class)***	
Limited	Less than Sufficient	Limited or Inadequate	**Possibly carcinogenic to humans (Group 2B)**
Inadequate	***Sufficient***	Strong (b)(3), Limited, or Inadequate	
Inadequate	Less than Sufficient	***Strong b(1–3)***	
Limited	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	
Inadequate	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	**Not classifiable as to its carcinogenicity to humans (Group 3)**
All other situations not listed above			

[a] Human cancer(s) with highest evaluation

[b] The *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* must specifically be for the tumour sites supporting the classification of *sufficient evidence in experimental animals*.

• *Strong evidence that the agent exhibits key characteristics of carcinogens.*

Because this category can be based on evidence from studies in experimental animals alone, there is **no** requirement that the strong mechanistic evidence be in exposed humans or in human cells or tissues. This category may be based on *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens.*

As with Group 2A, additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2B.

The agent is not classifiable as to its carcinogenicity to humans (Group 3)

Agents that do not fall into any other group are generally placed in this category.

This includes the case when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites in experimental animals, the remaining tumour sites do not support an evaluation of *sufficient evidence in experimental animals*, and other categories are not supported by data from studies in humans and mechanistic studies.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent is of unknown carcinogenic potential and that there are significant gaps in research.

If the evidence suggests that the agent exhibits no carcinogenic activity, either through *evidence suggesting lack of carcinogenicity* in both humans and experimental animals, or through

evidence suggesting lack of carcinogenicity in experimental animals complemented by strong negative mechanistic evidence in assays relevant to human cancer, then the Working Group may add a sentence to the evaluation to characterize the agent as well-studied and without evidence of carcinogenic activity.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is summarized so that the basis for the evaluation offered is transparent. This section integrates the major findings from studies of cancer in humans, cancer in experimental animals, and mechanistic evidence. It includes concise statements of the principal line(s) of argument that emerged in the deliberations of the Working Group, the conclusions of the Working Group on the strength of the evidence for each stream of evidence, an indication of the body of evidence that was pivotal to these conclusions, and an explanation of the reasoning of the Working Group in making its evaluation.

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GENERAL REMARKS

This one-hundred-and-twenty-fourth volume of the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* contains evaluations of the carcinogenic hazard to humans of night shift work.

This agent was considered previously by a Working Group as "shift work that involves circadian disruption" in Volume 98 (IARC, 2010) and was evaluated as "*probably carcinogenic to humans* (Group 2A)". A substantial proportion of the working population is exposed to night shift work. In Volume 98 of the *IARC Monographs* (IARC, 2010), evidence related to cancer in humans and cancer in experimental animals formed the basis of the Working Group's evaluation of "shift work that involves circadian disruption" as Group 2A. Since the previous evaluation, new data have become available for these areas and for carcinogen mechanisms, and these data have been included and considered in the present volume.

A summary of the findings of this volume appears in *The Lancet Oncology* (Ward et al., 2019).

Scope of systematic review

Volume 124 of the *IARC Monographs* represents a milestone for the *IARC Monographs* programme, as the first volume to be published under the amended Preamble to the *IARC Monographs* adopted in 2019 (IARC, 2019; Samet et al., 2020; available from: https://monographs.iarc.fr/iarc-monographs-preamble-preamble-to-the-iarc-monographs/). An important aspect of the Preamble is the enhanced documentation of systematic review practices to identify, screen, and select the studies related to cancer in humans, cancer in experimental animals, and mechanistic evidence for each agent. For Volume 124, the scope of the systematic review encompassed a comprehensive search of the literature, focusing on an agent name reflecting variations on "night shift work", "transmeridian travel", or "circadian disruption", and standardized terms for each of the relevant outcomes (cancer and mechanisms). As a result of the sparse and inconsistent evidence regarding cancer risk associated with variations in melatonin secretion (see "Melatonin in humans" below), the Working Group elected not to evaluate melatonin as part of the agent name in relation to cancer risk in humans. The literature tree, including the full set of search terms for the agent name and each outcome type, is available at: https://hawcproject.iarc.who.int/assessment/605/.

Agent name

For Volume 124, the Working Group re-evaluated an agent previously considered in Volume 98 (IARC, 2010) and entitled "shift work that involves circadian disruption". For the current evaluation, the Working Group elected to change the agent name to "night shift work" in order to better reflect the main evidence base for the studies of cancer in humans, and to avoid mixing the exposure with the potential health effects or mechanisms. Furthermore, as noted in Section 1 of the monograph, measuring circadian disruption itself proves challenging, which argued against invoking it as part of the agent name. The Working Group was careful to note that this new agent name encompasses workers in fixed locations (e.g. hospital, call centre, or factory) as well as those involved in transmeridian air travel (e.g. aircrew).

Working at night involves work during the regular sleeping hours of the general population. This alters exposure to the regular photoperiod and may disrupt circadian rhythms in humans. Working at night is connected to the perturbation of the natural cycle of sleep and wakefulness, and related patterns of activity and rest (e.g. mealtimes, social life), as staying awake at night and trying to sleep during the day is not a physiological condition for "diurnal" creatures like humans.

Trends in night shift work

The nature of night shift work is changing, with decreases in traditional work arrangements, but also increases in irregular and temporary work arrangements. This is likely to have an impact on researchers' ability to accurately assess exposures over the lifespan, and on the development of evidence-based recommendations to support worker health. This further supports the need for strong methodological approaches to assess exposure to night shift work in epidemiological studies.

Regulation with respect to cancer patients

Regulations on shift work are in place in many countries. These regulations do not address explicitly the question regarding return to shift work for cancer patients after treatment. Particularly considering increasing survival rates (e.g. for cancers of the breast and prostate), evidence-based research on this topic was a notable gap.

Exposure assessment quality

The Working Group has noted improvements in exposure assessment methods in epidemiological studies of night shift work and cancer since Volume 98 and the subsequent IARC workshop on exposure assessment of shift work (Stevens et al., 2011). The recommendations made in Stevens et al. (2011) have been incorporated in several case–control studies, allowing assessment of aspects of shift work (e.g. number of consecutive shifts, number of shifts per week or month) that may have an impact on health. The recommendations made by Stevens and colleagues have not been adopted to the same extent in cohort studies, with some exceptions (e.g. Pijpe et al., 2014). Therefore, it remains unclear whether the observed differences in associations between night shift work and breast cancer in case–control versus cohort studies are related to differences in exposure assessment quality across these study designs. In addition to continuing research using case–control studies, the quality of exposure assessment in cohort studies should be improved through implementation

of the recommendations made by Stevens et al. (2011). This is important to reduce heterogeneity in results between studies, allowing for better comparisons of evidence, and facilitating the development of effective public health interventions. To advise on work schedules that may be more or less detrimental for health, evidence-based insight into the most important aspects of night shift work is imperative.

Harmonization of terminology for aircrew studies

The Working Group noted the wide variation in terminology describing aircraft cockpit and cabin crew occupations. To better harmonize this terminology throughout the monograph, the Working Group adopted the following terms throughout (except where giving more specific description of the studied group): "aircrew" was used to designate cockpit and cabin crew, when used collectively; "cockpit crew" was used to designate pilots and flight engineers; and "cabin crew" was used to designate flight attendants and other airborne workers not in the cockpit.

Considerations regarding studies of cancer in humans

The Working Group considered but ultimately decided not to conduct a new meta-analysis of breast or other cancers for the present monograph, despite the existence of a relatively large number of studies for some cancer sites. The rationale was 2-fold: (1) the existence of a recent, large pooled case–control study that combined the most informative studies on breast cancer; and (2) the heterogeneity of the exposure methods used in the cohort studies, which presented a considerable challenge when pooling effect estimates.

The Working Group noted that differentiating the effects of age at exposure from age at risk is very difficult (if not impossible) in the studies of cancer in humans, hampering interpretation of some of the animal bioassay evidence and its relevance to humans (e.g. stronger effects were seen in some animal bioassays after exposures before or near puberty). Health effects of night shift work may differ across latitude and season. Similarly, factors related to night shift work (and also, potentially, to cancer) such as sunlight exposure and physical activity may also differ across latitude and season.

General comments on experimental systems

Studies in a variety of experimental systems were available to the Working Group, including the traditional experimental rodent species – rats (usually *Rattus norvegicus*), mice (usually *Mus musculus*), and hamsters (usually *Mesocricetus auratus*). These species are considered nocturnal (National Research Council, 2011). Certain strains of mice (e.g. BALB/c, C57BL/6J) do not synthesize endogenous melatonin because of a mutation in the *Aanat* gene, resulting in non-functional arylalkylamine *N*-acetyltransferase (AANAT), an enzyme involved in melatonin synthesis (Roseboom et al., 1998; Kasahara et al., 2010). A limited number of studies have used nonhuman primates including capuchin monkey (*Cebus apella*) and rhesus macaques (*Macaca mulatta*). Monkeys demonstrate diurnal behaviour patterns. Several studies also used diurnal rodents (e.g. fat sand rats, *Psammomys obesus*; Sudanian grass rats, *Arvicanthis ansorgei*) and one nocturnal marsupial species (tammar wallaby, *Macropus eugenii*). Some inconsistencies were seen between these various model systems and traditional laboratory animals.

The Working Group also noted that direct experimental evidence for night shift work in experimental models is incomplete since the experimental systems rely instead on alterations in the light–dark schedule as a proxy for night shift work. Experimental designs used with experimental systems can vary significantly from short-term alterations in the light–dark schedule to continuous light or continuous darkness over one or more days. Exposure in animal models can involve the following experimental conditions:

- Light exposure involving visible light intensity for a variable time duration that occurs during the period of darkness in animals kept under artificial schedules consisting of 12 hours of light followed by 12 hours of darkness (LD12:12), such as those in current use in research animal facilities.
- Light exposure can occur repeatedly during the period of darkness or can be repeated during multiple periods of darkness at any frequency.
- Continuous light exposure, as part of the light-at-night paradigm
- The suppression of melatonin secretion by the pineal gland (includes pinealectomy)
- Phase shift of physiological and molecular circadian rhythms in the whole organism
- Disruption of the circadian timing system, as defined by the suppression and/or the internal desynchronization of circadian rhythms in behaviour, physiology, expression of clock genes, or other molecular or biochemical parameters in various tissues.

Experimental details concerning light intensity during animal husbandry procedures were sometimes lacking in the reviewed studies. Increases in daytime room illumination for maintenance purposes have been shown to change photoreceptor physiology and can alter circadian regulation (Remé et al., 1991; Terman et al., 1991; National Research Council, 1996). In addition, many studies used a light–dark schedule consisting of 12 hours of light followed by 12 hours of darkness as the control situation. Abrupt light and dark transitions are common in animal housing facilities, and do not reflect natural lighting conditions.

Circadian rhythm and clock genes

Hormone secretion, cellular function, and metabolism fluctuate throughout the day (Gamble et al., 2014; Tsang et al., 2016; Neumann et al., 2019). Circadian rhythm is generated through circadian variation in the expression of clock genes. Light and related melatonin production is one of several factors affecting circadian rhythm. Light signals detected by the eyes can synchronize through the retinohypothalamic tract the phase of the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN sends synchronization signals to other cells putatively by hormone secretion, sympathetic innervation, and indirect cues including body temperature, feeding time, and activity (Herzog, 2007). While the light–dark information is not critical for the SCN to orchestrate behavioural and physiological rhythms, the photic inputs are essential for the resetting the circadian phase in the SCN pacemaker, and, hence, synchronization of the peripheral clocks (Dallmann et al., 2016).

The first mammalian clock gene, clock circadian regulator, *Clock*, was cloned in 1997 (King et al., 1997). Since then at least 14 core clock genes have been reported, including *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *Bmal1*, *Tim, Ck1ε*, *Npas2*, *Rev-Erbs*, *Dec1*, *Dec2*, and *Rors*. These genes demonstrate oscillating expression with a rhythmicity of 24 hours (e.g. Hamada et al., 2016). Clock genes help coordinate and synchronize different physiological processes. Interdependent transcriptional–translational feedback loops exist

in cells that contribute to circadian cycles (Bozek et al., 2009). For example, the transcription factor heterodimer Clock:Bmal1 activates the expression of period circadian regulator genes (*Per1*, *Per2,* and *Per3*), cryptochrome genes (*Cry1* and *Cry2*), and nuclear receptors (*Rev-erbα*, *Rorα*). Per and Cry proteins form complexes and repress their own expression by interacting with the Clock:Bmal1 dimer. Rev-erbα and Rorα regulate the transcription of *Bmal1* in a separate feedback loop through retinoic acid receptor-related orphan receptor (ROR) regulatory elements (Solt et al., 2011). Clock output genes (e.g. *Dbp*, *Hlf*, *Tef*, *E4bp4*) regulate clock-controlled genes. Other cell cycle genes are under the direct influence of the circadian clock and include *Wee1*, *Myc*, cyclin D1, and *Tp53* (Hassan et al., 2018). Circadian genes are involved in the regulation of cell division (Hunt & Sassone-Corsi, 2007; Li et al., 2016). Mutant mice deficient in a second clock gene, *Per2*, results in disrupted circadian rhythms, alterations in the expression of genes (e.g. cyclin D1, cyclin A, *Mdm2*, and *GADD45a*) involved in cell proliferation and tumour suppression, and increased tumour incidence (Fu et al., 2002; Matsuo et al., 2003). Mutations in clock genes, such as *Per, Cry,* or *Bmal1,* or chronic disruption of circadian homeostasis, promote genomic instability, induce immune suppression and metabolic dysfunction, and increase the risk of cancer in experimental animals (Fu et al., 2002; Anisimov et al., 2004; Yang et al., 2009; Lee et al., 2010; Anisimov et al., 2012; Geyfman et al., 2012; Kettner et al., 2016; Papagiannakopoulos et al., 2016).

Melatonin in humans

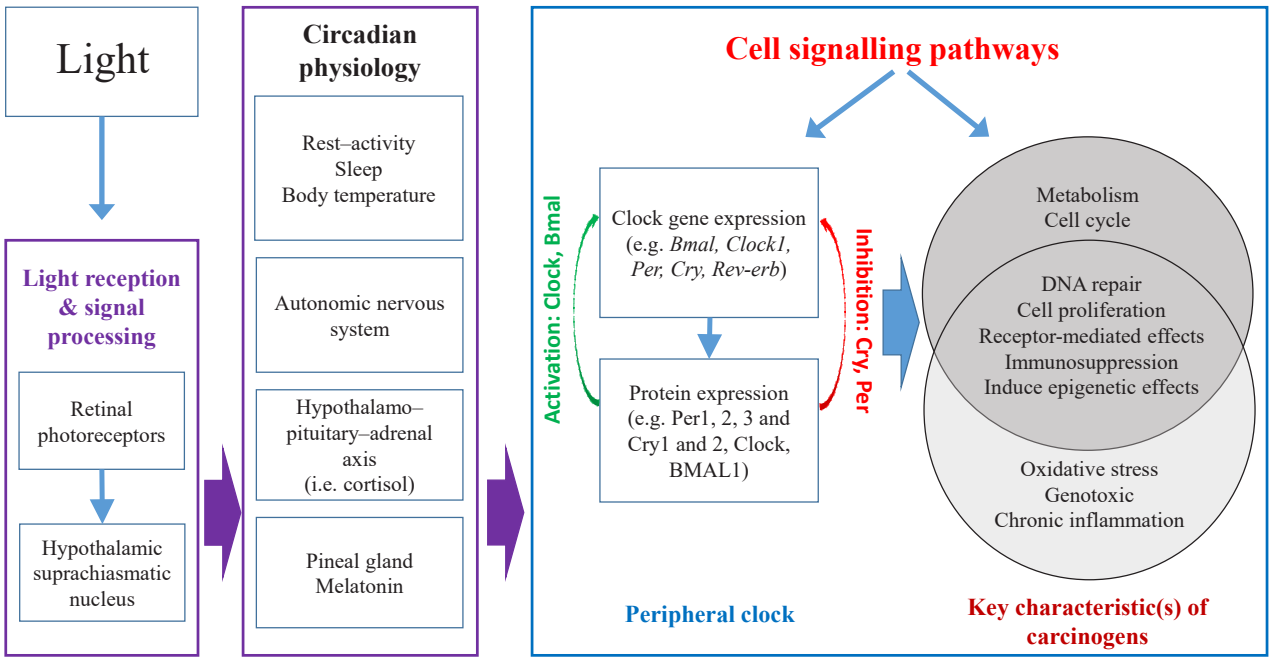
Production of melatonin (*N*-acetyl-5-methoxytryptamine), a hormone secreted by the pineal gland, is rhythmically regulated by the SCN in the hypothalamus. Under the regular alterations of light and darkness over 24 hours, melatonin is the main synchronizer of circadian rhythms. Melatonin secretion increases at night and reaches highest plasma concentrations near 02:00 on average in humans. Melatonin secretion is generally suppressed in the presence of light at night (Bojkowski et al., 1987; Lewy et al., 1980). Even brief (i.e. minutes) exposure to light during hours of natural darkness can alter melatonin production in mammals. Light exposure can also shift the phase of the melatonin rhythm, with exposure to bright light intensities during morning hours being associated with a phase advance, while exposure during evening hours is associated with a phase delay (Duffy & Wright, 2005). Recent data highlight the critical role of blue light in eliciting melatonin responses (e.g. Tanito et al., 2018).

Melatonin metabolism occurs mainly in the liver, where it is hydroxylated and then conjugated as sulfate and excreted mainly as 6-sulfatoxymelatonin (Claustrat et al., 2005). Urinary and salivary 6-sulfatoxymelatonin excretion has been used as a means of monitoring melatonin circadian rhythmicity (Nowak et al., 1987).

Melatonin has diverse pharmacological effects, many of which are mediated through melatonin receptors found in multiple tissues and organs (Reiter et al., 2017; Bondy & Campbell, 2018; Favero et al., 2018). Melatonin also has antioxidant properties secondary to its action as a free-radical scavenger (Tan et al., 2003; Tosini et al., 2014).

Studies linking melatonin secretion to cancer risk are few, and results are inconsistent. For example, a pooled analysis of six independent studies of breast cancer indicated that urinary concentration of 6-hydroxymelatonin sulfate (aMT6s) in the morning hours was not associated with risk of breast cancer (relative risk, 0.97; 95% confidence interval, CI, 0.88–1.08). This result did not vary by menopausal status, estrogen receptor status, or when using 12-hour overnight urine sampling. Time lag between measurement

Fig. 1 Effects of light on circadian physiology and key characteristics of carcinogens



and degree of invasiveness did not affect the results, and no publication bias was detected (Xu et al., 2017); however, in the majority of studies, melatonin measurement followed diagnosis, which might have induced bias.

Fig. 1 illustrates some of the effects of light on circadian physiology, including alterations in sleep, rest, and eating patterns, impacts on the autonomic nervous system and behaviour, disruption of the circadian timing system, as well as changes in body temperature and in melatonin secretion by the pineal gland. The effects on expression of clock genes and other molecular or biochemical parameters are shown as an illustration of the association with key characteristics of carcinogens.

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1. EXPOSURE DATA

1.1 Identification of the agent

"Night shift work" involves work, including transmeridian travel, that occurs during the regular sleeping hours of the general population. This alters exposure to the natural light–dark schedule and disrupts circadian rhythms.

"Night" or "night time" is generally defined as the period from sunset to sunrise in each 24 hours. Human biological night depends on individual circadian rhythms, but normally includes the timeframe from 23:00 to 07:00 that most adults use for sleeping; this can vary according to, for example, cultural and other differences.

Shift work is defined by the International Labour Organization (ILO) (ILO, 1990a, b) as "a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers". According to the European Working Time Directive No. 2003/88/EC (WTD) concerning certain aspects of the organization of working time, "shift work means any method of organising work in shifts whereby workers succeed each other at the same work stations according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks" and "shift worker means any worker whose work schedule is part of shift work" (European Commission, 2003).

Shift work arrangements may extend work to all 24 hours of the day, including night hours, by alternating different workers and/or teams.

As defined by the ILO, night work means "all work which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 a.m."; consequently, "night worker means an employed person whose work requires performance of a substantial number of hours of night work which exceeds a specified limit" (ILO, 1990a, b).

The European Union (EU) WTD definition of "night time" is the same as that set by the ILO, and the "night worker" is someone who (a) "during night time, works at least three hours of his daily working time as a normal course" or (b) "is likely during night time to work a certain proportion of his annual working time, as defined at the choice of the Member State concerned" by national legislation or by collective agreements, or agreement between two sides of industry (European Commission, 2003) (see Section 1.4).

In the present "24/7 society" (24 hours per day, 7 days per week), shift work may involve various forms of flexible, variable, irregular, and non-standard working hours, including evening and night work, split shifts, staggered working hours, compressed work weeks, weekend work, on-call work, and on-demand work. There exists a myriad of shift systems that can differ widely according to the following main features (Knauth, 1993, 1996, 1998; Kogi, 2001; Bambra et al., 2008).

1. *With or without night work*. The working time can be extended to all or part of the night, and the number of nights worked per week, month, or year can vary considerably. "Night work" is generally considered to be work performed during the usual sleeping hours, but the legal "period of night work" varies between countries; for example, it ranges between 19:00–22:00 and 05:00–08:00 in some countries, and between 23:00 to midnight and 05:00–06:00 in others (see Section 1.4).

2. *Continuous or discontinuous*. In the case of continuous shift work, every day of the week is covered by the shift system; in the case of discontinuous shift work, work does not occur every day of the week (e.g. no work takes place during the weekend).

3. *Permanent or rotating*. For permanent shift work, the same shift is always worked by any particular employee (morning, afternoon, or night); for rotating shift work, the shift assigned to a particular employee changes regularly.

4. *Length of the shift cycle*. A "cycle" includes all shifts and rest days up until the series of shifts and rest days restarts from the same point; cycles may range in length from days to weeks or months.

5. *Duration of individual shifts*. In many cases, shift duration is approximately 8 hours; however, it can range from less than 8 hours (more common in part-time work) to 12 hours or longer. [The Working Group noted that long commuting hours can further prolong work time (e.g. Costa et al., 1988).]

6. *Start and end time of individual shifts*. Morning shift may start between 04:00 and 08:00, and night shift may start between 18:00 and midnight. End times vary according to type of shift schedule and duration of shifts.

7. *Number of consecutive shifts*. The number of consecutive night shifts is relevant for both permanent and rotating night work. In studies of rotating night work, "speed of rotation" is sometimes used to describe this concept. A "fast" speed of rotation indicates fewer consecutive night shifts than a "slow" speed of rotation (exact definitions vary).

8. *Direction of shift rotation*. This can be clockwise (also called "forward" or "delaying", i.e. changing from a morning to an afternoon shift, or from an afternoon to a night shift) or counter-clockwise (also called "backward" or "advancing", i.e. changing from an afternoon to a morning shift, or from a morning to a night shift), producing different periods of rest between shifts.

9. *Number and position of rest days along the shift cycle and between shifts*. The number and position of rest days is relevant for both permanent and rotating shift work, with the potential for "quick returns", generally defined as less than 11 hours between shifts.

10. *Regularity or irregularity of the shift schedule*.

A circadian disruption (Haus & Smolensky, 2006; Stevens et al., 2011; Vetter, 2020 of the harmonic organization and synchronization of biological processes can occur to a greater or lesser degree according to the specific characteristics of different shift systems (see Section 1.3.1(b)).

Transmeridian flights typically involve night work and rapid travel across multiple time zones for aircrew. The related interference with circadian rhythms, in terms of both de- and resynchronization, depends on flight direction (i.e. resynchronization is slower and jetlag is more severe when flying eastwards rather than westwards), number of time zones crossed, length of rest period, and the circadian characteristics of the individual (Wegmann et al., 1983; Härmä et al., 1994; Sack et al., 2007).

1.2 Applications and drivers of night shift work

In past decades, shift and night work were essentially used for guaranteeing round-the-clock activities related to the provision of essential basic services to the general population (e.g. supply of light, water, and gas; health care; transport; security; and telecommunications), to address technological constraints (e.g. power plants, metallurgy, and the chemical industry), and to increase the labour productivity and economic profitability of enterprises (e.g. the manufacturing industry).

In the modern 24/7 society, shift and night shift work are key features of work organization. They permit globalization of the labour market and enhance economic competition by enabling nonstop activities favoured by the development of new technologies (e.g. information and communication technologies) and productive and commercial strategies (e.g. just-in-time operation and logistics), and the increased exploitation of leisure time (e.g. tourism and entertainment) (Presser, 2003; Anttila & Oinas, 2018).

Shift and night shift work are therefore the cornerstones of the so-called "temporal flexibility" that characterizes current trends in the diversification of working time patterns of modern society. Such working time patterns are rapidly changing in terms of both economic and productive strategies (e.g. the "gig economy"), as well as social organization and individual behaviour (ILO, 2018).

At present, there are large variations in the conceptualization and approaches to "flexible working hours" among countries, industries, and companies, according to different cultures, history, socioeconomic conditions, work sectors, the power of unions, and industrial relations (ILO, 2018). Furthermore, there are different perspectives concerning "temporal flexibility" between employers and employees: employers may view "temporal flexibility" in terms of prompt adaptation of production and/or service systems to market demands and to technological and organizational innovations, whereas employees may tend to view it in terms of decreasing work constraints and increasing control over working time (Costa et al., 2004).

Atypical and irregular working hours may also vary with type of employment. In recent years, increasing numbers of workers have been engaged in temporary jobs (particularly in the tertiary sector, e.g. services), which are often associated with unpredictable and variable working hours (e.g. split shifts, on-call work), including night shift work (Marmot et al., 2006). Consequently, the interaction between employment status and various working time patterns may have a different impact on the health and well-being of workers, depending on different degrees and combinations of job insecurity, self-employment, work intensity, time pressure, and low control over working time experienced by temporary workers (Bartley et al., 2006; Hall, 2017).

Furthermore, there is an increasing global trend for new forms of work organization connected to modern information and communication technologies, which have revolutionized everyday work and life in the 21st century (Boulin et al., 2006). Evolving information and communication technologies have led to the extension of shift and night work to sectors previously not or only marginally involved, such as banking and insurance, radio and television broadcasting, and technical assistance (e.g. call centres) (ILO, 2018). A recent joint ILO–Eurofound report indicated that the working hours of teleworking and/or mobile information and communication technologies workers were typically longer than their office-based counterparts, with blurred lines between work and private life. This was particularly the case for workers who performed supplemental work on top of office work (as opposed to those who substituted work at home for office work) (EuroFound/ILO, 2017).

Because the variability and irregularity of working hours of such work arrangements are also partially linked to autonomous choices of workers, they are difficult to monitor and can elude the usual methods of recording and also assessment in terms of impact on human health.

Section 1.3.1(b) contains additional sector-specific information on night shift work prevalence and trends.

1.3 Exposure characterization

1.3.1 Prevalence and trends

The definitions, quality, and extent of statistical data on the number of shift and night shift workers vary worldwide, making direct comparisons between regions difficult. It should also be noted that, particularly in countries with economies in transition, shift work, and night shift work are often associated with poor living and working conditions, high workloads, and long working hours (Ahasan et al., 1999; Fischer, 2001), which may exacerbate the impact of shift and night shift work on health.

(a) General summary

In Europe, results from the latest EU Labour Force Survey (Eurostat, 2019), covering 28 European countries, indicated that 16.7% of employed men and 9.4% of employed women worked night shifts in 2018. The overall percentage of employed people working nights decreased slightly between the 2009 and 2018 surveys (from 14.9% to 13.3%). The most prevalent types of shift work are alternating or rotating shifts, followed by permanent shifts (EuroFound, 2017). "Atypical work", including night work, weekend work (working both Saturday and Sunday), and shift work, is more prevalent among men than women, among the self-employed than the non-self-employed, and during the earliest stage of working life; within Europe, it is most prevalent in the Anglo-Saxon, Central–Eastern, and Southern country clusters (EuroFound, 2017).

In Africa, a survey conducted in Senegal in 2005 found that of the nine companies interviewed (covering the business sectors of chemicals, food, oil and gas, energy, agribusiness, metallurgy, textiles, and fishing), 89% used shift systems and 20% of employees reported working at least one night per week (Ndiaye, 2006).

In the USA, the Bureau of Labor Statistics reported that in 2004 over 27 million full-time wage and salary workers had flexible work schedules, with 14.8% usually working a shift other than a daytime schedule: 4.7% worked evening shifts (any time between 14:00 and midnight), 3.2% worked night shifts (anytime between 21:00 and 08:00), 3.1% worked employer-arranged irregular schedules, and 2.5% worked rotating shifts including evenings or nights (US Bureau of Labor Statistics, 2005). More recent estimates from a different data source, the 2015 National Health Interview Survey – Occupational Health Supplements survey (NIOSH, 2015) based on 19 456 adults, indicated that 27% of the working population are involved in shift work ("any alternative shift" including evening, night, and rotating shifts); the unadjusted prevalence is 28% for men and 25% for women. Approximately 11 million adults (7.4% of the working population) were estimated to perform night work (any time between 01:00 and 05:00) frequently ("more than 5 times in the past 30 days"). This was more common among men (9.1% versus (vs) 5.6% for women), blacks (10.5% vs 7.1% for whites and 6.5% for "other"), non-Hispanics (7.6% vs 6.6% for Hispanics), workers with a high school education (10.1% vs 7.7% for less than high school and 6.6% for beyond high school education), and in younger age groups (8.6% of those aged 18–29 years vs 7.8% of those aged 30–44 years, 6.9% of those aged 45–64 years, and 3.7% of those aged 65 years and older) (unadjusted prevalences) (NIOSH, 2015).

In Canada, according to the Survey of Labour and Income Dynamics carried out in 2011, 2.0% of workers were engaged in regular night or graveyard shifts, 9.4% in rotating shifts, and 12.3% in irregular schedules (Statistics Canada, 2013). From 1996 to 2011, decreasing proportions of Canadian workers reported regular day schedules (from 68.4% to 66.1%) and rotating shifts (from 10.1% to 9.4%), and slight increases were noted in the proportions of workers reporting regular night shifts (from 1.7% to 2.0%) and irregular schedules (from 9.7% to 12.3%) (Statistics Canada, 2009a, b, 2013; Hall, 2017).

In South America in 2002, 23% of companies in Chile use shift systems; 61% of these include night work, suggesting that 15% of all employees in this country perform night shift work (Echeverría, 2002). According to the national survey carried out in Brazil in 2016, 7.6% of the working population (or approximately 7 million individuals) performed work at night (PNAD, 2016).

In China, a working time survey of 300 enterprises in three major cities (Beijing, Changsha, and Guangzhou) undertaken between 2003 and 2004 found that 17.5% of employees performed night work at least once per month (Zeng et al., 2005). In Japan, a recent study based on government surveys reported that the prevalence of night shift work among Japanese employees increased over the last two decades from 13.3% in 1997 to 17.8% in 2002, 17.9% in 2007, and 21.8% in 2012 (Kubo, 2014). It was estimated that, in 2012, 12 million workers were engaged in night work (defined as an average of at least 4 times per month during the previous 6 months) (Kubo, 2014).

In Australia, 1.5 million workers (excluding owners and/or managers of incorporated enterprises), or 16% of all workers, usually worked shifts in their main job in 2012; the most common type of shift worked was a rotating shift (45% of those performing shift work). Men were more likely to usually work in shifts (18%, compared with 14% of women) (Australian Bureau of Statistics, 2012).

The globalization of the labour market, and the outsourcing of many productive activities of multinational companies, has led to the increasing use of shift and night shift work in low- and middle-income countries at levels similar to, or even higher than, those of high-income countries; this is particularly the case for the manufacturing and construction sectors. The growing populations of some low- and middle-income countries mean that a large number of workers are involved in shift and night shift work (ILO, 2011b).

(b) Industry sector

Shift systems may differ between industry sectors according to their specific requirements and work organization (EuroFound, 2017).

In health-care sectors worldwide, shift work is mainly based on continuous shift systems, managed with both clockwise and counter-clockwise rotation, variable start and end times, and different blocks of night shifts in succession. Slowly rotating systems were mainly used in the past, but rapidly rotating (every 1–3 days) systems have increased during recent decades; a growing number of workers are also engaged in 12-hour shifts (European Trade Union Confederation, 2011; EuroFound/ILO, 2017).

In manufacturing sectors (e.g. mechanical, graphic, textile, food, and paper), shift work including nights is generally organized in both semi-continuous and continuous three-shift systems, where workers alternate regularly between day and night shifts with relatively stable start and finish times, and fairly homogeneous duty periods (8–9 hours). Semi-continuous shift systems are mainly based on a weekly rotation that involves 5 consecutive night shifts; continuous systems are more variable in terms of shift cycle. In recent decades, faster rotating systems that imply fewer nights in succession (e.g. 3, 2, or 1) have increasingly been adopted. Permanent or

slowly rotating (every 15–30 days) shift systems are used in some subsectors (e.g. oil and gas overseas platforms) (EuroFound, 2015).

In the transport sector, particularly in rail and air travel and long-haul driving, individual shift schedules are often irregular with rapid rotation and high variability in shift duration, start and end time of duty periods, and position and number of rest days (which may be spent away from home and family) (European Agency for Safety and Health at Work, 2010). Flight personnel can experience additional disruption in relation to the variable number of time zones crossed (Grajewski et al., 2003).

In the retail sector, the decline of small shops and the proliferation of larger supermarkets, hypermarkets, and shopping centres are associated with a liberalization in opening hours (longer hours and more frequent service at weekends) and the adoption of semi-continuous and continuous rotating shift systems; operating times have been extending into the evening and, in some cases, night time (EuroFound, 2012).

In agriculture, shift and night work are also increasingly used in connection with more intensive and extensive work, mainly linked to livestock breeding, large plantations, and fishing. This can be associated with long working hours (ILO, 2011a).

In Europe, according the 4th EU Working Conditions Survey (EuroFound, 2007), night shift work is used in many work sectors, particularly in: hotels and restaurants (> 45% of the workforce); transport and communication (> 35%); health care (> 30%); public administration and defence (> 25%); manufacturing (> 20%); and electricity, gas, and water (> 20%).

In the USA, the estimated prevalence (adjusted for age, sex, and race using the 2000 United States population) of frequent night work (working between 01:00 and 05:00 more than 5 times per month) by work sector in 2015 was: 18.1% in mining; 15.5% in transportation, warehousing, and utilities; 11.8% in health care and social assistance; 10.8% in manufacturing; 9.8% in agriculture, forestry, and fishing; 6.6% in wholesale and retail trade; 5.3% in services; and 1.3% in construction (NIOSH, 2015).

In Canada, the industry groups with the highest numbers of people working regular night or rotating shifts in 2011 were trade (396 000 workers; 15% of industry), health care and social assistance (318 000 workers; 18% of industry), manufacturing (261 000 workers; 17% of industry), and accommodation and food services (222 000 workers; 20% of industry). The majority of regular night or rotating shift workers in health care and social assistance, trade, and accommodation and food services were women, and men represented the majority in manufacturing and public administration (CAREX Canada, 2019).

Shift and night work are also widely used across sectors in Africa, Asia, and South America (Lee et al., 2007). A survey based in China found that shift work (with and without nights) was most highly concentrated in the manufacturing sector, followed by the wholesale and retail trade, food and beverage, and social services sectors (Zeng et al., 2005). In the Republic of Korea, the proportions of shift work including night work were observed to be highly concentrated in the service sectors, including: 64.9% in transportation, storage, and communications; 48.3% in community, social, and personal services; and 30.2% in the wholesale and retail trade, and hotels and restaurants subsectors (Yoon, 2001). In Jamaica, shift work was the dominant working time arrangement in most industry sectors in 2004, particularly in the service subsectors of transport, storage, communications, wholesale and retail trade, and hotels and restaurants (Taylor, 2004).

1.3.2 Methods of measurement

Night shift work is the most common observational proxy for circadian disruption (Vetter, 2020). Transmeridian flights are associated with

night shift work and additional circadian disruption as a result of rapid travel over time zones (Härmä et al., 1994).

In relation to measuring exposure to night shift work, a focus on the measurement of exposure to work occurring during the normal sleeping hours of the general population is recommended. Concerning the measurement of exposure to night shift work among aircrew, it is important to consider the cumulative time spent working in the standard sleep interval, as well as the number of time zones crossed.

Subjective methods for detecting and quantifying exposure to night shift work and flying over time zones include questionnaires, interviews, or diary techniques, where workers themselves report on past or current exposures. Objective methods are normally based on historical registry data of individual working hours or company-based flight history records of the aircrew, for example, flight or block hours. It is also possible to estimate past exposure to night shift work using a job-exposure matrix (JEM); this method combines information based on job title with information on average exposure to shift work for each job title, usually based on an earlier evaluation by questionnaire in other populations (e.g. Schwartzbaum et al., 2007).

For aircrew, exposure estimation may be based on subjective or objective data concerning flights to and from specific airports. The exposure data concerning flying over time zones typically include information on the number of time zones crossed in a certain time period, or information on the number of flights crossing time zones, or the number of hours worked during a time period, for example, the standard sleep interval (Grajewski et al., 2003).

The use of objective day-to-day data describing exposure to night shift work (payroll data of working hours; e.g. Härmä et al., 2015; Vistisen et al., 2017) is most accurate, because this is suitable for multidimensional exposure assessment (e.g. Stevens et al., 2011) and is less sensitive to attrition and reporting bias, especially in studies with a long follow-up. However, although objective data on working hours are normally more precise and can provide quantitative information on different dimensions of night shift work over time, good correlation has been observed between self-reported and objective data in relation to some work schedules; examples include permanent night work and rotating shift work with night shifts (Härmä et al., 2018a), and duration of employment as a flight attendant (Schubauer-Berigan et al., 2015). Further, although company-based registry data are more representative for the target population (100% coverage), the availability of such data can vary across regions, sectors, and occupations. The use of questionnaires and/or interviews can yield additional information compared with such registry data, for example, total working hours associated with all jobs and/or unpaid working hours. Scheduled and executed work shifts often differ (e.g. as a result of double shifts or last-minute work shift changes). Analysis of past scheduled rotas is therefore less reliable than the use of registry data that reflect executed shifts (e.g. payroll data). Information on executed shifts offers the additional benefit of capturing and analysing irregular and complicated shift systems.

[The Working Group noted that a limitation of the use of company-based registry data describing working hours is a lack of information about working hours in other jobs in addition to the main job, or before entering the registry. A solution is to combine the objective exposure information on daily registry-based working hours with individual-based survey information, for example, night shift work and lifelong exposure.]

Data collected at the individual level are generally preferred over non-individual (grouped) data such as JEMs, because of their ability to capture inter-individual variability in exposure. Population-based JEMs are especially

prone to exposure misclassification, resulting in underestimation of the hypothesized relationship between exposure and outcome. For example, Schwartzbaum et al. (2007) classified day work as occupations in which "less than 30% were normally shift workers". [The Working Group noted that the JEM method is often applied without validation in the country, sector, or time period where it is used. Sensitivity and specificity are seldom reported, and job titles and shift schedules may differ across countries and over time. Industry-based JEMs, where jobs can be directly linked to shift work schedules that include nights, may provide a more accurate picture of shift work exposure compared with population-based JEMs.]

1.3.3 Factors that may influence the effects of night shift work on cancer

Exposure to night shift work may vary according to different schedule and job characteristics (see Sections 1.1, 1.2, and 1.3.1(b)). In addition, other variables, such as individual, lifestyle, and environmental factors (e.g. light exposure), may mediate, confound, or moderate cancer outcomes among night shift workers, including those who fly over time zones (e.g. Lunn et al., 2017) (Table 1.1). These factors may act alone or together, complicating the identification of causal risk factors for cancer in these populations.

Table 1.1 Factors that may influence the effects of night shift work on cancer

Individual characteristics	Lifestyle-related factors	Light exposure
Age	Smoking	Altered light patterns
Reproductive factors	Physical activity	
Chronotype or diurnal preference	Eating behaviour (timing)	
Sleep	Alcohol consumption	

(a) Individual characteristics

Individual characteristics that may influence the impact of exposure to night shift work on cancer include, among others, age, reproductive factors, chronotype or diurnal preference, and sleep patterns.

Exposure to night shift work, and its effects on the risk of chronic disease, may relate to age and its association with lifestyle factors and circadian timing (Duffy et al., 2015; Ramin et al., 2015). In turn, age is related to reproductive factors (e.g. parity, age at first child, and menopause) that have been postulated as potentially important confounders in some health risk analyses (e.g. for cancer of the breast) (Kelsey et al., 1993; Ban & Godellas, 2014). Some recent studies have indicated that such reproductive differences between day and night shift workers do exist, but are not strongly pronounced (Papantoniou et al., 2016; Wegrzyn et al., 2017).

Chronotype is a characteristic of the circadian timing system that varies according to the individual; it is related to individual preference of sleeping and waking hours. Chronotype and individual diurnal preferences have been proposed as important considerations in epidemiological studies of night shift work and cancer (e.g. Section 2.1.1(c)) (Hansen & Lassen, 2012; Erren et al., 2017).

In 1970, Oquist produced a questionnaire to differentiate between morning and evening persons, translated into English by Horne & Ostberg (1976). This questionnaire has five categories of "chronotypes": definitely morning, moderately morning, neither, moderately evening, and definitely evening. [The Working Group noted that this questionnaire measures individual diurnal preference rather than chronotype.] Other questionnaires were subsequently developed, such as those by Folkard et al. (1979) and Torsvall & Akerstedt (1980). More recently, Roenneberg et al. (2003) created

the Munich Chronotype Questionnaire that measures individual sleep phase differences (i.e. timing of sleep within the 24-hour day). [The Working Group noted that these questionnaires may be measuring distinct human characteristics; it is therefore relevant to consider which questionnaire was used in a study when interpreting obtained results.]

Night shift work is commonly associated with disturbed sleep (Åkerstedt, 2003; Sallinen & Kecklund, 2010). Disrupted sleep (and its characteristics, such as duration and timing) has been proposed as a potential risk factor for cancer (Haus & Smolensky, 2013; Irwin, 2015).

(b) Lifestyle-related factors

Lifestyle factors, including smoking behaviour, amount of physical activity, eating behaviour, and consumption of alcohol, may be affected by night shift work (Bøggild & Knutsson, 1999; Bushnell et al., 2010).

A cohort study with data from 2004 to 2006 observed increased odds of smoking relapse and reduced odds of smoking cessation in fixed night workers (Nabe-Nielsen et al., 2011). There is sufficient evidence for the carcinogenicity of tobacco smoking in humans, with links to several cancer end-points (IARC, 2004). Patterns of alcohol consumption may also vary according to work schedule timing (Dorrian & Skinner, 2012; Dorrian et al., 2015). Alcohol has been classified as carcinogenic to humans (IARC, 2012).

Several studies have investigated the association between body mass index and/or metabolic problems and night shift work (van Drongelen et al., 2011; Wang et al., 2014; Gan et al., 2015; Proper et al., 2016). Night shift work may impair metabolism, although it is unclear whether physical activity attenuates the effects on weight gain and/or body composition in night shift worker populations (van Drongelen et al., 2011; Marqueze et al., 2014; Neil-Sztramko et al., 2016). Excess body weight (increased body mass index) has been associated with the risk of cancer (Renehan et al., 2008). Some studies have shown differences between shift workers and non-shift workers in relation to eating behaviour (Lowden et al., 2010; Souza et al., 2019). Eating behaviour, including nocturnal nibbling, has also been investigated as a biological factor associated with weight gain and physical activity among night shift workers (Haus et al., 2016). Moreover, dietary intake may be affected by reduced sleep (Dashti et al., 2015). van de Langenberg et al. (2019) observed that, during a night shift, workers have a shorter maximum fasting interval, more eating moments, and a higher fat intake than during work without a night shift. Changes in timing of sleep and eating related to shift work may increase the risk of obesity, which has been linked to an increased risk of cancer (Calle & Kaaks, 2004; IARC, 2018).

(c) Light exposure

Night shift workers experience altered exposures to light during the 24-hour period. Exposure to artificial light at night (particularly in the blue wavelength region of the spectrum) inhibits the physiological nocturnal production of melatonin by the pineal gland (Lewy et al., 1980; Mirick & Davis, 2008), and has been hypothesized as a mechanism for increased risk of cancer (Stevens, 1987). Further details on melatonin are provided in Section 4. In addition, lack of sunlight exposure may increase risk of cancer via its effects on reducing vitamin D levels (Garland et al., 2006; Juzeniene et al., 2011).

Various methods have been used to assess exposure to light and its potential health impacts in night shift workers (Hunter & Figueiro, 2017; Cherrie, 2019). Quantitatively measured light-at-night levels in night shift workers have been shown to differ by season (Daugaard et al., 2019) and workplace characteristics, such as occupation and work site (Hall et al., 2017). Night shift workers in equatorial regions have been observed to experience shorter durations of natural light exposure compared with day workers during work days as well as days off

(Marqueze et al., 2015). In a Dutch study, night shift workers were exposed to daylight for longer durations compared with day workers during non-night shift sessions, but were less exposed to daylight during night shift sessions compared with non-night shift sessions (van de Langenberg et al., 2019). In a Danish investigation of average light exposures, Daugaard et al. (2019) observed higher intensities and durations of light exposures for night workers compared with day workers in the period between midnight and 05:59 and decreased intensities and durations in the 06:00–17:59 period during work days, but not during days off work.

1.3.4 Co-exposures in the workplace

(a) Introduction

Night shift workers may be occupationally exposed to chemical, physical, or biological agents and ergonomic stressors, and some of these exposures may be known or possible carcinogens (Costa, 2003; Fenga, 2016). The intensity or extent of an occupational co-exposure may differ by shift. Using telephone interviews, Jay et al. (2017) evaluated exposures to workplace hazards across a national sample of the New Zealand population, comparing people who worked a standard daytime work week with those who did not. Participants working non-standard hours were more likely to be exposed to workplace hazards and to multiple hazards than daytime workers. The prevalence of workplace hazards was reported for dusts (odds ratio, OR, 1.55; 95% confidence interval, CI, 1.29–1.87), smoke or fumes (OR, 1.88; 95% CI, 1.53–2.32), gases (OR, 3.35; 95% CI, 2.55–4.40), oils or solvents (OR, 1.50; 95% CI, 1.22–1.83), acids or alkalis (OR, 2.24; 95% CI, 1.72–2.91), fungicides, insecticides, herbicides, or timber preservatives (OR, 1.71; 95% CI, 1.31–2.24), and other chemical products (OR, 1.27; 95% CI, 1.00–1.61), as well as for two or more hazards (OR, 2.45; 95% CI, 2.01–3.0). [The Working Group noted that the observed differences in exposure prevalence did not account for differences in job distributions across night and day shifts.] A study of night shift work in 44 enterprises in Poland, spanning diverse industrial sectors such as manufacturing, printing, transport, sewerage, and electricity supply, indicated that night workers may be exposed to formaldehyde, mineral oils containing polycyclic aromatic hydrocarbons, silica dust, chromium (VI) compounds, vinyl chloride, nickel, benzene, cadmium, wood dust, and diesel exhaust, all of which are IARC Group 1 carcinogens (Pepłońska et al., 2013). [The Working Group noted that this study did not compare exposures in night workers with those in day workers within a single job or sector; differences in exposure prevalence between these groups therefore cannot be discerned.]

Night shift work could influence biological processes that increase the risk associated with exposure to xenobiotics as a result of both the circadian fluctuation in biological susceptibility to them, and the desynchronization of the mechanisms of detoxification (Claudel et al., 2007; Nagai et al., 2011; Lin et al., 2014; Carmona-Antoñanzas et al., 2017). Smolensky et al. (2017) reviewed how circadian time structure influences vulnerability to chemical xenobiotics. Human vaccination trials have demonstrated circadian time-dependent differences in response to bacterial and viral agents (Smolensky et al., 2019). In addition, the timing of drug administration affects the efficacy of treatment (Kaur et al., 2013; Ballesta et al., 2017).

Havet et al. (2017) evaluated varied exposures to carcinogenic, mutagenic, and reprotoxic (CMR) chemicals for French employees and found that over 2.2 million or 10.4% of employees were exposed to one or more CMR agents at their workplace and that 3.4% were exposed to multiple CMR chemicals. Carcinogens accounted for 97% of the CMR exposures. The most prevalent exposures were mineral oil, wood dust, crystalline silica, and, to a lesser extent, diesel exhaust and

formaldehyde. Night shift workers were found to be more frequently exposed to at least one CMR agent compared with occupations without night shift work, although comparisons were not restricted to those with the same occupation. Among shift workers and night workers, the prevalence of exposure to at least one CMR agent for more than 20 hours per week was 22% and 18%, respectively. [The Working Group noted that this study did not compare exposures in night workers with those in day workers within a single job or sector; differences in exposure prevalence between these groups therefore cannot be discerned.]

(b) Aircrew

Aircrew are exposed to cosmic ionizing radiation in addition to night shift work, crossing time zones, and long work hours (O'Brien & Friedberg, 1994; Hammer et al., 2014). Cosmic radiation from the sun and charged particles from the galaxy interact with the Earth's atmosphere and form secondary and subsequent particles including neutrons, protons, electrons, positrons, photons, and positive and negative muons (UNSCEAR, 2008). The Earth's magnetosphere concentrates radiation at higher latitudes. Radiation dose in aircraft depends on latitude, longitude, and the stage of the 11-year solar cycle. The most important determinant of the dose rate is altitude, with dose doubling every 1500 m (Paretzke & Heinrich, 1993). Neutrons are a major contributor to cosmic radiation dose at flight altitudes (Goldhagen, 2000).

Aircrew are one of the occupational groups with the highest radiation exposures (UNSCEAR, 2008). Depending on flight route patterns, annual doses range from 0.2 to 9.0 mSv in excess of the 2 mSv natural background radiation dose at sea level (UNSCEAR, 2008). Cumulative occupational lifetime doses of ionizing radiation generally remain less than 100 mSv (O'Brien & Friedberg, 1994). Aircrew represent the largest population of people exposed to high-energy neutrons and the only population exposed to high-energy protons (Wilson, 2000). Long-haul high-latitude flights, such as from New York to Hong Kong Special Administrative Region, may have single flight doses ranging from 52 to 102 μSv, depending on the stage of the 11-year solar cycle (Alvarez et al., 2016).

Studies of cancer summarized by the Working Group (see Section 2) that assessed exposure to cosmic radiation are described in Table 1.2, including the method used to estimate cosmic radiation doses. To calculate cumulative dose, a personal flying time metric is folded with a dose metric for the type of flight or aircraft. Flying time may be assessed by logbooks (in the case of pilots), company personnel records, or questionnaires. Studies reported cumulative radiation dose as either absorbed dose or effective dose. Absorbed dose is a measurable quantity of the amount of energy deposited by radiation in a mass, expressed in units of milligrays. Effective dose is a radiation protection quantity computed from the absorbed dose weighted by both radiation effectiveness and organ sensitivity over the whole body, expressed in millisieverts (ICRP, 2007).

(c) Health-care workers

Occupational hazards among health-care workers have been reviewed (Vecchio et al., 2003; Gambrell & Moore, 2006; Connor et al., 2010; Lawson et al., 2012; Graeve et al., 2017; Hall et al., 2017; Siama et al., 2019). Hazards include exposure to antineoplastic drugs, sterilizing agents, and ionizing radiation. Antineoplastic drugs are handled in hospitals in shipping and receiving areas, pharmacies, care wards, and laundry areas; exposures can occur during preparation, administration, cleaning, and contact with patient waste products (Hon et al., 2013; Hall et al., 2017). Exposure to antineoplastic drugs can also occur in non-hospital settings such as community pharmacies, veterinary-care facilities, and

Table 1.2 Estimation of cosmic radiation dose in aircrew epidemiological studies that assessed both night shift work and radiation dose[a]

Reference	Country	Aircrew type	Study type and population	Duration estimation method	Cosmic radiation dose estimation		
					Model	Method	Dose range
Pukkala et al. (2003)	Denmark, Finland, Iceland, Norway, Sweden	Cockpit	Cancer incidence study; national cohort (pilots, *n* = 10 211) followed through 1996 or 1997	Records of annual block hours[b] by aircraft	CARI-5E	Tveten et al. (2000) Aircraft type assigned dose rate per block hour for 5-yr periods from 1960 to 1994	Cumulative effective dose < 1 to > 20 mSv Four dose categories
Yong et al. (2014a)	USA	Cockpit	Cohort mortality study; company (Pan Am[c]) cohort (cockpit crew, *n* = 5964) followed through 2008	Records of annual flight hours[b]	CARI-6P	Waters et al. (2009); Anderson et al. (2011) Frequency-weighted domicile-based dose for 5-yr periods from 1930 to 1970, 1980, and 1990	Cumulative effective dose Mean, 28 mSv (median, 31 mSv; range, 0.0047–71.0 mSv) Six dose categories
Pinkerton et al. (2012)	USA	Cabin	Cohort mortality study; company (Pan Am, including transfers from National[c]) cohort (FAs, *n* = 11 311) followed through 2007	Questionnaire or interview with some proxy respondents	CARI-6P	Waters et al. (2009) Frequency-weighted domicile-based dose for 5-yr periods from 1930 to 1970, 1980, and 1990	Cumulative effective dose Median, 12.7 mSv (range, 0.33–102 mSv)
Pinkerton et al. (2016)	USA	Cabin	Breast cancer incidence study; company (Pan Am, including transfers from National[c]) cohort (female FAs participating, self or proxy, in a questionnaire study, *n* = 6093)	Questionnaire or interview with some proxy respondents	CARI-6P	Waters et al. (2009); Anderson et al. (2011)	Cumulative absorbed dose Cases: mean, 10 mGy; median, 5.5 mGy; IQR, 2.6–16 mGy Non-cases: mean, 12 mGy; median, 7.3 mGy; IQR, 2.7–17 mGy
Pinkerton et al. (2018)	USA	Cabin	Cancer (melanoma, thyroid, and gynaecological) incidence study; company (Pan Am, including transfers from National[c]) cohort (female FAs participating, self or proxy, in a questionnaire study, *n* = 6095)	Questionnaire or interview with some proxy respondents	CARI-6P	Waters et al. (2009); Anderson et al. (2011)	Cumulative absorbed dose Cohort: mean, 7.3 mGy; IQR, 2.7–17 mGy

Table 1.2 (continued)

Reference	Country	Aircrew type	Study type and population	Duration estimation method	Cosmic radiation dose estimation		
					Model	Method	Dose range
Pukkala et al. (2012)	Finland, Iceland, Norway, Sweden	Cabin	Cancer incidence study; national cohort (FAs, *n* = 8507) followed for cancer incidence	Records of annual block hours[b]	EPCARD	Tveten et al. (2000); Kojo et al. (2004) Aircraft type assigned dose rate per block hour for 5-yr periods from 1960 to 1994	Cumulative effective dose < 5 to > 35 mSv
Schubauer-Berigan et al. (2015)	USA	Cabin	Breast cancer incidence study; company (Pan Am, including transfers from National[c]) cohort (female FAs participating, self or proxy, in a questionnaire study, *n* = 6093)	Questionnaire or interview with some proxy respondents	CARI-6P	Waters et al. (2009); Anderson et al. (2011)	Cumulative absorbed dose Median, 7.2 mGy (range, 2.7–17 mGy)

CARI, computer program that estimates cosmic radiation dose received by an individual; EPCARD, European Program Package for the Calculation of Aviation Route Doses; FA, flight attendant; IQR, interquartile range; yr, year.

[a] Studies that were reviewed by the Working Group but provided no information on cosmic radiation exposure are not included.

[b] "Block hours" refers to gate departure to gate arrival (aircraft taxi time and air time); "flight hours" refers to wheels off the ground to wheels on the ground (air time).

[c] Pan American World Airways acquired National Airlines in 1980.

home care settings (Meijster et al., 2006; Hall et al., 2017).

A Dutch study of shift work and breast cancer risk among 59 947 nurses found that 27% reported work with antineoplastic drugs for at least 6 months, 26% with routine X-rays, 10% with anaesthetic gases, and 2% with radiotherapy; however, the co-occurrence of night shift work with other occupational exposures was not reported (Pijpe et al., 2014). Buschini et al. (2013) evaluated DNA damage in Italian nurses who worked with the antineoplastic drugs cyclophosphamide, chlorambucil, melphalan, busulfan, thiotepa, etoposide, and treosulfan, all IARC Group 1 carcinogens, but were unable to identify significant differences between exposed nurses and referents using three versions of the comet assay.

Sterilizing and disinfecting chemicals including formaldehyde and ethylene oxide are used to sterilize and disinfect medical and surgical equipment, and in pathology and anatomy laboratories (Kiran et al., 2010; Costa et al., 2011). Exposures to ionizing radiation in health care include gamma, X-rays, alpha particles, and beta rays (Gorman et al., 2013).

(d) Co-exposures in other occupations

Co-exposures for industries and occupations within the major sectors where night shift work is common (see Sections 1.2 and 1.3.1(b)) are summarized in Table 1.3. The sectors are manufacturing, transport (other than flying), retail and services, agriculture, and information and communications.

1.4 Regulations and guidelines

1.4.1 Introduction

Regulatory approaches for shift work vary widely between countries, industry sectors, and companies. Implementation of international regulations is dependent on national laws and collective agreements, and benefits from participatory strategies for local adjustment (Kogi, 1998). Gärtner et al. (2019) reviewed regulatory approaches towards shift work in four regions: Australasia, East Asia (China, Japan, and the Republic of Korea), Europe, and North America. The most prescriptive regulations are found in European countries, with a focus on limiting features of schedules such as the maximum number of work hours per day, the amount of rest time after shift work, and minimum break times (Gärtner et al., 2019). EU countries have sometimes implemented regulations in a different way at the national, sector, and company levels. Asian countries such as Japan and the Republic of Korea focus more specifically on protecting at-risk workers such as pregnant and nursing women, and requiring health examinations for night shift workers, without night work limits for the general working population. In all four regions, specific industries and occupations have separate regulations for shift work (Gärtner et al., 2019). Examples include: the transport sector, including highway commercial truck, bus, or coach; rail, aviation, and maritime operations; the health-care sector, particularly nurses; and nuclear power plant operations.

The USA is less regulated than Europe with respect to shift work, except for certain sectors such as transport, maritime, and nuclear power plant operation (Gärtner et al., 2019). In Australia, states and territories have adapted national workplace health and safety and labour laws to regulate shift work, with specific industries in the transport and mining sectors governed by an industry regulator. Japan and the Republic of Korea regulate aspects of night work; Japan has sector-specific regulations for drivers and nurses. International guidelines have been issued separately by the ILO and the European Council in the last several decades, addressing the organization of shift and night work. These guidelines are detailed in the following sections.

Table 1.3 Co-exposures in industries and occupations in which night shift work is common, other than aircrew

Type of industry or occupation	Agent(s)	Reference(s)
Manufacturing		
Oil refining and petrochemicals	Bitumen, benzene, 1,3-butadiene	Burstyn et al. (2000), Akerstrom et al. (2016)
Printing	Trichloroethylene, toluene, ethyl alcohol, ethyl acetate	Fischer et al. (2001), Bakke et al. (2007)
Textiles, cloth weaving, knitting, dyeing	Trichloroethylene, formaldehyde, dyes, solvents, metals, cotton and other dusts, pesticides	Wernli et al. (2006), Bakke et al. (2007)
Shoe manufacturing	PAHs	Costantini et al. (2009)
Rubber and rubber products manufacturing	1,3-Butadiene, carbon black, vinyl chloride, carbon disulfide, silicates, *N*-nitrosamines, PAHs, solvents	Kromhout et al. (1994), Oury et al. (1997), Dost et al. (2000), De Vocht et al. (2005), Hanley et al. (2012)
Plastics and composites manufacturing	Methylene chloride, styrene	Collins et al. (2013), Christensen et al. (2018)
Welding, metal working, soldering	Lead fume, lead oxide dust, metalworking fluids, metals, solvents, oil mist	Park et al. (2009a, b), Meeker et al. (2010), Behrens et al. (2012)
Metal plating and coating	Metal, acid mists, solvents	Pollán & Gustavsson (1999)
Smelting	Benzo[*a*]pyrene, PAHs	Healy et al. (2001), Tuominen et al. (2002), Sanderson et al. (2005)
Automobile electronics manufacturing	Fibreglass dust, coatings, lead-based solder, 1,1,1-trichloroethane, trichloroethylene, asbestos	DeBono et al. (2019)
Transportation other than flying		
Railway employees	Asbestos, diesel exhaust	Preller et al. (2008)
Seafarers	Diesel particulate, metal abrasion compounds, asbestos	Oldenburg et al. (2010)
Marine transportation	Diesel exhaust, PAHs	Pronk et al. (2009)
Large truck and bus drivers	Diesel exhaust, PAHs, gasoline, diesel fuel, asbestos, metals	Pronk et al. (2009), Boffetta (2012)
Retail and services		
Hairdressers, barbers	Dyes, solvents, talc, formaldehyde	Hollund & Moen (1998)
Butcher, meat cutter	PAHs, nitrosamines, animal viruses	Guo et al. (2017)
Tollbooth operators	Diesel exhaust, PAHs, gasoline, diesel fuel	Sapkota et al. (2005)
Agriculture		
Farmers	Pesticides, animal dust, fertilizers, metals, wood dust, solvents, gasoline and/or diesel fuel and/or exhaust	Band et al. (2000)
Greenhouse workers	Pesticides	Dolapsakis et al. (2001)
Information and communications		
Telephone industry	Non-ionizing radiation	Dosemeci & Blair (1994)
Radio and telegraph	Non-ionizing radiation	Tynes et al. (1996)

PAH, polycyclic aromatic hydrocarbon.

1.4.2 General working population

ILO night work guidelines include the ILO Night Work Convention, 1990 (No. 171), referred to as C171 (ILO, 1990a), and the ILO Night Work Recommendation, 1990 (No. 178) (ILO, 1990b), referred to as R178. ILO C171 and ILO R178 together establish a comprehensive system for the regulation of night work and the protection of night workers. Guidelines in C171 set the minimum standard for adoption by national authorities and carry more weight than the recommendations in R178. Regarding the length of night work, R178 contains detailed but non-binding guidelines; R178 also calls for night work overtime to be avoided as far as possible.

C171 and R178 (ILO, 1990a, b) define "night work" generally as all work that is performed during a period of not less than 7 consecutive hours, including the interval from midnight to 05:00. "Night worker" refers to employees working a substantial number of hours of night work exceeding a specified limit, although individual national authorities may implement this differently.

Both C171 and R178 apply to all employed persons, except those employed in agriculture, stock raising, fishing, maritime transport, and inland navigation. C171 does not specify limits to night work. R178 recommends that work for night workers should not exceed 8 hours in any 24-hour period, with additional specifications and exceptions.

The EU WTD "Concerning certain aspects of the organisation of working time" (European Commission, 2003) focuses on key aspects of night work in a less detailed manner than the ILO guidelines. The definition of "night" in the directive is similar to that of the ILO guidelines, but the definition of "night worker" in the directive is different from that of ILO C171 and R178.

The EU WTD (European Commission, 2003) sets minimum health and safety requirements for the organization of working time. Although Member States may opt out of certain provisions, they may not opt out of night and shift work limits. The directive is applicable to all sectors of activity with some derogation. "Night time" is defined as any period of not less than 7 hours, as defined by national law, and which must include, in any case, the period between midnight and 05:00. "Night worker" means (a) any worker who normally works at least 3 hours of their daily shift at night time or (b) any worker who works a certain proportion of their annual working time at night time, defined by either Member State legislation or collective agreement.

"Shift work" is defined as "any method of organizing work in shifts whereby workers succeed each other at the same work stations according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks". "Shift worker" means "any worker whose work schedule is part of shift work". "Shift workers" may also be "night workers" (European Commission, 2017).

The EU WTD defines binding parameters regarding the length of night work, and its Preamble states that night work overtime should be limited. Some European countries have implemented the EU WTD through national legislation, and these implementations vary.

General trends in the use of night work have been summarized by Lee et al. (2007).

1.4.3 Women during pregnancy and around childbirth

ILO R178 Section VI recommends that "at any point during pregnancy, once this is known, women night workers who so request should be assigned to day work, as far as is practical" (ILO, 1990b). ILO C171 Article 7 specifies that measures shall be taken to ensure that an alternative to night work is available to women workers before or after childbirth, or if medically necessary (ILO, 1990a).

The EU WTD does not specifically address pregnant or nursing women, but specifies that Member States may do so (European Commission, 2017, p. 14). EU Council Directive 92/85/EEC (EU-OSHA, 1992) forced Member States to ensure that women are not obliged to perform night work during their pregnancy and for a period after childbirth, as determined by the national authority competent for safety and health.

1.4.4 Young people

Night work by children or young people is not addressed by either ILO C171 or R178 (ILO, 1990a, b). ILO provisions for children and young people are found in Night Work of Young Persons (Industry) Convention No. 90 (Revised), 1948 (ILO, 1948); Night Work of Young Persons (Non-Industrial Occupations) Convention No. 79, 1946 (ILO, 1946); and Night Work of Children and Young Persons (Agriculture) Recommendation No. 14, 1921 (still in effect) (ILO, 1921). ILO Convention No. 79 applies to all occupations except for industrial, agricultural, or maritime occupations. ILO Convention No. 90 applies to all industries, but particularly to textiles, recycling, mining, construction, transport, shipbuilding, and power.

With some exceptions and additional specifications, the ILO advises that young people aged < 18 years should not be employed at night, with modifications for those aged < 14 years and 14 to < 18 years, and those in agricultural jobs (ILO, 1921, 1946, 1948).

1.4.5 Industry sector

(a) Long-distance drivers

The ILO has two sets of guidelines for long-distance drivers: Hours of Work and Rest Periods (Road Transport) Convention No. 153 (ILO, 1979a) and Hours of Work and Rest Periods (Road Transport) Recommendation No. 161 (ILO, 1979b). Both limit the maximum total driving time, including overtime, to less than 9 hours per day and 48 hours per week. Night work is not addressed.

In Europe, Regulation (EC) No. 561/2006 regulates driving times and rest periods for all drivers of road haulage and passenger transport vehicles, with specific exceptions and national derogations (European Commission, 2006). The rules limit driving to 9 hours per day (up to 10 hours twice a week), 56 hours per week, and 90 hours per fortnight. Daily rest period is at least 11 hours (9 hours up to 3 times a week) and can be split with specifications. In Australia, the Heavy Vehicle National Regulation governs drive time (Gärtner et al., 2019). Regulations permit either adhering to detailed prescriptive rules or using a fatigue management programme. Drive time is limited to 10 hours in any 11-hour period and 12 hours per 24-hour period. Additional rules govern cumulative work limits, and minimum and cumulative rest limits.

The United States Department of Transportation has established limits for drivers of property-carrying vehicles in interstate commerce (Gärtner et al., 2019). Time on-duty is limited to 14 hours with driving limited to 11 hours. Under "adverse conditions", up to 2 additional hours of driving are permitted. At least 10 hours of off-duty time is required between on-duty periods.

Brazil implemented limits for long-distance drivers in 2015 (Presidência da República Brasil, 2015). The maximum driving interval is limited to 5.5 consecutive hours, with a daily maximum of 14 hours and a minimum of 11 hours rest between two shifts.

(b) Seafarers

The ILO recommendations for maritime, fishing, or dock work do not address night work or shift work. ILO Convention No. 180 Concerning Seafarers' Hours of Work and the Manning of Ships (ILO, 1996) applies to seagoing ships and

commercial maritime fishing. It advises that the maximum hours of work must not exceed 14 hours in any 24-hour period, with additional specifications. The ILO Maritime Labour Convention No. 96 (ILO, 2006) specifies the same work limits and rest periods as ILO Convention No. 180 (ILO, 1996).

(c) Aviation

Shift work and night work are integral to civil aviation and are not directly regulated (Banks et al., 2012). The International Civil Aviation Organization (ICAO) uses a prescriptive approach with defined duty and rest time limits as well as a performance-based approach for fatigue risk management (ICAO, 2016). Missoni et al. (2009) summarized pilot duty time and rest time limits for 10 ICAO member countries. More recently, Banks et al. (2012) reviewed fatigue regulations, duty time limits, and sleep and/or rest requirements for 117 ICAO Member States. Some regulations limit the flight duty period during the circadian low (the period during which the body is programmed to sleep), or recommend avoiding scheduling crews for duty during this time.

An EU Directive (2000/79/EC) (EU-OSHA, 2000) addresses minimum standards for working time in civil aviation. The directive provides for a maximum annual working time of 2000 hours, with total flight time limited to 900 hours, per year.

(d) Railway

In both Europe and Australia, rail employee duty time limits are complex and regionalized; Australia also requires the use of a fatigue management system (Gärtner et al., 2019; ONRSR, 2019). The USA regulates duty for freight, passenger, signal, and dispatching train employees (Office of the Federal Register, 2019a, b). Duty time is limited to 12 hours maximum with a rest time of 10 hours per 24-hour period. Minimum rest periods differ by rail type (Gärtner et al., 2019).

(e) Maritime

United States non-defence maritime work must comply with Standards of Training, Certification and Watchkeeping for Seafarers (IMO, 2010; Office of the Federal Register, 2019c). Merchant mariners are required to receive a minimum of 10 hours rest within a 24-hour period in one or two periods, with additional limits per week. Watch worker duty limits range from 8–15 hours maximum within 24 hours, with a maximum of 36 hours working during any 72-hour period.

Canadian maritime duty time limits vary by vessel type and location. In general, work time is limited to 14 hours in any 24-hour period and 72 hours in any 7-day period. Workers must receive at least 6 hours of rest every 24 hours and 16 hours of rest during every 48-hour period, with no more than 18 hours between the end of a rest period and the beginning of the next rest period (Minister of Justice, Canada, 2019).

1.4.6 Country

A selection of country-specific regulations on night work are summarized in Table S1.4 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). Regulations vary widely between countries and regions (Lee et al., 2007).

1.5 Quality of exposure assessment in key epidemiological studies

Section 1.3.2 introduced the main methods used in the exposure assessment of night shift work and some of their quality issues. Table 1.5 provides recommendations for the categorization of the quality of exposure assessment methodologies, focusing on the type of assessment (objective, subjective, and JEM) and definition of night work.

This section also examines various shift domains, including several presented by the workgroup report of Stevens et al. (2011) that are recommended for the evaluation of exposure to night shift work and transmeridian flights in studies of cancer (Table 1.6). Suggestions for metrics to characterize the quality of various shift domains are also provided. Because the use of night shift work is critical in assessing the relationship between shift work and cancer, shift domains capturing exposure assessment for night work are prioritized. For aircrew, domains capturing exposure assessment for flying over time zones, which include night flying (night work), are considered.

Table 1.6 summarizes categories, definitions, epidemiological relevance, and justification for the different domains of exposure assessment examined. Most categories within domains in this table refer to the order of optimal information for exposure assessment; others provide information about the nature of the exposure that could influence the interpretation of the evidence.

1.5.1 *Quality of exposure assessment in primary studies*

See Tables S1.7–1.13 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593) for a quality appraisal of the exposure assessment in the studies of human cancer reviewed.

Quality appraisals were based on exposure information and analyses reported in the study under consideration. This does not preclude the possibility that additional information has been collected or reported in other studies based on the same cohorts or populations.

Domains for the review of the quality of the exposure assessment methodologies for night shift work and flying over time zones in epidemiological studies of cancer were evaluated as described above. In brief, "type of assessment" refers to how information on night shift work was collected in each study (i.e. objective, subjective, or JEMs). The "definition of night shift" was compatible with the definitions of the ILO (1990a, b), the EU WTD (European Commission, 2003), and Stevens et al. (2011).

Domains for the review of the quality of the exposure assessment for night shift work and flying over time zones in epidemiological studies of cancer were also assessed for each study as follows.

- *Reference group: past or present schedule includes night shift work* examines whether individuals performing night work could be included in the reference group. Contamination of the reference group can occur when it includes subjects with a limited intensity of night work (e.g. less than one shift per week or month) or those with an alternative schedule (e.g. permanent night workers included in the reference group in analyses of the effects on rotating night workers). It is important to note that contamination of the reference group can also occur as a result of missing information on lifetime tenure (this information is captured in the *duration of exposure to night shift work* domain).
- *Intensity of exposure to night shift work* refers to the number of night shifts performed within a certain period of time (e.g. week or month).
- *Duration of exposure to night shift work* refers to the number of years spent performing night shift work.
- *Temporality of exposure to night shift work* refers to information on start and end dates of night shift work. Such information allows age-specific risk analyses (e.g. stratified analyses by menopausal status).
- *Type of night shift work schedule* refers to the differentiation between, for example, permanent and rotating shift work schedules.

Table 1.5 Domains for the review of quality of exposure assessment methodologies for night shift work and flying over time zones in epidemiological studies of cancer

Domain	Categories	Definition/clarification	Epidemiological relevance	Justification
Type of assessment	1. Objective 2. Subjective 3. JEM	Objective data include registry data of actual individual-based working hours and analysis of document-based shift rota tables (note that planned and executed shifts may differ) Subjective data include surveys, interview, and diary data, where the information is obtained from the employees themselves JEMs in shift work research combine information on job title with information on estimated average exposure to shift work for each job title, based on earlier questionnaire-based evaluation in other populations	Objective data are generally more accurate than subjective information, as recall bias may affect the latter; however, objective data may be incomplete (e.g. by not capturing second jobs, or because temporary workers, contractors, and small- and medium-sized enterprises may not be captured by registries) General population studies using JEMs are generally less informative than industry-based JEMs (with specific links between occupation and night work) and objective and/or subjective data	The use of objective data is more accurate and less sensitive to selection, attrition, and reporting bias; however, there is a good correlation between self-reported and objective data for some work schedules (e.g. permanent night work and shift work with night shifts) (Härmä et al., 2018a)
Definition of night shift	1. Defined, includes exposure to night work for at least 3 hours between 23:00 and 06:00 (For aircrew studies: defined, includes a flight of at least 3 hours between 22:00 and 08:00 based on the local time before the flight) 2. Defined, other 3. Undefined	Category 1 includes the studies using the earlier recommendation by Stevens et al. (2011) and the definitions based on ILO C171 and R178 and the EU WTD, where the 3-hour exposure window is covered in a period of 7 hours that must include the period from midnight to 05:00	An operational definition of night work (as provided in Categories 1 and 2) is essential to enable comparisons between studies and to ensure coverage of work during the biological night Studies that do not define night shift (Category 3) should be given less weight, as it is unclear what exact exposure circumstance is covered	At least 3 hours from 23:00 to 06:00 is close to the biological night and compatible with ILO C171 and R178 and the EU WTD definitions, as well as with the Stevens et al. (2011) definition

C171, (ILO) Night Work Convention, 1990 (No. 171); EU, European Union; ILO, International Labour Organization; JEM, job-exposure matrix; R178, (ILO) Night Work Recommendation, 1990 (No. 178); WTD, European Working Time Directive No. 2003/88/EC.

Table 1.6 Domains for the review of quality of exposure assessment metrics for night shift work and flying over time zones in epidemiological studies of cancer

Domain	Categories	Definition/clarification	Epidemiological relevance	Justification
Reference group: past or present schedule includes night shift work	1. Yes 2. No 3. Undefined	This domain refers to the definition of the reference group used within an individual study; contamination of the reference group can occur when the applied exposure categorization of the reference group includes subjects with some degree of exposure to night shift work; this may include subjects exposed to a lower intensity of night shift work (e.g. < 1 shift/week or month) or with an alternative schedule (e.g. when permanent night workers are included in the reference group)	Reference populations in night shift work studies may have been exposed to night work, leading to contamination of the reference group; it is important to note that contamination of the reference group can also occur as a result of missing information on lifetime tenure, which is captured in another domain ("Duration of exposure to night shift work") Evidence of a contaminated reference group should be noted, but this is not necessarily a basis for exclusion; the impact of a contaminated control group should be judged on a study-by-study basis	Under the assumption that any form of night shift work increases cancer risk, a contaminated control group results in risk estimates that are biased towards the null
Intensity of exposure to night shift work	1. Precise information available (number of night shifts in a week, month, or year) 2. Imprecise, or limited, information available 3. No information available	Number of non-day shifts per unit of time (e.g. month or year)	Stevens et al. (2011) defined intensity for non-day shifts but not for night shifts, which are probably most important for circadian disruption; studies with information on intensity are of a higher quality than those without	Different shift working populations within and across studies may differ strongly in relation to intensity of night shift work

Table 1.6 (continued)

Domain	Categories	Definition/clarification	Epidemiological relevance	Justification
Duration of exposure to night shift work	1. Complete information (includes the number of cumulative exposure years) 2. Partial information (information available only for a limited time period of the subject's work history) 3. Partial information (information available at one time-point only e.g. "do you currently work night shifts?") 4. No information	Completeness of information in cohort studies refers to coverage of the time period up to the point of exposure data collection	Duration of exposure is generally believed to be an important component of risk; however, in some studies there is an extended time period between last exposure data collection and end of health follow-up, which results in incomplete exposure information; studies with partial or no information in this domain should therefore be given less weight	Information on long-term exposure to night shift work can be used to assess cancer risk (Hansen, 2017)
Temporality of exposure to night shift work	1. Complete information 2. Partial information 3. No information		Information on timing of exposure could be important to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of temporality of exposure and relevant exposure definitions (windows, lags), this criterion alone should not be used to evaluate informativeness of studies	Information on timing of exposure has been noted as a potentially important source of differences between studies (e.g. studies involving older people who had not been exposed to night work recently)
Type of night shift work schedule	1. Permanent night shift 2. Rotating night shift 3. Imprecise, or limited, information available 4. No information available		Information on type of night work schedule could be important to explain heterogeneity in epidemiological studies; studies with no information on the type of night work should be given less weight because of uncertainty about the definition of the exposure metric	

Table 1.6 (continued)

Domain	Categories	Definition/clarification	Epidemiological relevance	Justification
Number of consecutive night shifts (or speed of rotation)	1. Precise information available 2. Imprecise, or limited, information available 3. No information available	The number of consecutive night shifts is relevant for both permanent and rotating night work; in studies of rotating night work, "speed of rotation" is sometimes used to describe this concept	Information on number of consecutive night shifts could be important to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of the number of consecutive night shifts worked and relevant exposure definitions, this criterion alone should not be used to evaluate informativeness of studies	The number of consecutive night shifts is associated with circadian adjustment and/or disruption (Härmä et al., 2006, 2018b; Sallinen & Kecklund, 2010)
Direction of night shift rotation	1. Precise information available 2. Imprecise, or limited, information available 3. No information available	Using 8-hour shifts as an example, forward rotation means that morning or day shifts are followed by afternoon or evening shifts, and finally by night shifts (clockwise); backward rotation follows the opposite pattern (counter-clockwise)	Information on direction of night shift rotation could be important to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of night shift rotation direction and relevant exposure definitions, this domain alone should not be used to evaluate informativeness of studies	Direction of rotation, often interacting with the speed of rotation, can influence circadian disruption; quick forward rotating shift systems appear to be less disruptive because of faster re-adaptation after the night shift and fewer quick returns (< 11 hours between work shifts) (Driscoll et al., 2007; Bambra et al., 2008; Sallinen & Kecklund, 2010)
Start and end times of all shifts	1. Precise information available 2. Imprecise, or limited, information available 3. No information available		Information on start and end times of all shifts could be used to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of start and end times and relevant exposure definitions, this domain alone should not be used to evaluate informativeness of studies	Information on the start and end times of shifts (especially early morning and night) gives additional information on exposure to night work during the biological night; it also allows better estimation of on- and off-job (e.g. commuting) activities during the biological night

Table 1.6 (continued)

Domain	Categories	Definition/clarification	Epidemiological relevance	Justification
Flying over time zones	1. Information available on the mean number of time zones crossed in a time period, or information on cumulative number of time zones crossed 2. Imprecise, or limited, information available (e.g. the number of intercontinental flights in a year) 3. No information available		Accurate information on the number of time zones crossed is essential to judge the extent of circadian disruption, and precise information is preferred; studies with limited information should therefore be given less weight in epidemiological synthesis, and studies with no information (Category 3) are considered non-informative	Flying (quickly) over time zones (transmeridian travel) causes circadian disruption as a result of disparities between external time cues and internal circadian rhythms (Härmä et al., 1994)

- *Number of consecutive night shifts* refers to the number of successive shifts performed. In studies of rotating night work, "speed of rotation" is sometimes used to describe this concept.
- *Direction of night shift rotation* refers to the ordering of subsequent shifts (e.g. clockwise vs counter-clockwise rotation).
- *Start and end times of all shifts* provides additional information on exposure to night work during the biological night, as well as on- and off-job (e.g. commuting) activities during the biological night.

For each domain, the Working Group indicated whether information existed in detail, if some information was available, or if information was absent; additional detail was provided in some cases (e.g. type of night shift work schedule).

For epidemiological studies among aircrew, the Working Group also examined information on flying over time zones and cumulative time spent working in the standard sleep interval. In this case, a distinction is made between information on mean or cumulative time zones crossed, approximation of transmeridian travel by number of flights within a certain time frame, or other information.

The assessed studies are grouped according to cancer site and study design, with differentiation between aircrew studies and other.

(a) Cancer of the breast among night shift workers other than aircrew

(i) Cohort and nested case–control studies

Assessments for cohort and nested case–control studies of cancer of the breast among night shift workers other than aircrew are provided in Table S1.7 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). Most studies used objective or subjective methods (Schernhammer et al., 2001, 2006; Lie et al., 2011, 2013; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_EPIC; Travis et al., 2016_UK Biobank; Vistisen et al., 2017; Wegrzyn et al., 2017; Jones et al., 2019) with individual-level information on exposure. One study combined subjective and JEM methods (Pronk et al., 2010). The remaining studies used JEMs (Tynes et al., 1996; Lie et al., 2006; Li et al., 2015); these were all industry-based studies, for example, in textile workers (Li et al., 2015), in nurses subdivided into jobs with and without night work (Lie et al., 2006), and in radio and telegraph operators or those present in the radio room on ships (Tynes et al., 1996).

"Night shift" was defined as working for 3 hours or more between 23:00 and 06:00 in a small number of studies (Lie et al., 2011; Travis et al., 2016_Million Women; Travis et al., 2016_UK Biobank; Vistisen et al., 2017). Some studies defined "night shift" in other ways (Pronk et al., 2010; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Knutsson et al., 2013; Lie et al., 2013; Koppes et al., 2014; Li et al., 2015; Jones et al., 2019). "Night shift" was undefined in the remaining studies (Tynes et al., 1996; Schernhammer et al., 2001, 2006; Lie et al., 2006; Pronk et al., 2010; Åkerstedt et al., 2015; Travis et al., 2016_EPIC; Wegrzyn et al., 2017). [The Working Group noted that the study by Pronk et al. (2010) contains multiple definitions of "night shift".]

In some studies the reference group was assessed as not including night shift work (Hansen & Lassen, 2012; Hansen & Stevens, 2012; Lie et al., 2013; Li et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_UK Biobank). In the remaining studies, it was unclear if the reference group included night shift workers (Tynes et al., 1996; Schernhammer et al., 2001, 2006; Lie et al., 2006, 2011; Pronk et al., 2010; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_EPIC; Vistisen et al., 2017; Wegrzyn et al., 2017; Jones et al., 2019).

Precise information on intensity was available in some studies (Pronk et al., 2010; Lie et al., 2011, 2013; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Li et al., 2015; Jones et al., 2019), but the majority provided imprecise or no information on intensity (Tynes et al., 1996; Schernhammer et al., 2001, 2006; Lie et al., 2006; Pronk et al., 2010; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_EPIC; Travis et al., 2016_UK Biobank; Vistisen et al., 2017; Wegrzyn et al., 2017). [The Working Group noted that the study by Pronk et al. (2010) contains multiple types of information on intensity.]

Complete information on duration of exposure to night shift work, typically lifetime occupational history collected in interviews, was available in the following studies (Schernhammer et al., 2001, 2006; Pronk et al., 2010; Lie et al., 2011; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Åkerstedt et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_EPIC; Wegrzyn et al., 2017). Other studies reported partial information in terms of exposure assessment either over a limited time period (Tynes et al., 1996; Lie et al., 2006, 2013; Knutsson et al., 2013; Li et al., 2015; Vistisen et al., 2017; Jones et al., 2019) or at a single time-point only (Koppes et al., 2014; Travis et al., 2016_UK Biobank). [The Working Group noted that the study by Wegrzyn et al. (2017) contains multiple types of information on duration.]

Only a few studies included complete information on temporality of exposure (Pronk et al., 2010; Travis et al., 2016_Million Women; Vistisen et al., 2017; Jones et al., 2019).

Precise information on number of consecutive night shifts was provided in the studies by Lie et al. (2011, 2013).

Precise information on type of night shift work schedule was reported in Lie et al. (2011, 2013), Hansen & Stevens (2012), and Li et al. (2015).

Information on direction of night shift rotation and precise information on start and end time of shifts were not reported in any of the evaluated studies.

(ii) Case–control studies

Table S1.8 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593) provides summaries of case–control studies of cancer of the breast among night shift workers other than aircrew. A detailed description of exposure assessment considerations for the case–control study deemed most informative (i.e. Cordina-Duverger et al., 2018) is provided below, followed by such considerations across all case–control studies.

Cordina-Duverger et al. (2018) conducted a pooled analysis of five population-based case–control studies with complete work history; all were conducted using interview- or questionnaire-based exposure assessment. Information on work schedules was obtained for each job held longer than 6 months (12 months in Spain). The definition of night work exposure varied across studies; in the combined analyses night work was defined as any job that included 3 hours or more of work between midnight and 05:00. Based on this definition, exposure indicators included ever/never, duration in years, length of night shifts (hours), and years since last night shift. Additional analyses that considered shift frequency (including four of the five studies) examined intensity of night work (nights per week), lifetime cumulative number of night shifts, and number of night hours worked per week. Combined variables (intensity × duration of night work, intensity × length of night shift, and intensity × years since last night shift) were also considered.

All studies used objective or subjective methods (Davis et al., 2001; O'Leary et al., 2006; Pesch et al., 2010; Grundy et al., 2013; Menegaux et al., 2013; Rabstein et al., 2013, 2014; Wang et al., 2015a; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016; Fritschi et al., 2013,

2018; Yang et al., 2019) with individual-level information on exposure.

In the majority of studies, exposure to night shift was defined as at least 3 hours working time between 23:00 and 06:00 (Davis et al., 2001; Pesch et al., 2010; Menegaux et al., 2013; Rabstein et al., 2013, 2014; Wang et al., 2015a; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016; Fritschi et al., 2018). Three studies used other definitions (O'Leary et al., 2006; Fritschi et al., 2013; Grundy et al., 2013), and night shift work was undefined in the studies by Grundy et al. (2013) and Yang et al. (2019). [The Working Group noted that the study by Grundy et al. (2013) contains multiple definitions of night shift.]

In most studies the reference group was assessed as not including night shift work (Davis et al., 2001; Grundy et al., 2013; Menegaux et al., 2013; Wang et al., 2015a; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016; Fritschi et al., 2018; Yang et al., 2019); it was unclear if the reference group included night shift work in the remaining studies (O'Leary et al., 2006; Pesch et al., 2010; Fritschi et al., 2013; Rabstein et al., 2013, 2014).

Precise information on intensity was available in some studies (Davis et al., 2001; O'Leary et al., 2006; Grundy et al., 2013; Menegaux et al., 2013; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016); the remainder reported imprecise or no information on intensity (Pesch et al., 2010; Rabstein et al., 2013, 2014; Wang et al., 2015a; Fritschi et al., 2013, 2018; Yang et al., 2019).

Complete information on duration of exposure to night work was reported in some studies (Davis et al., 2001; Grundy et al., 2013; Menegaux et al., 2013; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016), typically in the form of lifetime occupational history collected in interviews. Others had partial information in terms of exposure assessment over a limited time period (O'Leary et al., 2006; Pesch et al., 2010; Rabstein et al., 2013, 2014; Fritschi et al., 2013, 2018). No information on duration of exposure to night work was noted in the studies by Wang et al. (2015a) and Yang et al. (2019).

Some studies included analysis using information on temporality of exposure (Davis et al., 2001; O'Leary et al., 2006; Pesch et al., 2010; Grundy et al., 2013; Menegaux et al., 2013; Cordina-Duverger et al., 2016, 2018), for example, time since last night shift (Cordina-Duverger et al., 2018), whether night work had been undertaken before first pregnancy (Cordina-Duverger et al., 2018), and night work in the 10 years before diagnosis (Davis et al., 2001).

Precise information on type of night shift work schedule was reported in Davis et al. (2001), O'Leary et al. (2006), and Papantoniou et al. (2016).

Precise information on start and end time of shifts was available in the studies by Davis et al. (2001), Menegaux et al. (2013), Cordina-Duverger et al. (2018), Fritschi et al., 2013, 2018).

No information on number of consecutive night shifts and direction of night shift rotation was provided in any of the studies evaluated.

(b) Cancer of the prostate among night shift workers other than aircrew

Summaries of studies of cancer of the prostate among night shift workers other than aircrew (any design) are reported in Table S1.9 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used objective or subjective methods (Kubo et al., 2006, 2011; Conlon et al., 2007; Parent et al., 2012; Gapstur et al., 2014; Yong et al., 2014a, b; Hammer et al., 2015; Papantoniou et al., 2015; Dickerman et al., 2016; Åkerstedt et al., 2017; Behrens et al., 2017; Tse et al., 2017; Wendeu-Foyet et al., 2018; Barul et al., 2019; Kogevinas et al., 2019) with individual-level information on exposure.

Exposure to night shift was defined as at least 3 hours of work between 23:00 and 06:00 in some studies (Parent et al., 2012; Yong et al., 2014a, b; Hammer et al., 2015; Barul et al., 2019); most

studies used other definitions (Kubo et al., 2011; Gapstur et al., 2014; Papantoniou et al., 2015; Behrens et al., 2017; Tse et al., 2017; Wendeu-Foyet et al., 2018; Kogevinas et al., 2019) and night shift was undefined in the remainder (Kubo et al., 2006; Conlon et al., 2007; Dickerman et al., 2016; Åkerstedt et al., 2017).

In most studies the reference group was assessed as not including those exposed to night shift work (Kubo et al., 2011; Parent et al., 2012; Yong et al., 2014a, b; Papantoniou et al., 2015; Behrens et al., 2017; Tse et al., 2017; Wendeu-Foyet et al., 2018; Barul et al., 2019). It was unclear if the reference group included those exposed to night shift work in the following studies: (Kubo et al., 2006; Conlon et al., 2007; Gapstur et al., 2014; Dickerman et al., 2016; Åkerstedt et al., 2017). The reference group included those exposed to night shift work in the studies by Hammer et al. (2015) and Kogevinas et al. (2019).

A few of the studies had precise information on intensity of night shift work (Wendeu-Foyet et al., 2018; Barul et al., 2019; Kogevinas et al., 2019); all other studies had imprecise or no information.

Most studies had complete information on duration of exposure to night shift work, typically in the form of lifetime occupational history collected in interviews (Parent et al., 2012; Hammer et al., 2015; Papantoniou et al., 2015; Åkerstedt et al., 2017; Behrens et al., 2017; Wendeu-Foyet et al., 2018; Barul et al., 2019; Kogevinas et al., 2019). Other studies had partial information in terms of assessment over a limited time period (Conlon et al., 2007; Kubo et al., 2011; Yong et al., 2014a, b) or at a single time-point (Gapstur et al., 2014). No information on duration of exposure was available from the remainder of the studies (Kubo et al., 2006; Dickerman et al., 2016; Tse et al., 2017).

Some studies included analyses using complete information on temporality (Conlon et al., 2007; Parent et al., 2012; Yong et al., 2014a, b; Kogevinas et al., 2019).

Precise information on the number of consecutive night shifts worked was available in the studies by Wendeu-Foyet et al. (2018) and Barul et al. (2019). Direction of night shift rotation was reported in the studies by Kubo et al. (2011), Hammer et al. (2015), Wendeu-Foyet et al. (2018), and Barul et al. (2019).

Precise information on type of night shift work schedule was reported by Kubo et al. (2006, 2011), Gapstur et al. (2014), Yong et al. (2014a, b), Hammer et al. (2015), Papantoniou et al. (2015), Wendeu-Foyet et al. (2018), Barul et al. (2019), and Kogevinas et al. (2019).

Precise information on start and end time of shifts was available in the studies by Hammer et al. (2015) and Wendeu-Foyet et al. (2018).

(c) Cancer of the colon and rectum among night shift workers other than aircrew

Assessments of studies of cancer of the colon and rectum among night shift workers other than aircrew (any design) are reported in Table S1.10 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used objective or subjective methods (Schernhammer et al., 2003; Parent et al., 2012; Yong et al., 2014a, b; Gu et al., 2015; Devore et al., 2017; Jørgensen et al., 2017; Papantoniou et al., 2017, 2018) with individual-level information on exposure.

Exposure to night shift was defined as at least 3 hours of work between 23:00 and 06:00 in studies by Yong et al. (2014a, b) and Papantoniou et al. (2017). Parent et al. (2012) and Jørgensen et al. (2017) used other definitions for night shift, and it was undefined in the remaining studies (Schernhammer et al., 2003; Gu et al., 2015; Devore et al., 2017; Papantoniou et al., 2018).

The reference group was assessed as not including those exposed to night shift work in some studies (Parent et al., 2012; Yong et al., 2014a, b; Papantoniou et al., 2017), but it was unclear if the reference group included those exposed to night shift work in others (Schernhammer

et al., 2003; Gu et al., 2015; Devore et al., 2017; Jørgensen et al., 2017; Papantoniou et al., 2018).

One study reported precise information on intensity (Papantoniou et al., 2017); all other studies had imprecise or no information on intensity.

Complete information on duration of exposure to night shift work, typically in the form of lifetime occupational history collected in interviews, was reported in some studies (Schernhammer et al., 2003; Parent et al., 2012; Devore et al., 2017; Papantoniou et al., 2017, 2018). The remaining studies had partial information on duration of exposure to night shift work, assessed either for a limited time period (Yong et al., 2014a, b; Gu et al., 2015) or at a single time-point (Jørgensen et al., 2017).

Some studies included analysis using complete information on temporality of exposure (Yong et al., 2014a, b; Parent et al., 2012).

Precise information on type of night shift work schedule was reported by Yong et al. (2014a, b) and Papantoniou et al. (2017).

None of the studies provided information on the number of consecutive night shifts worked, the direction of night shift rotation, or start and end times of shifts.

(d) Cancer at other organ sites among night shift workers other than aircrew

Assessments of studies of cancer of other sites among night shift workers other than aircrew (any design) are reported in Table S1.11 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used objective or subjective methods with individual information on exposure.

Exposure to night shift was defined as 3 hours or longer of work between 23:00 and 06:00 in some studies (Bhatti et al., 2013; Carter et al., 2014; Yong et al., 2014a, b; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016). Different definitions were used in other studies (Parent et al., 2012; Lin et al., 2013, 2015; Carreón et al., 2014; Carter et al., 2014; Leung et al., 2019), and night shift work was undefined in the remainder of the studies (Viswanathan et al., 2007; Poole et al., 2011; Schernhammer et al., 2013; Gu et al., 2015; Heckman et al., 2017). [The Working Group noted that the study by Carter et al. (2014) contains multiple definitions of night shift.]

In several studies the reference group was assessed as not including those exposed to night shift work (Parent et al., 2012; Bhatti et al., 2013; Yong et al., 2014a, b; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Leung et al., 2019). In other studies it was unclear if the reference group included those exposed to night shift work (Viswanathan et al., 2007; Poole et al., 2011; Lin et al., 2013, 2015; Schernhammer et al., 2013; Carreón et al., 2014; Carter et al., 2014; Gu et al., 2015; Heckman et al., 2017).

Some studies reported precise information on intensity of night shift work (Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Leung et al., 2019); all other studies had imprecise or no information on intensity.

Most studies had complete information on duration of exposure to night shift work, typically in the form of lifetime occupational history collected in interviews (Viswanathan et al., 2007; Poole et al., 2011; Parent et al., 2012; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Heckman et al., 2017; Leung et al., 2019). Other studies reported partial information on duration of exposure, assessed either over a limited period (Bhatti et al., 2013; Schernhammer et al., 2013; Carreón et al., 2014; Yong et al., 2014a, b; Gu et al., 2015) or at a single time-point (Carter et al., 2014), or did not report any information (Lin et al., 2013, 2015).

Some studies included analysis using complete information on temporality (Parent et al., 2012; Bhatti et al., 2013; Carreón et al., 2014; Yong et al., 2014a, b; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Leung et al., 2019).

Precise information on the number of consecutive night shifts worked and direction of night shift rotation was provided by Carreón et al. (2014) only.

Precise information on type of night shift work schedule was available in studies by Carreón et al. (2014), Carter et al. (2014), Yong et al. (2014a, b), Kwon et al. (2015), Costas et al. (2016), Gyarmati et al. (2016), and Leung et al. (2019).

Precise information on start and end time of shifts was not available in any of the studies reviewed.

(e) Cancer among aircraft cockpit crew

Assessments of studies of cancer among aircraft cockpit crew (Rafnsson et al., 2000; Pukkala et al., 2003; Yong et al., 2014c) are reported in Table S1.12 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used JEMs based on information on block hours and flight hours [The Working Group noted that "block hours" refers to gate departure to gate arrival (aircraft taxi time and air time), and "flight hours" refers to wheels off the ground to wheels on the ground (air time).] All studies reported limited or no information on flying over time zones, and night shift work was undefined. Whether the reference group included those exposed to night shift work was also unreported in all studies, and none provided precise information on intensity of night shift work. One study (Rafnsson et al., 2000) had complete information on duration of work as a pilot. One study (Pukkala et al., 2003) had complete information on temporality of exposure.

(f) Cancer among aircraft cabin crew

Summaries of studies of cancer among aircraft cabin crew are reported in Table S1.13 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used JEMs based on information on aircraft type or airport, for example.

Some studies defined exposure to night shift as at least 3 hours of work between 22:00 and 08:00 local time at origin (Pinkerton et al., 2012, 2016, 2018; Schubauer-Berigan et al., 2015), and night shift work was undefined in other studies (Reynolds et al., 2002; Linnersjö et al., 2003; Pukkala et al., 2012).

The reference group was assessed as not including those exposed to night shift work in studies by Schubauer-Berigan et al. (2015) and Pinkerton et al. (2016, 2018); in other studies, the reference group included those exposed to night shift work (Pinkerton et al., 2012) or this was not reported (Reynolds et al., 2002; Linnersjö et al., 2003; Pukkala et al., 2012).

Precise information on intensity of night shift work was available in studies by Pinkerton et al. (2012), Pukkala et al. (2012), and Schubauer-Berigan et al. (2015).

Schubauer-Berigan et al. (2015) and Pinkerton et al. (2016, 2018) provided complete information on duration of work as a flight attendant from individual interviews; the other studies had partial information (limited period) on duration of work as a flight attendant.

Most studies had precise information on time zones crossed (Pinkerton et al., 2012, 2016, 2018; Pukkala et al., 2012; Schubauer-Berigan et al., 2015); the remainder had limited information on flying over time zones (Reynolds et al., 2002; Linnersjö et al., 2003).

Temporality of exposure to night shift work was not available in any of the studies assessed.

1.5.2 Quality of exposure assessment in meta-analyses

(a) Cancer of the breast

In the study by Liu et al. (2018), the analyses of multiple cancers were stratified by sex. Work schedules were divided into rotating shift (working a regular shift schedule), fixed shift

(permanent night work), and mixed (with no clear work schedule) when this information was available for each study; in some cases, "evening" work was also considered. There were no definitions of night shift. The exposure indicators for analyses were the odds ratios of the longest (from ≥ 0.6 years to ≥ 30 years) versus shortest exposure time when this was reported in the articles considered. When exposure time was not reported, the authors used "ever versus never" exposure to the work schedule evaluated (which occurred for 10 of the 26 studies included on cancer of the breast). [The Working Group noted that 37 risk estimates for cancer of the breast are summarized in table 2 of Liu et al. (2018), although only 26 studies are described in table 1; the summary description of the exposure assessment may therefore be incomplete.] Other specific shift work properties were not characterized. Most study exposure assessments were subjective (9 based on questionnaires, 15 based on interviews, and 2 from databases).

Liu et al. (2016) examined breast cancer outcomes among female cabin crew, where this occupational title (yes/no) was used as the exposure variable. No detail on exposure assessment was provided. Specific shift work variables (e.g. time zones crossed or individual duration of exposure) and co-exposure to cosmic radiation were not considered.

Travis et al. (2016) examined 10 prospective studies (defined as those where exposure data were recorded before the onset of cancer of the breast), including 3 prospective UK studies and 7 other studies located through a literature search. Shift work schedules involving nights were variably defined across studies. The exposure indicator of ever/never worked night shifts included individual studies with varying types of indicators; for example, detail provided for the three UK studies indicated that "ever versus never exposure to night shift work" was reported in two of the studies, while "yes/no current exposure to night shift work" was reported in the other. Additional analyses assessed relative risks associated with duration of exposure to long-term shift work of 20 years or longer (eight studies included) and 30 years or longer (four studies included). Other shift work properties were not characterized.

The meta-analysis conducted by He et al. (2015) included 28 studies that evaluated the association between risk of cancer of the breast and any type of circadian disruption. Studies with differing exposures, including shift work (assessed in 15 studies), exposure to light at night (6 studies), sleep deficiency (7 studies), and employment as a flight attendant (3 studies), were grouped within one overall meta-analysis. Shift work schedules, including those involving nights, were not clearly defined. Subgroup analyses were conducted by source of circadian disruption (yes/no) as described above. Additional subgroup analyses examined studies of shift work and flight attendants combined and all studies except for those of flight attendants. Dose–response meta-analyses examined increments of 10 years of shift work (reference group: never exposed).

(b) Other cancers

Studies of cancer of the prostate where the exposure of interest was shift work were examined by Du et al. (2017) and Gan et al. (2018).

Gan et al. (2018) included 15 studies; of these, 3 reported more than one shift work category. Shift work schedules were classified as rotating shifts (six studies), night shifts (eight studies), mixed schedules (four studies, three of which were aircrew populations), and evening shifts (one study). Shift work schedules, including those involving nights, were not clearly defined in most original studies included in the analyses. Exposure indicators used in full analyses were ever versus never exposure; a subset of three studies (including four reports) with information on duration of exposure was also examined in a separate analysis. Subgroup analyses by shift schedule were performed.

Nine cohort studies were included in the meta-analysis conducted by Du et al. (2017). Exposure was to shift work (six studies), night work (three studies), or occupations "related with shift work", such as aircrew (three studies) (some studies included both shift and night work). The shift work schedules under consideration, including those involving nights, were not clearly defined. The exposure indicator used was ever versus never exposure; other shift work characteristics (e.g. duration) were not assessed. Subgroup analyses examined night work and shift work separately.

Wang et al. (2015b) conducted a meta-analysis of six studies focused on night shift work and cancer of the colon and rectum. Exposure assessment was conducted via interview (four studies), questionnaire (one study), and database (one study). The shift work schedules under consideration, including shift work involving nights, were not clearly defined. The exposure indicator used in the main analyses was longest versus shortest period of night shift work reported; this consisted of ever/never exposure for four of the six studies. In a "dose-response meta-analysis" examining duration of night shift work, it was not clear which studies were included. Other specific shift work properties were not characterized. In additional analyses, stratification was conducted by exposure assessment type (e.g. self-administered questionnaire or interview).

The methods used in the meta-analysis by Liu et al. (2018) for cancers other than breast are described in the previous section on meta-analyses of cancer of the breast. When exposure time was not reported, the authors used "ever versus never" exposure to the work schedule evaluated (which occurred for 24 of the 58 studies included in this meta-analysis). Most study exposure assessments were subjective (28 based on questionnaire, 24 based on interview, and 6 from databases), with no information available on individual- versus group-level assessment. Dose information from ordinal categorical data (three or more levels of the exposure category) was used in a dose–response meta-analysis.

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2. CANCER IN HUMANS

A systematic search was conducted of PubMed and Web of Science databases to identify cohort, case–control, and nested case–control studies evaluating exposure to night shift work or work involving transmeridian air travel (i.e. aircrew studies) with cancer as an outcome. Search terms and the resulting literature are available online (https://hawcproject.iarc.who.int/assessment/605/). Case reports, studies using ecological designs, and studies that did not include cancer as an end-point were not considered further.

Since the review of the carcinogenicity of shift work by the Working Group as part of *IARC Monographs* Volume 98 (Straif et al., 2007; IARC, 2010), numerous studies have been published on cancer incidence or mortality among night shift workers and aircrew. The Working Group considered studies that only compared incidence or mortality rates with the general population to be uninformative for the present evaluation because of the lack of control for potential confounding. All other studies were considered potentially eligible for the evaluation, and were divided into studies of shift workers other than aircrew (Section 2.1), studies of aircrew (Section 2.2), and meta-analyses (Section 2.3). The evidence regarding human cancer from all these sources is synthesized in Section 2.4.

2.1 Studies among night shift workers other than aircrew

2.1.1 Cancer of the breast

(a) Cohort studies (including nested case–control studies)

See Table 2.1.

In *IARC Monographs* Volume 98 (IARC, 2010), three cohort studies (Schernhammer et al., 2001, 2006; Schwartzbaum et al., 2007) and two nested case–control studies (Tynes et al., 1996; Lie et al., 2006) provided data on the risk of breast cancer in night shift workers. Since the publication of this volume, nine additional cohort studies reported in seven publications (Pronk et al., 2010; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016; Vistisen et al., 2017; Jones et al., 2019), one case–cohort study (Li et al., 2015), three nested case–control studies (Lie et al., 2011; Hansen & Lassen, 2012; Hansen & Stevens, 2012), and results (Wegrzyn et al., 2017) from the expanded follow-up of two cohorts considered in the previous IARC monograph have been published. After excluding one insufficiently informative study that provided only standardized incidence ratios for cancer of the breast in occupations with probable exposure to shift work and no adjustment for potential confounders (Schwartzbaum et al., 2007), the Working Group reviewed the most recent data from 17 cohort, case–cohort,

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schernhammer et al. (2001) 11 states of USA June 1988–May 1998 (follow-up) Cohort	78 562 women: nurses included in NHS-I who responded to the 1988 questionnaire on night shift work and who were free of cancer at that time Exposure assessment method: subjective assessment; night shift undefined	Rotating night shift work history at baseline (RR): Never 1–14 yr 15–29 yr ≥ 30 yr Trend test *P* value, 0.02 Rotating night shift work history at baseline, premenopausal (RR): Never 1–14 yr ≥ 15 yr Trend test *P* value, 0.12 Rotating night shift work history at baseline, postmenopausal (RR): Never 1–14 yr 15–29 yr ≥ 30 yr Trend test *P* value, 0.05	 925 1324 134 58 121 174 14 801 1146 120 58	 1 1.08 (0.99–1.18) 1.08 (0.90–1.30) 1.36 (1.04–1.78) 1 1.23 (0.97–1.55) 1.34 (0.77–2.33) 1 1.06 (0.97–1.16) 1.05 (0.87–1.27) 1.36 (1.04–1.78)	Age, age at menarche, parity, age at first birth, weight change between age 18 yr and menopause, BMI at age 18 yr, family history of breast cancer, benign breast disease, OC, alcohol, time period, age at menopause, postmenopausal hormone therapy, menopausal status, height	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments:* analysis of years of employment with night work; data included in the study by Wegrzyn et al. (2017) Strengths: prospective study; large population size; breast cancer diagnoses confirmed through review of medical records; full consideration of potential confounders Limitations: women on permanent night shift not classified; no updated information on exposure during follow-up (1988–1998)

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schernhammer et al. (2006) USA 1989–2001 Cohort	115 022 nurses in NHS-II, age 25–42 yr at enrolment in 1989 Exposure assessment method: subjective assessment; night shift undefined	Duration of rotating night shift work (RR):			Age, age at menarche, menopausal status, age at menopause, age at first birth and parity, BMI, alcohol, contraceptive use, postmenopausal hormone, smoking, benign breast disease, family history of breast cancer, physical activity	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments:* analysis of years of employment with night work Strengths: prospective study; large population size; exposure information updated during follow-up; breast cancer diagnoses confirmed from pathology reports; full consideration of potential confounders Limitations: women on permanent night shift not classified; part of the updated exposure information was obtained retrospectively at the end of follow-up
		Never worked rotating night shift	441	1		
		1–9 yr	816	0.98 (0.87–1.1)		
		10–19 yr	80	0.91 (0.72–1.16)		
		≥ 20 yr	15	1.79 (1.06–3.01)		
		Trend test *P* value, 0.65				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Wegrzyn et al. (2017) USA NHS-I follow-up, 1988–2012; NHS-II follow-up, 1989–2013 Cohort	NHS-I, 78 516, NHS-II, 114 559: nurses NHS-I: women free of cancer when enrolled at baseline in 1988, who responded to the shift work questionnaire NHS-II: women aged 25–42 yr, free of cancer when enrolled at baseline in 1989, who responded to the shift work questionnaire Exposure assessment method: subjective assessment; night shift undefined	NHS-I rotating nightshift work history (at baseline) (HR):			Age, height, BMI, BMI aged 18 yr, body size at adolescence, age at menarche, age at first birth and parity, breastfeeding, menopausal status, age at menopause, duration of hormone therapy and type, family history of breast cancer, history of benign breast disease, alcohol consumption, physical activity, mammography	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete (NHS-II) or Partial (NHS-I). No other information available. *Other comments:* analysis of years of employment with night work; updated follow-up of NHS-I and NHS-II cohorts (Schernhammer et al., 2001, 2006) Strengths: large population size; 24 yr of follow-up; full adjustment for confounders Limitations: updated information on exposure not available during follow-up for NHS-I; permanent night work not considered
		Never	2382	1		
		1–14 yr	3162	1.01 (0.96–1.07)		
		15–29 yr	331	1.06 (0.94–1.19)		
		≥ 30 yr	96	0.95 (0.77–1.17)		
		Trend test *P* value, 0.63				
		NHS-II 1989 rotating nightshift work history (at baseline) (HR):				
		Never	1318	1		
		1–9 yr	2071	1.05 (0.98–1.13)		
		10–19 yr	168	1.00 (0.85–1.17)		
		≥ 20 yr	13	2.15 (1.23–3.73)		
		Trend test *P* value, 0.23				
		NHS-II cumulative rotating night shift work history (updated to end of follow-up) (HR):				
		Never	950	1		
		1–9 yr	2002	1.04 (0.96–1.12)		
		10–19 yr	201	0.94 (0.81–1.1)		
		≥ 20 yr	35	1.40 (1.00–1.97)		
		Trend test *P* value, 0.74				
		NHS-I rotating nightshift work history (at baseline), follow-up period ≤ 10 yr (HR):				
		None	977	1		
		1–14 yr	1415	1.09 (1.00–1.18)		
		15–29 yr	146	1.07 (0.90–1.28)		
		≥ 30 yr	60	1.26 (0.97–1.64)		
		Trend test *P* value, 0.04				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Wegrzyn et al. (2017) (cont.)		NHS-I rotating nightshift work history (at baseline), follow-up period > 10 yr (HR):				
		None	1405	1		
		1–14 yr	1747	0.96 (0.89–1.03)		
		15–29 yr	185	1.05 (0.90–1.23)		
		≥ 30 yr	36	0.68 (0.49–0.95)		
		Trend test *P* value, 0.25				
		NHS-II 1989 rotating nightshift work history (at baseline), follow-up period ≤ 10 yr (HR):				
		None	416	1		
		1–9 yr	637	1.02 (0.90–1.15)		
		10–19 yr	57	0.96 (0.73–1.27)		
		≥ 20 yr	6	2.35 (1.04–5.31)		
		Trend test *P* value, 0.71				
		NHS-II 1989 rotating nightshift work history (at baseline), follow-up period > 10 yr (HR):				
		None	902	1		
		1–9 yr	1434	1.07 (0.98–1.16)		
		10–19 yr	111	1.01 (0.83–1.24)		
		≥ 20 yr	7	1.95 (0.92–4.15)		
		Trend test *P* value, 0.24				
		NHS-II cumulative rotating nightshift work (updated), follow-up period ≤ 10 yr (HR):				
		None	341	1		
		1–9 yr	621	0.97 (0.85–1.11)		
		10–19 yr	60	0.94 (0.71–1.23)		
		≥ 20 yr	12	2.13 (1.19–3.81)		
		Trend test *P* value, 0.75				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Wegrzyn et al. (2017) (cont.)		NHS-II cumulative rotating nightshift work (updated), follow-up period > 10 yr (HR):				
		None	609	1		
		1–9 yr	1381	1.07 (0.97–1.18)		
		10–19 yr	141	0.95 (0.79–1.14)		
		≥ 20 yr	23	1.19 (0.78–1.81)		
		Trend test *P* value, 0.89				
		NHS-II duration of rotating nightshift work (updated) (HR):				
		Per year of shift work before menopause	NR	1.00 (0.99–1.01)		
		Per year of shift work after menopause	NR	0.98 (0.90–1.06)		
		NHS-II cumulative rotating nightshift work (updated) exposure for ≥ 20 yr vs not exposed (HR):				
		ER+ and PR+	NR	1.62 (1.07–2.45)		
		ER+	NR	1.50 (1.01–2.22)		
		PR+	NR	1.57 (1.04–2.37)		
		Trend test *P* value, 0.89				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Tynes et al. (1996) Norway 1961–1991 Nested case–control	50 cases: women with breast cancer from the cohort of radio and telegraph operators (Telecom Cohort) 259 controls: women in the same cohort matched to the cases on year of birth and alive at the time of diagnosis (4–7 controls per case) Exposure assessment method: JEM assessment; night shift undefined	Cumulative exposure to shift work (categories × year), age < 50 yr (OR): None Low (> 0.0–3.1) High (> 3.1–20.7) Trend test *P* value, 0.97 Cumulative exposure to shift work (categories × year), age ≥ 50 yr (OR): None Low (> 0.0–3.1) High (> 3.1–20.7) Trend test *P* value, 0.13	 12 5 12 3 6 12 	 1 0.3 (0.1–1.2) 0.9 (0.3–2.9) 1 3.2 (0.6–17.3) 4.3 (0.7–26) 	Duration of employment	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (limited period). No other information available. *Other comments:* analysis of combined measure of shift work category × years of exposure to night work Strengths: nested case–control study based on high-quality registers Limitations: very small sample size; categories of exposure to shift work (0, 1, 2, 3) not defined; no adjustment for fertility factors and other breast cancer risk factors

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Lie et al. (2006) Norway Follow-up, 1960–1982 Nested case–control	537 cases: cohort of 44 835 Norwegian nurses; cancer cases identified from Cancer Registry of Norway 2143 controls: 4 controls per case individually matched on year of birth Exposure assessment method: JEM assessment; night shift undefined	Years with night work (OR):			Total employment time as a nurse, parity	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (limited period). No other information available. *Other comments:* analysis of years of night work Strengths: large cohort based on a nationwide registry of nurses; high-quality registries; 22 yr of follow-up; adjustment for parity known from Statistics Norway. Limitations: duration of night work based on imputation data; no adjustment for potential confounders (except parity).
		0 yr	50	1		
		> 0–14 yr	362	0.95 (0.67–1.33)		
		15–29 yr	101	1.29 (0.82–2.02)		
		≥ 30 yr	24	2.21 (1.10–4.45)		
		Trend test *P* value, 0.01				
		Years with night work, age < 50 yr (OR):				
		0 yr	21	1		
		> 0–14 yr	185	1.02 (0.60–1.71)		
		≥ 15 yr	13	1.72 (0.56–5.26)		
		Trend test *P* value, 0.52				
		Years with night work, age ≥ 50 yr (OR):				
		0 yr	29	1		
		> 0–14 yr	177	0.86 (0.54–1.37)		
		15–29 yr	88	1.17 (0.68–2.00)		
		≥ 30 yr	24	2.01 (0.95–4.26)		
		Trend test *P* value, 0.02				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Lie et al. (2011) Norway 1990–2007 Nested case–control	699 cases: diagnosed from January 1990 to December 2007, aged 35–74 yr at diagnosis, alive in February 2009; identified from Norwegian Cancer Registry 895 controls: frequency-matched within each 5-yr age stratum for each diagnostic year (1990, …, 2007), alive in February 2009 Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Duration of work in schedules including ≥ 3 nights/mo (OR):			Age, period of diagnosis, parity, family history of breast cancer, alcohol consumption	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Precise. Duration: Complete. Temporality: Complete. Rotation speed: Precise. Schedule type: Rotating, Undefined. No other information available. *Other comments:* analysis of: employment duration with ≥ 3 night shifts/mo; duration of employment with night; lifetime number of night shifts; lifetime average number of night shifts/mo No overlap with the previous study by Lie et al. (2006) on Norwegian nurses, as the follow-up periods are distinct Strengths: large cohort based on a nationwide registry of nurses; high-quality registries; 18 yr of follow-up; exposure data collected by detailed questionnaire; adjustment for the main potential confounders Limitations: study based on living prevalent cases in February 2009 at the time of data collection
		Never night work	102	1		
		Never ≥ 3 nights/mo	28	1.4 (0.8–2.6)		
		1–14 yr	390	1.2 (0.9–1.6)		
		15–29 yr	152	1.2 (0.9–1.7)		
		≥ 30 yr	27	0.8 (0.5–1.4)		
		Trend test *P* value, 0.69				
		Duration of work in schedules including night work (OR):				
		Never night work	102	1		
		1–11 yr	410	1.2 (0.9–1.5)		
		≥ 12 yr	187	1.3 (0.9–1.8)		
		Trend test *P* value, 0.17				
		Cumulative number of lifetime night shifts (OR):				
		Never night work	102	1		
		< 1007 nights	396	1.2 (0.9–1.6)		
		≥ 1007 nights	201	1.2 (0.9–1.7)		
		Trend test *P* value, 0.24				
		Lifetime average number of night shifts/mo (OR):				
		Never night work	102	1		
		< 4 nights/mo	415	1.2 (0.9–1.6)		
		≥ 4 nights/mo	182	1.2 (0.8–1.6)		
		Trend test *P* value, 0.51				
		Duration of work in schedules including ≥ 3 consecutive night shifts (OR):				
		Never night work	102	1		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Lie et al. (2011) (cont.)		Never 3 consecutive nights	125	1.4 (1–2.1)		
		< 5 yr with ≥ 3 consecutive nights	194	1.1 (0.8–1.6)		
		≥ 5 yr with ≥ 3 consecutive nights	278	1.1 (0.8–1.5)		
		Trend test *P* value, 0.92				
		Duration of work in schedules including ≥ 6 consecutive night shifts (OR):				
		Never night work	102	1		
		Never 6 consecutive nights	414	1.1 (0.8–1.5)		
		< 5 yr with ≥ 6 consecutive nights	119	1.2 (0.8–1.7)		
		≥ 5 yr with ≥ 6 consecutive nights	64	1.8 (1.1–2.8)		
		Trend test *P* value, 0.02				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Lie et al. (2013) Norway 1990–2007 Nested case–control	590 cases: diagnosed from January 1996 to December 2007, aged 35–74 yr at diagnosis, alive in February 2009; identified from Norwegian Cancer Registry 757 controls: frequency-matched within each 5-yr age stratum for each diagnostic year (1996, …, 2007), alive in February 2009 Exposure assessment method: subjective assessment; night shift defined (other)	Duration of work in schedules including ≥ 6 consecutive night shifts, PR+ (OR):			Age, period of diagnosis, parity, family history of breast cancer, hormonal treatment in previous 2 yr, alcohol consumption	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Precise. Duration: Complete. Temporality: Complete. Rotation speed: Precise. Schedule type: Permanent, Rotating. No other information available. *Other comments*: analysis of: employment duration with ≥ 6 night shifts/mo; duration of employment with night work; lifetime number of night shifts; lifetime average number of night shifts/mo No overlap with the previous study by Lie et al. (2006) on Norwegian nurses, as the follow-up periods are distinct Strengths: large cohort based on a nationwide registry of nurses; high-quality registries; 18 yr follow-up; exposure data collected from a detailed questionnaire; adjustment for the main potential confounders Limitations: study based on living prevalent cases in February 2009 at the time of data collection
		Never night work	45	1		
		Never worked 6 consecutive nights	203	1.3 (0.9–2)		
		< 5 yr with ≥ 6 consecutive nights	57	1.4 (0.9–2.4)		
		≥ 5 yr with ≥ 6 consecutive nights	33	2.4 (1.3–4.3)		
		Trend test *P* value, 0.01				
		Duration of work in schedules including ≥ 6 consecutive night shifts, PR– (OR):				
		Never night work	22	1		
		Never worked 6 consecutive nights	114	1.4 (0.8–2.4)		
		< 5 yr with ≥ 6 consecutive nights	26	1.2 (0.7–2.3)		
		≥ 5 yr with ≥ 6 consecutive nights	9	1.2 (0.5–2.8)		
		Trend test *P* value, 0.76				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Lie et al. (2013) (cont.)		Duration of work in schedules including ≥ 6 consecutive night shifts, ER– (OR):				
		Never night work	6	1		
		Never worked 6 consecutive nights	45	2.0 (0.8–4.8)		
		< 5 yr with ≥ 6 consecutive nights	10	1.7 (0.6–4.8)		
		≥ 5 yr with ≥ 6 consecutive nights	6	2.8 (0.8–9.2)		
		Trend test *P* value, 0.19				
Pronk et al. (2010) Shanghai, China Enrolment, 1996–2000; follow-up, through 2007 Cohort	73 049 women aged 40–70 yr in seven urban communities of Shanghai Exposure assessment method: two analyses: (1) subjective assessment with night shift defined (other) ; and (2) JEM assessment with night shift undefined	Ever working night shifts according to JEM (HR):			Age, education, family history of breast cancer, number of pregnancies, age at first birth, occupational physical activity	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Precise (survey based); Imprecise (JEM based). Duration: Complete. Temporality: Complete. No other information available. *Other comments*: analysis of: ever/never night work; number of night shifts/mo; lifetime number of night shifts; age at starting night shift Strengths: large size of cohort; population-based study involving a large range of occupations; high participation rate; adjustment for the main potential confounders Limitations: poor exposure assessment
		Never	423	1		
		Ever	294	1.0 (0.9–1.2)		
		Ever working night shifts according to self-report (HR):				
		Never	276	1		
		Ever	73	0.9 (0.7–1.1)		
		Duration of working in jobs with score > 0 according to JEM (HR):				
		0 yr	423	1		
		> 0 to ≤ 14 yr	108	1.1 (0.9–1.3)		
		> 14 to ≤ 25 yr	89	0.9 (0.7–1.1)		
		> 25 yr	97	1 (0.8–1.3)		
		Trend test *P* value, 0.72				
		Average night shift score defined by JEM (HR):				
		0	423	1		
		> 0 to ≤ 1.29	102	1 (0.8–1.2)		
		> 1.29 to ≤ 2.38	109	1.1 (0.9–1.3)		
		> 2.38	83	0.9 (0.7–1.2)		
		Trend test *P* value, 0.73				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Pronk et al. (2010) (cont.)		Frequency (number of night shifts/mo, self-reported (HR):				
		0 shifts/mo	276	1		
		> 0 to < 8 shifts/mo	8	0.6 (0.3–1.2)		
		8 shifts/mo	45	0.9 (0.7–1.3)		
		> 8 shifts/mo	20	0.9 (0.5–1.3)		
		Trend test *P* value, 0.29				
		Duration of working night shifts, self-reported (HR):				
		Never shift work	276	1		
		Ever shift work	73	0.9 (0.7–1.1)		
		> 0 to ≤ 5 yr	25	0.9 (0.6–1.3)		
		> 5 to ≤ 17 yr	29	0.9 (0.6–1.4)		
		> 17 yr	19	0.8 (0.5–1.2)		
		> 20 yr	NR	0.7 (0.4–1.2)		
		> 30 yr	NR	0.9 (0.4–2)		
		Trend test *P* value, 0.26				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Hansen & Stevens (2012) Denmark July 2001 to June 2003 Nested case–control	267 cases: nurses with a histologically confirmed primary breast cancer diagnosed during follow-up, still alive at the time of interview, identified from Danish Cancer Registry 1035 controls: cohort members randomly selected from the cohort matched by year of birth and interviewed in the same period as the cases Exposure assessment method: subjective assessment; night shift defined (other)	Shift work system (OR):			Age, weight regularity, use of HRT, age at menarche, menstrual regularity, menopausal status, age at first birth, breast cancer in mother or sister, total duration of lactation	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Schedule type: Permanent night, Rotating. Shift start/end times: Imprecise. No other information available. *Other comments*: analysis of: lifetime duration of permanent and rotating schedules; duration of night work (yr); lifetime number of night shifts Strengths: large cohort; identification of cases from high-quality cancer register; telephone interview using a detailed questionnaire on shift work; high participation rate Limitations: short period of follow-up and limited number of cases
		Permanent day shift, never evening or night shift	28	1		
		Ever evening shift, never night	9	0.9 (0.4–1.9)		
		Ever after-midnight rotating shift, never permanent night shift	212	1.8 (1.2–2.8)		
		Ever permanent night in addition to rotating night shifts	18	2.9 (1.1–8.0)		
		Duration of graveyard shifts (working after midnight (~8 h of work between 19:00 and 09:00) for ≥ 1 yr) (OR):				
		Never graveyard shift	37	1		
		1–5 yr	55	1.5 (0.99–2.5)		
		5–10 yr	70	2.3 (1.4–3.5)		
		10–20 yr	66	1.9 (1.1–2.8)		
		≥ 20 yr	39	2.1 (1.3–3.2)		
		OR per year worked graveyard shift	267	1.018 (1.010–1.027)		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Hansen & Stevens (2012) (cont.)		Cumulative number of graveyard shifts (working after midnight (~8 h of work between 19:00 and 09:00) for ≥ 1 yr) (OR):				
		Never graveyard shift	37	1		
		< 468 shifts	63	1.6 (1–2.6)		
		468–1095 shifts	80	2 (1.3–3)		
		≥ 1096 shifts	87	2.2 (1.5–3.2)		
		Rotating shifts (cumulative number of shifts by shift system) (OR):				
		Permanent day shifts	28	1		
		Day–evening shifts < 732	34	1.4 (0.9–2.2)		
		Day–evening shifts ≥ 733	4	1 (0.4–2.4)		
		Day–night shifts < 732	30	1.5 (0.9–2.4)		
		Day–night shifts ≥ 733	11	2.6 (1.8–3.8)		
		Day–evening–night shifts < 732	127	1.8 (1.2–3.1)		
		Day–evening–night shifts ≥ 733	86	1.9 (1.1–3.3)		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Hansen & Lassen (2012) Denmark 1990–2003 Nested case–control	141 cases: 329 incident cases of breast cancer (among a cohort of 18 551 Danish female military employees born in 1929–1968) were diagnosed during 1990–2003 from the Danish Cancer Registry; 218 were alive at the time of interview, of which 141 participated in the study 551 controls: 899 live controls were frequency-matched to cases by year of birth, of which 551 participated in the study Exposure assessment method: subjective assessment; night shift defined (other)	Ever night shift work vs never (OR):			Age, HRT, number of child births, age at menarche, years of education, occasional sunbathing, tobacco smoking	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Schedule type: Imprecise. No other information available. *Other comments:* analysis of: ever/never night work; duration of work with night work; lifetime number of night shifts; a combined measure of intensity (number of shifts/wk) and duration Sensitivity analyses showed that selection bias is possible but unlikely Strengths: well-defined cohort; identification of cancer cases from a high-quality cancer register Limitations: no inclusion of deceased cases and controls; low participation rate among live cases (65%) and controls (61%); small numbers
		Never	89	1		
		Ever	43	1.4 (0.9–2.1)		
		Duration of night shift work (OR):				
		Never	88	1		
		1.0–5.9 yr	13	0.9 (0.4–1.7)		
		6.0–14.9 yr	18	1.7 (0.9–3.2)		
		≥ 15.0	12	2.1 (1–4.5)		
		Trend test *P* value, 0.03				
		Cumulative number of night shifts (OR):				
		Never	82	1		
		< 416 shifts	9	0.8 (0.4–1.9)		
		416–1560 shifts	14	1.4 (0.7–2.9)		
		> 1560 shifts	17	1.9 (1.2–4.6)		
		Trend test *P* value, 0.02				
		Frequency and duration of night shifts (OR):				
		Never	82	1		
		1–2 times/wk, all durations	15	1 (0.5–1.9)		
		≥ 3 times/wk, 1–5.9 yr	9	1.1 (0.5–2.3)		
		≥ 3 times/wk, 6–14.9 yr	11	2.1 (1–4.8)		
		≥ 3 times/wk, ≥ 15 yr	9	2.5 (1.0–6.6)		
		Trend test *P* value, 0.02				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Hansen & Lassen (2012) (cont.)		Cumulative number of night shifts, morning chronotype (OR):				
		Never	36	1		
		< 884 shifts	6	1.3 (0.5–3.7)		
		≥ 884 shifts	12	3.9 (1.6–9.5)		
		Cumulative number of night shifts, evening chronotype (OR):				
		Never	21	1		
		< 884 shifts	5	0.8 (0.2–3)		
		≥ 884 shifts	10	2 (0.7–5.8)		
		Cumulative number of night shifts, neither morning nor evening chronotype (OR):				
		Never	23	1		
		< 884 shifts	4	1 (0.3–4)		
		≥ 884 shifts	3	0.7 (0.1–3)		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Li et al. (2015) Shanghai, China Enrolment, 1989–1991; follow-up through July 2000 Case–cohort	1709 cases: 1763 incident cases (among a cohort of 267 400 textile workers residing in Shanghai, born during 1925–1958) identified from factory medical records, annual medical reports, and the Shanghai Cancer Registry; 54 cases excluded because of missing data 4780 non-cases: 3139 cancer-free women randomly selected from the cohort by age strata and 1697 controls selected for two other nested case–control studies; 56 excluded because of missing data Exposure assessment method: JEM assessment; night shift defined (other)	Duration worked rotating night shift (HR): 0 yr > 0–12.8 yr > 12.8–19.92 yr > 19.92–27.67 yr > 27.67 yr Trend test *P* value, 0.095 Cumulative number of night shifts (HR): 0 shifts > 0–1316 shifts > 1316–2018 shifts > 2018–2880 shifts > 2880 shifts Trend test *P* value, 0.155	 557 286 290 289 287 557 288 287 288 289	 1 0.99 (0.83–1.17) 0.97 (0.82–1.15) 0.90 (0.76–1.06) 0.88 (0.74–1.05) 1 0.96 (0.81–1.14) 1.00 (0.84–1.19) 0.88 (0.74–1.04) 0.89 (0.75–1.07)	Age	*Exposure assessment critique:* NSW in ref. group: No. Intensity: Precise. Duration: Partial (limited period). Schedule type: Rotating. No other information available. *Other comments:* analyses of duration of employment with night work (yr) and lifetime total number of night shifts, conducted using a case–cohort design Strengths: large population size; high participation rate Limitations: adjustment for a limited number of factors; no individual information on shift work

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Knutsson et al. (2013) Sweden Enrolment, 1992–1995, 1996–1997, 2000–2003; follow-up, through 2008 Cohort	4036 women with information on shift work in the Work, Lipids and Fibrinogen (WOLF) occupational cohort study, including employees in different public and private companies Exposure assessment method: subjective assessment; night shift defined (other)	Type of work schedule (HR):			Number of children, alcohol consumption	*Exposure assessment critique:* NSW in ref. group: Undefined. Duration: Partial (limited period). Schedule type: Imprecise. No other information available. *Other comments*: information on working hours was combined into day work (ref. group), shift work without night work, and shift work with night work Strengths: prospective study; identification of cancer cases from a high-quality cancer register Limitations: small sample size; limited information on duration of exposure
		Day shift only	60	1		
		Shift without night	20	1.23 (0.70–2.17)		
		Shift with night	14	2.02 (1.03–3.95)		
		Type of work schedule, age < 60 yr (HR)				
		Day shift only	NR	1		
		Shift without night	17	1.18 (0.67–2.07)		
		Shift with night	12	2.15 (1.1–4.21)		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Koppes et al. (2014) The Netherlands Enrolment, 1996–2009; follow-up through 2009 Cohort	285 723 female participants of the 14 Dutch Labor Force Surveys conducted during 1996–2009, randomly sampled from the national household registers Exposure assessment method: subjective assessment; night shift defined (other)	Categories of night work exposure (HR): No night work Occasional night work Regular night work Categories of night work exposure, job tenure ≥ 20 yr (HR): No night work Occasional night work Regular night work	 2312 102 117 NR NR NR	 1 1.04 (0.85–1.27) 0.87 (0.72–1.05) 1 0.78 (0.48–1.28) 0.95 (0.62–1.45)	Age, origin, number of children in household, education, occupation, job tenure, contractual working hours	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (one time-point). No other information available. *Other comments*: analyses were made for occasional or regular night work vs no night work for total population, and stratified by tenure (not related to night work) Strengths: very large sample size; prospective study Limitations: exposure assessment at baseline only; limited to current night work; adjustment for potential confounders limited to suboptimal surrogates (e.g. number of children living at home)

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Vistisen et al. (2017) Denmark Enrolment, January 2007–December 2011; follow-up, through December 2012 Cohort	155 540 women aged ≥ 18 yr with at least one registration of work in the Danish Working Hour Database (started in January 2007) and free of breast cancer at the start of follow-up Exposure assessment method: objective assessment; night shift defined (exposed for ≥ 3 h between midnight and 05:00)	Categories of exposure (RR):			Calendar year, age, age at first birth, number of births, family history of breast or ovarian cancer, oral contraception, HRT, medication related to alcoholism, mammography screening attendance, highest family educational level	Exposure assessment critique: NSW in ref group: Undefined. Duration: Partial (limited period). Temporality: Complete. No other information available *Other comments*: analysis of ever/never night shift (and trend test for number of night shifts in the previous 1–5-yr time window) Strengths: large population; exposure assessment based on the Danish Working Hour Database that covers individual information on day, hour, and minute of every work shift; definition of night shift ≥ 3 h work between midnight and 05:00; use of high-quality nationwide registers to assess potential confounders (age at first birth, number of children, education, medications used) Limitations: exposure to night shift work not available before January 2007 (left-truncation); follow-up period maximum of 5 yr
		Only day shifts	751	1		
		Ever non-day, non-night shifts	69	0.94 (0.73–1.2)		
		Ever night shifts	425	0.90 (0.80–1.01)		
		Trend test *P* value, 0.10				
		Categories of shifts during past 1 yr (RR):				
		Only day shifts	748	1		
		Ever night shifts	220	0.8 (0.89–0.93)		
		Trend test *P* value, 0.01				
		Categories of shifts during past 1–3 yr (RR):				
		Only day shifts	397	1		
		Ever night shifts	170	0.83 (0.69–1)		
		Trend test *P* value, 0.04				
		Number of night shifts per month during the past 1–5 yr (RR):				
		Only day shifts	113	1		
		< 1 night shift	40	1.00 (0.69–1.45)		
		1 to < 4 night shifts	22	0.91 (0.57–1.46)		
		4 to < 10 night shifts	7	1.32 (0.61–2.85)		
		≥ 10 night shifts	NR	NC		
		Trend test *P* value, 0.70				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Vistisen et al. (2017) (cont.)		Ever night shift (vs only day shifts) since start of follow-up, combined ER and HER2 status (RR):				
		ER–/HER2–	49	0.85 (0.59–1.23)		
		ER+/HER2–	250	0.8 (0.68–0.95)		
		ER–/HER2+	37	1.49 (0.93–2.39)		
		ER+/HER2+	48	1.26 (0.84–1.89)		
		Night shift work since entry, first employed in 2008 or later (RR):				
		Only day shifts	144	1		
		Ever non-day, non-night shifts	17	1.15 (0.69–1.91)		
		Ever night shifts	69	0.88 (0.66–1.17)		
		Night shift work during past 1 yr, first employed in 2008 or later (RR):				
		Only day shifts	128	1		
		Ever night shifts	37	0.82 (0.56–1.18)		
		Night shift work during last 1–3 yr, first employed in 2008 or later (RR):				
		Only day shifts	43	1		
		Ever night shifts	29	1.33 (0.82–2.17)		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Åkerstedt et al. (2015) Sweden Enrolment, 1998–2003; follow-up through December 2010 or when women reached age 60 yr Cohort	13 656 female twins born before 1959 who participated in the Screening Across the Lifespan Twin study and were aged 41–60 yr at the time of interview Exposure assessment method: subjective assessment; night shift undefined	No night work vs ever night work (HR):			Age, education, tobacco consumption, BMI, having children, coffee, previous cancer, use of hormones	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Complete. No other information available. *Other comments*: analysis of employment duration with night (5-yr increments) Strengths: linkage with high-quality cancer registry Limitations: single question about the number of years when the participant worked at night at least "now and then"; relatively small size
		No night work	354	1		
		Ever night work	109	0.94 (0.73–1.22)		
		Duration of night work, results for complete follow-up through December 2010 (HR):				
		No night work	354	1		
		1–5 yr	57	0.92 (0.65–1.29)		
		6–10 yr	16	0.79 (0.45–1.37)		
		11–20 yr	18	0.77 (0.43–1.38)		
		21–45yr	18	1.68 (0.98–2.88)		
		Duration of night work, results for follow-up until age 60 yr (HR):				
		No night work	354	1		
		1–5 yr	57	0.93 (0.66–1.31)		
		6–10 yr	16	0.79 (0.45–1.38)		
		11–20 yr	18	0.8 (0.45–1.42)		
		21–45 yr	18	1.77 (1.03–3.04)		
Travis et al. (2016) UK, Million Women Study Baseline, 2009–2012; follow-up, through December 2013 Cohort	522 246 women in the Million Women Study who answered the 4th survey questionnaire in 2009–2012 Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Years of night shift work (RR):			Age underlying time variable, socioeconomic status, parity and age at first birth, BMI, alcohol intake, strenuous physical activity, family history of breast cancer, age at menarche, OC use, smoking, living with a partner, use of MHT	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Imprecise. Duration: Complete. Temporality: Complete. No other information available. *Other comments*: analyses include: ever/never night work; years of night shift work; night shift work within past 10 yr Strengths: very large prospective study Limitations: old age of participants at baseline (> 68 yr); short follow-up period (average, 2.8 yr)
		Never worked at night	4136	1		
		Ever worked at night	673	1.00 (0.92–1.08)		
		< 10 yr	400	0.93 (0.83–1.03)		
		10–19 yr	140	1.14 (0.96–1.35)		
		≥ 20 yr	89	1.00 (0.81–1.23)		
		≥ 30 yr	32	0.98 (0.69–1.39)		
		Trend test *P* value, 0.68				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Travis et al. (2016) (cont.)		Years of night shift work, ≥ 10 yr since last worked night shifts (RR):				
		Never worked at night	4136	1		
		Ever worked at night	474	0.96 (0.87–1.06)		
		< 10 yr	329	0.92 (0.82–1.03)		
		10–19 yr	83	1.01 (0.81–1.26)		
		≥ 20 yr	41	0.96 (0.7–1.3)		
		Trend test *P* value, 0.61				
		Duration of night shift work, < 10 yr since last worked night shift (RR):				
		Never worked at night	4136	1		
		Ever worked at night	156	1.10 (0.94–1.30)		
		< 10 yr	55	0.97 (0.74–1.26)		
		10–19 yr	52	1.41 (1.07–1.86)		
		≥ 20 yr	42	0.98 (0.72–1.33)		
		Trend test *P* value, 0.42				
		Duration of night shift work, nursing tenure ≥ 10 yr (RR):				
		Never worked at night	80	1		
		Ever worked at night	319	0.96 (0.75–1.23)		
		< 10 yr	180	0.95 (0.73–1.24)		
		10–19 yr	72	1.00 (0.73–1.38)		
		≥ 20 yr	53	0.88 (0.62–1.25)		
		Trend test *P* value, 0.60				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Travis et al. (2017) UK, Million Women Study Baseline, 2009–2012; follow-up, 3.5 yr Cohort	522 246 women in the Million Women Study who answered the 4th survey questionnaire in 2009–2012 Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Ever worked night shift in the last 10 yr (RR): Never worked at night Ever worked at night	 5841 212	 1 1.07 (0.93–1.23)	Age underlying time variable, socioeconomic status, parity and age at first birth, BMI, alcohol intake, strenuous physical activity, family history of breast cancer, age at menarche, OC use, smoking, living with a partner, use of MHT	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Imprecise. Duration: Complete. Temporality: Complete. No other information available. *Other comments*: analyses include: ever/never night work; years of night shift work; and night shift work within past 10 yr Strengths: very large prospective study Limitations: old age of participants at baseline (> 68 yr); short follow-up period (average, 3.5 yr)
Travis et al. (2016) UK, EPIC-Oxford Baseline, 2010; follow-up through December 2013 Cohort	22 559 women enrolled in EPIC-Oxford who answered the 4th survey questionnaire in 2009–2012 Exposure assessment method: subjective assessment; night shift undefined	Years of night shift work (RR): Never worked at night Ever worked at night < 10 yr 10–19 yr ≥ 20 yr Trend test *P* value, 0.75	 153 28 15 11 1	 1 1.07 (0.71–1.62) 1.18 (0.69–2.01) 1.92 (1.03–3.57) 0.22 (0.03–1.61)	Age underlying time variable, socioeconomic status, parity and age at first birth, BMI, alcohol intake, strenuous physical activity, age at menarche, OC use, smoking, living with a partner, use of MHT	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments*: analyses include: ever/never night work; years of night shift work; night shift work within last 10 yr Strengths: prospective investigation Limitations: relatively small cohort; old age at baseline (> 55 yr); short follow-up period (mean, 3.1 yr)

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Travis et al. (2017) UK, EPIC-Oxford Baseline, 2010; 4.1 yr follow-up Cohort	22 559 women enrolled in EPIC-Oxford who answered the 4th survey questionnaire in 2009–2012 Exposure assessment method: subjective assessment; night shift undefined	Years of night shift work within the past 10 yr (RR): Never worked at night Ever worked at night	 212 10	 1 1.16 (0.61–2.22)	Age underlying time variable, socioeconomic status, parity and age at first birth, BMI, alcohol intake, strenuous physical activity, age at menarche, OC use, smoking, living with a partner, use of MHT	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments*: analyses include: ever/never night work; years of night shift work; night shift work within past 10 yr Strengths: prospective investigation Limitations: relatively small cohort; old age at baseline (> 55 yr); short follow-up period (mean, 3.1 yr)
Travis et al. (2016) UK, UK Biobank Baseline, 2006–2010; follow-up, through December 2012 Cohort	251 045 women enrolled in UK Biobank study who provided information on shift work in current job at baseline Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Night shift work at recruitment (RR): Never/rarely Yes, at least sometimes	 2653 67	 1 0.78 (0.61–1.00)	Age underlying time variable, socioeconomic status, parity and age at first birth, BMI, alcohol intake, strenuous physical activity, family history of breast cancer, age at menarche, OC use, smoking, living with a partner, use of MHT	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Imprecise. Duration: Partial (one time-point). No other information available. *Other comments*: analyses include: ever/never night work; intensity of night work Strengths: large prospective cohort Limitations: age at baseline > 50 yr; short follow-up period (mean, 3.8 yr); information on shift work available only for the job held at baseline

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Jones et al. (2019) UK Enrolment, 2003–2014; follow-up through March 2018 Cohort	102 869 women participating in the Generations Study Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Night shift work within the past 10 yr (HR):			Attained age, time since recruitment to cohort, birth cohort, benign breast disease, family history of breast cancer, socioeconomic score, birth weight, height at age 20 yr, age at menarche, BMI at age 20 yr, age at first pregnancy, parity, breastfeeding, current use of OCs, alcohol consumption, age when started smoking, physical activity, postmenopausal BMI, menopausal HRT, menopausal status, age at menopause	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Precise. Duration: Partial (limited period). Temporality: Complete. No other information available. *Other comments*: night shift work defined as late evening or night between 22:00 and 07:00 Strengths: large study size; updated exposure information during follow-up up to 6 yr after baseline Limitations: wide definition of night work (any time 22:00 to 07:00); exposure assessed during the last 10 yr before recruitment
		None	1845	1		
		Yes	214	1.00 (0.86–1.15)		
		Average hours worked per night (HR):				
		None	1845	1		
		< 7 h	91	1.04 (0.84–1.28)		
		≥ 7 h	103	0.96 (0.78–1.17)		
		Unknown	20	1.02 (0.65–1.58)		
		Trend test *P* value, 0.62				
		Average nights per week on night shift (HR):				
		None	1845	1		
		< 4 nights/wk	152	0.96 (0.81–1.14)		
		4–7 nights/wk	55	1.18 (0.90–1.55)		
		Unknown	7	0.7 (0.33–1.47)		
		Trend test *P* value, 0.066				
		Average hours per week on night shift (HR):				
		None	1845	1		
		< 10 h/wk	70	0.88 (0.69–1.12)		
		10 to < 20 h/wk	61	1.07 (0.83–1.39)		
		20 to < 30 h/wk	35	1.05 (0.75–1.48)		
		≥ 30 h/wk	26	1.27 (0.86–1.87)		
		Unknown	22	0.91 (0.60–1.38)		
		Trend test *P* value, 0.035				
		Cumulative years of employment as NSW (HR):				
		None	1845	1		
		< 10 yr	89	0.92 (0.74–1.14)		
		10 to < 20 yr	65	1.09 (0.85–1.4)		
		20 to < 30 yr	36	0.97 (0.70–1.35)		
		≥ 30 yr	24	1.12 (0.75–1.69)		
		Trend test *P* value, 0.51				

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Jones et al. (2019) (cont.)		Cumulative hours of night shift work (10 000 h) (HR):				
		None	1845	1		
		0 to < 1	103	1.00 (0.82–1.23)		
		1 to < 2	36	1.04 (0.74–1.44)		
		2 to < 3	22	1.24 (0.82–1.9)		
		≥ 3	21	1.07 (0.70–1.66)		
		Unknown	32	0.79 (0.56–1.13)		
		Trend test *P* value, 0.51				
		Age started night shift work (HR):				
		None	1845	1		
		< 25 yr	71	1.03 (0.80–1.32)		
		25–34 yr	45	0.84 (0.62–1.14)		
		35–44 yr	63	1.24 (0.96–1.6)		
		≥ 45 yr	35	0.84 (0.60–1.18)		
		Trend test *P* value, 0.89				
		Night work in relation to first pregnancy, parous women (HR):				
		No night work	1593	1		
		Started night work before first pregnancy	58	0.95 (0.73–1.25)		
		Started night work after first pregnancy	111	1.01 (0.83–1.23)		

Table 2.1 Cohort and nested case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Jones et al. (2019) (cont.)		Time since last night shift work (HR):				
		None	1845	1		
		Current	84	1.01 (0.80–1.26)		
		0 to < 5 yr	60	1.05 (0.81–1.36)		
		5 to < 10 yr	70	0.94 (0.74–1.2)		
		Trend test *P* value, 0.38				

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, estrogen receptor; h, hour; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRT, hormone replacement therapy; JEM, job-exposure matrix; MHT, menopausal hormone therapy; mo, month; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; NC, not calculable; NR, not reported; NSW, night shift worker(s); OC, oral contraceptive; OR, odds ratio; PR, progesterone receptor; RR, rate ratio or relative risk; vs, versus; wk, week; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

and nested case–control studies, including 13 in European countries, 2 in China, and 2 in the USA. A detailed description of the studies is provided in chronological order.

(i) Nested case–control study within a cohort of Norwegian radio and telegraph operators

Tynes et al. (1996) published results from a nested case–control study of breast cancer incidence in a cohort of 2619 certified Norwegian radio and telegraph operators exposed to shift work. During follow-up (1961–1991), they identified 50 cases of cancer of the breast that were matched by age to 259 controls. On the basis of detailed work history, shift work was scored as none, low, or high to reflect frequency of presence in the radio room both at night and during the day, with possible exposure to light at night. In women younger than 50 years, shift work was not associated with the incidence of cancer of the breast. In women aged 50 years and older, the odds ratio (OR) for cancer of the breast, associated with a high score for shift work (12 cases) relative to none (3 cases), was 4.3 (95% confidence interval, CI, 0.7–26). [The Working Group noted that this study was limited by the very small number of cases, the loose definitions of categories of shift work used for calculating exposure, and the adjustment for confounding being only for the duration of employment.]

(ii) Nested case–control study of Norwegian nurses

Lie et al. (2006) conducted a case–control study of cancer of the breast nested within a cohort of 44 835 Norwegian nurses followed up between 1960 and 1982. The study included 537 incident cases of breast cancer identified from the Cancer Registry of Norway and 2143 age-matched controls. The number of years during which night work was undertaken was estimated from information on dates of employment and work site, available from the Norwegian registry of nurses and from census data. Compared with women who had never worked at night, women with 30 years or more of night work had an increased odds ratio of 2.21 (95% CI, 1.10–4.45) based on 24 exposed cases (*P* for trend with increasing number of years of night work, 0.01). [The Working Group considered that the small numbers of cases and controls who had performed night shift work for 30 years or more led to a lack of precision in the odds ratio.]

(iii) Cohort of Chinese women in Shanghai

Pronk et al. (2010) reported on the risk of cancer of the breast associated with night shift work in a population-based cohort of 73 049 Chinese women in Shanghai (mean age at entry into the cohort, 52.5 years), who were followed up for an average of 9 years between 1996 and 2007. A total of 717 breast cancer cases were identified. In-person interviews were conducted at baseline to elicit information on sociodemographic factors, breast cancer risk factors, and occupational history. Exposure to night work was assessed using a job-exposure matrix (JEM) that scored each job in the work history according to the probability of night work. During follow-up, women were also asked whether they had ever held a job involving night shift work, defined as starting work after 22:00 at least 3 times a month for over 1 year. Information on the number of night shifts per week, duration in years, and the years of starting and ending night work was also obtained. The hazard ratios (HRs) for ever versus never working night shift were 1.0 (95% CI, 0.9–1.2) and 0.9 (95% CI, 0.7–1.1) when exposure was assessed from the JEM and from self-reported data, respectively. Whichever method of exposure assessment was used, there was no association between risk of cancer of the breast and the number of years in jobs involving night work (HR for > 17 years, 0.8; 95% CI, 0.5–1.2 based on self-reported data), the frequency of night shifts, or lifetime cumulative exposure to night work.

[The Working Group noted that the comparison between exposure assessment methods (JEM and self-reported exposure) indicated important exposure misclassification of the JEM, making the JEM-based analysis less informative.]

(iv) Second nested case–control study within a cohort of Norwegian nurses

Lie et al. (2011) conducted another case–control study on cancer of the breast, nested within the cohort of Norwegian nurses including 49 402 women. There was no overlap with the previous study (Lie et al., 2006) as the periods of follow-up were distinct. The most recent study (Lie et al., 2011) included 699 cases of cancer of the breast diagnosed during 1990–2007 and 895 controls frequency matched by 5-year age stratum. Cases and controls who were alive in 2009 answered a questionnaire on work history and potential risk factors for cancer of the breast. Using several metrics for measuring exposure to night work, there was no clear association with duration of work in schedules including night work (OR for ≥ 12 years, 1.3; 95% CI, 0.9–1.8), duration of work in schedules including at least 3 night shifts per month (OR for ≥ 30 years, 0.8; 95% CI, 0.5–1.4), lifetime average number of night shifts per month, or cumulative number of lifetime night shifts. Increased risks of cancer of the breast were observed in nurses with a long duration (≥ 5 years) of work in schedules including a high intensity of consecutive night shifts (≥ 6 consecutive nights). In a separate publication, the reported association with ever worked at least 6 consecutive night shifts versus never worked night shift was stronger for progesterone-receptor (PR)-positive than for PR-negative cases, with a borderline statistically significant heterogeneity (P = 0.05) (Lie et al., 2013). [The Working Group noted that the limitations of this study included: the relatively small study size; possible recall bias as a result of the collection of night work exposure information in 2009 after cancer diagnosis; and suboptimal participation, with recruitment of 74% of the breast cancer cases who were alive at the time of data collection and 65% of the controls. The association between breast cancer and the number of consecutive nights worked was noted, and is the only significant finding out of 10 different exposure metrics.]

(v) Nested case–control study within a cohort of Danish nurses

Hansen & Stevens (2012) conducted a case–control study on cancer of the breast nested in a cohort (Kjaer & Hansen, 2009) of 58 091 Danish nurses followed up between July 2001 and June 2003. The study included 267 incident cases of breast cancer identified from the Danish Cancer Registry and 1035 age-matched controls. Detailed information on shift work and potential confounders was obtained by telephone interviews between 2002 and 2005, after cancer diagnosis. Participation rate was high among eligible cases (92%) and controls (91%). For each job held for at least 1 year, the questionnaire elicited information to characterize the shift work system and was used to assess the lifetime duration of each shift system. When compared with nurses who performed permanent day work, the odds ratio in nurses who ever worked after-midnight rotating shifts and had never worked permanent night shift was 1.8 (95% CI, 1.2–2.8) and the odds ratio for nurses who ever worked permanent night shift in addition to rotating night shifts was 2.9 (95% CI, 1.1–8.0). Risk tended to increase with increased duration of exposure to night shifts (OR for ≥ 20 years, 2.1; 95% CI, 1.3–3.2) and with increased cumulative exposure to night shifts (OR per year, 1.018; 95% CI, 1.010–1.027). [The Working Group noted that this study provided evidence that the most disruptive shifts (i.e. rotating shifts including night, with or without permanent nights) provide the largest risk. The main limitations of the study included the small study size and possible recall bias as a result of

exposure information collection after breast cancer diagnosis.]

(vi) Nested case–control study within a cohort of women in the Danish military

A case–control study of cancer of the breast was nested in a cohort of 18 551 women in the Danish military (Hansen & Lassen, 2012). The analysis was based on 141 incident cases of breast cancer, out of the 329 cases diagnosed during follow-up between 1990 and 2003, and 551 age-matched controls. All participating cases and controls responded to a postal questionnaire eliciting information on occupational exposures including shift work (defined as work beginning after 17:00 and ending before 09:00) for each job held during work history, education level, reproductive and lifestyle factors, and diurnal preference of the participant. The overall odds ratio for ever versus never night shift work was 1.4 (95% CI, 0.9–2.1). The risks tended to increase with increasing number of years of night shift (*P* for trend, 0.03) and increasing cumulative number of night shifts (*P* for trend, 0.02). The incidence of cancer of the breast was also positively associated with performing at least 3 night shifts per week for at least 15 years (OR, 2.5; 95% CI, 1.0–6.6). [The Working Group noted that the limitations of the study were the small sample size, potential recall bias as a result of the use of a questionnaire after cancer diagnosis, and potential selection bias as a result of the low participation rate among cases (67%) and controls (61%). A sensitivity analysis for the potential selection bias showed that selection bias alone was not likely to explain the association with duration of night shift work.]

(vii) Cohort of women in the Swedish Work, Lipids and Fibrinogen study

Knutsson et al. (2013) assessed the risk of breast cancer according to shift work category among 4036 women in the Work, Lipids and Fibrinogen (WOLF) cohort study that included employees of different public and private companies in Sweden. Women were enrolled between 1992 and 2003 and followed up for breast cancer incidence through 2008. Ninety-four breast cancer cases were identified from the Swedish Cancer Registry and included in the analysis. The type of work schedule was assessed from a questionnaire at baseline and, for a subset of women, at the end of follow-up. When compared with women working only day shifts, the hazard ratio for cancer of the breast was 2.02 (95% CI, 1.03–3.95) for shift workers working night shifts. A slight increase in risk was also observed for shift workers not working night shifts. [The Working Group noted that the limitations of this study included the small number of cases (14 exposed and 60 unexposed), the inconsistencies in exposure assessment revealed by comparing exposure information obtained from the questionnaires at baseline with that obtained at the end of the follow-up, and a lack of data on risk of breast cancer in relation to duration of exposure to night shift.]

(viii) Population-based cohort study in the Netherlands

Koppes et al. (2014) conducted a population-based prospective cohort study in the Netherlands that included 285 723 women randomly sampled from the Dutch population to be included in one of the 14 Dutch Labor Force Surveys between 1996 and 2009. A personal interview was conducted at enrolment in the survey to collect information on relationships between people and the labour market. Night work information was also collected at the enrolment interview, asking women if they worked at night "occasionally" or "regularly" in their current job. A total of 2531 cases of women admitted to hospital with cancer of the breast were identified from the National Medical Registration system. No increased risk of cancer of the breast was observed among women who declared occasional night work or regular night work, compared with non-night workers. Results were similar for women with at

least 20 years of work tenure: HR for tenure of ≥ 20 years including occasional night work, 0.78 (95% CI, 0.48–1.28), and HR for tenure of ≥ 20 years including regular night work, 0.95 (95% CI, 0.62–1.45), compared with non-night workers. [The Working Group noted that the null findings of this large population-based study may be explained by its important limitations, including: case definition being based on hospital admission; poor exposure assessment with night work defined as occasional or regular and known only at baseline, preventing any relevant analysis based on exposure duration (in addition, only one third had a regular full-time job); and weak control for confounding (e.g. number of children in household was used as a proxy for parity).]

(ix) Case–cohort study of textile workers in Shanghai

In a case–cohort study conducted in a cohort of 267 400 active and retired employees from 503 textile factories in Shanghai, China, Li et al. (2015) reported on the risk of cancer of the breast associated with night shift work. The study included 1709 cases of cancer of the breast diagnosed between 1989 and 2000, and 4780 non-cases selected from the cohort and from previous nested case–control studies. All participants were interviewed at baseline about their reproductive history, duration of breastfeeding, and alcohol consumption. Shift work was assessed by combining individual-level information on employment in specific manufacturing processes within a particular factory (from factory personnel records for 80% of participants) with data on night shift work associated with each specific process in that factory. Night shifts were exclusively part of a rotating shift work pattern, as no job involved permanent night shifts. No association with either duration of night shift work (HR for > 27.67 years, 0.88; 95% CI, 0.74–1.05) or number of nights worked during the entire employment period (HR for > 2880 nights, 0.89; 95% CI, 0.75–1.07) was observed. Similar patterns were observed in women younger than 50 years and in women aged 50 years and older. [This was a study based on a relatively large sample size. The Working Group noted the possibility of exposure misclassification as a result of using an aggregate, and not individual, level of exposure assessment, although the collection of information at the factory level minimized the magnitude of information bias.]

(x) Cohort of twins in Sweden

Åkerstedt et al. (2015) reported on a cohort of 13 656 women included in the Swedish Twin Registry who were followed from enrolment during 1998–2003 through 2010. Exposure was assessed at baseline from a questionnaire that elicited the number of years the women had worked at night at least occasionally. During follow-up, 463 cases of cancer of the breast were identified in the cohort. Overall, the hazard ratio for women who had ever worked at night compared with those who had never worked at night was 0.94 (95% CI, 0.73–1.22). In terms of duration of exposure, the hazard ratio for women who declared 21–45 years of night work was 1.68 (95% CI, 0.98–2.88), but no trend of increasing risk with increasing duration was observed. Similar results were observed when restricting the follow-up to the age of 60 years. [The Working Group noted that this was a relatively small cohort, and the loose definition of exposure possibly led to exposure misclassification.]

(xi) Population-based prospective cohort studies in the UK

Travis et al. (2016) reported results from three population-based prospective cohort studies in the UK. The Million Women Study included 522 246 women who responded to a questionnaire at baseline to obtain information on night work. The main aim was to assess whether regular night shift work, particularly long-term night shift work, was associated with an increased risk

of cancer of the breast. Participants were asked "Have you ever regularly worked at night or on night shifts (at any time between midnight and 6:00 hours), for at least 3 nights per month?" If the response was "yes", they were then asked "Over how many years in total?" and "When did you last work at night?" During the follow-up period (for an average of 2.8 years until December 2013), 4809 breast cancer cases were identified. The rate ratio (RR) comparing women who ever worked night shifts with never night workers was 1.00 (95% CI, 0.92–1.08). Breast cancer risk was not associated with long-duration night work; the rate ratio associated with 20 years or more of night work was 1.00 (95% CI, 0.81–1.23; 89 exposed cases) and with 30 years or more was 0.98 (95% CI, 0.69–1.39; 32 exposed cases) (Travis et al., 2016_Million Women). Results were also null for recent night shift work; the rate ratio for night work within the last 10 years was 1.10 (95% CI, 0.94–1.30; 156 exposed cases) and, in a subsequently published updated analysis based on 3.5 years of follow-up, was 1.07 (95% CI, 0.93–1.23; 212 exposed cases) (Travis et al., 2017). For recent night work by duration, rate ratios for night work for less than 10 years, 10–19 years, and 20 years or more were 0.97 (95% CI, 0.74–1.26), 1.41 (95% CI, 1.07–1.86), and 0.98 (95% CI, 0.72–1.33), respectively (Travis et al., 2016_Million Women). In analyses restricted to women who had worked as a nurse for 10 years or more, null associations were observed for ever night work and 20 years or more of night work (53 exposed cases) (Travis et al., 2016_Million Women). [The Working Group noted that, with a mean age at baseline of more than 68 years, the Million Women Study assessed the association between night shift work and risk of breast cancer in older women when most had retired; therefore, it could not assess cancer risks for younger women or for women whose first exposure was more recent.]

The EPIC-Oxford study included 22 559 women at baseline who responded to a similar questionnaire (Travis et al., 2016_EPIC). A total of 181 incident cases of cancer of the breast were identified during follow-up (an average of 3 years until December 2013). The rate ratio for women who ever worked night shifts compared with those who never worked nights was close to unity (RR, 1.07; 95% CI, 0.71–1.62; 28 exposed cases); ever night shift workers worked on average 8.8 nights per month, for 10.2 hours per night, and for 9.5 years. Almost half reported working as a nurse and working rotating shifts (Travis et al., 2016_EPIC). The relative risk for night shift work within the last 10 years was 1.16 (95% CI, 0.61–2.22), but was based on only 10 exposed cases (Travis et al., 2017). [The Working Group noted that the limitations of the study by Travis et al. (2017) included a small number of exposed cases and, although the study collected information on duration of night work, it was not powered to study the effect of long duration of exposure to night work.]

The UK Biobank study included 251 045 women at baseline who answered a questionnaire on whether they worked night shifts during their current employment (Travis et al., 2016_UK Biobank). A total of 2720 incident cases of cancer of the breast were identified during the follow-up (an average of 3.8 years until December 2012). Current night shift work was not associated with risk of cancer of the breast (RR, 0.78; 95% CI, 0.61–1.00). [The Working Group noted that information on duration and recentness of night work was not available in the UK Biobank study.]

(xii) Cohorts of nurses in the USA: Nurses' Health Study I and II

Following the previous reports of breast cancer risk in rotating night shift workers in the Nurses' Health Study (NHS-I) (Schernhammer et al., 2001) and in the second Nurses' Health Study (NHS-II) (Schernhammer et al., 2006), Wegrzyn et al. (2017) published an update based on an extended follow-up period of 24 years in the two cohorts. NHS-I included 78 516 nurses who responded to the shift work questionnaire

at baseline in 1988 and who were followed up through 2012. NHS-II included 114 559 nurses who responded to the questionnaire on shift work history at baseline in 1989, and who regularly provided updated information about shift work during follow-up through 2013. Exposure was measured as the number of years during which the nurses worked rotating night shifts for at least 3 nights per month in addition to days and/or evenings in that month. In NHS-I (5971 cases of cancer of the breast), the number of years of shift work during work history was not found to be associated with the incidence of cancer of the breast (HR for ≥ 30 years of shift work, 0.95; 95% CI, 0.77–1.17). In NHS-II (3570 cases of cancer of the breast), the risk of breast cancer was significantly increased in women with 20 years or more of shift work at baseline (HR, 2.15; 95% CI, 1.23–3.73; 13 cases), and marginally increased in women with 20 years or more of cumulative shift work using updated exposure information (HR, 1.40; 95% CI, 1.00–1.97; 35 cases). After stratification by period of follow-up, a small increasing trend of breast cancer risk was found in NHS-I during the first 10 years of follow-up (*P* for trend, 0.04). In NHS-II, the risk (hazard ratio) of cancer of the breast for 20 years or more of exposure was higher in the first 10 years of follow-up (2.35 for rotating night shift work history at baseline and 2.13 for cumulative rotating night shift work, updated during follow-up) than in the later period of follow-up (1.95 and 1.19, respectively). The results reported in the initial follow-up period of NHS-I from 1988 to 1998 by menopausal status (Schernhammer et al., 2001) showed a risk of breast cancer associated with duration of exposure, with a *P* for trend of 0.12 in premenopausal women and 0.05 in postmenopausal women. Wegrzyn et al. (2017) also conducted analyses by menopausal status in NHS-II, but the interaction with rotating night shift work was not significant, and duration of shift work in pre- and postmenopausal women was not associated with risk of cancer of the breast. There was no evidence of heterogeneity between estrogen receptor (ER) and PR status in the NHS-I and NHS-II cohorts. However, in the NHS-II cohort, a statistically significant association was found between incidence of cancer of the breast in ER- and PR-positive women and having worked 20 years or more of cumulative shift work (HR, 1.62; 95% CI, 1.07–2.45). [The Working Group noted that some of the participants who were permanent night workers may have been included in the reference group of non-night workers, meaning that the risk estimate is biased towards the null.]

(xiii) Population-based cohort study in Denmark

Vistisen et al. (2017) reported on the association between recent exposure to night shifts and risk of cancer of the breast in a cohort of 155 540 Danish women registered in the Danish Working Hour Database. This database contains information on individual employees in the five administrative regions that are responsible for all public hospitals in Denmark. The largest groups of employees are health-care workers, that is, nurses and physicians. The database includes information from payroll data on day, hour, and minute of every work shift, and was started in January 2007. Night shifts were defined as work shifts with at least 3 hours between midnight and 05:00. Information on reproductive factors, education, and use of medication was also obtained for all cohort members from nationwide registers. During follow-up from the date of first registration in the database to 31 December 2012, 1245 cases of cancer of the breast were identified, primarily through linkage with the clinical database of the Danish Breast Cancer Cooperative Group. The ER and human epidermal growth factor 2 (HER2) status of the tumour was also obtained for 90% of the cases. When comparing women who ever worked night shift during follow-up with women who worked only day shifts, the adjusted rate ratio was 0.90 (95% CI, 0.80–1.01; *P* for trend by number of night shifts, 0.10), suggesting that recent night

shift work is not a risk factor for cancer of the breast. Adjusted rate ratios were similar when considering night shifts worked during the last 1, 1–2, and 1–5 year(s) before the end of follow-up. Similar results were also observed in the subcohort (35.6%) of women first employed by January 2008 or later, where no confounding from long-term exposure to night work could be expected. In the analyses by breast cancer subtype, modest increases in the rate ratio were seen for HER2-positive breast cancer subtypes. [The Working Group noted that information on covariates was from nationwide registers and data were available only on some potential confounders. A major limitation of the study is that exposure data were available only for 5 years of working life, leading to substantial misclassification of exposure. The study did not account for the included healthcare workers who were exposed to night work, at least in their early career before 2007, or for those who worked outside the five administrative regions.]

(xiv) UK Generations Study

Jones et al. (2019) investigated the risk of cancer of the breast in relation to night shift work in the Generations Study cohort study conducted in the UK. The cohort comprised 102 869 women recruited from 2003 to 2014 who completed a questionnaire at baseline. By the end of follow-up in March 2018 (median, 9.5 years), 2059 cases of invasive cancer of the breast were identified from follow-up questionnaires, National Health Service Central Register, cancer registries, general practitioners, and pathology reports. Information on night shift work was obtained by asking women who completed the recruitment questionnaire if, "over the past 10 years", they had had "any jobs that regularly involved work in the late evening or night (between 10 pm and 7 am)". For each episode of night work, information was also obtained on type of job, starting and ending year, average number of nights per week working at night or late evening, and average number of hours worked between 22:00 and 07:00. Updated information was obtained during follow-up 6 years after recruitment. Being a night worker within the last 10 years was not associated with an increased incidence of cancer of the breast (HR, 1.00; 95% CI, 0.86–1.15). No association was observed with average hours worked per night, cumulative years of employment as a night shift worker, or cumulative hours of night shift work. The hazard ratio for breast cancer increased slightly with the average number of nights per week (*P* for trend, 0.066) and the average hours per week on night shift (*P* for trend, 0.035). Further analyses did not show any association of breast cancer incidence with age at start of night work, night work in relation to first pregnancy, or time since last worked night shifts. Stratification by menopausal status or by breast cancer subtypes defined by ER, PR, or HER2 status did not show associations with night shift work in the last 10 years. [The Working Group noted that this study lacked information on night shift work that ended before the 10-year period before recruitment, and the consequent inclusion of night shift workers employed 10 years or more before recruitment in the unexposed group. Stratified analyses by duration or intensity measures did not overcome this problem. The wide definition of late evening/night work may have led to the dilution of workers exposed to night shift work with workers who performed evening shift.]

(b) Case–control studies

See Table 2.2.

Conference abstracts and papers without original results for the association between night shift work and cancer of the breast were not considered, which included two conference abstracts (Menegaux et al., 2011; Ren, 2014), a study description (Menegaux & Guénel, 2012), a duplication of previously reported (Fritschi et al., 2013) results for night shift work and cancer of the breast (Lizama et al., 2017), and

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) Australia, Canada, France, Germany, Spain 2000–2013 Case–control	6093 cases: enrolled from hospitals (Canada, France, Germany, Spain) or registries (Australia, Canada) 6933 controls: general (Australia, France, Germany) or patient (Canada, Spain) populations and frequency-matched to cases by age Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Night work (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT, menopausal status	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Shift start/end times: Precise. No other information available. *Other comments*: analyses include: ever/never night work; duration of night work (yr); length of night shifts; intensity; time since last night shift; lifetime number of night shifts; lifetime average number of night shifts per week; intensity × duration of night work; intensity × length of night shift; intensity × time since last night shift Strengths: pooled data to create uniform exposure assessment, allowing for more detailed subanalyses; large sample; various metrics to assess shift work Limitations: self-reported data; some data collected after 2007, the date of the previous evaluation of shift work by the IARC Working Group (IARC, 2010)
		Never	5322	1		
		Ever	771	1.12 (1.00–1.25)		
		Night work, premenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco smoking	
		Never	1669	1		
		Ever	324	1.26 (1.06–1.51)		
		Night work, postmenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco smoking, MHT	
		Never	3652	1		
		Ever	447	1.04 (0.90–1.19)		
		Duration of night work (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT, menopausal status	
		Never worked at night	5322	1		
		< 10 yr	461	1.18 (1.03–1.36)		
		10–19 yr	154	0.98 (0.78–1.22)		
		≥ 20 yr	151	1.10 (0.87–1.39)		
		Length of night shifts (OR):				
		Never worked at night	5322	1		
		< 8 h	84	1.06 (0.78–1.43)		
		8–9 h	324	1.15 (0.98–1.34)		
		≥ 10 h	344	1.12 (0.96–1.31)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Time since last night shift (OR):				
		Never worked at night	5322	1		
		0–2 yr	206	1.26 (1.02–1.55)		
		3–9 yr	123	1.09 (0.84–1.4)		
		10–19 yr	172	1.1 (0.88–1.36)		
		≥ 20 yr	268	1.07 (0.90–1.27)		
		Intensity of night work (OR):				
		Never worked at night	4373	1		
		< 1 night/wk	122	0.94 (0.73–1.21)		
		1–2 nights/wk	254	1.01 (0.84–1.22)		
		≥ 3 nights/wk	132	1.26 (0.97–1.63)		
		Lifetime cumulative number of night shifts (OR):				
		Never worked at night	4373	1		
		< 300 shifts	170	1.06 (0.85–1.32)		
		300–999 shifts	174	0.99 (0.80–1.23)		
		≥ 1000 shifts	164	1.11 (0.88–1.39)		
		Number of night hours per week (OR):				
		Never worked at night	4373	1		
		< 11 h/wk	150	0.99 (0.79–1.26)		
		11–19 h/wk	179	0.96 (0.77–1.18)		
		≥ 20 h/wk	173	1.28 (1.01–1.61)		
		Duration of night work, premenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco	
		Never worked at night	1669	1		
		< 10 yr	210	1.33 (1.07–1.65)		
		10–19 yr	69	1.05 (0.74–1.47)		
		≥ 20 yr	42	1.34 (0.85–2.13)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Length of night shifts, premenopausal (OR):				
		Never worked at night	1669	1		
		< 8 h	37	1.03 (0.65–1.64)		
		8–9 h	111	1.2 (0.91–1.6)		
		≥ 10 h	167	1.36 (1.07–1.74)		
		Time since last night shift, premenopausal (OR):				
		Never worked at night	1669	1		
		0–2 yr	118	1.41 (1.06–1.88)		
		3–9 yr	68	1.21 (0.84–1.72)		
		10–19 yr	85	1.22 (0.88–1.68)		
		≥ 20 yr	52	1.11 (0.74–1.65)		
		Intensity of night work, premenopausal (OR):				
		Never worked at night	1393	1		
		< 1 night/wk	62	1.31 (0.89–1.93)		
		1–2 nights/wk	108	1.03 (0.78–1.36)		
		≥ 3 nights/wk	68	1.80 (1.20–2.71)		
		Lifetime cumulative number of night shifts, premenopausal (OR):				
		Never worked at night	1393	1		
		< 300 shifts	92	1.2 (0.88–1.65)		
		300–999 shifts	87	1.27 (0.92–1.76)		
		≥ 1000 shifts	59	1.31 (0.88–1.94)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Cross-classification of intensity (nights/wk) and duration (yr) of night work (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, MHT, menopausal status	
		Never worked at night	4373	1		
		< 3 nights/wk and < 10 yr	201	0.99 (0.81–1.21)		
		< 3 nights/wk and ≥ 10 yr	175	0.99 (0.79–1.23)		
		≥ 3 nights/wk and < 10 yr	92	1.23 (0.90–1.67)		
		≥ 3 nights/wk and ≥10 yr	40	1.34 (0.83–2.15)		
		Cross-classification of intensity (nights/wk) and duration (yr) of night work, premenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco	
		Never worked at night	1393	1		
		< 3 nights/wk and < 10 yr	106	1.19 (0.89–1.6)		
		< 3 nights/wk and ≥ 10 yr	64	1.01 (0.71–1.45)		
		≥ 3 nights/wk and < 10 yr	52	1.66 (1.05–2.6)		
		≥ 3 nights/wk and ≥ 10 yr	16	2.55 (1.03–6.30)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Cross-classification of intensity (nights/wk) and duration (yr) of night work, postmenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, MHT	
		Never worked at night	2979	1		
		< 3 nights/wk and < 10 yr	95	0.84 (0.63–1.11)		
		< 3 nights/wk and ≥ 10 yr	111	0.98 (0.74–1.3)		
		≥ 3 nights/wk and < 10 yr	40	0.88 (0.57–1.37)		
		≥ 3 nights/wk and ≥ 10 yr	24	1.00 (0.56–1.77)		
		Cross-classification of intensity (nights/wk) and length (h) of night shift (OR):				
		Never worked at night	4373	1		
		< 3 nights/wk and < 10 h	200	0.96 (0.78–1.17)		
		< 3 nights/wk and ≥ 10 h	173	1.03 (0.82–1.27)		
		≥ 3 nights/wk and < 10 h	60	1.34 (0.91–1.98)		
		≥ 3 nights/wk and ≥ 10 h	69	1.35 (0.93–1.94)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Cross-classification of intensity (nights/wk) and length (h) of night shift, premenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco, MHT, menopausal status	
		Never worked at night	1393	1		
		< 3 nights/wk and < 10 h	78	0.96 (0.69–1.32)		
		< 3 nights/wk and ≥ 10 h	91	1.28 (0.93–1.77)		
		≥ 3 nights/wk and < 10 h	28	1.56 (0.86–2.8)		
		≥ 3 nights/wk and ≥ 10 h	38	2.15 (1.21–3.84)		
		Cross classification of intensity (nights/wk) and length (h) of night shift, postmenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco, MHT	
		Never worked at night	2979	1		
		< 3 nights/wk and < 10 h	122	0.98 (0.75–1.27)		
		< 3 nights/wk and ≥ 10 h	82	0.83 (0.61–1.13)		
		≥ 3 nights/wk and < 10 h	32	1.17 (0.69–1.99)		
		≥ 3 nights/wk and ≥ 10 h	31	0.9 (0.55–1.48)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Cross classification of intensity (nights/wk) and time since last night shift (yr) (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco, MHT, menopausal status	
		Never worked at night	4373	1		
		< 3 nights/wk and ≤ 2 yr	121	1.16 (0.89–1.52)		
		< 3 nights/wk and > 2 yr	255	0.93 (0.75–1.11)		
		≥ 3 nights/wk and ≤ 2 yr	44	2.21 (1.3–3.76)		
		≥ 3 nights/wk and > 2 yr	88	1.04 (0.77–1.41)		
		Cross classification of intensity (nights/wk) and time since last night shift (yr), premenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco	
		Never worked at night	1393	1		
		< 3 nights/wk and ≤ 2 yr	68	1.28 (0.89–1.85)		
		< 3 nights/wk and > 2 yr	102	1.03 (0.77–1.37)		
		≥ 3 nights/wk and ≤ 2 yr	28	2.76 (1.38–5.53)		
		≥ 3 nights/wk and > 2 yr	40	1.43 (0.87–2.35)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Cordina-Duverger et al. (2018) (cont.)		Cross classification of intensity (nights/wk) and time since last night shift (yr), postmenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco, MHT	
		Never worked at night	2979	1		
		< 3 nights/wk and ≤ 2 yr	53	1.07 (0.71–1.6)		
		< 3 nights/wk and > 2 yr	153	0.87 (0.69–1.09)		
		≥ 3 nights/wk and ≤ 2 yr	16	1.58 (0.68–3.64)		
		≥ 3 nights/wk and > 2 yr	48	0.82 (0.55–1.21)		
		Night work, ER+/HER2+ (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco, MHT, menopausal status	
		Never night work	378	1		
		Ever night work	73	1.7 (1.3–2.23)		
		Night work, ER+/HER2+, premenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco	
		Never night work	126	1		
		Ever night work	32	1.77 (1.16–2.70)		
		Night work, ER+/HER2+, postmenopausal (OR):			Age group, study, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol intake, tobacco, MHT	
		Never night work	252	1		
		Ever night work	41	1.59 (1.11–2.28)		

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Davis et al. (2001) Seattle, Washington, USA 1992–1995 Case–control	813 cases: identified from cancer register, aged 20–74 yr 792 controls: population controls frequency-matched to cases by age Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Quartiles of years of sleep that did not occur when the peak melatonin level typically occurs (OR):			Parity, family history of breast cancer (mother or sister), OC use (ever), recent (< 5 yr) discontinued use of HRT	*Exposure assessment critique:* NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Schedule type: Rotating. Shift start/end times: Precise. No other information available. *Other comments*: analyses of: ever/never night work; hours of night work/wk; number of years with at least 1 night shift/wk in the 10 yr before the diagnosis Strengths: good detail on night shifts; strong population-based methods Limitations: small numbers of exposed; exposure window limited and excludes early exposures among older women
		Reference	682	1		
		< 1	19	1.2 (0.6–2.3)		
		1.0–3.0	20	1.4 (0.7–2.8)		
		3.0–4.6	9	0.6 (0.3–1.5)		
		≥ 4.6	33	2.3 (1.2–4.2)		
		Trend test *P* value, 0.01				
		At least 3 nights/wk not sleeping at the typical peak nocturnal melatonin time (OR):				
		No	682	1		
		Yes	81	1.4 (1–2)		
		Ever worked the graveyard shift in the 10 yr before the reference date (OR):				
		No	713	1		
		Yes	54	1.6 (1.0–2.5)		
		Hours per week worked the graveyard shift in the 10 yr before the reference date (OR):				
		Never	713	1		
		< 1.2 h/wk	11	1.3 (0.5–3.1)		
		1.2–2.7 h/wk	13	1.4 (0.6–3.2)		
		2.7–5.7 h/wk	13	1.5 (0.6–3.6)		
		≥ 5.7 h/wk	17	2.3 (1–5.3)		
		Trend test *P* value, 0.04				
		Years worked the graveyard shift in the 10 yr before the reference date (OR):				
		Reference	733	1		
		< 3 yr	15	1.4 (0.6–3.2)		
		≥ 3 yr	19	1.6 (0.8–3.2)		
		Trend test *P* value, 0.04				

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
O'Leary et al. (2006) Long Island, New York, USA 1996–1997 Case–control	487 cases: study of electromagnetic fields and breast cancer on Long Island; registry-identified cases who worked at some time during the 15 yr before diagnosis 509 controls: population-based controls frequency-matched to cases by 5-yr age group and who worked at some time during 15 yr before reference date Exposure assessment method: subjective assessment; night shift defined (other)	Shift work exposure in the past 15 yr (OR): No evening or overnight shift work Any evening of overnight shift work Any evening shift work Evening shift work only Any overnight shift work Overnight shift work only	 313 174 164 148 26 10	 1 1.04 (0.79–1.38) 1.08 (0.81–1.44) 1.21 (0.90–1.64) 0.55 (0.32–0.94) 0.64 (0.28–1.45)	Age, parity, family history of breast cancer, education, history of benign breast disease	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Precise. Duration: Partial (limited period). Temporality: Complete. Schedule type: Permanent night, Rotating. No other information available. *Other comments*: analyses of: type of shift work; combined measure of intensity (< 1 and ≥ 1 shift/wk) and duration of evening (< 5 and ≥ 5 yr) and night shift (< 8 and ≥ 8 yr) work Strengths: subjective assessment; night shift defined (other) Limitations: limited power; limited time window information; potential for information and selection bias
Rabstein et al. (2014) Bonn, Germany 2000–2004 Case–control	857 cases: population-based, age ≤ 80 yr with known ER status 892 controls: population-based controls frequency-matched to cases by age in 5-yr categories Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	*CLOCK* polymorphism rs10462028, shift workers (OR): GG GA AA GA+AA	 35 36 12 48	 1 0.94 (0.48–1.85) 3.53 (1.09–11.42) 1.19 (0.63–2.25)	Age, family history of breast cancer, hormone replacement use, number of mammograms	*Exposure assessment critique:* NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (limited period). No other information available.

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yang et al. (2019) Jiujiang, China January 2013, December 2016 Case–control	401 cases: female permanent residents of Xunyang and Lushan districts of Jiujiang aged 18–74 yr; histologically confirmed invasive breast cancers identified through local cancer registries; cases confirmed through home visits and further review of medical charts by clinical and/or pathological experts 401 controls: female permanent residents of Xunyang and Lushan districts of Jiujiang matched to cases 1:1 by sex, year of birth (within 1 yr), and region of residence Exposure assessment method: questionnaire; subjective assessment; night shift undefined	Night/shift work (OR):			Age in three age groups, education, family income, occupation, menopausal status, number of live births, use of menopausal hormones, age at menarche, age at first birth, marital status, family history of breast cancer, smoking, alcohol intake, fruit and vegetable consumption, physical activity, BMI, sleep duration in hours per day (< 6, 6, 7, 8, > 8), sleep quality, light exposure at night, sleep medication	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Imprecise. No other information available. Strengths: good response fractions for cases Limitations: small number of cases and controls; response fractions for controls not stated
		Never	360	1		
		Ever	41	1.38 (1.04–2.71)		
		Night/shift work, premenopausal (OR):				
		Never	128	1		
		Ever	19	1.33 (0.85–3.55)		
		Night/shift work, postmenopausal (OR):				
		Never	232	1		
		Ever	22	1.4 (0.92–3.21)		
		1 hour-year increase of night/shift work (OR):				
		1 hour-year increase of night/shift work	NR	1.15 (1.07–2.62)		
		Trend test *P* value, 0.03				

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Wang et al. (2015a) Guangzhou, China 2010–2012 Case–control	661 cases: histologically diagnosed primary breast cancers from two hospitals and one university cancer centre; women with metastasized breast cancer or previous history of any cancers were excluded 714 controls were recruited from a health check-up clinic in the same two hospitals during the same period; frequency-matched in 5-yr age groups to cases; women with chronic diseases or self-reported history of cancer were excluded Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Night shift work (OR): Never Ever	 443 218	 1 1.34 (1.05–1.72)	Age, education, BMI, age at menarche, menopausal status, parity, physical activity, breastfeeding, family history of breast cancer, other sleep factors (24-h sleep duration, daytime napping)	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Imprecise. No other information available. *Other comments*: exposure assessment includes activities outside work; analyses of ever/never night work Strengths: high proportion of shift workers Limitations: eligibility criteria not well defined; participation fractions not stated; 30% of cases aged ≤ 40 yr; hospital-based controls

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Fritschi et al. (2018) Australia 2009–2011 Case–control	1205 cases: women aged 18–80 yr with a histologically confirmed first incident invasive breast cancer identified from population-based cancer registry 1789 controls: women aged 18–80 yr frequency-age-matched from electoral roll Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Late circadian disruption (OR): Never Ever	 947 254	 1 1.17 (0.98–1.41)	Age	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Shift start/end times: Precise. No other information available. Limitations: low participation fractions, especially for controls

Table 2.2 Case–control studies of cancer of the breast among female shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2016) Spain 2008–2013 Case–control	1708 cases: women aged 25–85 yr with histologically confirmed first incident breast cancer identified; resident for at least 6 mo in the catchment area of the hospitals were they were identified 1778 controls: randomly selected from the rosters of general practitioners at the primary health centres participating in the study; frequency-matched by 5-yr age and study area Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Night work, morning chronotype (OR):			Age, centre, education level, parity, menopausal status, family history of breast cancer, BMI, smoking status, OC use, leisure time physical activity, alcohol consumption	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Schedule type: Permanent night, rotating. Shift start/end times: Imprecise. No other information available. Limitations: low participation fractions for controls
		Never	425	1		
		Ever	89	1.17 (0.83–1.65)		
		1–4 yr	24	2.09 (1.03–4.22)		
		5–14 yr	32	1.14 (0.66–1.98)		
		≥ 15 yr	31	0.91 (0.54–1.51)		
		Night work, neither chronotype (morning, evening) (OR):				
		Never	459	1		
		Ever	77	1.17 (0.82–1.69)		
		1–4 yr	19	0.97 (0.49–1.89)		
		5–14 yr	34	1.18 (0.68–2.03)		
		≥ 15 yr	24	1.38 (0.76–2.51)		
		Night work, evening chronotype (OR):				
		Never	275	1		
		Ever	56	1.27 (0.81–2.00)		
		1–4 yr	13	0.95 (0.44–2.03)		
		5–14 yr	20	1.17 (0.55–2.48)		
		≥ 15 yr	23	1.76 (0.85–3.67)		

BMI, body mass index; CI, confidence interval; h, hour; HRT, hormone replacement therapy; IARC, International Agency for Research on Cancer; MHT, menopausal hormone therapy; mo, month; NR, not reported; OC, oral contraceptive; OR, odds ratio; wk, week; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

an examination of light at night as the exposure (Garcia-Saenz et al., 2018). In addition, three studies with insufficient information on study design and analysis to evaluate the study quality were excluded: Datta et al. (2014) reported an odds ratio of 1.51 (95% CI, 0.27–8.52) for risk of cancer of the breast for "women working at night shift", based on 50 hospital cases and matched controls from a screening department, with no further information provided; the case–control study (4033 cases and 5314 controls) of McElroy et al. (2006) reported only on sleep, providing no analysis of shift workers because there were "too few women" even though shift work was assessed; the hospital-based case–control study (500 cases and 500 controls) by Qiu et al. (2012) provided an odds ratio of 1.003 (95% CI, 1.001–1.006) for "period of night shifts" and risk of cancer of the breast, but methods were inadequately reported for a full assessment of study quality.

Case–control studies deemed eligible for review and that investigated the association between night shift work and cancer of the breast are discussed below, starting with the most informative study and subsequently in chronological order. Of the case–control studies summarized, the largest contribution comes from a study that pooled five previously reported population-based case–control studies, allowing for detailed examination of various exposure metrics and stratified analyses to evaluate potentially vulnerable time periods.

(i) Overview of included studies

Nine case–control studies reported in several papers (Davis et al., 2001; O'Leary et al., 2006; Pesch et al., 2010; Fritschi et al., 2013, 2018; Grundy et al., 2013a; Menegaux et al., 2013; Rabstein et al., 2013, 2014; Wang et al., 2015a; Cordina-Duverger et al., 2016; Papantoniou et al., 2016; Yang et al., 2019) were included in the evaluation, as well as one pooled case–control study (Cordina-Duverger et al., 2018), which comprised five of the nine case–control studies (Pesch et al., 2010; Fritschi et al., 2013; Grundy et al., 2013a; Menegaux et al., 2013; Papantoniou et al., 2016). A case–control study by Hansen (2001), which was not considered informative for the current evaluation because of its use of a JEM-based night shift work exposure assessment approach in a population-based study, is noted as the first observational study addressing the hypothesis of an association between night shift work and risk of cancer of the breast.

Several other published papers present additional analyses from existing study populations, including: Rabstein et al. (2013), which stratified results by ER status from Pesch et al. (2010); Rabstein et al. (2014), which evaluated the interaction of circadian genes from Pesch et al. (2010); Cordina-Duverger et al. (2016), which stratified results by ER status from Menegaux et al. (2013); Truong et al. (2014), which showed the interaction of circadian genes from Menegaux et al. (2013); Grundy et al. (2013b), which studied the interaction of circadian genes from Grundy et al. (2013a); and Fritschi et al. (2018), which incorporated chronotype into the exposure assessment from Fritschi et al. (2013). Of these, Grundy et al. (2013b), Rabstein et al. (2014), Truong et al. (2014), and Fritschi et al. (2018) present analyses not already represented by the pooled analysis (Cordina-Duverger et al., 2018).

Most studies were conducted in Europe (Denmark, France, Germany, and Spain), and the remainder were conducted in Australia, Canada, China, and the USA. Of the 14 studies, 13 were general-population studies and a single study (Wang et al., 2015a) was hospital-based.

The individual case–control studies included in the pooled case–control study of Cordina-Duverger et al. (2018) (Pesch et al., 2010; Fritschi et al., 2013; Grundy et al., 2013a; Menegaux et al., 2013; Rabstein et al., 2013; Cordina-Duverger et al., 2016; Papantoniou et al., 2016) are described in detail in Annex 2, Supplementary material for Section 2, web only; available from: http://publications.iarc.fr/593. All other

individual studies, including those in the pooled study that examined interactions between night shift work and either chronotype or clock genes, are detailed after the description of the pooled study.

(ii) Pooled case–control study of Cordina-Duverger et al. (2018)

Of the case–control studies that contributed to this section, the most informative and rigorous study comes from a pooled analysis (Cordina-Duverger et al., 2018) of five case–control studies (Pesch et al., 2010 and Rabstein et al., 2013; Fritschi et al., 2013; Grundy et al., 2013a; Menegaux et al., 2013 and Cordina-Duverger et al., 2016; Papantoniou et al., 2016) with a total of 6093 cases of cancer of the breast and 6933 population controls. The individual case–control studies were conducted in Australia, Canada, France, Germany, and Spain. All five studies included in the pooled analysis had a lifetime work history; exposure was assessed by interview or questionnaire in all five studies. Information on work schedules was obtained for each job held for longer than 6 months (12 months in Spain). The definition of exposure to night work varied between studies, and protocols were harmonized to develop an exposure evaluation common to all studies. In the combined analyses, night work was defined as any job that included at least 3 hours of work between midnight and 05:00. On the basis of this definition, exposure indicators included ever/never, duration in years, length of night shifts (hours), and years since last night shift. Additional analyses incorporating considerations of shift frequency (including four of the five studies) examined intensity of night work (number of nights per week), lifetime cumulative number of night shifts, and number of night hours per week. Further, combined variables (intensity × duration of night work, intensity × length of night shift, and intensity × years since last night shift) were considered. Overall, Cordina-Duverger et al. (2018) reported a pooled odds ratio for cancer of the breast in women who ever worked at night (for at least 3 hours between midnight and 05:00), compared with never night workers, of 1.12 (95% CI, 1.00–1.25). Risks were reported for having 20 years or more of night work (OR, 1.10; 95% CI, 0.87–1.39), having worked night shifts that lasted 10 hours or more (OR, 1.12; 95% CI, 0.96–1.31), a period of 0–2 years since last night shift worked (OR, 1.26; 95% CI, 1.02–1.55), a period of 20 years or more since last night worked (OR, 1.07; 95% CI, 0.90–1.27), working night shift at least 3 nights per week (OR, 1.26; 95% CI, 0.97–1.63), having a lifetime cumulative number of night shifts of at least 1000 (OR, 1.11; 95% CI, 0.88–1.39), and having worked at least 20 night-hours per week during nights (OR, 1.28; 95% CI, 1.01–1.61), all compared with never working night shifts. Cancer of the breast in postmenopausal women (447 cases) was not associated with night work, irrespective of exposure metric used. However, among premenopausal women (324 cases), the odds ratio for ever night work was 1.26 (95% CI, 1.06–1.51), and the highest risks were observed for persistent night work (i.e. most nights per week or greatest number of night hours per week). The odds ratio for long-duration night work (i.e. for 20 years or more of night work, based on 42 exposed cases) was 1.34 (95% CI, 0.85–2.13) and for cumulative nights worked (i.e. ≥ 1000 cumulative lifetime nights) was 1.31 (95% CI, 0.88–1.94). There was an elevated risk for night shifts ≥ 10 hours (OR, 1.36; 95% CI, 1.07–1.74), for work ≥ 3 nights per week (OR, 1.80; 95% CI, 1.20–2.71), and for both duration of night work ≥ 10 years and exposure intensity ≥ 3 nights per week (OR, 2.55; 95% CI, 1.03–6.30, based on 16 exposed cases). Among premenopausal women, the odds ratio for cancer of the breast was higher in current or recent night workers than in those who had stopped night work more than 2 years ago, compared with women who had never worked night shifts. For ER- and/or HER2-positive tumours, the risk of cancer of the breast was significantly

elevated in both premenopausal (OR, 1.77; 95% CI, 1.16–2.70) and postmenopausal (OR, 1.59; 95% CI, 1.11–2.28) women. [The Working Group noted that the strength of this pooled study was the uniform methods applied to the individual study data. The limitations of this study included the small sample size in subgroups (particularly tumour subtypes) and, for some exposure categories in analyses of exposure metrics other than ever/never night shift work.]

(iii) Seattle case–control study, USA

A population-based case–control study (Davis et al., 2001) was conducted in Seattle, Washington, USA, enrolling 813 women with cancer of the breast and 793 random-digit dialled controls. Participation rates were 75% among the controls and 78% among eligible cases. Lifetime occupational history and lighting conditions in the bedroom were queried using standardized questionnaires. The number of night ("graveyard") shifts worked per week (one shift being 8 hours), defined as beginning work after 19:00 and leaving work before 09:00, was assessed. An increased risk of cancer of the breast was observed among women who worked any night shift (OR, 1.6; 95% CI, 1.0–2.5), with a positive trend for with increasing number of years (*P* for trend, 0.04) and with more hours per week of night shift work (*P* for trend, 0.04).

(iv) Long Island case–control study, USA

The case–control study by O'Leary et al. (2006) conducted in Long Island, New York, USA (487 cases and 509 population-based controls, frequency matched by age group) included women who were also part of a larger case–control study (Long Island Breast Cancer Study Project). Overall, the proportion of shift workers in the final sample was 36.3%, with only a small proportion of women working overnight shifts (e.g. at least one overnight shift per week: 11 cases and 16 controls for duration < 8 years, 6 cases and 16 controls for duration ≥ 8 years). The main finding was that there was no positive (but actually an inverse) association between night shift work and risk of cancer of the breast; a multivariable-adjusted odds ratio of 0.55 (95% CI, 0.32–0.94) was reported for any overnight shift work versus no evening or overnight shift work. [The Working Group noted that this study was of limited power and used information from a limited time window; there was also a potential for information and selection bias. Because of the subsequent sampling of cases and controls from undefined initial populations, it was not possible to calculate accurate response rates in this study]

(v) Guangzhou case–control study, China

Wang et al. (2015a) reported a hospital-based case–control study of 661 cases and 714 age-matched controls, conducted during 2010–2012 in Guangzhou, China. Controls were recruited from a health check-up clinic in the same hospital from which consecutive cases of cancer of the breast were enrolled. There was a relatively high proportion of shift workers in this population (33% among the cases, 26.2% among controls), and ever night shift work was associated with an increased risk of breast cancer (OR, 1.34; 95% CI, 1.05–1.72). There was no evidence of heterogeneity in the association with night work by menopausal status (*P* for interaction, 0.26). Risks were slightly higher for ER-positive than for ER-negative tumours (*P* for interaction, 0.03), but there was no evidence of heterogeneity by HER2 status. Participation rates were 75–85% for cases (depending on recruitment site) and 78.2% for controls.

(vi) Jiujiang Breast Cancer Study, China

In Jiujiang, China, a community-based case–control study (the Jiujiang Breast Cancer Study) was conducted of 401 cases from the local cancer registry individually matched (on age and area) to 401 controls (Yang et al., 2019). Participants in the study were asked whether they had ever had "night/shift" work (yes/no) and, if yes, the

frequency (per week), the amount in hours per day, and the duration (years) of night/shift work were recorded. The study assessed the cumulative influence of night/shift work in "hour-years" by evaluating the product of hours of night/shift work per day and the duration of night/shift work. An increased risk of cancer of the breast (OR, 1.38; 95% CI, 1.04–2.71) was reported based on 41 cases and 30 controls who had ever worked nights/shifts. Further, an increase of 1 hour-years of night/shift work was associated with an OR of 1.15 (95% CI, 1.07–1.62; *P* for trend, 0.03). Risks did not vary by hormone receptor status of the tumour, or menopausal status. [The Working Group noted that night shift work (i.e. "night/shift work") was undefined in this study. The study reported a participation rate of 93% for the cases, but did not report the participation rate of neighbourhood controls.]

(c) Studies evaluating the interaction between night work and chronotype

Two cohort studies evaluated whether chronotype modified the association between night work and cancer of the breast (Table 2.1). In the nested case–control study among women in the Danish military, the cumulative number of night shifts was more strongly associated with cancer of the breast in those with morning preference than in those with evening preference (Hansen & Lassen, 2012). In the NHS-II cohort, chronotype was not found to modify the effect of night shift work on breast cancer risk (Ramin et al., 2013). Two population-based case–control studies on night work and risk of cancer of the breast considered chronotype in their analyses (Papantoniou et al., 2016; Fritschi et al., 2018) (Table 2.2). Both were set within studies that contributed to the pooled case–control study (Cordina-Duverger et al., 2018). Fritschi et al. (2018) observed virtually no change in the odds ratio for night shift work (compared with that observed in Fritschi et al., 2013) after reclassifying exposure by incorporating chronotype (OR, 1.17; 95% CI, 0.98–1.41 with chronotype; OR, 1.16; 95% CI, 0.97–1.38 without chronotype). Chronotype was assessed using the Morningness-Eveningness Questionnaire designed by Horne & Ostberg (1977). Papantoniou et al. (2016) examined the association between night shift work and risk of cancer of the breast stratified by chronotype (estimated as the midsleep time on free days corrected for oversleep on free days compared with working days) and found that the risk for ever compared with never night workers was only slightly higher among evening types than among other types (OR, 1.27; 95% CI, 0.81–2.00 for evening types, versus 1.17, 95% CI, 0.83–1.65 for morning types, and 1.17, 95% CI, 0.82–1.69 for neither chronotype. When considering lifetime cumulative duration of night work, a larger difference in risk was observed between morning types (OR, 0.91; 95% CI, 0.54–1.51) and evening types (OR, 1.76; 95% CI, 0.85–3.67) for those with 15 years or more duration compared with those who had never worked nights. [The Working Group noted there were only a few studies on and diverging assessments of chronotype, which precluded a comprehensive evaluation of its importance as a modifier of the risk of cancer of the breast.]

(d) Studies evaluating gene–environment interactions with night shift work

In a subset of 1318 women from the NHS-II cohort, Monsees et al. (2012) investigated the interaction between genes in the circadian genes pathway and night shift work, and observed that the association between risk of cancer of the breast and night shift work differed according to genotype in the *NPAS2* gene.

In a study conducted within the nested case–control study of Norwegian nurses by Lie et al. (2011), Zienolddiny et al. (2013) found that several polymorphisms in genes involved in the circadian clock gene pathway may modify breast cancer risk in women who worked 3 or more consecutive nights.

Three studies (Grundy et al., 2013b; Rabstein et al., 2014; Truong et al., 2014), set within studies that were part of the pooled case–control study by Cordina-Duverger et al. (2018), evaluated whether variants in clock or related genes interacted with night shift work in its effect on breast cancer risk. Using the same data from the Gene ENvironment Interaction and Breast CAncer (GENICA) study (described in Annex 2, Supplementary material for Section 2, web only; available from: http://publications.iarc.fr/593) (Pesch et al., 2010; Rabstein et al., 2013), Rabstein et al. (2014) examined the interactions between seven polymorphisms in clock genes, as well as genes involved in melatonin metabolism, and night shift work. The study found some suggestive evidence for interactions primarily for a CLOCK single-nucleotide polymorphism (SNP) (rs10462028), with an increased risk of cancer of the breast among shift workers for AA versus GG (OR, 3.53; 95% CI, 1.09–11.42); however, the finding was based on only 12 shift worker cases with the genotype of interest. The publication by Truong et al. (2014), a report of the "Cancer du Sein: Etude épidémiologique en Côte d'Or et en Ille-et-Vilaine sur l'Environnement" (CECILE) study conducted in France and described in Annex 2 (web only; available from: http://publications.iarc.fr/593), focused on 23 circadian clock genes and included 1126 cases of cancer of the breast and 1174 controls. The study reported "some evidence of an interaction between PER1 and nightwork in breast cancer in the whole sample, P=0.024", with a *P* value that was no longer significant after Bonferroni correction. [The Working Group noted that, in general, this study did not report a positive finding, but was likely underpowered to address the research question at hand. The Working Group further noted the limited precision as a result of the small numbers in some of the stratified analyses.] A study (Grundy et al., 2013b) set within the Canadian case–control study (Grundy et al., 2013a) found no significant interaction between night shift work and 100 SNPs of 14 clock-related genes among 1042 cases and 1051 controls of any ancestry, and of European ancestry specifically (645 cases, 806 controls).

[The Working Group noted that no consistent or particularly compelling evidence emerged from these few studies, which had low power and used scattered assessments of various SNPs.]

2.1.2 Cancer of the prostate

See Table 2.3.

Eligible studies on cancer of the prostate include five general-population cohort studies (Kubo et al., 2006; Gapstur et al., 2014; Dickerman et al., 2016; Åkerstedt et al., 2017; Behrens et al., 2017); two industrial cohort studies, one in Japan (Kubo et al., 2011) and one in Germany (Yong et al., 2014a, b; Hammer et al., 2015); five population-based case–control studies (Conlon et al., 2007; Parent et al., 2012; Papantoniou et al., 2015; Wendeu-Foyet et al., 2018; Barul et al., 2019); and one hospital-based case–control study (Tse et al., 2017). Three studies were conducted in Asia, six in Europe, and four in North America. These studies do not include those on aircrew reviewed in Section 2.2.1. Another study that used only population-based JEMs (Schwartzbaum et al., 2007) was considered uninformative and is not described further. There are several qualitative reviews (Sigurdardottir et al., 2012; Wendeu-Foyet & Menegaux, 2017) and meta-analyses (Rao et al., 2015; Du et al., 2017; Gan et al., 2018; Mancio et al., 2018) on shift work and cancer of the prostate; the meta-analyses are reviewed in Section 2.3.

(a) Cohort studies

A total of 14 052 men from 21 areas in Japan, employed and aged 40–65 years at baseline in 1988–1990, were extracted as a subcohort of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Kubo et al., 2006). A self-administered questionnaire was used to record

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Åkerstedt et al. (2017) Sweden Enrolment, 1998–2003; follow-up, through 2010 Cohort	12 322 general population; members of Swedish Twin Registry; men aged 41–60 yr at interview and followed for incident prostate cancer (Swedish Cancer Registry and Cause of Death Register) through 2010 Exposure assessment method: subjective assessment; night shift undefined	No night work vs ever night work, incidence (HR):			Age, education, tobacco, BMI, children, coffee consumption, previous cancer	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Complete. No other information available. *Other comments*: analysis of: ever/never night work; total duration of employment with night work
		Never	294	1		
		Night work for 1–45 yr	160	0.91 (0.74–1.12)		
		Duration of night work, incidence (HR):				
		Never	294	1		
		1–5 yr	55	0.86 (0.63–1.17)		
		6–10 yr	31	1.09 (0.74–1.61)		
		11–20 yr	38	1.12 (0.78–1.63)		
		21–45 yr	36	0.72 (0.50–1.05)		
Behrens et al. (2017) Germany 2000–2014 Cohort	1757 randomly selected men aged 45–74 yr and residing in the Ruhr area of Germany (recruited during 2000–2003); followed-up with a detailed questionnaire on shift and night work (2011–2014) and followed for incident prostate cancer through September 2014 Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Duration of night work, incidence (HR):			Age, smoking, family history of prostate cancer, education, income	*Exposure assessment critique*: NSW in ref. group: No. Duration: Complete. Temporality: Partial. No other information available. Strengths: able to differentiate between shift and night work Limitations: small number of incident cases, such that stratified analysis by duration of shift or night work could not be performed for all subgroups
		0 to < 1 yr	44	1		
		Ever ≥ 1 yr	32	2.27 (1.42–3.64)		
		1 to < 10 yr	11	1.72 (0.88–3.35)		
		10 to < 20 yr	5	1.68 (0.66–4.26)		
		≥ 20 yr	16	3.76 (2.04–6.93)		
		Trend test *P* value, < 0.0001				
		Ever ≥ 1 yr shift work, incidence (HR):				
		0 to < 1 yr of shift work	38	1		
		Ever ≥ 1 yr	38	2.29 (1.43–3.67)		

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2015) Spain 2008–2013 Case–control	1095 cases: histologically confirmed incident prostate cancer cases identified from 11 hospitals; resident in the catchment area of each hospital for at least 6 mo before diagnosis 1388 controls: men free of prostate cancer, randomly selected from the rosters of GPs at primary health centres; frequency-matched to cases on 5-yr age group and study area Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Cumulative duration of night work (yr), incidence (OR):			Age, centre, education, family history of prostate cancer, level of physical activity, smoking, sun exposure, daily meat consumption	*Exposure assessment critique*: NSW in ref. group: Yes. Intensity: Precise. Duration: Complete. Schedule type: Permanent night, Rotating. No other information available. *Other comments*: analyses of: ever/never night work; permanent and rotating night; lifetime cumulative duration of employment with night; age of first shift work; years since last shift work Includes information on lifetime cumulative duration and frequency of night work; regularity of night work assessed Strengths: includes information on severity of prostate cancer and chronotype Limitations: participation fraction for controls was low (average, 54%)
		Never	733	1		
		≤ 10 yr	128	1.10 (0.83–1.45)		
		11–27 yr	92	0.94 (0.69–1.27)		
		≥ 28 yr	138	1.38 (1.05–1.81)		
		Trend test *P* value, 0.047				
		Cumulative duration of permanent night work (yr), incidence (OR):				
		Never night work	733	1		
		≤ 10 yr	75	1.07 (0.75–1.51)		
		11–27 yr	41	1.01 (0.65–1.56)		
		≥ 28 yr	36	1.40 (0.83–2.37)		
		Trend test *P* value, 0.251				
		Cumulative duration of rotating night work (yr), incidence (OR)				
		Never night work	733	1		
		≤ 10 yr	73	1.21 (0.85–1.74)		
		11–27 yr	47	0.84 (0.56–1.26)		
		≥ 28 yr	85	1.37 (0.97–1.94)		
		Trend test *P* value, 0.158				
		Cumulative duration of night work (yr), incidence of high-risk cancer (RRR):				
		Never night work	168	1		
		≤ 10 yr	35	1.32 (0.86–2.02)		
		11–27 yr	30	1.26 (0.80–1.98)		
		≥ 28 yr	40	1.63 (1.08–2.45)		
		Trend test *P* value, 0.027				

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2015) (cont.)		Cumulative frequency of night work (night shifts), incidence (OR):				
		Never night work	733	1		
		≤ 1152 night shifts	85	1.03 (0.75–1.42)		
		1153–2856 night shifts	71	1.09 (0.78–1.52)		
		≥ 2857 night shifts	100	1.3 (0.97–1.74)		
		Trend test *P* value, 0.084				
		Cumulative frequency of permanent night work (night shifts), incidence (OR):				
		Never night work	733	1		
		≤ 1152 night shifts	28	0.97 (0.59–1.59)		
		1153–2856 night shifts	17	1.06 (0.63–1.77)		
		≥ 2857 night shifts	38	1.27 (0.85–1.91)		
		Trend test *P* value, 0.247				
		Cumulative frequency of rotating night work (night shifts), incidence (OR):				
		Never night work	733	1		
		≤ 1152 night shifts	71	1.08 (0.78–1.5)		
		1153–2856 night shifts	48	1.18 (0.78–1.77)		
		≥ 2857 night shifts	42	1.26 (0.80–1.99)		
		Trend test *P* value, 0.254				
		Cumulative frequency of night work (night shifts), incidence of high-risk cancer (RRR):				
		Never night work	168	1		
		≤ 1152 night shifts	24	1.17 (0.73–1.87)		
		1153–2856 night shifts	23	1.26 (0.76–2.07)		
		≥ 2857 night shifts	33	1.78 (1.17–2.69)		
		Trend test *P* value, 0.007				

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2015) (cont.)		Night work (ever vs never), incidence (OR):			Age, centre, education, family history of prostate cancer, physical activity over the past decade, tobacco, sun exposure, daily meat consumption	
		Never	733	1		
		Ever	362	1.14 (0.94–1.37)		
		Night work (ever vs never), incidence of high-risk cancer (RRR):				
		Never	168	1		
		Ever	106	1.40 (1.05–1.86)		
		Night shift type, incidence (OR):				
		Never night shift	733	1		
		Permanent night work	156	1.10 (0.85–1.43)		
		Rotating night work	206	1.16 (0.92–1.46)		
Kogevinas et al. (2019) Spain 2008–2013 Case–control	1093 cases: histologically confirmed incident prostate cancer cases, identified from 11 hospitals, resident in the catchment area of each hospital for at least 6 mo before diagnosis 1387 controls: men free of prostate cancer, randomly selected from the rosters of GPs at primary health centres, frequency-matched to cases by 5-yr age group and study area Exposure assessment method: questionnaire; subjective assessment; night shift	Time since last night shift (yr), incidence (OR):			Age, centre, education	*Exposure assessment critique*: NSW in ref. group: Yes. Intensity: Precise. Duration: Complete. Temporality: Complete. Schedule type: Permanent night, Rotating. No other information available. *Other comments*: same study as Papantoniou et al. (2015) Strengths: includes information on severity of prostate cancer and chronotype Limitations: participation fraction for controls was low (average, 54%)
		Never night work	733	1		
		≥ 20 yr	155	1.02 (0.8–1.3)		
		3–19 yr	138	1.23 (0.95–1.60)		
		0–2 yr	67	1.25 (0.86–1.80)		

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014a) Germany 1995–2009 Cohort	27 828 (12 609 shift workers and 15 219 day workers) male production workers employed for a least 1 yr in a chemical company Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Rotating shift work compared with day work, incidence (HR): Day workers Rotating shift workers	 191 146	 1 0.93 (0.71–1.21)	Age, job level, cigarette smoking, employment duration	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Temporality: Complete. Schedule type: Rotating. No other information available. *Other comments*: exposure misclassification (day vs shift worker) tested ad hoc with overall accuracy 97% Strengths: large study Limitations: imputation of exposure before 1995; no information on number of cases
Hammer et al. (2015) Germany 1995–2009 Cohort	Cases and controls as for Yong et al. (2014b) above Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Compared with the general population, incidence (SIR): Day workers Rotating shift workers Shift workers vs daytime workers, cancer stage (HR): Day workers Stage 1 Stage 2 Stage 3 Stage 4 Stage unknown	 191 146 191 10 84 32 3 17	 1.44 (1.22–1.70) 1.51 (1.30–1.74) 1 1.18 (0.40–3.75) 0.8 (0.58–1.09) 0.87 (0.51–1.48) 1.19 (0.21–5.52) 1.45 (0.64–3.39)	Age, job level, cigarette smoking, employment duration Smoking status	*Exposure assessment critique*: NSW in ref. group: Yes. Intensity: Imprecise. Duration: Partial (limited period). Temporality: Partial. Rotation speed: Imprecise. Rotation direction: Precise. Schedule type: Rotating. Shift start/end times: Precise. *Other comments*: exposure misclassification (day vs shift worker) tested ad hoc with overall accuracy 97% Strengths: large study Limitations: imputation of exposure before 1995; no information on number of cases

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Parent et al. (2012) Canada 1979–1985 Case–control	400 cases: histologically confirmed incident cases aged 35–70 yr identified from 18 major hospitals 512 controls: randomly selected from the electoral roll, matched to cases in 5-yr age group and residential area Exposure assessment method: questionnaire; subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Night work, incidence (OR):			Age, ancestry, education, income, respondent status, smoking, alcohol intake, BMI, farming, occupational physical activity	*Exposure assessment critique*: NSW in ref. group: No. Duration: Complete. Temporality: Complete. No other information available. *Other comments*: analysis of: ever/never night work; cumulative duration of employment with night work; timing of night work (cut-off, 20 yr) Strengths: lifetime job history, wide range of jobs Limitations: 18% cases and 13% controls not interviewed (proxies used instead); multiple comparisons)
		Never	268	1		
		Ever	132	2.77 (1.96–3.92)		
		Cumulative duration of night work (yr), incidence (OR):				
		Never	268	1		
		< 5 yr	68	3.13 (1.98–4.95)		
		5–10 yr	27	2.11 (1.11–3.99)		
		> 10 yr	36	2.68 (1.45–4.95)		
		Timing of night work, incidence (OR):				
		Never	268	1		
		Recent past (≤ 20 yr before diagnosis or interview)	55	3.17 (1.89–5.31)		
		Distant past (> 20 yr before diagnosis or interview)	57	3.01 (1.83–4.93)		
Dickerman et al. (2016) Finland 1981–2012 Cohort	11 370 male, same-sex twin individuals born before 1958 with both twins alive in 1974 Exposure assessment method: questionnaire; subjective assessment; night shift undefined	Type of work schedule, incidence (HR):			Age, education, BMI, physical activity, social class, smoking status, alcohol intake, snoring, zygosity	*Exposure assessment critique*: NSW in ref. group: Undefined. No other information available. Strengths: large population-based sample with long follow-up Limitations: shift work assessed only for current or latest work type
		Fixed day work	509	1		
		Fixed night work	2	0.5 (0.1–1.9)		
		Rotating shift work	80	1.0 (0.7–1.2)		
		Missing	11	1.1 (0.6–2.1)		

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Gapstur et al. (2014) USA 1982–2010 Cohort	305 057 employed men aged ≥ 29 yr and free of cancer at baseline, followed for prostate cancer mortality through 2010 Exposure assessment method: questionnaire; subjective assessment; night shift defined (for permanent night workers)	Type of work schedule, mortality (RR): Fixed day Rotating Fixed afternoon/evening Fixed night	 4497 268 55 16	 1 1.08 (0.95–1.22) 1.27 (0.97–1.65) 0.72 (0.44–1.18)	Age, race, education, BMI, smoking status, family history of prostate cancer, painful or frequent urination	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (one time-point). Schedule type: Permanent night, Rotating. No other information available Strengths: large prospective study Limitations: non-random sample; mortality outcome; shift work assessed only for current job
Kubo et al. (2006) Japan 1988–1997 Cohort	14 052 employed men aged 40–65 yr at recruitment Exposure assessment method: questionnaire; subjective assessment; night shift undefined	Type of work schedule, incidence (RR): Daytime Fixed night Rotating	 21 3 7	 1 2.3 (0.6–9.2) 3.0 (1.2–7.7)	Age, study area, family history of prostate cancer, BMI, tobacco, alcohol intake, job type, usual physical activity at work, workplace, perceived stress, education, marital status	*Exposure assessment critique*: NSW in ref. group: Undefined. Schedule type: Rotating. No other information available Strengths: large study sample Limitations: lack of statistical power; short follow-up for prostate cancer; limited information on exposure to shift work
Conlon et al. (2007) Canada 1995–1998 Case–control	760 cases: aged 45–85 yr 1632 controls: frequency-matched to cases by age Exposure assessment method: questionnaire; subjective assessment; night shift undefined	Full-time rotating shift status, incidence (OR): Never full-time rotating shift Ever full-time rotating shift Duration of full-time rotating shift work (OR): Never ≤ 7 yr 7.1–22.0 yr 22.1–34.0 yr > 34.0 yr Trend test *P* value, 0.4202	 391 369 391 115 87 81 86	 1 1.19 (1.00–1.42) 1 1.44 (1.1–1.87) 1.14 (0.86–1.52) 0.93 (0.7–1.23) 1.3 (0.97–1.74)	Age, family history of prostate cancer	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (limited period). Temporality: Complete. No other information available. Limitations: lack of detailed information on shift work

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Conlon et al. (2007) (cont.)		Age worked first full-time rotating shift (OR):				
		Never	391	1		
		11–19 yr	98	1.04 (0.79–1.36)		
		20–22 yr	67	1.11 (0.81–1.52)		
		23–29 yr	107	1.38 (1.05–1.8)		
		≥ 30 yr	97	0.13 (0.94–1.65)		
		Trend test *P* value, 0.0521				
Wendeu-Foyet et al. (2018) France 2012–2013 Case–control	818 cases: men aged < 75 yr with histologically confirmed incident prostate cancer, residing in the Hérault region at the time of diagnosis 875 controls: men randomly selected from the general population; residing in the same region and frequency-matched to the cases by 5-yr age groups Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Night work, incidence (OR):			Age, family history of prostate cancer, race, education	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Partial. Rotation speed: Precise. Rotation direction: Precise. Schedule type: Permanent night, Rotating. Shift start/end times: Precise. *Other comments*: analyses of: ever/never night work; total duration of employment with night; lifetime number of night shifts; number of consecutive night shifts; direction and speed of rotation; shift length; combinations; also assessed early morning and late evening shift work Strengths: detailed information on work schedules for each job; information on prostate cancer aggressiveness; good response rates (cases, 75%; controls, 79%)
		Never	532	1		
		Ever	286	0.97 (0.79–1.19)		
		Permanent night work (OR):				
		Never night work	532	1		
		Ever	210	1.04 (0.82–1.32)		
		Rotating night work (OR):				
		Never night work	532	1		
		Ever	84	0.81 (0.59–1.16)		
		Night work shift length (OR):				
		Never night work	532	1		
		< 8 h	18	0.44 (0.25–0.78)		
		8–10 h	97	0.79 (0.59–1.07)		
		> 10 h	54	1.57 (1.01–2.44)		
		Trend test *P* value, 0.94				
		Permanent night work shift length (OR):				
		Never night work	532	1		
		< 8 h	11	0.32 (0.16–0.64)		
		8–10 h	23	0.86 (0.48–1.53)		
		> 10 h	38	1.88 (1.08–3.26)		
		Trend test *P* value, 0.29				
		Night work, evening chronotype (OR):				
		Never night work	60	1		
		Ever	53	1.83 (1.05–3.19)		

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Wendeu-Foyet et al. (2018) (cont.)		Duration of permanent night work (yr), Gleason score of ≥ 7 (OR):				
		Never night work	107	1		
		< 20 yr	23	1.09 (0.66–1.81)		
		≥ 20 yr	35	1.76 (1.13–2.75)		
		Trend test *P* value, 0.003				
Kubo et al. (2011) Japan 1981–2009 Cohort	4995 male workers aged 49–65 yr with annual health check-up information since 2006, and either always a day shift worker or having undertaken rotating three-shift work for > 80% of career Exposure assessment method: records; objective assessment; night shift defined (other)	Career working pattern, incidence (RR):			Age, BMI, alcohol intake, tobacco, physical activity, marital status	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Temporality: Partial. Rotation speed: Imprecise. Rotation direction: Precise. Schedule type: Rotating. No other information available. Strengths: long follow-up Limitations: small number of cases
		Daytime only	13	1		
		Rotating three-shift for > 80% of career	4	1.79 (0.57–5.68)		
Yong et al. (2014b) Germany 1995–2005; follow-up, 2000–2009 Cohort	31 143 (14 038 rotating shift workers and 17 105 day workers); retrospective mortality study of male production workers employed for at least 1 yr in a chemical company Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	No night work vs ever night work, mortality (HR):			Age at entry, cigarette smoking	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Temporality: Complete. Schedule type: Rotating. No other information available. Strengths: large industrial cohort Limitations: exposure classification was dichotomous (≥ 1 yr of shift work vs never shift work) at the time of study entry
		Never	NR	1		
		Ever	NR	0.59 (0.27–1.3)		
		No night work vs ever night work (HR):			Age at entry	
		Never	NR	1		
		Ever	NR	0.70 (0.33–1.50)		

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Barul et al. 2019 Canada 2005–2007 Case–control	1904 cases: histologically confirmed primary prostate cancers from seven (out of nine) hospitals 1965 controls: population controls from continually updated electoral lists Exposure assessment method: questionnaire; subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Night work, incidence (OR):			Age, ancestry, education	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Rotation speed: Precise. Rotation direction: Precise. Schedule type: Permanent night, Rotating. Shift start/end times: Imprecise. No other information available. *Other comments*: analyses included: ever/never night work/permanent night work/rotating schedule night work; cumulative duration of night work and night work with rotating schedule; intensity of night work and night work with rotating schedule; cumulative number of night shifts and rotating night shifts; direction and rate of shift rotation; number of night shifts with rotation Limitations: crude age adjustment (dichotomous)
		Never	1453	1		
		Ever	439	1.07 (0.92–1.26)		
		Direction of shift rotation (OR):				
		Never	1453	1		
		Always forward	158	1.23 (0.96–1.58)		
		Always backward	1	0.29 (0.03–2.8)		
		Both	69	0.92 (0.66–1.29)		
		Not classifiable	19	0.94 (0.50–1.77)		
		Rate of shift rotation (OR):				
		Never	1453	1		
		Daily or 2, 3, or 4 days/wk	19	1.70 (0.81–3.57)		
		Weekly	169	1.00 (0.80–1.27)		
		More than weekly	39	1.4 (0.85–2.31)		
		Not classifiable	20	0.94 (0.50–1.75)		
		Permanent night shift work without rotation (OR):				
		Never	1453	1		
		Ever	12	1.22 (0.76–1.95)		
		Night shift work with rotation (OR):				
		Never night shift	1453	1		
		Never night shift with rotation	192	1.12 (0.89–1.4)		
		Ever	247	1.04 (0.86–1.27)		
		Night work with a minimum frequency of 7 nights/mo (OR):				
		Never	1453	1		
		Ever	277	1.05 (0.87–1.26)		
		Night work, low-grade cancer (OR):				
		Never	1127	1		
		Ever	338	1.08 (0.91–1.28)		
		Night work, high-grade cancer (OR):				
		Never	326	1		
		Ever	101	1.07 (0.82–1.39)		

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Barul et al. 2019 (cont.)		Cumulative duration of night work (yr) (OR):				
		Never	1453	1		
		≤ 4 yr	120	1.1 (0.84–1.44)		
		> 4 to 10 yr	111	1.01 (0.76–1.34)		
		11–21 yr	105	1.17 (0.86–1.59)		
		> 21 yr	103	1.04 (0.77–1.38)		
		Trend test *P* value, 0.61				
		Cumulative duration of night shift with rotation work (yr) (OR):				
		Never	1453	1		
		≤ 4 yr	59	0.9 (0.63–1.27)		
		> 4 to 10 yr	64	1.04 (0.72–1.5)		
		11–21 yr	56	1.1 (0.74–1.64)		
		> 21 yr	68	1.19 (0.83–1.72)		
		Trend test *P* value, 0.64				
		Cumulative duration of night work with a minimum frequency of 7 nights/mo (yr) (OR):				
		Never	1453	1		
		≤ 6 yr	117	1.09 (0.87–1.37)		
		> 7 to 15 yr	74	1.08 (0.82–1.42)		
		> 15 yr	86	1.05 (0.82–1.34)		
		Trend test *P* value, 0.98				
		Cumulative duration of night work (yr), low-grade cancer (OR):				
		Never	1127	1		
		≤ 4 yr	93	1.08 (0.81–1.44)		
		> 4 to 10 yr	83	0.98 (0.72–1.34)		
		11–21 yr	81	1.2 (0.87–1.66)		
		> 21 yr	81	1.08 (0.79–1.47)		
		Trend test *P* value, 0.49				

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Barul et al. 2019 (cont.)		Cumulative duration of night work (yr), high-grade cancer (OR):				
		Never	326	1		
		≤ 4 yr	27	1.17 (0.73–1.87)		
		> 4 to 10 yr	28	1.08 (0.69–1.68)		
		11–21 yr	24	1.09 (0.68–1.75)		
		> 21 yr	22	0.91 (0.56–1.48)		
		Trend test *P* value, 0.88				
		Intensity of night work (nights/yr) (OR):				
		Never	1453	1		
		≤ 83.33 nights/yr	108	1.1 (0.82–1.47)		
		83.34–122.50 nights/yr	133	1.2 (0.92–1.56)		
		122.51–240.00 nights/yr	92	0.91 (0.68–1.22)		
		> 240.00 nights/yr	106	1.09 (0.81–1.46)		
		Trend test *P* value, 0.69				
		Intensity of night shift work with rotation (nights/yr) (OR):				
		Never	1453	1		
		≤ 81.67 nights/yr	81	1.14 (0.81–1.59)		
		81.68–84.00 nights/yr	63	1.14 (0.78–1.65)		
		84.01–125 nights/yr	62	0.96 (0.65–1.4)		
		> 125 nights/yr	41	0.93 (0.60–1.44)		
		Trend test *P* value, 0.67				
		Intensity of night shift work (nights/yr), low-grade cancer (OR):				
		Never	1127	1		
		≤ 83.33 nights/yr	85	1.12 (0.83–1.52)		
		83.34–122.50 nights/yr	106	1.25 (0.94–1.66)		
		122.51–240 nights/yr	71	0.90 (0.65–1.24)		
		> 240 nights/yr	76	1.03 (0.75–1.43)		
		Trend test *P* value, 0.83				

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Barul et al. 2019 (cont.)		Intensity of night shift work (nights/yr), high-grade cancer (OR):				
		Never	326	1		
		≤ 83.33 nights/yr	23	1.03 (0.63–1.67)		
		83.34–122.50 nights/yr	27	1.03 (0.66–1.61)		
		122.51–240 nights/yr	21	0.95 (0.58–1.56)		
		> 240 nights/yr	30	1.25 (0.80–1.94)		
		Trend test *P* value, 0.56				
		Cumulative number of night shifts (total number of nights) (OR):				
		Never	1453	1		
		≤ 588 nights	119	1.10 (0.84–1.46)		
		588–1332 nights	116	1.20 (0.90–1.59)		
		1333–2575 nights	115	1.10 (0.83–1.46)		
		> 2575 nights	89	0.88 (0.65–1.2)		
		Trend test *P* value, 0.97				
		Cumulative number of night shifts (total number of nights), low-grade cancer (OR):				
		Never	1127	1		
		≤ 588 nights	94	1.1 (0.83–1.47)		
		588–1332 nights	85	1.14 (0.84–1.56)		
		1333–2575 nights	91	1.15 (0.85–1.56)		
		> 2575 nights	68	0.90 (0.65–1.26)		
		Trend test *P* value, 0.83				
		Cumulative number of night shifts (total number of nights), high-grade cancer (OR):				
		Never	326	1		
		≤ 588 nights	25	1.11 (0.68–1.82)		
		588–1332 nights	31	1.37 (0.88–2.12)		
		1333–2575 nights	24	0.95 (0.60–1.52)		
		> 2575 nights	21	0.83 (0.50–1.36)		
		Trend test *P* value, 0.72				

Table 2.3 Studies of cancer of the prostate among shift workers other than aircrew (cont.)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method[a]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Barul et al. 2019 (cont.)		Cumulative number of night shifts with rotation (total number of nights) (OR):				
		Never	1453	1		
		≤ 490 nights	61	0.99 (0.68–1.44)		
		491–1111 nights	60	1.1 (0.75–1.63)		
		1112–2292 nights	68	1.07 (0.75–1.53)		
		> 2292 nights	58	1.02 (0.69–1.49)		
		Trend test *P* value, 0.93				
Tse et al. (2017) Hong Kong Special Administrative Region, China 2011–2016 Case–control	431 cases: histologically confirmed incident prostate cancer cases registered in one regional hospital 402 controls: hospital controls without a history of cancer or benign prostate hyperplasia Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Night work (OR):			Age at interview, marital status, employment status, family history of prostate cancer, consumption of deep-fried food, consumption of pickled vegetable, green tea consumption, bisphenol A exposure index	*Exposure assessment critique*: NSW in ref. group: No. No other information available. Limitations: lack of detailed information on night work
		Never	366	1		
		Ever	58	1.76 (1.07–2.89)		

BMI, body mass index; CI, confidence interval; GP, general practitioner; h, hour ; HR, hazard ratio; mo, month; OR, odds ratio; RR, relative risk or rate ratio; RRR, relative risk ratio; SIR, standardized incidence ratio; vs, versus; wk, week; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

information at baseline on exposures related to lifestyle and work. At baseline, study participants were asked to indicate the work schedule they had engaged in the longest: daytime work, fixed night work, or alternate night and day work (which is referred to as rotating shift work). Of the 14 052 men, 11 269 (80.2%) reported day work, 982 (7.0%) reported fixed night work, and 1801 (12.8%) reported rotating shift work. In total, 31 cases of cancer of the prostate were documented from cancer registries during follow-up, based on 111 974 person-years (mean, 8.0 years from baseline until the end of 1997). Multivariate-adjusted relative risk (based on Cox proportional hazards models) for fixed night shifts was 2.3 (95% CI, 0.6–9.2; 3 exposed cases) and for rotating shifts was 3.0 (95% CI, 1.2–7.7; 7 exposed cases), compared with day workers. [The Working Group noted that the major limitations of the study were a lack of statistical power, the short follow-up for cancer of the prostate, and limited information on exposure to shift work.]

Kubo et al. (2011) examined the risk of cancer of the prostate among shift workers in an industry-based retrospective cohort study in Japan. The study was based on the health-care database of a Japanese manufacturing corporation. Work schedules of 4995 male workers (mean age, 55.5 years) were evaluated retrospectively for a mean follow-up period of 25.0 years. Among participants, 4168 had previously undertaken only daytime work whereas 827 had undertaken rotating three-shift work for more than 80% of their career, representing a mean duration of shift work of 25.9 years. Data on the incidence of cancer of the prostate were obtained from health insurance records (13 cases among day workers; 4 cases among night shift workers). Compared with daytime workers, the rate ratio for cancer of the prostate among shift workers was 1.79 (95% CI, 0.57–5.68). [The Working Group noted the small number of cases and limited information on night shift work.]

Cancer incidence (Yong et al., 2014a; Hammer et al., 2015) and mortality (Yong et al., 2014b) were examined in a cohort of male production workers employed at a chemical factory in Germany for 1 year or more between 1995 and 2005. For the cancer incidence analysis (Yong et al., 2014a; Hammer et al., 2015), the cohort included 12 609 shift and 15 219 day male production workers residing in the German federal state of Rhineland-Palatinate (approximately 90% of the total cohort). Incident cancer cases from 2000 to 2009 were identified through record linkage with the cancer registry of Rhineland-Palatinate. The completeness of reported cancer cases was estimated to be about 80%. Information on exposure to shift work and potential confounders, including age, smoking status, job level, and employment duration, was extracted from the personnel and health records. The accuracy of the exposure classification into shift or day workers was estimated to be 97%. Information on direction of rotation and duration was available. [The Working Group noted that results were not presented for these exposure variables.] The hazard ratio for shift workers compared with day workers was 0.93 (95% CI, 0.71–1.21) (Yong et al., 2014a). Compared with the general population, both day workers (standardized incidence ratio, SIR, 1.44; 95% CI, 1.22–1.70; n = 191 cases) and shift workers (SIR, 1.51; 95% CI, 1.30–1.74; n = 144 cases) had an increased incidence rate of cancer of the prostate (Hammer et al., 2015). Further analysis (Hammer et al., 2015) did not indicate differences by cancer stage between day and shift workers. In the analysis on mortality (Yong et al., 2014b), the risk for all cancers and for cancer of the prostate (HR, 0.70; 95% CI, 0.33–1.50) was lower among shift workers when adjusting for age at entry, and was even lower when adjusting for smoking. [The Working Group noted that the definition of shift work was dichotomous and, although information on duration of shift work was available, risk estimates were not presented. The shift work group had an unexplained lower

mortality from all causes and cancer when compared with day workers.]

Gapstur et al. (2014) examined associations between mortality from cancer of the prostate and work schedule, sleep duration, and insomnia frequency in the American Cancer Society Cancer Prevention Study II, a large prospective cohort study of adults in the USA. Work schedule (i.e. rotating shift work, fixed night, and fixed afternoon/evening shift work) was self-reported in 1982. The baseline self-administered questionnaire elicited information on current occupation, and participants were asked "Do you work rotating shifts?" and "What time of day do you start working?" The rotating shift work and time-of-day variables were combined to create a five-level variable for work schedule: fixed day (starting work between 06:00 and 10:00; *n* = 274 702, 90%), rotating (*n* = 18 126, 5.9%), fixed afternoon/evening (starting work between 14:00 and 16:00; *n* = 2921, 1%), fixed night (starting work between 21:00 and midnight; *n* = 1612, 0.5%), and other fixed shift (starting work at any other time; *n* = 7696, 2.5%). Among 305 057 employed men aged 29 years or older who were free of cancer at baseline, there were 4974 deaths from cancer of the prostate during follow-up through 2010. At completion of the 1988 follow-up via direct contact, vital status was known for 98.2% of the cohort. Deaths among 21 704 individuals who were lost to follow-up in 1988 and deaths occurring from September 1988 through December 2010 were identified through linkage with the United States National Death Index. Work schedule was not associated with risk of fatal cancer of the prostate for rotating workers (adjusted RR, 1.08; 95% CI, 0.95–1.22) or for fixed night workers (adjusted RR, 0.72; 95% CI, 0.44–1.18), compared with fixed day workers. [The Working Group noted that exposure information was collected at baseline for current job at the time of enrolment with no data on intensity or duration, and no information regarding prior history of shift work or shift work during subsequent years of follow-up. There was a very low percentage of rotating and fixed night shift workers in this cohort, probably because of an overrepresentation of participants with high socioeconomic status, and the category "rotating" included workers who did not work at night.]

Dickerman et al. (2016) examined midlife sleep- and circadian-related parameters including shift work and later incidence of and mortality from cancer of the prostate in a population-based cohort of Finnish twins (Older Finnish Twin Cohort). They included 11 370 twins followed from 1981 to 2012. Over the study period, 602 incident cases of cancer of the prostate and 110 deaths from cancer of the prostate occurred. [The Working Group noted that the follow-up rate was not reported but, based on other publications of the same cohort, should be nearly 100%.] Data on shift work were obtained by assessing the respondent's current or latest work type and were classified into four categories: fixed days, fixed nights (0.8% of the population), rotating shift (16%), and missing (0.9%). Rotating shift work referred to work that rotated through morning, evening, or night shifts in either a two-shift or three-shift pattern. Only two cases were reported in the night shift group, with a hazard ratio of 0.5 (95% CI, 0.1–1.9) compared with day workers; there was no association with rotating shift (HR, 1.0; 95% CI, 0.7–1.2; 80 exposed cases). Results were similar in a co-twin analysis. Chronotype significantly modified the relationship between shift work and risk of cancer of the prostate (*P* value for interaction, < 0.001), with evening types working rotating shift having a high risk. [The Working Group noted the limited information on night shift work exposure in this study, which was based on current or more recent work type at baseline, as well as the very small number of night shift workers in this study. The rotating shift work category included workers who did not work at night.]

Behrens et al. (2017) evaluated the incidence of cancer of the prostate in the population-based

Heinz Nixdorf Recall cohort study that included a random sample of inhabitants (aged 45–74 years) of the highly industrialized Ruhr area in Germany. Participants of the baseline survey were recruited between 2000 and 2003, and a follow-up survey including a detailed interview on shift and night work was conducted from 2011 to 2014. The response rate for the follow-up was 63% (participants, n = 1481), but information on shift work could be recovered from the baseline interview for another 319 men (overall number of participants, 1757 men who did not report a history of cancer of the prostate at baseline; follow-up rate, 75%). Exposure to shift and night work was assessed up to the time of the baseline interview. Shift work was defined as any regular employment in shift systems including work hours outside the period 07:00–18:00, whereas night work was defined as a shift that included work between midnight and 05:00. Incident cases of cancer of the prostate (n = 76) were recorded from baseline through September 2014. Hazard ratios were calculated for exposure to shift and night work using Cox proportional hazards regression with age at event as timescale, adjusting for smoking status, family history of cancer of the prostate, education (≤ 13, 14–17, or ≥ 18 years), and income (low, medium, or high). Including body mass index (BMI), level of physical activity, and alcohol consumption as confounders changed the effect estimates minimally, and models adjusting for these variables were not reported. Total serum 25-hydroxyvitamin D, 25(OH)D, at baseline was measured in 2007 on thawed samples using Liaison assay (DiaSorin), and vitamin D status was categorized as "low" or "high" based on a cut-off at the median concentration (15.3 ng/mL). Ever employment in shift work was associated with a hazard ratio of 2.29 (95% CI, 1.43–3.67), and ever night work was associated with a hazard ratio of 2.27 (95% CI, 1.42–3.64). The hazard ratio increased with duration of employment in night work, and was 3.76 (95% CI, 2.04–6.93) for men employed for 20 years or more in night work. [The Working Group noted that, although this is a cohort study, detailed shift work information was collected retrospectively and, for most of the study population, the analysis used the exposure data collected in 2011–2014, when most of the incident cases of cancer of the prostate would have been aware of their diagnosis.]

Åkerstedt et al. (2017) reported on a cohort of 12 322 men who participated in the Screening Across the Lifespan Twin study of the Swedish Twin Registry. Participants were twins born in Sweden before 1959 and aged 41–60 years at the time of the interview. Participants responded to a computer-assisted telephone interview once between 1998 and March 2003, with a response rate of 74%. Those who had worked at night for 1–45 years, according to the response to the question "For how many years have you had working hours that meant that you worked nights at least now and then", were classified as night shift workers (n = 4816). Follow-up was nearly 100%, the mean follow-up time was 8.7 years (range, 0–13 years), and cancer of the prostate occurred in 454 men. Overall, men who had ever worked at night were not at increased risk of cancer of the prostate compared with never night workers (adjusted HR, 0.91; 95% CI, 0.74–1.12). Adjustment for several factors made a small difference. There was no association between risk and duration of night shift work exposure, with a hazard ratio of less than 1 reported for most strata. Results were similar when the analysis was restricted to twin pairs discordant for cancer of the prostate. [The Working Group noted the limited information on night shift work that was self-reported, on the basis of a single question.]

(b) Case–control studies

A case–control study based on a cancer registry among residents of north-eastern Ontario, Canada, included 760 cases of cancer of the prostate in men aged 45–84 years, diagnosed during 1995–1998 (Conlon et al., 2007). Controls

(n = 1632) were frequency matched to cases by age and sex. A comprehensive mailed questionnaire was designed to gather information on exposure to lifestyle factors and on each job held for 1 year or more, including information on usual work time (daytime shift, evening/night shift, rotating shift, or other). The adjusted odds ratio for ever working rotating shifts on a full-time basis (compared with never working such shifts on a full-time basis) was 1.19 (95% CI, 1.00–1.42; 369 cases). There was no pattern of risk with duration of years of full-time rotating shifts. A trend (P for trend, 0.0521) was observed for age of working a first full-time rotating shift, with higher odds ratios for older ages, but the pattern was not monotonic. [The Working Group noted the lack of detailed information on night shift work, and that the proportion of cases and controls classified with rotating shift work seemed unusually high. Analyses were adjusted only for age and family history of cancer of the prostate.]

Parent et al. (2012) studied the association between night work and risk of cancer among men in a population-based case–control study conducted in Montreal, Quebec, Canada, between 1979 and 1985. Analyses included 3137 men with incident cancer at one of 11 anatomic sites (400 with cancer of the prostate) and 512 controls who provided information about shift work (84% of all cases and 96% of controls). For each job held, the participant was asked whether the job entailed shift work and, if so, the start and finish times of this work shift. A job entailing night work was defined as one that included working between 01:00 and 02:00 for at least 6 months. A cumulative index of night work exposure was calculated by totalling the number of years of night work in all jobs held. Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for the risk of cancer among men who had ever held a job entailing night work. Analyses were also conducted according to the cumulative duration (< 5, 5–10, or > 10 years) and timing (recent or distant) of night work over the participant's lifetime. Time since last night work was classified as "recent" if jobs were held during the 20-year period before the date of diagnosis or interview, and "distant" if jobs were held more than 20 years ago. In analyses for cancer of the prostate, ever performing night work was associated with increased risk (OR, 2.77; 95% CI, 1.96–3.92); however, risk did not increase with increasing cumulative duration of night work from less than 5 years (OR, 3.13; 95% CI, 1.98–4.95) to 5–10 years (OR, 2.11; 95% CI, 1.11–3.99), to 10 years or more (OR, 2.68; 95% CI, 1.45–4.95). Odds ratios were similar for those with recent and distant night work. [The Working Group noted that a higher proportion of cases (16%) than controls (4%) were excluded because of a lack of information about night shift work. A higher proportion of cases than controls had proxy respondents.]

Papantoniou et al. (2015) evaluated the risk of cancer of the prostate in relation to shift work history in the population-based multicase–control (MCC-) Spain study. The study assessed incident cases of cancer of the breast, colon and rectum, prostate, and stomach, and of chronic lymphocytic leukaemia diagnosed during 2008–2013 in 23 public hospitals distributed within 12 Spanish regions. For the analysis of cancer of the prostate, cases were recruited in 11 hospitals from seven Spanish regions. Cases were aged 27–85 years, had a new histologically confirmed diagnosis of cancer of the prostate, and had been living in the catchment area of the participating hospitals for at least 6 months before diagnosis. Controls had no history of cancer of the prostate and lived in the same catchment area as cases for the same period of time. Response rates were, on average, 74% among cases and 54% among controls. Shift work was assessed through lifetime occupational history consisting of all jobs held for at least 1 year, and included information on age at the beginning and end of each job, job title, and the main task of the job. Participants

self-classified each job as day, night, or rotating. Exact time schedules were assessed for all rotating night shift jobs reported by the workers. Permanent night shift work was defined as a fixed schedule that involved working partly or entirely between midnight and 06:00 at least 3 times per month. Rotating shift work was defined as any rotation between morning, evening, and/or night shifts. The reference group consisted of participants who had never worked shift work (i.e. only day workers). Chronotype was evaluated with the use of the Munich Chronotype Questionnaire. Clinical information was collected from medical records, including anatomopathological and clinical stage, prostate-specific antigen levels, and Gleason score. The association between shift work and cancer of the prostate was evaluated using unconditional logistic regression models, and odds ratios with 95% confidence intervals were estimated for different shift work metrics (ever shift work, lifetime cumulative duration, and lifetime cumulative frequency). The study included 1095 cancer cases and 1388 population controls with complete shift work data. Participants who had worked night shift for at least 1 year had a slightly higher risk of cancer of the prostate (OR, 1.14; 95% CI, 0.94–1.37) compared with never night workers. Odds ratios were 1.10 (95% CI, 0.85–1.43) for permanent night workers and 1.16 (95% CI, 0.92–1.46) for rotating night work. Risk increased with increasing duration of exposure (OR for highest tertile of ≥ 28 years, 1.38; 95% CI, 1.05–1.81; *P* for trend, 0.047), with similar odds ratios for permanent and rotating night workers. In an analysis by time since last exposure (Kogevinas et al., 2019), it was found that participants with current or recent night shift work (0–2 years) had an odds ratio of 1.25 (95% CI, 0.86–1.80) compared with never night shift workers; a similar risk was observed for night shift workers who had last worked night shift 3–19 years ago (OR, 1.23; 95% CI; 0.95–1.60). At 20 years since last exposure, there was no increased risk (OR, 1.02; 95% CI, 0.8–1.3). The *P* value for trend by time since last night shift was 0.08. Relative risk ratios (RRRs) (D'Amico classification) were higher for high-risk tumours (RRR, 1.40; 95% CI, 1.05–1.86), particularly among participants with a longer duration of exposure (RRR for exposure of ≥ 28 years, 1.63; 95% CI, 1.08–2.45; *P* for trend, 0.027) (Papantoniou et al., 2015). Overall risk was higher among participants with an evening chronotype, but also increased in morning chronotypes after long-term night work. [The Working Group noted the low response rate among controls.]

Wendeu-Foyet et al. (2018) reported results on cancer of the prostate from the Epidemiological Study of Prostate Cancer (EPICAP) in France. This population-based case–control study included 818 incident cases of cancer of the prostate and 875 frequency-matched controls. Eligible cases were men younger than 75 years, newly diagnosed with histologically confirmed cancer of the prostate in 2012–2013, who were residing in the Hérault region at the time of diagnosis. Controls were randomly selected from the general population residing in the same region, frequency matched to the cases by 5-year age groups, who had no history of prostate cancer. Participants were interviewed face-to-face on several potential risk factors, including lifetime occupational history. Response rates were 75% for cases and 79% for controls. Detailed information on work schedules for each job (permanent or rotating night work, duration, total number of nights, length of the shift, number of consecutive nights), as well as sleep duration and chronotype, was recorded. The aggressiveness of the cancer was assessed by the Gleason score. Overall, 36% of the cases and controls had ever worked at night (OR, 0.97; 95% CI, 0.79–1.19), with 28% on permanent night work (OR, 1.04; 95% CI, 0.82–1.32) and 15% on rotating night work (OR, 0.81; 95% CI, 0.59–1.16). There was no overall association with aggressiveness of cancer of the prostate. A shift length longer than 10 hours was associated with an elevated risk of

prostate cancer (OR, 1.57; 95% CI; 1.01–2.44), especially among permanent night workers (OR, 1.88; 95% CI, 1.08–3.26). Other exposure parameters, including type of night shift (early morning, late evening, or overnight shift), total duration of night work, total frequency of night work, and number of consecutive nights, either on permanent or rotating night work, were not found to be associated with cancer of the prostate. A duration of 20 years or more of permanent night work was associated with aggressive cancer of the prostate (OR, 1.76; 95% CI, 1.13–2.75). Stratified analyses by chronotype showed an elevated risk of cancer of the prostate among ever night workers with an evening chronotype (OR, 1.83; 95% CI, 1.05–3.19).

A population-based case–control study conducted during 2005–2012 in Montreal, Canada enrolled 1904 cases of cancer of the prostate (432 high-grade cancers) and 1965 population controls (Barul et al., 2019). Detailed work schedules for each job held for at least 2 years (n = 15 724) by each case and control were elicited in face-to-face interviews. Night shift work was defined as having ever worked for 3 hours or more between midnight and 05:00 for 1 year or more, for 3 nights or more per month. Odds ratios and 95% confidence intervals for the association between night shift work and cancer of the prostate were adjusted for age (dichotomous), ancestry, and education. The odds ratios for ever compared with never having worked night shift was 1.07 (95% CI, 0.92–1.26). There was no clear pattern of risk with any of the exposure metrics evaluated, including duration, intensity, cumulative exposure, rotating shifts, and early morning shifts. The highest risks were observed in men on rapid shift rotation (OR, 1.70; 95% CI, 0.81–3.57) for daily or 2–3–4 days per week shift rotation, and for men having only worked on night shift schedules involving forward rotation (OR, 1.23; 95% CI, 0.96–1.58). There was no evidence of heterogeneity in odds ratios between low- and high-grade cancers. Sensitivity analyses considering screening history yielded similar results. [The Working Group noted that the age adjustment was crude (dichotomous), although it was not clear whether this would have affected odds ratios and, if so, in which direction.]

A hospital-based case–control study in Hong Kong Special Administrative Region, China, enrolled 431 newly diagnosed cases of cancer of the prostate and 402 controls randomly selected from various departments of the same hospital, frequency matched by age (Tse et al., 2017). Night shift work was defined as ever worked night shift any hour between midnight and 05:00 more than once a month for more than 1 year. An odds ratio of 1.76 (95% CI, 1.07–2.89) was observed for ever having worked night shift (fully adjusted model). [The Working Group noted that information on exposure was limited.]

2.1.3 Cancer of the colon and rectum

Cohort studies of the incidence of or mortality from cancer of the colon and rectum with individual-level (self-reported or record-based) assessment of shift work exposure include cancer incidence studies in two cohorts of female nurses in the USA (Schernhammer et al., 2003; Papantoniou et al., 2018), mortality studies in female nurses in the USA (Gu et al., 2015) and Denmark (Jørgensen et al., 2017), and incidence and mortality studies in a cohort of male chemical workers in Germany (Yong et al., 2014a, b). A study of the incidence of colorectal adenoma in a cohort of female nurses in the USA is included because adenomas of the colon and rectum are a precursor of cancer of the colon and rectum (Devore et al., 2017). Population-based case–control studies with individual (self-reported) assessment of shift work exposure were conducted among men in Montreal, Canada (Parent et al., 2012), and among men and women in Spain (Papantoniou et al., 2017). Population-based studies in Sweden (Schwartzbaum et al., 2007) and Australia (Walasa et al., 2018) that

used JEMs to classify probability of exposure were considered uninformative because of the high potential for misclassification, and two other studies were considered uninformative because no analyses of the risk of cancer of the colon and rectum by shift work exposure were presented (Tynes et al., 1996; Wickremaratne et al., 2017). Among the more informative studies that have information on duration of shift work exposure, NHS-I and NHS-II considered rotating shift work only (Schernhammer et al., 2003; Gu et al., 2015; Papantoniou et al., 2018), one case–control study examined risks associated with rotating shift work and permanent night work (Papantoniou et al., 2017), and one case–control study examined night work only (Parent et al., 2012).

(a) Prospective cohort studies

See Table 2.4.

Studies of the incidence of cancer of the colon and rectum were included in the NHS-I and NHS-II cohorts; these cohorts and study methodologies are described in Section 2.1.1(a)(xii). In brief, self-reported diagnoses of cancer of the colon and rectum were obtained on biennial questionnaires and confirmed through medical records. In 1988, NHS-I participants were asked how many years in total they had worked rotating shifts, defined as working "at least 3 nights per month in addition to days or evenings in that month", using eight pre-specified categories. The first report of incidence of cancer of the colon and rectum from the NHS-I cohort (Schernhammer et al., 2003) included 78 586 women who were followed up from 1988 through 1998, and documented 602 incident cases of cancer of the colon and rectum. The study found an excess risk of colorectal cancer among women who reported working 15 years or more of rotating shifts at baseline (RR, 1.35; 95% CI, 1.03–1.77), with no excess among women who worked rotating shifts for 1–14 years, compared with those who never worked rotating shifts. In subsite analyses, the highest risk was observed for cancer of the rectum (RR, 1.51; 95% CI, 0.82–2.81). Mortality from cancer of the colon and rectum was also studied in the NHS-I cohort (Gu et al., 2015), with mortality follow-up through 2010. Among the 74 862 women included in the mortality study, 464 deaths from cancer of the colon and rectum were identified. An increased risk of colorectal cancer mortality (HR, 1.33; 95% CI, 0.97–1.83) was observed among women with 15 years or more of night shift work in multivariate adjusted models.

A subsequent report (Papantoniou et al., 2018) analysed the incidence of cancer of the colon and rectum among 77 439 women in the NHS-I cohort and 113 371 in the NHS-II cohort, with cases of cancer of the colon and rectum identified from 1 June 1988 to 31 May 2012 in NHS-I and from 1 June 1989 to 31 May 2013 in NHS-II. In addition to the baseline assessment, shift work information was updated periodically in the NHS-II cohort and used to derive an estimate of the total duration of shift work. A total of 59% of women in NHS-I and 62% of women in NHS-II reported a history of rotating shift work. Because assessments of exposure to shift work differed by cohort (i.e. not updated in NHS-I; updated in NHS-II), models were presented separately. In the NHS-I cohort, secondary analyses were performed by anatomical subsite of cancer of the colon and rectum. A total of 1965 cases of cancer of the colon and rectum (1527 in NHS-I and 438 in NHS-II) were included in analyses.

In the NHS-I cohort, based on fully adjusted models, no increase in the incidence of cancer of the colon and rectum with increasing years of rotating night shift was observed (*P* for trend, 0.14). Compared with women who had never worked rotating night shifts, the hazard ratio for risk of cancer of the colon and rectum after exposure for 15 years or more was 1.15 (95% CI, 0.95–1.39). In subsite analyses, risks associated with long-term night shift work (≥ 15 years) tended to increase towards the distal parts of the colorectal tract (HR for proximal colon, 1.00;

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schernhammer et al. (2003) USA 1988; 1988–1998 Cohort	78 586; prospective cancer incidence study of female registered nurses aged 30–55 yr from 11 large states Exposure assessment method: subjective assessment; night shift undefined	Colon and rectum combined	Years of rotating night shift work at baseline (RR):			Age; pack-years of smoking before age 30 yr; BMI; physical activity; regular aspirin use; colorectal cancer in parent or sibling; screening endoscopy during the study period; consumption of beef, pork, or lamb; total caloric intake; use of postmenopausal hormones; menopausal status; height	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. Strengths: large prospective cohort study; confirmation of diagnosis through medical records; large number of colorectal cancer cases allowing separate analyses for colon and rectum; very complete information on covariates Limitations: no information on rotating shift exposure after baseline
			Never	229	1		
			1–14 yr	303	1.00 (0.84–1.19)		
			≥ 15 yr	70	1.35 (1.03–1.77)		
			Trend test *P* value, 0.04				
		Colon, right	Years of rotating night shift work at baseline (RR):				
			Never	73	1		
			1–14 yr	93	0.97 (0.71–1.32)		
			≥ 15 yr	23	1.41 (0.88–2.27)		
			Trend test *P* value, 0.31				
		Colon, left	Years of rotating night shift work at baseline (RR):				
			Never	64	1		
			1–14 yr	76	0.89 (0.63–1.24)		
			≥ 15 yr	18	1.22 (0.72–2.09)		
			Trend test *P* value, 0.44				
		Colon, combined	Years of rotating night shift work at baseline (RR)				
			Never	137	1		
			1–14 yr	169	0.93 (0.74–1.17)		
			≥ 15 yr	41	1.32 (0.93–1.87)		
			Trend test *P* value, 0.20				
		Rectum	Years of rotating night shift work at baseline (RR):				
			Never	41	1		
			1–14 yr	48	0.86 (0.56–1.3)		
			≥ 15 yr	14	1.51 (0.82–2.81)		
			Trend test *P* value, 0.15				

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Gu et al. (2015) USA 1988–2010 Cohort	74 862; prospective cohort mortality study of female registered nurses (NHS-I) aged 30–55 yr from 11 large states, established in 1976 Exposure assessment method: questionnaire; subjective assessment; night shift undefined	Colon and rectum	Baseline year of rotating night shift work (HR): Never rotating night shift 1–5 yr 6–14 yr ≥ 15 yr Trend test *P* value, 0.07	 180 176 56 52	 1 0.98 (0.79–1.21) 1.05 (0.77–1.42) 1.33 (0.97–1.83)	Age, alcohol consumption, physical exercise, multivitamin use, menopausal status, postmenopausal hormone use, physical examination in the past 2 yr, healthy eating score, smoking status, pack-years, husband's education, BMI	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (limited period). No other information available. Strengths: large prospective cohort study; very complete information on covariates Limitations: exposure assessment limited to years of rotating shift work at baseline
Papantoniou et al. (2018) USA 1988–2012 Cohort	121 701 at enrolment; 77 439 meeting inclusion criteria for colorectal study; prospective cancer incidence study of female registered nurses (NHS-I) aged 30–55 yr from 11 large states, established in 1976 Exposure assessment method: subjective assessment; night shift undefined	Colon and rectum	Baseline rotating night shift work history in years (HR): Never worked rotating shifts 1–2 yr 3–4 yr 5–9 yr 10–14 yr 15–19 yr 20–29 yr ≥ 30 yr Trend test *P* value, 0.14	 584 346 269 112 73 45 59 39	 1 1.04 (0.91–1.19) 1.05 (0.91–1.22) 1.06 (0.87–1.3) 1.01 (0.79–1.29) 1.02 (0.75–1.39) 1.26 (0.96–1.65) 1.17 (0.84–1.63)	Age, BMI, physical activity, alcohol intake, menopausal status, menopausal hormone use, height, education level, first-degree family history of colorectal cancer, smoking status, colonoscopy and/or sigmoidoscopy in the past 2 yr, current regular aspirin or NSAIDs use, folate consumption, daily calorie intake, red or processed meat servings per day	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments*: analysis of years of employment with night work Strengths: large prospective cohort study; confirmation of diagnosis through medical records; large number of colorectal cancer cases, allowing separate analyses for colon and rectum; very complete information on covariates Limitations: no information on rotating shift exposure after baseline
		Colon and rectum	Baseline rotating night shift work history in years (HR): Never worked rotating shifts 1–14 yr ≥ 15 yr	 584 800 143	 1 1.04 (0.94–1.16) 1.15 (0.95–1.39)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2018) (cont.)		Colon	Baseline rotating night shift work history in years (HR):				
			Never worked rotating shifts	403	1		
			1–14 yr	542	1.02 (0.90–1.16)		
			≥ 15 yr	93	1.09 (0.87–1.37)		
			Trend test *P* value, 0.62				
		Colon, proximal	Baseline rotating night shift work history in years (HR):				
			Never worked rotating shifts	271	1		
			1–14 yr	347	0.98 (0.83–1.14)		
			≥ 15 yr	57	1.00 (0.75–1.34)		
			Trend test *P* value, 0.90				
		Colon, distal	Baseline rotating night shift work history in years (HR)				
			Never worked rotating shifts	132	1		
			1–14 yr	195	1.12 (0.90–1.4)		
			≥ 15 yr	36	1.27 (0.87–1.85)		
			Trend test *P* value, 0.32				
		Rectum	Baseline rotating night shift work history in years (HR):				
			Never worked rotating shifts	111	1		
			1–14 yr	156	1.05 (0.82–1.34)		
			≥ 15 yr	36	1.60 (1.09–2.34)		
			Trend test *P* value, 0.02				

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2018) USA 1989–2013 Cohort	116 430 at recruitment; 113 371 meeting inclusion criteria for colorectal study; prospective cancer incidence study of female registered nurses (NHS-II) aged 25–42 yr Exposure assessment method: subjective assessment; night shift undefined	Colon and rectum	NHS-II baseline rotating night shift work history in years (HR):			Age, BMI, physical activity, alcohol intake, menopausal status, menopausal hormone use, height, education level, first-degree family history of colorectal cancer, smoking status, colonoscopy and/ or sigmoidoscopy in the past 2 yr, current regular aspirin or NSAIDS use, folate consumption, daily calorie intake, red or processed meat servings per day	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments*: analysis of years of employment with night work Strengths: very large prospective study; colorectal cancers confirmed by medical records; exposure assessment at baseline and in follow-up questionnaires includes duration of working rotating shifts; very complete information on covariates Limitations: some of the updated exposure information was obtained retrospectively
			Never worked rotating shifts	183	1		
			1–2 yr	102	0.75 (0.59–0.95)		
			3–4 yr	83	0.90 (0.70–1.17)		
			5–9 yr	42	1.02 (0.72–1.43)		
			10–14yr	21	1.15 (0.73–1.81)		
			≥ 15 yr	7	0.97 (0.45–2.09)		
			Trend test *P* value, 0.49				
		Colon and rectum	NHS-II baseline rotating night shift work history in years (HR):				
			Never worked rotating shifts	183	1		
			1–14 yr	248	0.86 (0.71–1.04)		
			≥ 15 yr	7	0.97 (0.45–2.09)		
		Colon and rectum	NHS-II updated rotating night shift work history in years (HR):				
			Never worked rotating shifts	149	1		
			1–4 yr	187	0.77 (0.62–0.95)		
			5–9 yr	60	0.90 (0.66–1.21)		
			10–14 yr	27	1.00 (0.66–1.51)		
			≥ 15 yr	15	0.96 (0.56–1.64)		
			Trend test *P* value, 0.88				
		Colon and rectum	NHS-II updated rotating night shift work history in years (HR):				
			Never worked rotating shifts	149	1		
			1–14 yr	274	0.81 (0.66–0.99)		
			≥ 15 yr	15	0.96 (0.56–1.64)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Devore et al. (2017) USA 1989; 1999–2011 Cohort	116 430 at recruitment; 56 275 meeting inclusion criteria for colorectal adenoma study; prospective study of female registered nurses aged 25–42 yr; cancer-free participants of the NHS-II who had their first colonoscopy or sigmoidoscopy between 1991 and 2011 Exposure assessment method: questionnaire; subjective assessment; night shift undefined	Colon and rectum (adenoma)	NHS-II updated rotating night shift work history (RR):			Age, time-period of first lower endoscopy, reason for endoscopy, family history of colorectal cancer, height, BMI, physical activity, pack-years of smoking, alcohol intake, menopausal status, menopausal hormone use, OC use, multivitamin use, total calcium intake, supplemental vitaminD intake, red meat intake, aspirin use, NSAID use, predicted vitamin D score	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. Strengths: very large prospective study; colorectal cancers confirmed by medical records; exposure assessment at baseline and in follow-up questionnaires includes duration of working rotating shifts; very complete information on covariates; control for potential confounding factors related to endoscopy Limitations: some of the updated exposure information was obtained retrospectively
			None	936	1		
			1–4 yr	1425	0.93 (0.85–1.01)		
			5–9 yr	409	0.98 (0.87–1.11)		
			≥ 10 yr	244	0.96 (0.83–1.11)		
			Trend test *P* value, 0.5				
		Colon, proximal (adenoma)	NHS-II updated rotating night shift work history (RR):				
			None	427	1		
			1–4 yr	653	0.93 (0.82–1.05)		
			5–9 yr	210	1.08 (0.91–1.28)		
			≥ 10 yr	115	0.95 (0.77–1.18)		
			Trend test *P* value, 0.9				
		Colon, distal (adenoma)	NHS-II updated rotating night shift work history (RR):				
			None	430	1		
			1–4 yr	680	0.96 (0.85–1.08)		
			5–9 yr	196	1.02 (0.86–1.21)		
			≥ 10 yr	122	1.04 (0.85–1.28)		
			Trend test *P* value, 0.7				
		Rectum (adenoma)	NHS-II updated rotating night shift work history (yr) (RR): rectum				
			None	177	1		
			1–4 yr	241	0.83 (0.69–1.01)		
			5–9 yr	65	0.85 (0.64–1.13)		
			≥ 10 yr	43	0.93 (0.66–1.3)		
			Trend test *P* value, 0.3				

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014a) Germany Enrolment, 1995–2005; follow-up 2000–2009 Cohort	27 828 (12 609 shift workers (≥ 1 yr of rotating shift work); 15 219 day workers (excluding office workers); retrospective incidence study of male production workers employed for ≥ 1 yr in a chemical company and residents of Rhineland-Palatinate Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Colon and rectum	Shift work status (1995–2005), incidence (HR):			Age at entry, job level, cigarette smoking, employment duration	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Temporality: Complete. Schedule type: Rotating. No other information available. Strengths: large industrial cohort; exposure assessment from records; incident cases identified through regional cancer registry Limitations: exposure classification was dichotomous (≥ 1 yr of shift work vs never shift work) at the time of study entry
			Day work only	NR	1		
			Shift work (≥ 1 yr)	NR	1.33 (0.86–2.06)		
		Colon and rectum	Shift work status (1995–2005), incidence (SIR):			Age, calendar year	
			Day work only	68	0.87 (0.67–1.1)		
			Shift work (≥ 1 yr)	69	1.08 (0.84–1.36)		
			SIR ratio (shift vs day)	NR	1.24 (0.88–1.77)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014b) Germany 1995–2005; follow-up, 2000–2009 Cohort	31 143 (14 038 rotating shift workers and 17 105 day workers); retrospective mortality study of male production workers employed for ≥ 1 yr in a chemical company Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Colon and rectum	Shift work status (1995–2005), mortality (HR): Day work only Shift work (≥ 1 yr)	 NR NR	 1 1.04 (0.50–2.14)	Age at entry, cigarette smoking	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Temporality: Complete. Schedule type: Rotating. No other information available. Strengths: large industrial cohort; exposure based on records Limitations: exposure classification was dichotomous (≥ 1 yr of shift work vs never shift work) at the time of study entry
Jørgensen et al. (2017) Denmark 1993 or 1999 to 2013 Cohort	18 015; prospective cohort mortality study of female members of the Danish Nurses Organization aged > 44 yr and in the workforce at recruitment Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Colon and rectum	Shift type at recruitment (HR): Day shifts Evening shifts Night shifts Rotating shifts	 76 12 9 20	 1 0.85 (0.46–1.59) 1.02 (0.5–2.11) 0.83 (0.5–1.36)	Age, smoking, pack-years, physical activity, BMI, alcohol consumption, diet (vegetables and fruit, fatty meat consumption), pre-existing diseases (hypertension, diabetes, myocardial infarction), self-reported health, stressful work environment, marital status, female reproductive factors (birth, use of hormone therapy, OCs)	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (one time-point). No other information available. Strengths: large study size Limitations: exposure assessment based on usual work with no estimate of intensity or duration

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Parent et al. (2012) Montreal, Quebec, Canada 1979–1985 Case–control	Cases: 439 colon and 236 rectum; male patients aged 35–70 yr residing in the greater Montreal area who had been diagnosed at any of the 18 major Montreal hospitals with incident, pathologically confirmed cancer 512 controls: recruited from the general population using electoral lists, randomly selected from the same age groups (± 5 yr) and residential areas (districts of about 40 000 electors) Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Colon	Night work exposure (OR):			Age (years continuous), ancestry, educational level, family income, respondent status, ever smoking, number of cigarette-years, number of years since quitting, BMI, beta-carotene index, occupational physical activity, alcohol consumption	*Exposure assessment critique*: NSW in ref. group: No. Duration: Complete. Temporality: Complete. Schedule type: Imprecise. No other information available. *Other comments*: analysis of: ever/never night work; cumulative duration of employment with night work; timing of night work (cut-off, 20 yr) Strengths: large population-based case–control study; information on cumulative duration and timing of night work; histological confirmation of cancers; detailed lifetime work histories; good information on potential covariates Limitations: no information on rotating shift work; a higher proportion of cases (16%) than controls (4%) were excluded because of a lack of information about shift work
			Never	329	1		
			Ever	110	2.03 (1.43–2.89)		
			Duration < 5 yr	61	2.32 (1.47–3.68)		
			Duration 5–10 yr	20	1.43 (0.73–2.8)		
			Duration > 10 yr	29	2.11 (1.13–3.94)		
		Colon	Timing of night work (OR):				
			Never	329	1		
			Recent past (≤ 20 yr)	53	2.5 (1.51–4.14)		
			Distant past (> 20 yr)	45	2.08 (1.24–3.47)		
		Rectum	Night work exposure (OR):			Age (years continuous), ancestry, educational level, family income, respondent status, ever smoking, number of cigarette-years, number of years since quitting, BMI, beer consumption	
			Never	178	1		
			Ever	58	2.09 (1.40–3.14)		
			Duration < 5 yr	35	2.58 (1.53–4.33)		
			Duration 5–10 yr	10	1.42 (0.64–3.18)		
			Duration > 10 yr	12	1.67 (0.77–3.61)		
		Rectum	Timing of night work (OR):				
			Never	178	1		
			Recent past (≤ 20 yr)	25	2.27 (1.27–4.05)		
			Distant past (> 20 yr)	26	2.35 (1.32–4.2)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2017) Spain (12 regions) 2008–2013 Case–control	1626 cases: incident colorectal cancer cases from 23 hospitals and primary care centres in 12 provinces of Spain 3378 controls: population-based controls frequency-matched to cases by age, sex, and region of residence Exposure assessment method: questionnaire; subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Colon and rectum	Shift work type (OR):			Age (continuous), centre, educational level, sex, history of colorectal cancer in first-degree relatives, BMI, smoking status, leisure time activity, past alcohol consumption, total energy intake, all red meat consumption, sleep duration, aspirin/NSAID use	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Partial. Schedule type: Permanent night, Imprecise. No other information available. *Other comments*: analysis of: ever/never night work; permanent versus rotating; cumulative duration of employment (yr) and cumulative number of night shifts; rotating shift work undefined, but involved on average 10 nights/mo; lifetime cumulative duration (yr); age at first shift work; years since last shift work considered Strengths: large population-based study; information on both rotating and permanent night shift work; exposure metrics include cumulative years, age at starting, and years since last worked; very complete information on covariates; able to analyse colon and rectum separately; histological confirmation of tumours
			Never shift work	1071	1		
			Rotating shift work	426	1.22 (1.04–1.43)		
			Permanent night shift work	129	0.79 (0.62–1.00)		
		Colon and rectum	Rotating shift work and nights per month (OR):				
			Never shift work	1071	1		
			Rotating shift work for ≥ 3 nights/mo	242	1.10 (0.91–1.32)		
			Rotating shift work for < 3 nights/mo	148	1.50 (1.18–1.92)		
		Colon	Shift work type (OR):				
			Never shift work	721	1		
			Rotating shift work	282	1.22 (1.02–1.46)		
			Permanent night shift work	83	0.79 (0.60–1.11)		
		Rectum	Shift work type (OR):				
			Never shift work	339	1		
			Rotating shift work	143	1.26 (0.99–1.58)		
			Permanent night shift work	42	0.76 (0.53–1.11)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2017) (cont.)		Colon and rectum	Years of rotating shift work (OR):				Limitations: lack of detail on rotating shift schedules; lower response rate for controls than for cases; potential for differential selection bias
			Never shift work	1071	1		
			< 8 yr	89	1.14 (0.85–1.51)		
			8–19 yr	87	1.12 (0.84–1.49)		
			20–34 yr	119	1.38 (1.06–1.81)		
			≥ 35 yr	127	1.36 (1.02–1.79)		
			Trend test *P* value, 0.005				
		Colon and rectum	Fixed categories of years of rotating shift work (OR):				
			Never shift work	1071	1		
			< 15 yr	147	1.19 (0.95–1.49)		
			≥ 15 yr	274	1.28 (1.06–1.56)		
		Colon and rectum	Years of permanent night shift work (OR):				
			Never shift work	1071	1		
			< 4 yr	22	0.64 (0.38–1.08)		
			4–9 yr	33	0.71 (0.45–1.11)		
			10–19 yr	33	0.76 (0.49–1.18)		
			≥ 20 yr	40	1.01 (0.65–1.55)		
			Trend test *P* value, 0.599				
		Colon and rectum	Fixed categories of years of permanent night shift work (OR):				
			Never shift work	1071	1		
			< 15 yr	75	0.7 (0.52–0.96)		
			≥ 15 yr	53	0.91 (0.64–1.3)		
		Colon and rectum	Age (yr) at first rotating shift work (OR):				
			Never shift work	1071	1		
			< 25 yr	166	1.24 (0.99–1.56)		
			≥ 25 yr	99	0.95 (0.72–1.25)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2017) (cont.)		Colon and rectum	Age (yr) at first permanent night shift work (OR):				
			Never shift work	1071	1		
			< 25 yr	75	0.80 (0.58–1.08)		
			≥ 25 yr	53	0.76 (0.53–1.09)		
		Colon and rectum	Years since last rotating night shift work (OR):				
			Never shift work	1071	1		
			< 15 yr	89	1.12 (0.83–1.52)		
			≥ 15 yr	136	0.97 (0.76–1.24)		
		Colon and rectum	Years since last permanent night shift work (OR):				
			Never shift work	1071	1		
			< 15 yr	44	0.91 (0.61–1.34)		
			≥ 15 yr	72	0.74 (0.54–1.01)		
		Colon and rectum	Ever rotating shift work, men (OR):				
			Never shift work	NR	1		
			Ever rotating shift work	NR	1.32 (1.10–1.59)		
		Colon and rectum	Ever rotating shift work, women (OR):				
			Never shift work	NR	1		
			Ever rotating shift work	NR	0.93 (0.57–1.50)		

Table 2.4 Studies of cancers and adenomas of the colon and rectum among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Papantoniou et al. (2017) (cont.)		Colon and rectum	Ever rotating shift work by age group (OR):				
			Never shift work, < 50 yr	NR	1		
			Ever rotating shift work, < 50 yr	NR	0.93 (0.51–1.69)		
			Never rotating shift work, 50–70 yr	NR	1		
			Ever rotating shift work, 50–70 yr	NR	1.43 (1.15–1.78)		
			Never shift work, > 70 yr	NR	1		
			Ever rotating shift work, > 70 yr	NR	1.02 (0.79–1.32)		

BMI, body mass index; CI, confidence interval; h, hour; HR, hazard ratio; mo, month; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; OC, oral contraceptive; OR, odds ratio; RR, relative risk or rate ratio; SIR, standardized incidence ratio; vs, versus; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

95% CI, 0.75–1.34; *P* for trend, 0.90; HR for distal colon, 1.27; 95% CI, 0.87–1.85; *P* for trend, 0.32; HR for rectum, 1.60; 95% CI, 1.09–2.34; *P* for trend, 0.02).

In the NHS-II cohort, no association was observed between rotating night shift work and risk of cancer of the colon and rectum. In analyses using only shift work history at baseline or using shift work information updated through follow-up, hazard ratios very close to 1.00 were observed for women working rotating shifts for 15 years or more compared with those never working rotating shifts. Devore et al. (2017) investigated the associations between rotating night shift work history and risk of adenoma of the colon and rectum among 56 275 cancer-free participants of the NHS-II cohort who had their first colonoscopy or sigmoidoscopy between 1991 and 2011. No association was found between duration (none, 1–4, 5–9, and ≥ 10 years) of rotating night shift work and occurrence of adenoma of the colon and rectum (*P* for trend across shift work categories, 0.5). [The Working Group noted that a limitation of the NHS-I cohort was that night shift work information was not updated after 1988. However, much of the follow-up was accrued at midlife or around retirement, so it is likely that cumulative rotating shift exposure was complete for most participants. Other limitations applying to both the NHS-I and the NHS-II cohorts are that some nurses working permanent night shifts may have been included in the control group, potentially biasing findings towards the null, and there is no information on number of nights worked per month. The conclusions of the NHS-II cohort study were limited by the relatively small number of cases of cancer of the colon and rectum in the exposure category of 15 years or more, and the related inability to examine risks by subsite. Lack of information on intensity of exposure was a limitation in both studies. However, exposure assessment was more complete than for the NHS-I cohort as a result of periodic updates.]

Yong et al. (2014a) studied the incidence of cancer in a cohort of male production workers (12 609 shift and 15 219 day workers) employed at a chemicals factory in Germany for at least 1 year between 1995 and 2005; a description of this study and its methods is provided in Section 2.1.2(a). Exposure classification was based on review of personnel records, with shift workers defined as having completed at least 1 year of rotating shift work between 1995 and 2005, and a referent population who never performed shift work (excluding office workers) was identified. A total of 69 colorectal cancers were observed in shift workers and 68 in day workers, yielding a hazard ratio of 1.33 (95% CI, 0.86–2.06). Yong et al. (2014b) studied cancer mortality in a similarly defined male cohort of shift and day workers at the same facility. Mortality from cancer of the colon and rectum was not elevated in rotating shift workers compared with day workers (HR, 1.04; 95% CI, 0.50–2.14). [The Working Group noted that in both studies the definition of shift work was dichotomous with no information on duration of shift work, and there was only a short (5–15 years) follow-up interval. In the mortality study, the number of deaths from cancer of the colon and rectum among shift and day workers was not given, the number of total deaths from cancer of the colon and rectum was small, and the shift work group had an unexplained lower mortality from all causes and cancer compared with day workers.]

Jørgensen et al. (2017) studied overall and cause-specific mortality in a cohort of female Danish nurses. Shift work data were self-reported by nurses who were in the workforce at the time of recruitment, and who were asked whether they normally worked day, evening, night, or rotating shifts. No association was found between working evening, night, or rotating shifts and mortality from cancer of the colon and rectum. [The Working Group noted that the exposure assessment was based on usual work, with no information on duration or intensity.]

(b) Case–control studies

Parent et al. (2012) studied the association between night work and risk of cancer among men in a multisite population-based case–control study conducted in Montreal, Quebec, Canada, between 1979 and 1985. The response rate was 82% among cases and 72% among controls. Analyses included 439 men with cancer of the colon and 236 men with cancer of the rectum, and 512 controls who provided information about shift work (84% of all cases and 96% of controls). For each job held, the participant was asked whether the job entailed shift work and, if so, the start and finish times of the work shift. A job entailing night work was defined as one that included working between 01:00 and 02:00 for at least 6 months. Analyses were also conducted according to the cumulative duration (< 5, 5–10, or > 10 years) and timing (recent, distant) of night work over the participant's lifetime. Separate regression models were fitted for cancer of the colon and rectum; each included a set of known or potential non-occupational and occupational confounding factors specific to each cancer type. In analyses for cancer of the colon, ever performing night work was associated with an increased risk (OR, 2.03; 95% CI, 1.43–2.89); however, risk did not increase with increasing cumulative duration of night work. Odds ratios were similar for those with recent and distant night work. In analyses for cancer of the rectum, ever performing night work was associated with an increased risk (OR, 2.09; 95% CI, 1.40–3.14); however, risk did not increase with increasing cumulative duration of night work. Odds ratios were similar for those with recent and distant night work. [The Working Group noted that proxy information was collected from a higher proportion of cases (17.6%) than controls (12.9%), and a higher proportion of cases (16%) than controls (4%) were excluded because of a lack of information about shift work.]

Papantoniou et al. (2017) evaluated the risk of cancer of the colon and rectum in relation to shift work history in the population-based MCC-Spain study, the methods of which are described in Section 2.1.2(b). For the colorectal cancer analysis, response rates were 68% among cases and 54% among controls. Shift work was assessed through lifetime occupational history, and participants self-classified each job as day, night, or rotating. Permanent night shift work was defined as a fixed schedule that involved working partly or entirely (≥ 1 hour) between midnight and 06:00 at least 3 times per month, and rotating shift work was defined as any rotation between morning, evening, and/or night shifts. The study included 1626 cases of cancer of the colon and rectum (1136 men and 490 women) and 3378 randomly selected population controls (1833 men and 1545 women) with complete shift work data (information on shift work was missing or incomplete for 18% of cases and 12% of controls). Participants who had ever worked in rotating work had an increased risk of cancer of the colon and rectum (adjusted OR, 1.22; 95% CI, 1.04–1.43) compared with day workers, and participants having ever worked in permanent night work had a lower risk of cancer of the colon and rectum (OR, 0.79; 95% CI, 0.62–1.00). In subsite analyses for rotating shift work, the adjusted odds ratio was 1.22 (95% CI, 1.02–1.46) for cancer of the colon and 1.26 (95% CI, 0.99–1.58) for cancer of the rectum. Additional analyses, conducted only for cancer of the colon and rectum combined, did not find an increase in risk associated with a higher frequency of rotating shift work (greater versus less than 3 nights per month). However, risk of cancer of the colon and rectum increased with increasing lifetime cumulative duration of rotating shift work (*P* for trend, 0.005), with increases in the top quartiles of exposure (OR for 3rd quartile, 20–34 years, 1.38; 95% CI, 1.06–1.81; OR for 4th quartile, ≥ 35 years, 1.36; 95% CI, 1.02–1.79). The odds ratio for cumulative duration of permanent night shift work,

age at first exposure, and years since last exposure were mostly negative or null. In a stratified analysis by sex, the odds ratio for rotating shift work was increased among men (OR, 1.32; 95% CI, 1.10–1.59) but not among women (OR, 0.93; 95% CI, 0.57–1.50) with a *P* value for interaction of 0.065. [The Working Group noted that response rates were lower among controls than among cases, and information on shift work was missing from a higher percentage of cases than controls. However, results were similar when analyses were restricted to study centres with high response rates among controls, and basic sociodemographic characteristics were similar among respondents and non-respondents to shift work questions.]

2.1.4 Other cancers

The most informative studies were case–control and cohort studies that had shift or night work exposure information at the individual level for a large proportion of the working life of the study participants, clarity that exposure occurred before cancer outcome, and control for relevant confounders. These studies are from Canada (Parent et al., 2012; Leung et al., 2019), China (Kwon et al., 2015), Spain (Costas et al., 2016; Gyarmati et al., 2016), and the USA (NHS-I and NHS-II cohorts: Viswanathan et al., 2007; Poole et al., 2011; Bhatti et al., 2013; Schernhammer et al., 2013; Gu et al., 2015; Heckman et al., 2017). Studies of cancer of the lung and of cancer of the ovary had high-quality evidence that merited more consideration than studies of other cancer sites; these cancers are therefore presented first in this section, with other sites following in order according to the 10th International Classification of Diseases (WHO, 2004).

The following studies were considered to be uninformative because shift and/or night work was not specifically assessed: Alguacil et al. (2003), Perez-Gomez et al. (2004), Pukkala et al. (2014), Rana et al. (2014a, b), and Lee et al. (2016). Three additional studies were not considered because of their poor-quality assessment of exposure to shift and/or night work that was not at the level of individual study participants, likely leading to a large magnitude of exposure misclassification (Schwartzbaum et al., 2007; Lahti et al., 2008; Talibov et al., 2018).

See Table 2.5.

(a) Cancer of the lung

In the Montreal multisite case–control study of men described in detail in Sections 2.1.2(b) and 2.1.3(b), ever performing night work was associated with an increased risk of incidence of cancer of the lung (761 cases); however, risk did not increase with increasing cumulative duration of night work, and odds ratios were similar for those with recent and distant night work (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

Incident cancer of the lung among 78 612 female registered nurses in the USA was investigated in the NHS-I cohort (Schernhammer et al., 2013). Increased risk was apparent for 15 years or more of rotating night shift work compared with women who never worked night shifts (HR, 1.28; 95% CI, 1.07–1.53; 164 exposed cases). When the analysis was stratified by smoking status (never, former, current), the elevated risk only remained for the subgroup of current smokers who had 15 years or more of rotating night shift work (80 cases; *P* for trend, 0.0006; *P* for interaction between shift work and smoking, 0.03). According to histological type, suggestive increased risks of 1.5-fold were seen for the duration category of 15 years or more among those with small cell and squamous cell types, but not for adenocarcinomas. A mortality study of 74 862 women in the NHS-I cohort observed 5413 cancer deaths among 14 181 deaths, and an increased risk of

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Parent et al. (2012) Montreal 1979–1985 Case–control	3137 cases: over 11 cancer sites among men aged 35–70 yr residing in Montreal and diagnosed with incident, pathologically confirmed cancer in 18 major hospitals 512 population controls: randomly selected from electoral lists, matched on age (± 5 yr) and residential area Exposure assessment method: subjective assessment; night shift defined (other)	Lung	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, smoking, beta-carotene, occupational exposure to asbestos and/or silica	*Exposure assessment critique*: NSW in ref. group: No. Duration: Complete. Temporality: Complete. No other information available. *Other comments*: analysis of: ever/never night work; cumulative duration of employment with night work; timing of night work (cut-off, 20 yr) Strengths: lifetime job history, wide range of jobs Limitations: 18% cases and 13% controls not interviewed (proxies used instead); multiple comparisons
			Never	545	1		
			Ever	216	1.76 (1.25–2.47)		
			Duration < 5 yr	110	1.93 (1.22–3.03)		
			Duration 5–10 yr	52	1.51 (0.80–2.85)		
			Duration > 10 yr	54	1.67 (0.90–3.09)		
			In recent past (≤ 20 yr) only	91	1.76 (1.07–2.89)		
			In distant past (> 20 yr) only	79	1.88 (1.13–3.14)		
		Urinary bladder	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, smoking, coffee, beta-carotene, occupational exposure to aromatic amines	
			Never	333	1		
			Ever	106	1.74 (1.22–2.49)		
			Duration < 5 yr	62	1.98 (1.24–3.16)		
			Duration 5–10 yr	15	1.06 (0.51–2.2)		
			Duration > 10 yr	29	1.98 (1.05–3.76)		
			In recent past (≤ 20 yr) only	54	2.19 (1.3–3.66)		
			In distant past (> 20 yr) only	42	1.8 (1.06–3.04)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Parent et al. (2012) (cont.)		Stomach	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, smoking, alcohol, beta-carotene, birthplace	
			Never	185	1		
			Ever	43	1.34 (0.85–2.1)		
			Duration < 5 yr	24	1.5 (0.83–2.7)		
			Duration 5–10 yr	7	0.89 (0.34–2.33)		
			Duration > 10 yr	12	1.45 (0.64–3.26)		
			In recent past (≤ 20 yr) only	14	1.04 (0.51–2.13)		
			In distant past (> 20 yr) only	23	1.93 (1.03–3.58)		
		NHL	Night work exposure (OR):			Age, ancestry, education, family income, respondent status	
			Never	150	1		
			Ever	47	2.31 (1.48–3.61)		
			Duration < 5 yr	21	2.25 (1.23–4.12)		
			Duration 5–10 yr	15	2.41 (1.14–5.1)		
			Duration > 10 yr	11	2.32 (1.03–5.23)		
			In recent past (≤ 20 yr) only	25	2.51 (1.36–4.64)		
			In distant past (> 20 yr) only	13	1.91 (0.94–3.9)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Parent et al. (2012) (cont.)		Kidney	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, smoking, coffee, alcohol, BMI	
			Never	128	1		
			Ever	30	1.42 (0.86–2.35)		
			Duration < 5 yr	15	1.43 (0.73–2.79)		
			Duration 5–10 yr	9	1.81 (0.77–4.29)		
			Duration > 10 yr	6	1.05 (0.39–2.8)		
		Skin (malignant melanoma)	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, beta-carotene, sports and/or outdoor activities	
			Never	82	1		
			Ever	12	1.04 (0.49–2.22)		
			Duration < 5 yr	7	1.16 (0.44–3.11)		
			Duration 5–10 yr	5	2.77 (0.89–8.58)		
			In recent past (≤ 20 yr) only	8	2.24 (0.84–5.95)		
			In distant past (> 20 yr) only	2	0.51 (0.11–2.23)		
		Pancreas	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, smoking, coffee, alcohol, beta-carotene, BMI	
			Never	70	1		
			Ever	24	2.27 (1.24–4.15)		
			Duration < 5 yr	10	1.91 (0.81–4.52)		
			Duration 5–10 yr	6	2.77 (0.97–7.9)		
			Duration > 10 yr	8	2.43 (0.91–6.47)		
			In recent past (≤ 20 yr) only	14	3.81 (1.75–8.28)		
			In distant past (> 20 yr) only	7	1.49 (0.55–4.06)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Parent et al. (2012) (cont.)		Oesophagus	Night work exposure (OR):			Age, ancestry, education, family income, respondent status, smoking, coffee, tea, alcohol, beta-carotene	
			Never	70	1		
			Ever	21	1.51 (0.80–2.84)		
			Duration < 5 yr	10	1.53 (0.64–3.63)		
			Duration 5–10 yr	4	1.27 (0.38–4.28)		
			Duration > 10 yr	7	1.71 (0.59–4.93)		
Schernhammer et al. (2013) USA 1976 onwards; 1988–2008 Cohort	78 612 women in NHS-I aged 30–55 yr (at enrolment in 1976) with exposure to rotating night shift information in 1988, and no prior reports of cancer Exposure assessment method: subjective assessment; night shift undefined	Lung	Years of rotating night shift work (HR):			Age, smoking status, age at smoking initiation, cigarettes smoked per day, time since quitting, fruit intake, vegetable intake, BMI, parent smoked, lived with smoker, workplace exposure to smoking, home exposure to smoking	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (limited period). No other information available. *Other comments*: analysis of years of employment with (rotating) night work Strengths: large cohort, 20-yr follow-up Limitations: no information on permanent nights
			None	542	1		
			1–5 yr	572	1.03 (0.91–1.16)		
			6–14 yr	177	0.96 (0.81–1.14)		
			≥ 15 yr	164	1.28 (1.07–1.53)		
			Trend test *P* value, 0.03				
		Lung	Years of rotating night shift work, never smokers (HR):			Age, fruit intake, vegetable intake, BMI	
			None	52	1		
			1–5 yr	63	1.19 (0.82–1.73)		
			6–14 yr	11	0.75 (0.39–1.45)		
			≥ 15 yr	11	1.00 (0.51–1.94)		
			Trend test *P* value, 0.65				

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schernhammer et al. (2013) (cont.)		Lung	Years of rotating night shift work, current smokers (HR):			Age, fruit intake, vegetable intake, BMI, parent smoked, lived with smoker, workplace exposure to smoking, home exposure to smoking, menopausal status, hormone use, OC use	
			None	191	1		
			1–5 yr	203	1.01 (0.82–1.24)		
			6–14 yr	84	1.16 (0.89–1.52)		
			≥ 15 yr	80	1.61 (1.21–2.13)		
			Trend test *P* value, 0.0006				
		Lung (adeno-carcinoma)	Years of rotating night shift work (HR):			Age, smoking status, age at smoking initiation, cigarettes smoked per day, time since quitting, fruit intake, vegetable intake, BMI, parent smoked, lived with smoker, workplace exposure to smoking, home exposure to smoking, menopausal status, hormone use, OC use	
			None	249	1		
			1–5 yr	263	1.03 (0.87–1.24)		
			6–14 yr	74	0.92 (0.71–1.2)		
			≥ 15 yr	50	0.91 (0.67–1.24)		
			Trend test *P* value, 0.40				
		Lung (squamous cell carcinoma)	Years of rotating night shift work (HR):				
			None	75	1		
			1–5 yr	75	0.96 (0.69–1.33)		
			6–14 yr	25	1.01 (1.01–1.6)		
			≥ 15 yr	26	1.45 (0.92–2.3)		
			Trend test *P* value, 0.13				
		Lung (small cell/oat cell)	Years of rotating night shift work (HR):				
			None	65	1		
			1–5 yr	73	1.11 (0.79–1.57)		
			6–14 yr	34	1.4 (0.91–2.15)		
			≥ 15 yr	29	1.56 (0.99–2.47)		
			Trend test *P* value, 0.03				

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Gu et al. (2015) USA 1976; 1988–2010 Cohort	74 862; NHS-I Exposure assessment method: subjective assessment; night shift undefined	All cancers combined (mortality)	Years of rotating night shift work (HR):			Age, alcohol consumption, physical exercise, multivitamin use, menopausal status, postmenopausal hormone use, physical examination in the past 2 yr, healthy eating score, smoking status, pack-years, BMI, husband's education	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (limited period). No other information available. *Other comments*: analysis of years of employment with (rotating) night work; sleep duration considered; stratification by smoking Strengths: high proportion of rotating NSWs Limitations: not possible to distinguish between rotating and permanent NSWs; night shift work unknown after single assessment in 1988
			None	2087	1		
			1–5 yr	2148	1.03 (0.97–1.09)		
			6–14 yr	672	1.04 (0.95–1.13)		
			≥ 15 yr	506	1.08 (0.98–1.19)		
			Trend test *P* value, 0.11				
		Other cancers (mortality)	Worked ≥ 15 yr rotating night shift (vs never) (HR):				
			Lung	150	1.25 (1.04–1.51)		
			Ovarian	30	0.82 (0.55–1.22)		
			Pancreas	33	1.03 (0.70–1.51)		
			NHL	26	1.06 (0.71–1.58)		
			Other cancers	32	0.94 (0.63–1.38)		
		Lung: (mortality)	Years of rotating night shift work, current smokers (HR):				
			Never	140	1		
			1–5 yr	149	1.11 (0.86–1.42)		
			6–14 yr	60	1.16 (0.84–1.61)		
			≥ 15 yr	67	1.88 (1.36–2.62)		
			Trend test *P* value, < 0.001				

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014a) Germany Enrolment, 1995–2005; follow-up, 2000–2009 Cohort	27 828 (12 609 shift workers with ≥ 1 yr rotating shift work and 15 219 day workers excluding office workers); retrospective incidence study of male production workers employed for ≥ 1 yr in a chemical company, and residents of Rhineland-Palatinate Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Lung and bronchus	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	*Exposure assessment critique*: NSW in ref. group: No. Duration: Partial (limited period). Temporality: Complete. Schedule type: Rotating. No other information available. Strengths: large industrial cohort; exposure assessment from records; incident cases identified through regional cancer registry Limitations: exposure classification was dichotomous (≥ 1 yr of shift work vs never shift work) at the time of study entry
			Day work only	39	1		
			Shift work (≥ 1 yr)	46	0.93 (0.54–1.63)		
		Lung and bronchus	Shift work status (SIR):			Age, calendar period	
			Day work only	39	0.48 (0.34–0.66)		
			Shift work (≥ 1 yr)	46	0.70 (0.51–0.94)		
			SIR ratio (shift vs day)	NR	1.46 (0.93–2.3)		
		Oesophagus	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	7	1		
			Shift work (≥ 1 yr)	14	2.85 (1.01–8.81)		
		Oesophagus	Shift work status (SIR):			Age, calendar period	
			Day work only	7	0.51 (0.21–1.06)		
			Shift work (≥ 1 yr)	14	1.28 (0.70–2.15)		
			SIR ratio (shift vs day)	NR	2.51 (0.94–7.31)		
		Stomach	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	16	1		
			Shift work (≥ 1 yr)	17	1.15 (0.49–2.72)		
		Stomach	Shift work status (SIR):			Age, calendar period	
			Day work only	16	0.81 (0.46–1.32)		
			Shift work (≥ 1 yr)	17	1.06 (0.62–1.7)		
			SIR ratio (shift vs day)	NR	1.31 (0.62–2.77)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014a) (cont.)		Pancreas	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	10	1		
			Shift work (≥ 1 yr)	12	1.05 (0.40–2.87)		
		Pancreas	Shift work status (SIR):			Age, calendar period	
			Day work only	10	0.66 (0.31–1.21)		
			Shift work (≥ 1 yr)	12	0.98 (0.50–1.71)		
			SIR ratio (shift vs day)	NR	1.48 (0.59–3.83)		
		Kidney	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	21	1		
			Shift work (≥ 1 yr)	24	1.21 (0.56–2.62)		
		Kidney	Shift work status (SIR):			Age, calendar period	
			Day work only	21	0.90 (0.56–1.38)		
			Shift work (≥ 1 yr)	24	1.27 (0.81–1.89)		
			SIR ratio (shift vs day)	NR	1.41 (0.75–2.66)		
		Urinary bladder	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	46	1		
			Shift work (≥ 1 yr)	49	1.01 (0.61–1.68)		
		Urinary bladder	Shift work status (SIR):			Age, calendar period	
			Day work only	46	1.24 (0.91–1.65)		
			Shift work (≥ 1 yr)	49	1.61 (1.19–2.13)		
			SIR ratio (shift vs day)	NR	1.3 (0.85–1.99)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014a) (cont.)		Urinary tract	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	25	1		
			Shift work (≥ 1 yr)	26	1.11 (0.54–2.29)		
		Urinary tract	Shift work status (SIR):			Age, calendar period	
			Day work only	25	0.98 (0.63–1.44)		
			Shift work (≥ 1 yr)	26	1.25 (0.81–1.83)		
			SIR ratio (shift vs day)	NR	1.28 (0.71–2.31)		
		Skin (malignant melanoma)	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	40	1		
			Shift work (≥ 1 yr)	27	0.53 (0.26–1.04)		
		Skin (malignant melanoma)	Shift work status (SIR):			Age, calendar period	
			Day work only	40	1.33 (0.95–1.81)		
			Shift work (≥ 1 yr)	27	1.09 (0.72–1.59)		
			SIR ratio (shift vs day)	NR	0.82 (0.49–1.38)		
		NHL	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	12	1		
			Shift work (≥ 1 yr)	15	1.57 (0.58–4.48)		
		NHL	Shift work status (SIR):			Age, calendar period	
			Day work only	12	0.71 (0.37–1.24)		
			Shift work (≥ 1 yr)	15	1.08 (0.60–1.78)		
			SIR ratio (shift vs day)	NR	1.52 (0.66–3.56)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Yong et al. (2014a) (cont.)		Leukaemia	Shift work status (HR):			Age, job level, cigarette smoking, employment duration	
			Day work only	6	1		
			Shift work (≥ 1 yr)	16	2.74 (0.89–9.98)		
		Leukaemia	Shift work status (SIR):			Age, calendar period	
			Day work only	6	0.47 (0.17–1.02)		
			Shift work (≥ 1 yr)	16	1.51 (0.87–2.46)		
			SIR ratio (shift vs day)	NR	3.21 (1.2–10.05)		
Yong et al. (2014b) Germany 1995–2005; follow-up, 2000–2009 Cohort	31 143 (14 038 rotating shift workers and 17 105 day workers); retrospective mortality study of male production workers employed for ≥ 1 yr at a chemical company Exposure assessment method: records; objective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Lung (mortality)	Shift work status (HR):			Age, cigarette smoking	*Exposure assessment critique*: NSW in ref group: No. Duration: Partial (limited period). Temporality: Complete. Schedule type: Rotating. No other information available. Strengths: large industrial cohort Limitations: exposure classification was dichotomous (≥ 1 yr of shift work vs never shift work) at the time of study entry
			Day work only	NR	1		
			Shift work (≥ 1 yr)	NR	1.02 (0.69–1.5)		
		All cancers combined (mortality)	Shift work status (HR):			Age, manual work, cigarette smoking, job duration	
			Day work only	NR	1		
			Shift work (≥ 1 yr)	NR	0.78 (0.62–0.99)		
		All cancers combined	Job duration (yr) (HR):			Age, job level, cigarette smoking	
			< 20 yr (shift vs day)	38	0.96 (0.49–1.87)		
			20– 25 yr (shift vs day)	41	0.83 (0.42–1.61)		
			26–33 yr (shift vs day)	56	0.6 (0.38–0.93)		
			≥ 34 yr (shift vs day)	62	1 (0.71–1.41)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Kwon et al. (2015) Shanghai, China 1989–2006 Nested case–control	1559 cases: incident lung cancer cases (determined through cancer registry) among 267 400 female textile workers from 526 factories actively employed or retired at enrolment (born 1925–1958) 3199 controls: randomly selected from cohort, frequency-matched to age group (± 5 yr) Exposure assessment method: objective and subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Lung	Years of rotating night shift work (HR): 0 yr > 0 to ≤ 17.1 yr 17.1 to ≤ 24.9 yr 24.9 to ≤ 30.6 yr > 30.6 yr Trend test *P* value, 0.29	 411 259 261 259 261	 1 0.76 (0.62–0.93) 0.89 (0.72–1.09) 0.94 (0.76–1.17) 0.82 (0.66–1.02)	Age, smoking, parity, endotoxin	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Rotation speed: Imprecise. Rotation direction: Imprecise. Schedule type: Rotating. No other information available. Strengths: large number of female workers labelled as exposed to rotating night shifts; 10-yr and 20-yr lag periods considered; control for age, smoking, parity, and endotoxins Limitations: probability of exposure based on JEM

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Poole et al. (2011) USA 1976–2007 Cohort	2 974 672 person-years; NHS-I and NHS-II Exposure assessment method: subjective assessment; night shift undefined	Ovary	Years of rotating night shift work, NHS-I and NHS-II (pooled) (HR): None 1–2 yr 3–5 yr 6–9 yr 10–14 yr 15–19 yr ≥ 20 yr Trend test *P* value, 0.74	 270 197 115 51 39 24 22	 1 1.07 (0.89–1.29) 0.90 (0.72–1.13) 0.92 (0.68–1.25) 1.14 (0.81–1.6) 1.28 (0.84–1.94) 0.80 (0.51–1.23)	Age, parity, duration of OC use, BMI, smoking status, tubal ligation, menopausal status, family history of ovarian cancer, cohort	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments*: analysis of years of employment with (rotating) night work Strengths: many covariates; several interactions and sensitivity analyses assessed; lag of 2 and 4 yr investigated; large number of cases Limitations: rotating night shift question asked only once (in 1988) for NHS-I

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Bhatti et al. (2013) Washington, USA 2002–2009 Case–control	1490 cases: population-based cancer registry (Cancer Surveillance System) in western Washington State, aged 35–74 yr (2002–2005) and 35–69 yr (2006–2009) 1832 controls: general population, obtained by random-digit dialling, frequency-matched by age, calendar period, and county of residence Exposure assessment method: subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Ovary: invasive	Worked night shift (OR):			Age, urban/rural status, number of pregnancies, BMI at age 30 yr, duration of OC use, reference year	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Imprecise. Duration: Partial (limited period). Temporality: Complete. No other information available. Strengths: good response for cases and controls; large number of cases; pathology information; high prevalence of night work (ever) among invasive cases (27%) and borderline cases (32%), and 23% among controls
			Never	808	1		
			Ever	293	1.24 (1.04–1.49)		
		Ovary: invasive	Worked night shift for less than half of all work days (OR):				
			Never	916	1		
			Ever	185	1.28 (1.03–1.59)		
		Ovary: invasive (*n* = 1101)	Cumulative night shift work years (OR):				
			Never	808	1		
			4 mo to 1 yr	55	1.03 (0.72–1.47)		
			> 1 to 3 yr	75	1.13 (0.82–1.57)		
			> 3 to 7 yr	94	1.95 (1.41–2.68)		
			> 7 yr	68	1.02 (0.74–1.42)		
		Ovary: invasive (*n* = 1101)	Worked night shift, aged ≥ 50 yr (OR):				
			Never	611	1		
			Ever	216	1.32 (1.07–1.63)		
		Ovary: borderline (*n* = 389)	Worked night shift (OR):				
			Never	263	1		
			Ever	126	1.48 (1.15–1.9)		
		Ovary: borderline (*n* = 389)	Worked night shift for less than half of all work days (OR):				
			Never	312	1		
			Ever	77	1.32 (0.98–1.78)		
		Ovary: borderline (*n* = 389)	Cumulative night shift work (OR):				
			Never	263	1		
			4 mo to 1 yr	27	1.44 (0.90–2.29)		
			> 1 to 3 yr	35	1.33 (0.87–2.02)		
			> 3 to 7 yr	44	2.37 (1.57–3.57)		
			> 7 yr	20	0.97 (0.58–1.61)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Bhatti et al. (2013) (cont.)		Ovary: borderline (n = 389)	Worked night shift, aged ≥ 50 yr (OR):				
			Never	150	1		
			Ever	67	1.57 (1.13–2.19)		
		Ovary: high-grade serous	Worked night shift (OR)				
			Never	606	1		
			Ever	228	1.29 (1.06–1.57)		
		Ovary: low-grade and borderline serous	Worked night shift (OR)				
			Never	161	1		
			Ever	79	1.51 (1.12–2.05)		
		Ovary: invasive and borderline mucinous	Worked night shift (OR)				
			Never	121	1		
			Ever	60	1.55 (1.1–2.17)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Carter et al. (2014) USA and Puerto Rico 1982–2010 Cohort	161 004 employed women from a prospective cohort mortality study in the USA and Puerto Rico, recruited in 1982 and followed for mortality through 2010; no prevalent cancer at baseline, non-menopausal, and with work schedule information Exposure assessment method: questionnaire; subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00) for permanent night shift work; night shift defined for rotating night shift work	Ovary (mortality)	Work schedule at baseline (HR): Fixed days Rotating shifts Fixed afternoon/ evenings Fixed night	 1126 101 11 15	 1 1.27 (1.03–1.56) 0.62 (0.34–1.12) 1.12 (0.67–1.87)	Age, OC use, age at menarche and menopause, tubal ligation, parity, postmenopausal estrogen use, race, family history of breast and/or ovarian cancers, exercise, BMI, height	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (one time-point). Schedule type: Permanent night, Rotating. Shift start/ end times: Imprecise. No other information available Strengths: large number of working women Limitations: definition of "night" shift is start of work between 21:00 and midnight, which is not conventional

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Leung et al. (2019) Montreal 2011–2016 Case–control	496 cases: women aged 18–79 yr with histologically confirmed epithelial ovarian cancer from seven hospitals (Canadian citizens, resident of Montreal, French and/or English speaking) 906 controls: electoral lists in same areas as hospitals, frequency-matched by age and electoral district Exposure assessment method: questionnaire; subjective assessment; night shift defined (other)	Ovary	Years of any shift work (OR):			Age, parity, education	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Schedule type: Permanent night, Imprecise. No other information available. *Other comments*: rotating including nights; number of night shifts/month; fixed days, 06:00–18:00; fixed evenings, 18:00 to midnight; fixed nights, midnight to 06:00; average number of consecutive nights/ month; 2-, 5-, and 10-yr lags Strengths: in-person interview with lifetime occupational histories; start and stop times for each job; wide diversity of occupations Limitations: too few cases working fixed nights, therefore not assessed; 56% response among controls
			Never	231	1		
			< 5 yr	93	1.21 (0.88–1.67)		
			5–12 yr	67	0.74 (0.53–1.03)		
			> 12 yr	105	1.21 (0.89–1.63)		
			Trend test *P* value, 0.75				
		Ovary	Years of shift work, morning chronotype (OR):				
			Never	101	1		
			< 5 yr	36	1.43 (0.87–2.34)		
			5–12 yr	24	0.82 (0.48–1.39)		
			> 12 yr	42	1.64 (1.01–2.65)		
			Trend test *P* value, 0.16				
		Ovary	Years of shift work, evening chronotype (OR):				
			Never	30	1		
			< 5 yr	13	0.56 (0.21–1.51)		
			5–12 yr	7	0.36 (0.12–1.1)		
			> 12 yr	20	0.37 (0.15–0.88)		
			Trend test *P* value, 0.02				
		Ovary	Years of night shift work (OR):				
			Never	231	1		
			< 5.5 yr	40	1.07 (0.70–1.64)		
			≥ 5.5 yr	38	0.88 (0.58–1.36)		
			Trend test *P* value, 0.69				

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Gyarmati et al. (2016) Spain 2008–2013 Case–control	374 cases: men and women aged 20–85 yr with histologically confirmed stomach cancer, diagnosed in any of 23 hospitals 2481 controls: population controls aged 20–85 yr randomly selected from the primary health centres in the study, frequency-matched to cases by sex and 5-yr age groups Exposure assessment method: questionnaire; subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	Stomach	Worked night shift (OR):			Sex, age, education, centre, BMI, cigarettes smoked, family history of cancer, physical activity level	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Schedule type: Permanent night, Rotating. No other information available. *Other comments*: men and women combined Strengths: exposure assessment based on lifetime occupational history and detailed patterns of night work Limitations: small number of exposed cases; no lag considered; 55% response among cases; 52% response among controls
			Never	278	1		
			Ever	96	1.1 (0.8–1.4)		
			Permanent nights	45	1.3 (0.9–1.9)		
			Rotating nights	51	1 (0.7–1.4)		
		Stomach	Duration of night shift (OR):				
			Never	278	1		
			< 10 yr	28	1.1 (0.7–1.6)		
			10–20 yr	21	1.1 (0.7–1.9)		
			≥ 20 yr	47	1.1 (0.8–1.6)		
			Trend test *P* value, 0.57				
		Stomach	Duration of permanent night shift (OR):				
			Never night shift	278	1		
			< 10 yr	14	1.1 (0.6–2.1)		
			10–20 yr	16	2 (1.1–3.8)		
			≥ 20 yr	15	1.1 (0.6–1.9)		
			Trend test *P* value, 0.24				
		Stomach	Duration of rotating night work (OR):				
			Never night shift	278	1		
			< 10 yr	14	1 (0.5–1.8)		
			10–20 yr	5	0.5 (0.2–1.2)		
			> 20 yr	32	1.1 (0.7–1.7)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Gyarmati et al. (2016) (cont.)		Stomach	Duration of permanent night shift, completed dietary questionnaire (OR):			Sex, age, education, centre, BMI, cigarettes smoked, family history of cancer, physical activity level, total energy intake, red meat grams, vegetable grams, fruit grams, alcohol consumption	
			Never night shift	242	1		
			< 10 yr	11	1.2 (0.6–2.5)		
			10–20 yr	16	3.4 (1.7–6.7)		
			≥ 20 yr	10	0.9 (0.4–2)		
			Trend test *P* value, 0.12				
Lin et al. (2013) Japan 1988–2009 Cohort	22 224 men aged 40–65 yr who reported working full-time or were self-employed (1988–1990) and with no history of cancer, followed prospectively for pancreatic cancer mortality through 2009 Exposure assessment method: subjective assessment; night shift defined (other)	Pancreas (mortality)	Work schedule for longest occupation (HR):			Age, BMI, diabetes, alcohol consumption, cigarette smoking, perceived stress, sleep time	*Exposure assessment critique*: NSW in ref. group: Undefined. Schedule type: imprecise. No other information available. *Other comments*: multiple publications as part of Japan Collaborative Cohort Study Strengths: large cohort Limitations: very small study with 127 cases; only one exposure question; baseline assessment only, and for longest-held occupation; mortality not incidence
			Daytime	111	1		
			Fixed nights	5	0.61 (0.22–1.60)		
			Rotating shifts	11	0.83 (0.43–1.60)		
		Pancreas (mortality)	Work schedule for longest occupation, employed full-time at baseline (HR):				
			Daytime	NR	1		
			Fixed nights	NR	NR		
			Rotating shifts	NR	1.34 (0.66–2.75)		
		Pancreas (mortality)	Work schedule for longest occupation excluding deaths in first 2 yr (HR):				
			Daytime	NR	1		
			Fixed nights	NR	NR		
			Rotating shifts	NR	0.84 (0.44–1.62)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Viswanathan et al. (2007) USA 1976; 1988–2004 Cohort	53 487: NHS-I, aged 30–55 yr Exposure assessment method: subjective assessment; night shift undefined	Endometrium	Years of rotating night shift work (HR):			Age, age at menarche, age at menopause, parity, OCs, postmenopausal hormone use, smoking, BMI, hypertension, diabetes	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. No other information available. *Other comments*: analysis of years of employment with (rotating) night work Strengths: large cohort Limitations: cannot distinguish permanent night workers among rotating night workers
			None	210	1		
			1–9 yr	224	0.89 (0.74–1.08)		
			10–19 yr	43	1.06 (0.76–1.49)		
			≥ 20 yr	38	1.47 (1.03–2.1)		
			Trend test *P* value, 0.04				
		Endometrium	Years of rotating night shift work, BMI of ≥ 30 (HR):				
			None	67	1		
			1–9 yr	85	1.09 (0.78–1.52)		
			10–19 yr	22	1.42 (0.86–2.37)		
			≥ 20 yr	23	2.09 (1.24–3.52)		
			Trend test *P* value, 0.003				
Lin et al. (2015a) Japan 1988–2009 Cohort	22 224 men aged 40–65 yr working full-time or self-employed Exposure assessment method: subjective assessment; night shift defined (other)	Bile duct/ gallbladder (mortality)	Work schedule for longest occupation (HR):			Age, BMI, history of cholelithiasis, history of diabetes, cigarette smoking, alcohol drinking, perceived stress, sleep time	*Exposure assessment critique*: NSW in ref. group: Undefined. Schedule type: Imprecise. No other information available. *Other comments*: multiple publications as part of Japan Collaborative Cohort Study Strengths: large cohort Limitations: very small study with 127 cases; only one exposure question; baseline assessment only, and for longest-held occupation; mortality not incidence
			Day	78	1		
			Fixed nights	4	0.86 (0.31–2.36)		
			Rotating shifts	12	1.5 (0.81–2.77)		
		Extrahepatic bile duct (mortality)	Work schedule for longest occupation (HR):				
			Day	56	1		
			Fixed nights	4	1.19 (0.43–3.31)		
			Rotating shifts	11	1.93 (1.00–3.72)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Heckman et al. (2017) 14 states in USA 2001–2011 Cohort	74 323 female registered nurses aged 25–42 yr at baseline (1989), with information on occupational exposure to rotating shift work between 1989 and 2001 and no report of cancer before 2001 (excluded African Americans, Asians, and those with Hispanic ethnicity); followed for cancer incidence (self-reported and confirmed by physician) Exposure assessment method: subjective assessment; night shift undefined	Skin (malignant melanoma)	Years on rotating shift schedule including ≥ 3 nights/mo (HR):			Age, years of shift work, hours of sleep per night, sleep adequacy, sleepy days per week, snoring, restless leg syndrome, family history of melanoma, hours in sun per week aged 25–35 yr, number of severe sunburns aged 15–20 yr, sunburn severity in childhood, artificial tanning aged 25–35 yr, annual UV at residence, moles on lower leg, hair colour in adolescence, marital status, financial status, BMI, physical activity, smoking status, menopausal status, postmenopausal hormone use, OC use, alcohol intake, alternate healthy eating index	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Complete. Temporality: Partial. No other information available. *Other comments*: analysis of years of employment with (rotating) night work; update of Schernhammer et al. (2011) Strengths: large population; many covariates
			Never	67	1		
			< 2 yr	54	0.85 (0.59–1.22)		
			2–5.9 yr	45	0.84 (0.57–1.23)		
			6–9.9 yr	28	1.13 (0.72–1.77)		
			≥ 10 yr	18	0.95 (0.55–1.61)		
		Skin (basal cell carcinoma)	Years on rotating shift schedule including ≥ 3 nights/mo (HR):				
			Never	1333	1		
			< 2 yr	1179	0.93 (0.86–1.01)		
			2–5.9 yr	1032	0.96 (0.88–1.04)		
			6–9.9 yr	416	0.83 (0.75–0.93)		
			≥ 10 yr	348	0.83 (0.74–0.94)		
		Skin (squamous cell carcinoma)	Years on rotating shift schedule including ≥ 3 nights/mo (HR):				
			Never	106	1		
			< 2 yr	93	0.94 (0.71–1.24)		
			2–5.9 yr	74	0.86 (0.63–1.16)		
			6–9.9 yr	34	0.85 (0.57–1.26)		
			≥ 10 yr	27	0.81 (0.53–1.25)		

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Carreón et al. (2014) New York state 1960–2007 Cohort	1739 men, 135 women: workers employed ≥ 1 d during 1946–2006 in one chemical manufacturing plant in New York state Exposure assessment method: objective assessment; night shift defined (other)	NHL (mortality)	Shift work status (SMR):			Sex, race, age, calendar time	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Imprecise. Duration: Partial (limited period). Temporality: Complete. Rotation speed: Precise. Rotation direction: Precise. Schedule type: Rotating. No other information available. *Other comments*: cancer mortality results are presented in relation to shift work for NHL only, not any other site Limitations: very small study; workers with short duration of employment (median, 1.6 yr); many possible concomitant exposures; too few deaths to assess most cancer sites
			Never (none)	3	2.59 (0.53–7.56)		
			Ever (≥ 1 d)	8	2.31 (1.00–4.55)		
			Shift work duration < 1 yr	3	2.22 (0.46–6.48)		
			Shift work duration ≥ 1 yr	5	2.37 (0.77–5.52)		
		NHL (mortality)	Shift work status (SRR):				
			Never (none)	3	1		
			Ever (≥ 1 d)	8	0.69 (0.18–2.69)		
			Shift work duration < 1 yr	3	0.41 (0.08–2.08)		
			Shift work duration ≥ 1 yr	5	0.61 (0.14–2.61)		
			Trend test *P* value, 0.93				

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Costas et al. (2016) Spain 2010–2013 Case–control	321 cases: men and women diagnosed with CLL in 11 hospitals 1728 controls: population controls randomly selected from centre rosters and frequency-matched by age, sex, and study area Exposure assessment method: questionnaire; subjective assessment; night shift defined (exposed for ≥ 3 h between 23:00 and 06:00)	NHL (CLL)	Worked night shift (OR):			Region, age, sex, worked on farm, family history of haematological malignancies, BMI, tobacco consumption, sleep problems, education	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Temporality: Complete. Schedule type: Permanent night, Rotating. No other information available. Strengths: lifetime occupational histories with start and stop times of each job; large number of population-based cases and controls for this site Limitations: perhaps residual confounding by working on farm, according to authors
			Never	225	1		
			Ever	79	1.06 (0.78–1.45)		
			< 6 yr	22	0.86 (0.52–1.43)		
			6–20 yr	17	0.65 (0.37–1.13)		
			> 20 yr	39	1.77 (1.14–2.74)		
			Trend test *P* value, 0.18				
		NHL (CLL)	Time since last night shift (OR):				
			Never night shift	225	1		
			Current	5	0.72 (0.27–1.94)		
			< 15 yr	30	1.34 (0.84–2.14)		
			15–30 yr	24	1.14 (0.69–1.88)		
			> 30 yr	19	0.80 (0.47–1.37)		
		NHL (CLL)	Worked rotating night shift (never permanent) (OR):				
			Never night shift	225	1		
			Ever	42	1.07 (0.72–1.6)		
			Duration < 8 yr	7	0.50 (0.22–1.14)		
			Duration 8–23 yr	9	0.66 (0.31–1.41)		
			Duration > 23 yr	26	2.29 (1.33–3.92)		
			Trend test *P* value, 0.07				

Table 2.5 Studies of cancer at other organ or tissue sites (excluding breast, prostate, colon, and rectum) among shift workers other than aircrew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type[b]	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Costas et al. (2016) (cont.)		NHL (CLL)	Worked permanent night shift (OR):				
			Never night shift	225	1		
			Ever	37	1.05 (0.69–1.59)		
			Duration < 4 yr	12	1.09 (0.55–2.15)		
			Duration 4–12 yr	11	0.85 (0.42–1.73)		
			Duration > 12 yr	13	1.16 (0.6–2.25)		
			Trend test *P* value, 0.86				

BMI, body mass index; CI, confidence interval; CLL, chronic lymphocytic leukaemia; d, day; h, hour; HR, hazard ratio; JEM, job-exposure matrix; mo, month; NHL, non-Hodgkin lymphoma; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; NR, not reported; NSW, night shift worker(s); OC, oral contraceptive; OR, odds ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; UV, ultraviolet radiation; vs, versus; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

[b] All outcomes are of incident cancers unless otherwise specified.

mortality from cancer of the lung for those working 15 years or more of rotating night shift (*P* for trend, 0.05) (Gu et al., 2015). Similar to the incidence study described above, when the analysis was stratified by smoking status (never, former, current), an elevated risk of mortality from cancer of the lung was seen only for the subgroup of current smokers who had 15 years or more of rotating night shift work.

As described in Section 2.1.2(a), a retrospective cohort study of chemical industry workers residing in the Rhineland-Palatinate region, Germany, evaluated cancer incidence (2000–2009) among 12 609 workers with 1 year or more of rotating shifts (1995–2005) and 15 219 day workers. No increased risk was apparent for shift workers for the incidence of cancer of the lung and/or bronchial system (46 exposed cases) compared with day workers (Yong et al., 2014a). No increased risk of mortality from cancer of the lung was observed among shift workers compared with day workers (Yong et al., 2014b). [The Working Group noted that, although this is a relatively large industrial cohort with exposure assessment from company records and incident cases identified through a regional cancer registry, exposure classification was assessed only as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry. The Working Group also noted that, although information on direction of rotation and duration was available, results were not presented for these exposure variables. With 518 incident cases of cancer among shift workers, the study power for specific sites was limited and resulted in imprecise risk estimates.]

Results for the risk of incidence of lung cancer were reported in a nested case–control study among a cohort of female workers (n = 276 400) in 526 textile factories in Shanghai, China. The probability of rotating shift including night work was ascertained by investigating these specific factories, and applied to the work history of participants through a JEM (Kwon et al., 2015). There were many exposed cases (n = 1040), and no increased risk of cancer of the lung was apparent for increased cumulative number of years of rotating night shifts or increased cumulative number of nights, whether a lag period was considered or not.

(b) Cancer of the ovary

After 20 years (2 974 672 person-years) of follow-up for two prospective cohorts of female registered nurses in the USA, NHS-I and NHS-II, 718 incident cases of cancer of the ovary were self-reported and confirmed through review of medical records by a pathologist blinded to exposure status (Poole et al., 2011). As described in Section 2.1.1(a) for the NHS-I and NHS-II cohorts, work patterns of duration of rotating shifts including at least 3 nights per month were analysed as never, 1–2, 3–5, 6–9, 10–14, 15–19, and ≥ 20 years. All results were null after adjusting for several confounders. Findings did not differ with the investigation of potential interactions or in several sensitivity analyses. Mortality from cancer of the ovary was also investigated in the NHS-I cohort, with 74 862 women included in the analysis and 5413 cancer deaths among 14 181 total deaths. There was no evidence of increased mortality from cancer of the ovary (425 deaths) with increased duration of night shift (Gu et al., 2015).

With participants aged 35–74 years recruited in western Washington State, USA, in 2002–2009, a case–control study was conducted with 1101 invasive and 389 borderline incident cases of cancer of the ovary, frequency matched by age, calendar period, and county to 1832 population controls (Bhatti et al., 2013). The response rate was 74% for cases and 79% for controls. Detailed lifetime occupational histories and covariate information were collected by in-person interviews, including all jobs from the age of 25 years of duration 4 months or longer, with start and stop times, average number of hours per week, and number of nights per week (defined as working between

midnight and 04:00). Ever performing night shift and cumulative work-years were analysed, the latter with quartiles (never, 4 months to 1 year, > 1–3 years, > 3–7 years, and > 7 years) determined by the frequency among controls. Elevated risks of cancer of the ovary were apparent for ever night shift for both invasive and borderline cases. When results were stratified by age (< 50 vs ≥ 50 years of age at the reference date), the increased risk for invasive and borderline cases remained only in the older age group. When results were stratified by tumour subtype (high-grade serous, low-grade and borderline serous, invasive and borderline mucinous, endometrioid, and clear cell), increased risk was apparent for ever night work in the serous and mucinous subtypes but not the endometrioid or clear cell subtypes. All of the analysis was repeated using cumulative night shift work-years as the exposure metric. No clear trend of increasing risk with increasing cumulative night shift was found in the main analysis or in either of the two stratified analyses (age and subtype); however, elevated odds ratios were found for a cumulative duration of > 3–7 years (but not > 7 years).

Fatal cancer of the ovary was investigated in a cohort established in 1982 with participants recruited by volunteers of the American Cancer Society (Carter et al., 2014). At baseline, participants were asked about work in rotating shifts and start time of job, with fixed shifts assumed if the answer to rotating shifts was negative. Assuming 8-hour work days, in addition to "rotating shifts", day shift was designated as starting between 06:00 and 10:00, afternoon/evening as starting between 14:00 and 16:00, and fixed nights as starting between 21:00 and midnight. After exclusions, the cohort for this analysis included 161 004 working women with a mean age of 50 years. With 6.6% of the cohort working rotating schedules in 1982, the highest risk for subsequent fatal cancer of the ovary was seen for those working rotating shifts (HR, 1.27; 95% CI, 1.03–1.56; 101 exposed cases). [The Working Group noted that exposure information was based on only one job ascertained at baseline and that the definition for fixed "nights" was atypical, with start times between 21:00 and midnight and unknown end times. The definition of "rotating shifts" was also not clear.]

In Montreal, Quebec, Canada, a population-based case–control study recruited histologically confirmed incident cases of cancer of the ovary and controls from electoral lists in 2011–2016, frequency matched to cases by age (Leung et al., 2019). In-person interviews collected lifetime occupational histories, starting at age 19 years, for every job held for 6 months or more. Patterns of work were determined using start and stop times – defined as fixed days (06:00–18:00), fixed evenings (18:00 to midnight), and fixed nights (midnight to 06:00) – and rotating shifts with or without nights, along with duration. Cumulative shift work-years, average number of nights per month, and average number of consecutive nights per month were assessed in the analysis, with 15 main-effect odds ratios presented for cancer of the ovary overall for 496 cases and 906 controls, plus 11 each for invasive and borderline types. An increased risk of cancer of the ovary overall was not apparent for increased cumulative years of shift work according to timing (ever night shift work, evening shift work only) or schedule (rotating shift work only, fixed shift work only), or any of these exposure parameters assessed separately for invasive and borderline cases versus controls. Interactions (selected a priori) between cumulative shift work and chronotype or menopausal status were also assessed. Increased risk of cancer of the ovary was seen for increased cumulative duration of exposure to any shift work of more than 12 years (but not in the < 5 or 5–12 years categories) among those self-reporting as "a morning person", with decreased risk at this exposure level for those reporting as "an evening person". No association was seen with menopausal status, and results calculated using various lag periods

and other sensitivity analyses did not change the conclusions.

(c) Cancer of the oesophagus

In the multisite population-based case–control study in Montreal, Canada, described in Section 2.1.4(c), no increased risk of cancer of the oesophagus was apparent for ever night work (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

In the retrospective cohort study of chemical industry workers in Germany, evaluating cancer incidence (2000–2009) among 12 609 workers with 1 year or more of rotating shifts (1995–2005) and among 15 219 day workers, an increased risk of cancer of the oesophagus was apparent when comparing shift workers with day workers (14 exposed cases) (Yong et al., 2014a). In this same cohort, rates of cancer of the oesophagus in shift workers were not elevated compared with the rate in the general population (Yong et al., 2014a). [The Working Group noted that exposure classification was assessed only as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and results for direction of rotation and duration were not presented. The study power for specific sites was limited, resulting in imprecise risk estimates.]

(d) Cancer of the stomach

In the multisite case–control study of men in Montreal, Canada, mentioned in Section 2.1.4(c), no association was observed between the incidence of cancer of the stomach and ever having performed night work or cumulative duration of night work in years. Increased risk was apparent for timing of night work in the "distant past", defined as more than 20 years before the date of diagnosis (for the 23 exposed cases) or interview (for controls), compared with those who never performed night work (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

The retrospective cohort study of male workers in the chemical industry in Germany did not show any increased risk of incidence of cancer of the stomach (Yong et al., 2014a). [The Working Group noted that exposure classification was assessed as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and that results for direction of rotation and duration were not presented. The study power for specific sites was limited.]

Permanent night work and rotating shift work with nights were assessed in the MCC-Spain study in five regions of Spain. Detailed lifetime occupational history, including start and stop times for each job, was collected via interview for incident cases of cancer of the stomach (n = 374) and population controls (n = 2481, frequency matched by age, sex, and centre) (Gyarmati et al., 2016). Night work was defined as working partly or entirely between midnight and 06:00, with duration in years of permanent night work and rotating shift work assessed (if both types of shifts occurred for an individual over time, they were allocated to permanent nights). With women and men combined in the analysis, there was no increased risk of cancer of the stomach for ever permanent or ever rotating night shifts, and no clear trend in risk according to increasing cumulative duration of permanent or rotating night shift work. Results were similar when the analysis was restricted to a subset of participants who had provided information on usual dietary intake. [The Working Group noted the low response rate among cases (55%) and controls (51%) as a study limitation.]

(e) Cancer of the liver and biliary tract

Using the same participants and exposure assessment methods as for the Japan Collaborative Cohort Study (Lin et al., 2013), mortality from cancer of the biliary tract including gallbladder (n = 94) and extrahepatic bile duct (n = 71) was investigated after 17 years of follow-up (Lin et al., 2015a). An increased relative risk was apparent for mortality from cancer of the extrahepatic bile duct among rotating shift workers (n = 11), compared with day workers. [The Working Group noted that exposure assignment was based on only one question for the longest-held occupation asked at baseline, too few participants were permanent night workers to assess relative risks for this exposure, and it was unclear if rotating shifts include nights.]

(f) Cancer of the pancreas

In the multisite case–control study of men in Montreal, Canada, mentioned in Sections 2.1.4(c) and (d), ever performing night work (94 cases) and timing of night work in the recent past (≤ 20 years) were associated with an increased risk of incident cancer of the pancreas (Parent et al., 2012). Suggestive increases of greater than 2-fold were also apparent for 5–10 years and more than 10 years cumulative duration of night work, although these estimates were imprecise. [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

In a cohort study in Japan, which used one question at baseline to assess work schedule exposure in participants' longest-held occupation, there were 127 deaths from cancer of the pancreas, of whom 5 were assessed as fixed night workers and 11 as rotating shift workers. No increased risk of cancer of the pancreas was apparent (Lin et al., 2013). [The Working Group noted that the exposure assignment was based on only one question asked at baseline about the longest-held occupation, there were too few participants who were permanent night workers for exposure–response assessment, and it was unclear whether rotating shifts included nights.]

The retrospective cohort study of male workers in the chemical industry in Germany did not show an increased risk of incident cancer of the pancreas for shift workers compared with day workers, or compared with the general population (Yong et al., 2014a). [The Working Group noted that exposure classification was assessed as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and that results for direction of rotation and duration were not presented. The study power for specific sites was limited.]

In the NHS-I cohort with 74 862 women included in the analysis and 5413 cancer deaths among 14 181 total deaths, there was no evidence of increased mortality from cancer of the pancreas with increased rotating night shift duration (Gu et al., 2015).

(g) Cancer of the endometrium

With data collection methods described in other sections (e.g. Section 2.1.1(a)(xii)), the NHS-I cohort included 53 487 registered nurses aged 30–55 years at enrolment (in 1976) after excluding those with a prior cancer diagnosis and those without an intact uterus (and therefore not at risk of cancer of the endometrium) (Viswanathan et al., 2007). A total of 720 698 person-years was observed with follow-up from June 1988 until May 2004, and 515 pathologically confirmed invasive cancers of the endometrium were identified. Increasing years of rotating shift work including at least 3 nights per month was associated with an increasing risk (P for trend, 0.04), with highest risk seen for duration of 20 years or more (38 exposed cases). When the results were stratified by BMI (< 30 or ≥ 30), the positive trend with duration was observed only

among the group of women with BMI of 30 or more (Viswanathan et al., 2007).

(h) Cancer of the kidney

In the multisite case–control study of men in Montreal, Canada, the risk of incident cancer of the kidney (158 total cases) was not associated with any parameter of night work (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

In the male chemical workers cohort study in Germany, no increased risk of the incidence of kidney cancer was apparent for shift workers (24 exposed cases) compared with day workers or with the local population (Yong et al., 2014a). [The Working Group noted that exposure classification was assessed as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and that results for direction of rotation and duration were not presented. The study power for specific sites was limited.]

(i) Cancer of the bladder and urinary tract

In the multisite case–control study of men in Montreal, Canada, ever night work was associated with an increased risk of incident cancer of the bladder (439 total cases). The shortest (< 5 years) and longest (> 10 years) categories of cumulative duration of night work also showed increased risk, but the middle category (5–10 years) did not and there was no evidence of an exposure–response trend. Both recent (≤ 20 years) and distant (> 20 years) timing of night work before date of diagnosis or interview showed increased risk (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

In the male chemical workers cohort study in Germany, an increased risk was apparent for shift workers for incident cancer of the bladder (49 exposed cases) compared with the local population, but not compared with day workers, and no increased risk of cancer of the urinary tract (26 exposed cases) was apparent for shift workers compared with day workers or the local population (Yong et al., 2014a). [The Working Group noted that exposure classification was assessed as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and that results for direction of rotation and duration were not presented. The study power for specific sites was limited.]

(j) Cancer of the skin

Incident malignant melanoma (94 total cases) was assessed for men in the multisite case–control study in Montreal, Canada, with no risk apparent for ever night work or for less than 5 years cumulative duration of night work. There was some indication of possible increased risks for a cumulative duration of 5–10 years and for timing of night work in the recent past (≤ 20 years), although effect estimates were imprecise (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

In the male chemical workers cohort study in Germany, no increased risk was apparent for shift workers for malignant melanoma (27 exposed cases) compared with day workers or the local population (Yong et al., 2014a). [The Working Group noted that exposure classification was assessed as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and that results for direction of rotation and duration

were not presented. The study power for specific sites was limited.]

Basal cell carcinoma (n = 4308), squamous cell carcinoma (n = 334), and malignant melanoma (n = 212) were the focus of an analysis of the NHS-II cohort including registered nurses from 14 states of the USA followed for 10 years (n = 74 323) (Heckman et al., 2017, updating Schernhammer et al., 2011). Outcomes were initially self-reported; only confirmed cases of invasive melanoma and invasive squamous cell carcinoma were included in the analyses, although pathology confirmation was not obtained for self-reported cases of basal cell carcinoma. Work patterns of rotating shifts including at least 3 nights per month were ascertained through questionnaires, with an additional question in a subsequent questionnaire including permanent nights for 6 months or more. Most results were null, with some decreased risks apparent for basal cell carcinoma only.

(k) Cancer of the haematopoietic and lymphoid tissues

Non-Hodgkin lymphoma (NHL) (197 cases) was assessed for men in the multisite case–control study in Montreal, Canada, with a greater than 2-fold increased risk apparent for ever night work for all three levels of cumulative duration and for timing of night work more recent than 20 years ago (Parent et al., 2012). [The Working Group noted that no information on type of shifts or intensity was available. Proxy interviews were conducted for 18% of cases and 13% of controls, and night work information was missing for a higher proportion of cases (16%) than controls (4%).]

In the NHS-I cohort described in Section 2.1.1(a)(xii), there was no evidence of increased mortality from NHL associated with night shift duration (Gu et al., 2015).

A study of cancer mortality was conducted among workers at a chemical manufacturing plant in New York State, USA, with follow-up from 1960–2007 (Carreón et al., 2014). A subgroup of job titles in the polyvinyl chloride and rubber chemical departments involved rotating shift work including some overnight shifts. Analyses considered ever exposure to shift work (77% of the cohort had ≥ 1 day of shift work) and duration of shift work exposure. Results for shift work were reported only for mortality from NHL in men, with an apparent increased risk compared with the USA population (n = 8 deaths with shift work exposure), but not compared with other workers in this cohort (n = 3 deaths without shift work exposure). [The Working Group noted the small number of deaths, short duration of employment (median, 1.6 years), and crude exposure assessment. There was also concern that some co-exposures were not taken into account, and that only one cancer site was reported.]

In the male chemical workers cohort study in Germany, no increased risk of NHL was apparent for shift workers (15 exposed cases) compared with day workers (Yong et al., 2014a). For leukaemia, an increased risk was apparent for shift workers compared with day workers. [The Working Group noted that exposure classification was assessed as dichotomous (≥ 1 year of shift work vs never shift work) at the time of cohort entry, and that results for direction of rotation and duration were not presented. The study power for specific sites was limited.]

In a case–control study in five regions of Spain, 321 incident cases of chronic lymphocytic leukaemia and 1728 population-based controls were compared using the same methods and exposure assessment as reported in Gyarmati et al. (2016) (Costas et al., 2016). About 25% of cases and 20% of controls had ever worked night shifts. Increased risks were apparent for ever rotating shift workers at the highest cumulative duration category (> 23 years, n = 26 exposed cases), without clear evidence of a dose–response relationship. Ever night work, duration of permanent night shift, time since last shift, and age at

first shift were not associated with increased risk of chronic lymphocytic leukaemia.

2.2 Studies among aircrew

2.2.1 Cockpit crew

See Table 2.6.

Aircraft pilots and other cockpit crew are regularly engaged in shift work and, particularly on long-distance flights, may cross several time zones during flying. The prime focus of cohort studies among cockpit crew has been their exposure to ionizing radiation of cosmic origin and the subsequent risk of cancer. Additional metrics aiming to quantify circadian rhythm disruption were also assessed in some studies, and these are reviewed here. Other studies that include exposure data which are not considered useful proxies of circadian rhythm disruption were not reviewed in detail. These include cohorts from Canada (Band et al., 1990, 1996), Denmark (Gundestrup & Storm, 1999), Germany (Zeeb et al., 2002, 2010; Hammer et al., 2012), Greece (Paridou et al., 2003), Iceland (Gudmundsdottir et al., 2017), Italy (Ballard et al., 2000), Norway (Haldorsen et al., 2000, 2002), the Republic of Bulgaria (Milanov et al., 1999), Sweden (Hammar et al., 2002), the UK (Irvine & Davies, 1992, 1999; De Stavola et al., 2012; dos Santos Silva et al., 2013), and the USA (Grayson & Lyons, 1996a, b; Nicholas et al., 1998; Rogers et al., 2011), as well as several other early studies (Salisbury et al., 1991; Kaji et al., 1993). A cohort study of Icelandic cockpit crew (Rafnsson et al., 2000) contained some information on flying across time zones, but the sample size was very small; this study was not considered further. Pooled cohort data analysed for mortality also did not include relevant exposure information, and respective studies were not considered further (Blettner et al., 2003; Langner et al., 2004; Hammer et al., 2014).

In a joint analysis of cockpit crew cohorts from Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), 10 051 men and 160 women were followed for cancer incidence in the respective national cancer registries, which are known for their completeness and high-quality data (Pukkala et al., 2003). Among the available exposure data, cumulative block hours (i.e. flight hours plus aircraft taxi time) on long-haul flights were estimated from annual job-history data and expert assessments of aircraft typology. The estimate of the standardized incidence ratio for all cancers combined was not statistically elevated for male cockpit crew with 10 000 hours or more on any aircraft type (SIR, 1.10; 95% CI, 0.97–1.24). In the same subgroup, an elevated risk of melanoma (SIR, 3.05; 95% CI, 2.04–4.38) and cancer of the prostate (SIR, 1.24; 95% CI, 0.89–1.68) was observed. For pilots aged 60 years and older, the incidence rate of cancer of the prostate was significantly elevated in those with 10 000 long-haul block hours or more compared with those with less than 5000 long-haul block hours (RR, 3.88; 95% CI, 1.26–11.9); this pattern was not seen in younger pilots. The risk of cancer of the prostate for all pilots with 10 000 long-haul block hours or more was also elevated (SIR, 1.56; 95% CI, 0.67–3.07). [The Working Group noted that the strengths of this study included its large size and the high-quality incidence follow-up. The cumulative hours of long-haul flying were seen as a reasonable proxy of circadian rhythm disruption, and the assessment of job history was relatively homogeneous across cohorts. There were limitations with regard to potential confounders, particularly for the estimates of risk of melanoma (e.g. leisure-time ultraviolet radiation). A high correlation between shift work and other occupational exposures, including cosmic radiation, needed to be taken into consideration, although ionizing radiation is not strongly associated with cancer of the prostate.]

Yong et al. (2014c) studied the mortality of 5964 former cockpit crew employed between 1953 and 1991 by a large United States airline on which international routes predominated, with

Table 2.6 Studies of cancer among aircraft cockpit crew

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled[a]	Comments[a]
Pukkala et al. (2003) Denmark, Finland, Iceland, Norway, Sweden Denmark, 1943–1996; Finland, 1953–1997; Iceland, 1984–1997; Norway, 1962–1996; Sweden, 1961–1996 Cohort	10 051 men and 160 women; eligibility criteria varied by country but in general cohort was identified from registers of pilots held by aviation authorities (Denmark, Finland, Iceland, Norway) or airline company registers (Sweden); cohorts identified from Iceland and Sweden included men only Exposure assessment method: JEM assessment; night shift undefined	All cancers combined	Categories of block hours[b] (SIR):			Not specified	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (limited period). Temporality: Complete. Information on flying over time zones: Limited. No other information available. *Other comments*: a reverse age-specific risk pattern was seen for prostate cancer with radiation dose: the RR for exposure category ≥ 20 mSv was elevated for age < 60 yr (RR, 9.13; 95% CI, 1.11–74.9; 8 cases; *P* for trend, 0.02), but not for age ≥ 60 yr (RR, 1.08; 95% CI, 0.55–2.12; 16 cases), which may be relevant for circadian disruption Strengths: large sample size with complete follow-up Limitations: unless otherwise specified, the block hours are not exclusively from long-haul flights
			≥ 10 000 h	257	1.10 (0.97–1.24)		
		Colon	Categories of block hours (SIR):				
			1–999 h	8	2.56 (1.11–5.05)		
			1000–4999 h	1	0.23 (0.01–1.26)		
			5000–9999 h	4	0.77 (0.21–1.97)		
			≥ 10 000 h	14	0.78 (0.42–1.3)		
		Lung	Categories of block hours (SIR):				
			1–999 h	1	0.19 (0.01–1.08)		
			1000–4999 h	10	1.31 (0.63–2.4)		
			5000–9999 h	6	0.62 (0.23–1.35)		
			≥ 10 000 h	30	0.78 (0.53–1.12)		
		Prostate	Categories of block hours (SIR):				
			1–999 h	4	0.76 (0.21–1.94)		
			1000–4999 h	5	0.89 (0.29–2.07)		
			5000–9999 h	7	1.27 (0.51–2.62)		
			≥ 10 000 h	42	1.24 (0.89–1.68)		
		Skin (malignant melanoma)	Categories of block hours (SIR):				
			1–999 h	2	0.78 (0.09–2.83)		
			1000–4999 h	9	1.79 (0.82–3.41)		
			5000–9999 h	14	2.55 (1.4–4.28)		
			≥ 10 000 h	29	3.05 (2.04–4.38)		
		Skin (non-melanoma skin cancer, excludes basal cell carcinoma and all non-melanoma skin cancer diagnosed in Denmark before 1979)	Categories of block hours (SIR):				
			1–999 h	2	1.59 (0.19–5.74)		
			1000–4999 h	2	1.12 (0.14–4.03)		
			5000–9999 h	3	1.55 (0.32–4.53)		
			≥ 10 000 h	19	2.69 (1.62–4.2)		

Table 2.6 Studies of cancer among aircraft cockpit crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled[a]	Comments[a]
Pukkala et al. (2003) (cont.)		CNS	Categories of block hours (SIR):				
			1–999 h	1	0.5 (0.01–2.8)		
			1000–4999 h	5	1.13 (0.01–2.8)		
			5000–9999 h	2	0.44 (0.37–2.63)		
			≥ 10 000 h	8	0.98 (0.42–1.93)		
		Leukaemia	Categories of block hours (SIR):				
			1–999 h	0	–		
			1000–4999 h	2	0.95 (0.11–3.41)		
			5000–9999 h	4	1.78 (0.48–4.55)		
			≥ 10 000 h	8	1.41 (0.61–2.79)		
		CLL	Categories of block hours (SIR)				
			1–999 h	0	–		
			1000–4999 h	0	–		
			5000–9999 h	0	–		
			≥ 10 000 h	4	1.74 (0.47–4.46)		
		Leukaemia: (non-CLL)	Categories of block hours (SIR):				
			1–999 h	0	–		
			1000–4999 h	2	1.17 (0.14–4.21)		
			5000–9999 h	4	2.41 (0.66–6.17)		
			≥ 10 000 h	4	1.19 (0.32–3.05)		
		Leukaemia (AML)	Categories of block hours (SIR):				
			1–999 h	0	–		
			1000–4999 h	0	–		
			5000–9999 h	3	3.67 (0.76–10.7)		
			≥ 10 000 h	2	1.12 (0.14–4.03)		
		Skin (basal cell carcinoma): only Denmark (1979–1996) and Finland (1953–1997)	Categories of block hours (SIR):				
			1–999 h	0	–		
			1000–4999 h	7	2.44 (0.98–5.02)		
			5000–9999 h	12	3.08 (1.47–4.97)		
			≥ 10 00 h	35	2.78 (1.93–3.86)		

Table 2.6 Studies of cancer among aircraft cockpit crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled[a]	Comments[a]
Pukkala et al. (2003) (cont.)		Skin (malignant melanoma of the head and neck)	Categories of block hours (SIR):				
			1–999 h	1	3.26 (0.08–18.2)		
			1000–4999 h	1	1.77 (0.04–9.87)		
			5000–9999 h	3	5.11 (1.05–14.9)		
			≥ 10 000 h	2	1.75 (0.21–6.32)		
		Skin (malignant melanoma of the trunk)	Categories of block hours (SIR):				
			1–999 h	1	0.69 (0.02–3.87)		
			1000–4999 h	7	2.54 (1.02–5.23)		
			5000–9999 h	4	1.3 (0.35–3.33)		
			≥ 10 000 h	19	3.5 (2.1–5.46)		
		Skin (malignant melanoma of the limbs)	Categories of block hours (SIR):				
			1–999 h	0	–		
			1000–4999 h	0	–		
			5000–9999 h	5	3.5 (1.13–8.16)		
			≥ 10 000 h	7	3.5 (1.29–6.59)		
		Prostate	Categories of block hours in long-haul aircraft, age ≥ 60 yr (RR):				
			< 5000 h	NR	1		
			5000 to < 9999 h	NR	NR		
			≥ 10 000 h	8	3.88 (1.26–11.9)		
			Trend test *P* value, 0.01				
		Prostate	Categories of block hours in long-haul aircraft (SIR):				
			≥ 10 000 h	8	1.56 (0.67–3.07)		
			Trend test *P* value, 0.07				

Table 2.6 Studies of cancer among aircraft cockpit crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled[a]	Comments[a]
Yong et al. (2014c) USA 1 January 1953–1990; follow-up to 31 December 2008 Cohort	5964 persons with 202 316 PYAR; 99.9% men; employed as a pilot or flight engineer with Pan Am after 1 January 1953 and for ≥ 1 yr before 1990; US citizens at the time of hire; worked ≥ 1 d Exposure assessment method: JEM-based, non-individual data in terms of block hours and flight type, but no definition of night shift	Leukaemia (non-CLL)	Cumulative radiation dose (mSv) quartiles, no lag (SRR):			Age and calendar period, sex, race	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (limited period). Temporality: Complete. No other information available. *Other comments*: cited evidence to support a strong correlation between estimated cumulative cosmic radiation and cumulative time zones crossed in this cohort Limitations: mortality rather than incident data; small number of cancer-specific deaths
			0 to < 22.9 mSv	5	1		
			22.9 to < 35.1 mSv	1	0.09 (0.01–0.77)		
			35.1 to < 44.8 mSv	10	1.04 (0.35–3.09)		
			≥ 44.8 mSv	3	0.30 (0.07–1.32)		
		Leukaemia (non-CLL)	Cumulative radiation dose (mSv) quartiles, 2-yr lag (SRR):				
			0 to < 22.3 mSv	5	1		
			22.3 to < 34.8 mSv	1	0.08 (0.01–0.72)		
			34.8 to < 44.7 mSv	10	0.98 (0.33–2.9)		
			≥ 44.7 mSv	3	0.31 (0.07–1.37)		
		CNS	Cumulative radiation dose (mSv) quartiles, no lag (SRR):				
			0 to < 22.9 mSv	7	1		
			22.9 to < 35.1 mSv	6	0.84 (0.27–2.63)		
			35.1 to < 44.8 mSv	11	1.5 (0.56–4.04)		
			≥ 44.8 mSv	8	1.27 (0.39–4.1)		
		CNS	Cumulative radiation dose (mSv) quartiles, 10-yr lag (SRR):				
			0 to < 18.1 mSv	9	1		
			18.1 to < 32.5 mSv	8	1.29 (0.41–4.00)		
			32.5 to < 43.7 mSv	6	1.13 (0.35–3.68)		
			≥ 43.7 mSv	9	3.84 (1.00–14.7)		

Table 2.6 Studies of cancer among aircraft cockpit crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled[a]	Comments[a]
Yong et al. (2014c) (cont.)		Skin (malignant melanoma)	Cumulative radiation dose (mSv) quartiles, no lag (SRR):				
			0 to < 22.9 mSv	6	1		
			22.9 to < 35.1 mSv	6	1.85 (0.53–6.51)		
			35.1 to < 44.8 mSv	6	1.66 (0.48–5.77)		
			≥ 44.8 mSv	5	0.71 (0.2–2.6)		
		Skin (malignant melanoma)	Cumulative radiation dose (mSv) quartiles, 10-yr lag (SRR):				
			0 to < 18.1	6	1		
			18.1 to < 32.5	8	2.92 (0.76–11.3)		
			32.5 < 43.7	5	1.4 (0.33–5.93)		
			≥ 43.7	4	0.73 (0.16–3.29)		
		Leukaemia (non-CLL)	Employment duration in years, no lag (SRR):				
			1 to < 18.9 yr	4	1		
			18.9 to < 26.4 yr	4	0.68 (0.13–3.51)		
			26.4 to < 31.8 yr	6	1.02 (0.28–3.76)		
			≥ 31.8 yr	5	1.65 (0.35–7.78)		
		Leukaemia (non-CLL)	Employment duration in years, 2-yr lag (SRR):				
			0 to < 18.5 yr	4	1		
			18.5 to < 26.2 yr	4	0.67 (0.13–3.47)		
			26.2 to < 31.7 yr	8	1.43 (0.42–4.92)		
			≥ 31.7 yr	3	0.25 (0.06–1.15)		
		CNS	Employment duration in years, no lag (SRR):				
			1 to < 18.9 yr	6	1		
			19.9 to < 26.4 yr	11	2.38 (0.78–7.23)		
			26.4 to < 31.8 yr	10	4.47 (1.46–13.71)		
			≥ 31.8 yr	5	1.53 (0.39–5.92)		
		CNS	Employment duration in years, 10-yr lag (SRR):				
			0 to < 15.5 yr	12	1		
			15.5 to < 25.0 yr	7	1.02 (0.32–3.22)		
			25.0 to < 31.3 yr	10	1.62 (0.62–4.26)		
			≥ 31.3 yr	3	0.37 (0.09–1.59)		

Table 2.6 Studies of cancer among aircraft cockpit crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled[a]	Comments[a]
Yong et al. (2014c) (cont.)		Skin (malignant melanoma)	Employment duration in years, no lag (SRR):				
			1 to < 18.9 yr	7	1		
			18.9 to < 26.4 yr	8	0.96 (0.24–3.83)		
			26.4 < 31.8 yr	5	0.59 (0.14–2.46)		
			≥ 31.8 yr	3	0.31 (0.06–1.57)		
		Skin (malignant melanoma)	Employment duration in years, 10-yr lag (SRR):				
			0 to < 15.5 yr	7	1		
			15.5 to < 25.0 yr	9	3.52 (1.00–12.42)		
			25.0 to < 31.3 yr	5	1.38 (0.37–5.1)		
			≥ 31.3 yr	2	0.70 (0.11–4.61)		

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; d, day; h, hour; JEM, job-exposure matrix; NR, not reported; Pan Am, Pan American World Airways; PYAR, person-years at risk; RR, relative risk or rate ratio; SIR, standardized incidence ratio; SRR, standardized rate ratio; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

[b] "Block hours" refers to gate departure to gate arrival (aircraft taxi time and air time).

follow-up for mortality through 2008. Although the focus was on exposure to cosmic radiation, the exposure reconstruction was based on detailed domicile-, era-, and flight-specific information, so that higher estimated doses are considered a proxy for circadian rhythm disruption through their high correlation with cumulative time zones crossed. The analysis focused on mortality from cancer of the central nervous system (CNS), leukaemia excluding chronic lymphocytic leukaemia (CLL), and malignant melanoma. The standardized rate ratio (SRR) was elevated for cancer of the CNS and malignant melanoma, but reduced for leukaemia excluding CLL. Using a 10-year lag, internal comparisons indicated an almost 4-fold increase in mortality from cancer of the CNS (SRR, 3.84; 95% CI, 1.00–14.74) for those cockpit crew in the highest versus the lowest dose quartile, a finding that was also reflected in exposure–response analyses using Cox proportional hazards regression. A positive trend was not observed between duration of employment and malignant melanoma. [The Working Group noted that the strengths of this study included the detailed cohort characterization and long-follow-up, spanning more than 50 years. However, the study had several limitations: the exposure assessment relied on cumulative radiation dose as a proxy, specific metrics related to circadian rhythm disruption were not used in the analysis, the number of cases in stratified and dose–response analyses was small in several instances, and the specific cancer entities on which this study focused were less relevant with respect to circadian rhythm disruptions.]

2.2.2 Cabin crew

See Table 2.7.

Similar to airline cockpit crew, cabin crew (e.g. flight attendants) may be exposed to shift work and associated circadian rhythm disturbance. This exposure is highly correlated with other work-related exposures, namely cosmic radiation. Exposure to cosmic radiation is a major confounder in the potential association between shift work and cancer; however, information about this confounder is not available in most cabin crew studies. This section reports on cabin crew studies that include an assessment of circadian rhythm disruption. Cabin crew studies that do not provide an approach to exposure assessment beyond the actual job title and duration of employment were not reviewed further, as well as studies without information on transmeridian travel. This includes the first report on the incidence of cancer of the breast among female cabin crew in Finland (Pukkala et al., 1995); a case–control study in the same population (Kojo et al., 2005); reports on German (Blettner et al., 2002; Zeeb et al., 2010), Greek (Paridou et al., 2003), Icelandic (Rafnsson et al., 2001, 2003), Italian (Ballard et al., 2002), and Norwegian (Haldorsen et al., 2001) cabin crew cohorts; and two pooled mortality analyses (Zeeb et al., 2003; Hammer et al., 2014).

Reynolds et al. (2002) studied a cohort of 8111 cabin crew from California, USA, identified via flight attendant union membership. Incident cases were followed up via the California Cancer Registry for the period 1988–1995. Domestic versus international flight assignments were differentiated. Of 60 cases of cancer of the breast, 31 (19.2 expected) occurred among cabin crew assigned to international routes. The risk was significantly elevated for attendants on international routes (SIR, 1.62; 95% CI, 1.10–2.30) compared with the risk for attendants on domestic routes (SIR, 1.10; 95% CI, 0.73–1.60). [The Working Group noted that this was a large cohort study with incidence follow-up through a high-quality cancer registry. The study provided standardized incidence ratios only, meaning that there was no control for potential confounders except for age. The study provided very limited information on circadian rhythm disruption or shift work, as only a crude dichotomized exposure variable (type of flight assignment), with

Table 2.7 Studies of cancer among aircraft cabin crew

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Linnersjö et al. (2003) Sweden 1961–1996 Nested case–control	48 cases: based on cancer registry; cabin attendants employed by SAS Sweden during 1957–1994, and resident of Sweden (and not formerly employed by Linjeflyg) 174 controls: randomly selected cohort members without cancer diagnosis at the time of case diagnosis, matched by sex and age group (± 5 yr) Exposure assessment method: records; JEM assessment; night shift undefined	Breast	High-altitude, long-distance flights, women (OR): Duty (yes/no) > 5000 h (yes/no)	 14 5	 1.79 (0.31–10.45) 3.27 (0.54–19.7)	NR	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (limited period). Information on flying over time zones: Limited. No other information available. *Other comments*: analysis of total block hours, aircraft type, and a combined measure of total block hours and aircraft type Strengths: nested in a well-characterized cohort Limitations: small number of cases (16 breast, 10 malignant melanoma); crude, non-individual exposure assessment
		Skin (malignant melanoma)	High-altitude, long-distance flights, women (OR): > 5000 h (yes/no)	 2	 2.59 (0.18–37.2)	NR	
		Skin (malignant melanoma)	High-altitude, long-distance flights, men (OR): > 5000 h (yes/no)	 3	 1 (0.03–31.97)	NR	
Pukkala et al. (2012) Finland, Iceland, Sweden, 1953–2005 Nested case–control	152 cases: based on cancer registry; among cabin attendant cohorts from three Nordic countries No. controls NR: cohort members matched by year of birth, alive, and free of breast cancer at date of incident case (all eligible controls) Exposure assessment method: JEM assessment; night shift undefined	Breast	Flights passing six or more time zones, women (OR): Per 100 flights passing six or more time zones	 152	 0.92 (0.77–1.11)	Parity	*Exposure assessment critique*: NSW in ref. group: Undefined. Intensity: Precise. Duration: Partial (limited period). Information on flying over time zones: Cumulative SSI and time zones crossed. No other information available. *Other comments*: follow-up times for underlying cohorts varied between countries, with Finland having the longest follow-up (1953–2005) Strengths: nested design in well-defined cohorts Limitations: limited exposure information

Table 2.7 Studies of cancer among aircraft cabin crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Reynolds et al. (2002) USA 1988–1995 Cohort	8111 cabin attendants residing in California Exposure assessment method: JEM assessment; night shift undefined	Breast	Type of routes flown (SIR): International Domestic	 31 28	 1.62 (1.10–2.3) 1.10 (0.73–1.60)	Age, calendar period	*Exposure assessment critique*: NSW in ref. group: Undefined. Duration: Partial (limited period). Information on flying over time zones: Limited. No other information available Strengths: large cohort with follow-up via high-quality cancer registry Limitations: limited exposure data; only domestic vs international flights; no covariate information
Pinkerton et al. (2012) USA 1979–2007 Cohort	11 311 flight attendants formerly employed by Pan Am Exposure assessment method: JEM assessment; night shift defined (exposed for ≥ 3 h between 22:00 and 08:00 local time at origin)	Breast	Cumulative number of time zones crossed, women (SMR): < 1100 1100 to < 2500 2500 to < 5600 ≥ 5600	 23 15 17 21	 1.17 (0.74–1.76) 1.02 (0.57–1.68) 1.12 (0.65–1.79) 1.1 (0.68–1.69)	Race, age, calendar period	*Exposure assessment critique*: NSW in ref. group: Yes. Intensity: Precise. Duration: Partial (limited period). Information on flying over time zones: Cumulative SSI and time zones crossed. No other information available Strengths: comprehensive cohort identification and long follow-up; specific focus on exposure metrics related to shift work and circadian rhythm disturbance Limitations: mortality only; short average duration of employment; small number of cases of melanoma and brain cancer (men)
		Breast	Cumulative hours spent working during SSI, women (SMR): < 410 h 410 to < 1100 h 1100 to < 2300 h ≥ 2300 h	 19 14 22 21	 1.04 (0.63–1.63) 0.95 (0.52–1.6) 1.31 (0.82–1.99) 1.11 (0.69–1.69)		

Table 2.7 Studies of cancer among aircraft cabin crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schubauer-Berigan et al. (2015) USA 1953–2005 Cohort	6093 female flight attendants formerly employed by Pan Am Exposure assessment method: JEM assessment; night shift defined (exposed for ≥ 3 h between 22:00 and 08:00 local time at origin)	Breast	Time spent working during SSI (h), 10-yr lag (SRR):			Race, age, calendar period	*Exposure assessment critique*: NSW in ref. group: No. Intensity: Precise. Duration: Complete. Information on flying over time zones: Cumulative SSI and time zones crossed. No other information available. Strengths: large study size; long follow-up; high number of breast cancer cases; availability of large set of covariates Limitations: moderate response proportion (64.4% of full cohort); highly correlated exposure metrics
			0 to < 318 h	69	1		
			318 to < 792 h	69	1.00 (0.69–1.45)		
			792 to < 1435 h	67	1.41 (0.98–2.05)		
			1435 to < 2642 h	70	1.13 (0.78–1.63)		
			≥ 2642 h	68	0.93 (0.64–1.36)		
			Trend test *P* value, 0.62				
		Breast	Cumulative number of time zones crossed, 10-yr lag (SRR):				
			0 to < 724	69	1		
			724 to < 1716	70	0.94 (0.66–1.36)		
			1716 to < 3201	67	1.17 (0.81–1.68)		
			3201 to < 6399	68	1.01 (0.69–1.47)		
			≥ 6399	69	0.87 (0.60–1.26)		
			Trend test *P* value, 0.25				
		Breast [95% CIs calculated using provided standard error]	Trend slope for 10-yr lagged hours flying in SSI (breast cancers per person-year × hours):				
			Parity 0	124	9.93×10^{-9} [(-2.94×10^{-7})–(3.14×10^{-7})]		
			Parity 1	63	-4.65×10^{-8} [(-5.37×10^{-7})–(4.44×10^{-7})]		
			Parity 2	111	1.52×10^{-7} [(-3.85×10^{-7})–(6.89×10^{-7})]		
			Parity ≥ 3	42	7.00×10^{-7} [(1.34×10^{-7})–(1.27×10^{-6})]		

Table 2.7 Studies of cancer among aircraft cabin crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schubauer-Berigan et al. (2015) (cont.)		Breast [95% CIs calculated using provided standard error]	Trend slope for 10-yr lagged cumulative time zones crossed (breast cancers per person-year × zones):				
			Parity 0	124	-6.74×10^{-8} [(-1.36×10^{-7})–(8.08×10^{-10})]		
			Parity 1	63	-7.43×10^{-8} [(-1.31×10^{-7})–(1.79×10^{-8})]		
			Parity 2	111	9.98×10^{-8} [(-1.57×10^{-7})–(3.57×10^{-7})]		
			Parity ≥ 3	42	6.22×10^{-7} [(1.26×10^{-7})–(1.12×10^{-6})]		
		Breast [95% CIs calculated using provided standard error]	Trend slope for 10-yr lagged hours flying in SSI (breast cancers per person-year × h), age at first birth for parous women:				
			Age 14 to < 25 yr at first birth	17	–		
			Age 25–29 yr at first birth	93	2.58×10^{-9} ((-8.25×10^{-7})–(8.30×10^{-7}))		
			Age 30–34 yr at first birth	65	-2.83×10^{-8} ((-4.44×10^{-7})–(3.87×10^{-7}))		
			Age ≥ 35 yr at first birth	41	-6.13×10^{-8} ((-3.85×10^{-7})–(2.62×10^{-7}))		

Table 2.7 Studies of cancer among aircraft cabin crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Schubauer-Berigan et al. (2015) (cont.)		Breast [95% CIs calculated using provided standard error]	Trend slope for 10-yr lagged cumulative time zones crossed (breast cancers per person-year × zones), age at first birth for parous women:				
			Age 14 to < 25 at first birth	17	2.18×10^{-7} ((2.00×10^{-8})–(4.16×10^{-7}))		
			Age 25–29 yr at first birth	93	1.44×10^{-7} ((-2.21×10^{-7})–(5.09×10^{-7}))		
			Age 30–34 yr at first birth	65	-1.07×10^{-7} ((-2.44×10^{-7})–(2.98×10^{-8}))		
			Age ≥ 35 yr at first birth	41	-3.16×10^{-8} ((-2.63×10^{-7})–(2.00×10^{-7}))		
Pinkerton et al. (2016) USA 1953–2005 Cohort	6093 female flight attendants formerly employed by Pan Am Exposure assessment method: JEM assessment; night shift defined (exposed for ≥ 3 h between 22:00 and 08:00 local time at origin)	Breast	Hours in SSI, parity ≥ 3 and 10-yr lag (ERR):			Age, age at menarche, age at first birth, height, alcohol status, menopausal status, use of HRT, family history of breast cancer	*Exposure assessment critique*: NSW in ref. group: No. Duration: Complete. Information on flying over time zones: Cumulative SSI and time zones crossed. No other information available Strengths: large study size; long follow-up; high number of breast cancer cases; availability of large set of covariates Limitations: moderate response proportion (64.4% of full cohort); highly correlated exposure metrics
			Per 2000 h	42	0.99 (–0.041 to 4.3)		
			Trend test *P* value, 0.04				
		Breast	Cumulative number of time zones crossed, parity ≥ 3 and 10-yr lag (ERR):				
			Per 4600 zones	42	1.5 (0.14–6.2)		
			Trend test *P* value, 0.02				

Table 2.7 Studies of cancer among aircraft cabin crew (cont.)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method[a]	Organ site or cancer type	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments[a]
Pinkerton et al. (2018) USA 1953–2005 Cohort	6093 female flight attendants formerly employed by Pan Am Exposure assessment method: JEM assessment; night shift defined (exposed for ≥ 3 h between 22:00 and 08:00 local time at origin)	Skin (malignant melanoma)	Hours in SSI (h), 10-yr lag (HR): Per 1000 h	125	1.08 (0.95–1.21)	Age, year of birth (± 5 yr), race and/or ethnicity, education	*Exposure assessment critique*: NSW in ref. group: No. Duration: Complete. Information on flying over time zones: Cumulative SSI and time zones crossed. *Other comments*: SIRs were also computed, but not relevant for shift work assessment Strengths: large study size; long follow-up; availability of large set of covariates; in-depth modelling and sensitivity analyses Limitations: moderate response proportion (64.4% of full cohort); highly correlated exposure metrics
		Skin (malignant melanoma)	Cumulative number of time zones crossed, 10-yr lag (HR): Per 2000 zones	125	1.01 (0.90–1.12)		
		Thyroid	Hours in SSI, 5-yr lag (HR): Per 1200 h	20	1.04 (0.70–1.41)		
		Thyroid	Cumulative number of time zones crossed, 5-yr lag (HR): Per 2600 zones	20	1.11 (0.82–1.37)		
		Uterus/ uterine corpus	Hours in standard sleep interval, 5-yr lag (HR): Per 515 h	43	0.9 (0.79–1)	Age, race and/or ethnicity, HRT status, parity, age at first birth	
		Uterus/ uterine corpus	Cumulative number of time zones crossed, 5-yr lag (HR): Per 935 zones	43	0.9 (0.81–0.99)		

CI, confidence interval; ERR, excess relative risk; h, hour; HR, hazard ratio; HRT, hormone replacement therapy; JEM, job-exposure matrix; NR, not reported; OR, odds ratio; Pan Am, Pan American World Airlines; SAS, Scandinavian Airlines System; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SSI, standard sleep interval; yr, year.

[a] The standardized terms used in the exposure assessment method and critique are explained in Table 1.5 and Table 1.6, Section 1.

unknown specificity with regard to shift work, was available.]

Linnersjö et al. (2003) analysed cancer incidence in the period 1961–1996 among 2324 female and 632 male cabin crew employed by Scandinavian Airlines in Sweden, a virtually complete cohort of all cabin crew employed between 1957 and 1994. In a nested case–control analysis, information about high-altitude, long-distance flight hours based on aircraft type flown was used to compare 48 cases of cancer and 174 controls. Overall, there were no clear associations observed for the two main cancers evaluated, malignant melanoma and cancer of the breast. For women with at least 5000 hours of high-altitude, long-distance flights, the odds ratio for cancer of the breast was 3.27 (95% CI, 0.54–19.7) compared with female cabin crew with no hours or less than 5000 hours of such flights. [The Working Group noted that the strengths of the study were the well-defined cohort and the follow-up based on high-quality cancer registry information. However, the limitations of the study included a lack of specific or individual information on circadian disruption, the small cohort size, the use of crew flight history to estimate exposure to shift work, and the use of aircraft type as a proxy for long-distance flights.]

Cabin crew cohorts from Finland, Iceland, Norway, and Sweden were pooled to assess the risk of cancer in relation to occupational factors (Pukkala et al., 2012). The overall pooled cohort comprised 8507 women and 1559 men. A nested case–control study included 152 cases of cancer of the breast and multiple matched controls from all cohorts except Norway. The average annual number of flights passing six or more time zones was used as a proxy for circadian rhythm disruption. This information was not available at an individual level; instead, historical airline timetables for every fifth year were used to obtain information on flight duration and frequency. The odds ratio per 100 flights passing six or more time zones for cancer of the breast was 0.92 (95% CI, 0.77–1.11). Sensitivity analyses using other exposure cut-offs showed similar results. [The Working Group noted that the strength of this case–control study was that it was nested in a large, pooled, registry-based cohort with incidence follow-up through virtually complete cancer registries. However, it was limited by the lack of individual data on circadian rhythm disruption or shift work.]

A series of studies on the risk of cancer associated with occupational factors, including cosmic radiation and circadian rhythm disruption, was conducted in a cohort of cabin crew formerly employed by a large United States airline for which international routes predominated. An initial study of mortality among 11 311 cabin crew employed between 1953 and 1991 (Pinkerton et al., 2012) was followed by studies of the incidence of cancer in the same cohort.

The incidence of cancer of the breast was assessed through a questionnaire study in which 6093 female cabin crew (64.4% of all women in the full cohort) could be included (Schubauer-Berigan et al., 2015). The identification of cases of cancer of the breast was based on self-report validated by medical records and cancer registry linkage. The cumulative number of time zones crossed and cumulative time spent working in the standard sleep interval were estimated based on domicile and flight schedule data that were specific to time periods. Overall, 343 cases of cancer of the breast were identified in the cohort, 37% more than expected based on national cancer incidence rates in the USA. [The Working Group noted that this excess appeared to be explained by lower parity and older age at first birth in the cohort compared with women overall in the USA.] In the full cohort, no risk differences were seen with respect to cumulative hours flown during the standard sleep interval or cumulative time zones crossed. In analyses of the exposure–response slope stratified by reproductive variables, women with parity of two or more showed a positive trend for both metrics.

For women with parity of three and more, the exposure–response trend was stronger but the numbers were small. Inconsistent results were seen when exposure metrics were stratified by age at first birth. The exposure–response in the same incidence cohort was further studied using an extended set of covariates in a Cox regression analysis (Pinkerton et al., 2016). In 10-year lagged analyses, a positive exposure–response was noted for number of time zones crossed and hours spent flying in the standard sleep interval, as well as for cumulative exposure to cosmic radiation, only in the subset of women with parity of three or more. In this high-parity subgroup, a statistically significant excess relative risk (ERR) of 1.5 (95% CI, 0.14–6.2) per 4600 time zones crossed and an ERR of 0.99 (95% CI, −0.041 to 4.3) per 2000 hours working during the standard sleep interval was observed. [The Working Group noted that excess relative risk is commonly used in radiation epidemiology studies, and is defined as relative risk minus 1. The statistical significance of excess relative risk estimates is indicated by the confidence interval excluding zero. The large study size, the high number of cases of cancer of the breast, and the ability to adjust for other risk factors were noted as being among the strengths of the study. Limitations included the moderate response proportion and the high correlation of circadian disruption metrics with cosmic radiation exposure. However, as there are data (e.g. Ronckers et al., 2005) suggesting that an increased risk of cancer of the breast associated with cosmic radiation would be expected in women with low or zero parity, the risk increase only among women with high parity is not explained by ionizing radiation.]

Pinkerton et al. (2018) also investigated the association of melanoma of the skin (125 cases), cancer of the thyroid gland (20 cases), and cancers of the female reproductive system (174 cases) with circadian rhythm disruption metrics in the United States cabin crew cohort. Ascertainment of cases of cancer, exposure assessment, and statistical analyses resembled the earlier studies in this cohort. The standardized incidence ratio was not elevated for any of the included cancers. In the exposure–response analysis, slightly elevated hazard ratios were reported for melanoma with travel during the standard sleep interval (HR per 1000 hours, 1.08; 95% CI, 0.95–1.21) and for cancer of the thyroid gland with number of time zones crossed (HR per 2600 zones crossed, 1.11; 95% CI, 0.82–1.37); negative associations with time zones crossed were seen for cancer of the uterus. [Beyond the strengths and limitations already discussed for Schubauer-Berigan et al. (2015) and Pinkerton et al. (2016), the Working Group noted that this study benefited from the in-depth modelling approaches and the assessment of different lag periods in sensitivity analyses. However, the study was limited by the relatively low percentage of cancer self-reports that were confirmed by cancer registry data, the low number of cases for most individual cancers, and the lack of data on potential confounders (e.g. sun exposure for melanoma).]

2.3 Meta-analyses of night shift workers, including aircrew

Several meta-analyses concerning night work and the risk of cancer were available to the Working Group for cancers of the breast, prostate, and colon and rectum, and for other cancers, including all cancers combined. These meta-analyses overlapped within each particular cancer site, but were different with respect to the number of included studies and in terms of the most recently published studies included. To cover as many relevant studies as possible, the Working Group selected for discussion those meta-analyses that were the most complete and the most recent, and that enhanced the analyses beyond those considered in the individual studies. Overall, nearly all the meta-analyses were limited by a lack of comparability between

the individual studies as a result of the different methods of exposure assessment and definitions of night work (see Section 1.5.2). This may have contributed to a high degree of heterogeneity in the calculated meta-relative risks.

2.3.1 Cancer of the breast

Multiple meta-analyses of shift work and cancer of the breast have been published (including Megdal et al., 2005; Ijaz et al., 2013; Jia et al., 2013; Kamdar et al., 2013; Wang et al., 2013; He et al., 2015; Lin et al., 2015b; Travis et al., 2016; Liu et al., 2018). The Working Group selected for review the most complete with respect to the inclusion of published individual studies of night work and risk of cancer of the breast (Liu et al., 2018), two other recent meta-analyses that provided aggregate relative risks from more detailed analyses (by study design) and further exposure metrics not available in the most recent meta-analysis (He et al., 2015; Travis et al., 2016, updated in Travis et al., 2017), and the most recent meta-analysis of studies of cancer of the breast in flight crews (Liu et al., 2016).

The most recent meta-analysis (Liu et al., 2018) included prospective and retrospective studies in men and women published up to May 2018, combined data on shift work and the risk of any cancer, and included results for cancer of the breast as a subgroup analysis only; based on results from 37 studies, the relative risk of cancer of the breast in female shift workers was 1.22 (95% CI, 1.08–1.38). [The Working Group noted that some of the included studies were overlapping (including the NHS cohorts). Separate meta-analyses of results for cancer of the breast from prospective and retrospective studies, or from cohort and case–control studies, were not conducted. The methods state that relative risks were extracted for the longest versus shortest exposure time (and dose information from ordinal categorical data for a dose–response meta-analysis); however, inspection of the tabulated extracted data indicates that this is not always accurate. No summary estimates for cancer of the breast were presented for night shift work by duration, frequency, or intensity.]

The most recently published meta-analysis to provide summary relative risks from results of prospective studies of night shift work and cancer of the breast (Travis et al., 2016) combined data from the 10 cohort and case–cohort prospective studies that were available by June 2015, with a total of 4660 cases of cancer of the breast in women reporting night shift work (1.4 million women in total). The meta-analysis was also repeated using updated results from the NHS cohorts, available at that time only in abstract form (Schernhammer, 2014) but subsequently published in a full article (Wegrzyn et al., 2017). Studies were considered eligible for meta-analysis if they included prospectively collected (i.e. collected before diagnosis) individual-level data on work history and on other relevant risk factors for cancer of the breast, or had equivalent information, for women who had worked night shifts and for female non-night workers. The identified studies were assessed for quality with respect to study design, exposure assessment, adjustment for confounders, and the potential for bias resulting from differential recall or participation. Compared with other women, the combined relative risk was 0.99 (95% CI, 0.95–1.03) for any night shift work. Information on the incidence of cancer of the breast associated with 20 years or more of night shift work was available for 8 of the 10 prospective studies, and the combined relative risk was 1.01 (95% CI, 0.93–1.10). Four prospective studies had data on the incidence of cancer of the breast associated with 30 years or more of night shift work, and the combined relative risk was 1.00 (95% CI, 0.87–1.14). Using the updated NHS results (Wegrzyn et al., 2017), the combined relative risk for 20 years or more was 0.97 (95% CI, 0.90–1.06). There was limited heterogeneity between study-specific results, despite differences in design, population studied, exposure

definition and assessment, night shift pattern, and control of potential confounders. This meta-analysis was subsequently updated in a published response (Travis et al., 2017) to correspondence; with the inclusion of extended follow-up in 2 cohort studies, relative risks from the updated meta-analyses of findings from the 10 prospective studies were 0.99 (95% CI, 0.95–1.04) for any night shift work and 1.00 (95% CI, 0.92–1.09) for 20 years or more of night shift work. The prospective studies meta-analysis includes data from cohort studies in older women; elevated risks may therefore not be observed if risks associated with night shift work in earlier life do not persist. Nonetheless, in a meta-analysis of findings from four prospective studies that examined recent night shift work, the combined relative risk was 0.99 (95% CI, 0.89–1.11) for night shift work in the previous 10 years versus none (for an average night work duration of 14 years in the two studies for which this information was available) (Travis et al., 2017).

[The Working Group noted that the summary relative risks provided were for the exposure metrics available in the majority of individual prospective studies (i.e. never and ever night shift work, night shift work duration, and recentness of night work), and these are less detailed than what was available in many retrospective studies (see, for example, results from the pooled study of Cordina-Duverger et al. (2018) discussed in Section 2.1.1(b)(ii)). Most study exposure assessments were self-reported and, although the exact definition of night work varied between prospective studies, the majority of data were from studies that used a definition broadly based on that used in the NHS cohorts (regular night work for at least 3 nights per month).

The Working Group further noted that all of the included studies were prospective in design, minimizing selection and recall bias. The risk of bias from confounding was low, with all included individual studies providing relative risks from multivariable-adjusted statistical models that included established risk factors for cancer of the breast (with some additionally stating that the addition of other covariates had not materially altered findings), although the covariates included varied. One cohort study, a registry-based retrospective cohort study based on record linkage to information from population censuses on occupation, was deemed ineligible because of the study design: limited information was available on night shift work exposure and no information was available on established risk factors for cancer of the breast.]

In a 2015 meta-analysis of circadian-disrupting exposures in relation to risk of cancer of the breast, He et al. (2015) combined estimates from 5 cohort and 10 case–control studies that evaluated risk of cancer of the breast in relation to shift work (RR, 1.19; 95% CI, 1.08–1.32). Based on published data from nine case–control and three cohort studies, He et al. (2015) also calculated a combined estimate for an increment of 10 years of exposure to shift work and found no significant dose–response relationship between shift work and overall risk of cancer of the breast (RR, 1.06; 95% CI, 0.98–1.15); a similar result was found from an analysis restricted to cohort studies (RR, 1.03; 95% CI, 0.95–1.11). In case–control studies, an increment of 10 years of exposure to shift work was associated with a 16% increased risk of cancer of the breast (RR, 1.16; 95% CI, 1.06–1.27). [The Working Group noted that the primary focus of this meta-analysis was circadian disruption; few details are included for shift work specifically, in terms of methods for deriving the overall estimate and results for subgroups, for example, by study design.]

In the most recent meta-analysis of cancer of the breast in flight crews (Liu et al., 2016), the results from 10 studies published up to 2015 were combined by a random-effect model to provide information on the incidence of cancer of the breast among female flight attendants, with occupational title used as the only exposure variable. [Because of the poor exposure assessment with

no relevant metrics, the Working Group considered this study uninformative.]

2.3.2 Cancer of the prostate

The most complete meta-analysis of cancer of the prostate included 15 studies published between 2002 and October 2017, including 9 prospective cohort, 2 retrospective cohort, and 4 case–control studies. Three of the included studies were overlapping studies of airline crew without information on night shift work (Gan et al., 2018). The reported meta-risk calculations did not separate these 3 studies from the 12 studies based on assessment of night shift work. Populations from Asia, Europe, and North America were involved. The majority of the individual studies included were based on incident cancer of the prostate; two studies were based on death certificates. Results were adjusted for various cofactors, such as age, tobacco smoking, and BMI, which only had a marginal influence on results. The overall relative risk for ever exposure to shift work was 1.23 (95% CI, 1.08–1.41) based on the 15 studies. Fixed- and random-effect models gave similar results. A high degree of heterogeneity exists (I^2, 82.70%; $P < 0.001$). In sensitivity analyses omitting one study at a time, the meta-relative risk was only marginally changed and gave meta-results from 1.12 (95% CI, 1.03–1.23) to 1.27 (95% CI, 1.10–1.46). For the 12 cohort studies, of which 11 were prospective cohorts, the relative risk for ever exposure to shift work was 1.10 (95% CI, 1.00–1.22). For the four case–control studies, the odds ratio for ever exposure to shift work was 1.58 (95% CI, 1.04–2.42). A random-effect dose–response analysis based on four reported results from three case–control studies showed a positive association with increasing duration of shift work (RR per 5 years of shift work, 1.06; 95% CI, 0.99–1.14); however, there was evidence of nonlinearity in the association ($P = 0.0001$). [The Working Group noted that the quality assessment of each of the 15 studies was performed using the Newcastle–Ottawa scale, but meta-results stratified by this were not shown.]

Another meta-analysis included nine cohort studies published through February 2017 on night shift work and the risk of cancer of the prostate (Du et al., 2017). All nine studies were also included in the meta-analysis by Gan et al. (2018). One included study was based on mortality, and another study included male airline pilots from Denmark, Finland, Iceland, Norway, and Sweden, without assessment of night shift work. The quality assessment of each study was based on the Newcastle–Ottawa scale. The meta-relative risk for ever working night shift was 1.05 (95% CI, 1.00–1.11) based on a fixed-effect model and 1.08 (95% CI, 0.99–1.17) based on a random-effect model. Studies with a high quality score ($n = 6$) yielded a meta-relative risk of 1.04 (95% CI, 0.95–1.14), whereas three studies assigned a quality score of low to moderate yielded a relative risk of 1.21 (95% CI, 1.03–1.41). [The Working Group noted that the quality scores assigned to each of the nine individual studies were not available, which limits the transparency of the assignment.]

2.3.3 Cancer of the colon and rectum

Wang et al. (2015b) summarized results from three cohort and three case–control studies published through March 2014 on the risk of cancer of the colon and rectum. [The Working Group noted that one cohort study of radio and telegraph operators in Norway (Tynes et al., 1996) was included among the three cohort studies, although it did not assess shift work in relation to cancer of the colon and rectum.] Two studies reported on both men and women, three studies included women only, and one study was restricted to men. Both the Norwegian study and a large census-based cohort study from Sweden (Schwartzbaum et al., 2007) had very limited confounder control [the Working Group noted

that the Swedish study is classified as interview-based in the report by Wang et al. (2015b)], although most other studies included information on tobacco smoking, alcohol drinking, and BMI as potential confounders. The overall meta-relative risk was 1.32 (95% CI, 1.12–1.55) for the group exposed to the longest period of night shift work compared with the group exposed to the shortest period of night shift work. [The Working Group noted that the longest period of night shift work was not consequently used for the meta-analysis calculation.] A high degree of heterogeneity was observed (I^2, 77.7%; $P < 0.001$). The meta-relative risk was 1.63 (95% CI, 1.32–2.01) based on the case–control studies, and 1.08 (95% CI, 0.96–1.22) based on the cohort studies. An analysis based on duration of night shift work showed an increased relative risk of cancer of the colon and rectum of 1.11 (95% CI, 1.03–1.20) per 5 years of night shift work. [The Working Group noted that the very small number of studies included were of very different designs, greatly reducing the utility of the evaluation of this group of cancers. Further, two of the most informative studies on cancer of the colon and rectum were published since this meta-analysis was conducted.]

2.3.4 All cancers

Liu et al. (2018) conducted meta-analyses of night shift work and different cancers based on 57 articles published through May 2018. [The Working Group noted that there was an overlap for some studies (e.g. the NHS cohorts) and that the reported exposure assessment method was incorrect for some studies (e.g. Hansen, 2001; Talibov et al., 2018).] The meta-analyses were based on 21 case–control, 6 nested case–control, and 31 cohort studies. Quality assessment of each study was based on the Newcastle–Ottawa scale (Liu et al., 2018). The random-effect model was used to estimate a meta-relative risk for all cancers combined, usually based on longest versus shortest exposure to night shift, of 1.15 (95% CI, 1.08–1.22). [The Working Group noted that for some studies the relative risk was based on an ever versus never comparison, although night work duration was available.] The heterogeneity was high (I^2, 76.2%; $P \leq 0.001$). Results were relatively similar for men (1.14; 95% CI, 1.05–1.25) and women (1.12; 95% CI, 1.04–1.20). A dose–response analysis based on all cancers and duration of night shift work, using data from 29 studies that included at least three levels of night shift work, revealed an increased meta-relative risk of 1.032 (95% CI, 1.013–1.051) for every 5 years of night shift work. A two-stage random-effect model was used to evaluate linearity ($P < 0.001$). Analyses stratified by study design found meta-relative risks of 1.28 (95% CI, 1.15–1.42), 1.30 (95% CI, 0.89–1.90), and 1.07 (95% CI, 1.00–1.15) for case–control studies ($n = 21$), nested case–control studies ($n = 6$), and cohort studies ($n = 31$), respectively. Based on quality scores, the meta-relative risk was 1.16 (95% CI, 0.98–1.37) and 1.14 (95% CI, 1.08–1.21) for studies with a low ($n = 17$) and high ($n = 41$) quality score, respectively. Meta-relative risks were also estimated for cancers of the digestive system (1.15; 95% CI, 1.01–1.32; $n = 11$), haematological system (1.08; 95% CI, 0.99–1.17; $n = 5$), prostate (1.26; 95% CI, 1.05–1.52; $n = 11$), breast (1.22; 95% CI, 1.08–1.38; $n = 37$), reproductive system (1.06; 95% CI, 0.85–1.32; $n = 6$), lung (1.08; 95% CI, 0.87–1.35; $n = 5$), and skin (0.93; 95% CI, 0.50–1.74; $n = 3$). [The Working Group noted that the number of included studies for each type of cancer was not reported and, as described in Section 1.5.2(b), exposure categories were not transparent.]

2.4 Evidence synthesis for cancer in humans

Numerous epidemiological studies have been conducted since the publication of *IARC Monographs* Volume 98 (IARC, 2010), providing an extensive body of evidence from large cohort and case–control studies on cancer and night shift work including transmeridian travel. The largest number of studies examined cancer of the breast, several studies examined cancers of the prostate and colon and rectum, and a few studies were conducted of other cancers, including common cancers such as of the lung or the hormone-related cancers (for example, those of the ovary and endometrium).

2.4.1 Studies evaluated

In assessing the human carcinogenicity of night shift work, several cohort and case–control studies were considered to be the most informative on the basis of quality of study design (e.g. participation rates and selection bias, power of the study, and control of confounding) and exposure assessment (see Section 2.4.3) that, in this context, were considered crucial in determining the weight given to each study when interpreting the evidence. For example, well-designed general-population studies that examined shift work without identifying whether participants worked at night or only worked day shift-rotations were reviewed but not further considered. Population-based studies that used JEMs exclusively when characterizing exposure were also excluded.

Several studies examined the risk of cancer for workers in occupations with a high prevalence of night shift work or transmeridian travel, such as firefighters or aircrew. Some of these studies did not provide a specific evaluation of shift work, but simply compared the risk of cancer for the occupational study group with that for the general population (local or national). In the absence of other human evidence these studies could have been reviewed and evaluated; however, given that evidence from high-quality cohort and case–control studies on night shift work (or transmeridian travel) and cancer are now available, these occupational studies were not considered here.

2.4.2 Meta-analyses

Numerous meta-analyses were published. Among the most recent, the largest provided meta-risk estimates for 57 studies examining night shift work and cancer, and reported statistically significant positive meta-risks for all cancers combined and for cancers of the breast, prostate, and gastrointestinal tract (Liu et al., 2018). This study and most other recent meta-analyses were considered weakly informative because inclusion criteria varied and were often not well described, the definitions of exposure were frequently vague and did not allow meaningful aggregation or stratification into exposure subcategories, and consistent (or at least well-described) criteria were not used for the selection of effect estimates that were subsequently pooled.

2.4.3 Exposure assessment and misclassification of exposure

Exposure assessment quality of night shift work was a key parameter for the evaluation of the studies, and an extensive report of the strengths and limitations of this aspect of the human cancer studies is provided in Section 1.5.

A main issue affecting several of the cohort studies was that exposure assessment was based on limited information on night shift work (ever or never, and duration) and usually from the baseline survey only. Studies that did not distinguish between rotation of shift during the day or the night were excluded from further consideration. In nearly all cohort studies with detailed exposure assessments, the information was collected retrospectively. This would not result in potential differential misclassification (bias due to

differential reporting by disease status) because the information was collected before the disease occurred, but would result in non-differential misclassification of exposure (bias due to inaccurate reporting independent of disease status) that would usually bias effect estimates towards the null. Because of a lack of detailed information on night shift work, some cohort studies may have included evening shift workers in the group of night shift workers; some may have included night shift workers in the comparison unexposed group; and some examined only recent time windows of exposure of the last 5–10 years and, as a consequence, included night shift workers during earlier periods among the unexposed (comparison) group. All of these limitations may have biased effect estimates towards the null. Some cohort studies had a low percentage of night shift workers, affecting the power to detect associations. Exposure assessment was more thorough in several case–control studies that included detailed questionnaires on type of shift work and on several time-related variables, including lifetime occupational history, duration in each job, time of start and end of each job, frequency of night shifts per week, whether permanent or rotating night shift work, and, in some studies, direction of rotation. Exposure information in these studies was collected retrospectively following diagnosis (for cases) and, while they may be more detailed (reducing non-differential misclassification), they could be affected by recall bias (cases and controls reporting differentially as a result of their disease status). However, there is little empirical evidence regarding the extent and impact of biases in cohort or case–control studies.

2.4.4 Confounding and selection bias

Some early studies on night shift work and transmeridian travel were criticized for a lack of control for potential confounding, particularly concerning when surveys revealed that night workers tended to have different lifestyles and reproductive characteristics than those of day workers or the general population. Lifestyle factors found to be different between day and night shift workers include reproductive history (particularly for transmeridian travel), sleep duration and sleep quality, smoking behaviour, obesity, diet, and physical exercise. Subsequent studies have shown that differences in these lifestyle factors do exist between day and night shift workers, but are frequently less pronounced than initially expected.

Most of the reviewed epidemiological studies have extensive information on lifestyle factors, reproductive history, obesity, and contextual factors such as socioeconomic status, and, to a lesser extent, nutrition and physical exercise. These studies have convincingly shown that confounding by the factors examined should not be considered a major bias, at least in the populations where these studies were conducted (predominantly in western Europe and North America). It is possible that there are other potential confounding factors that have not been examined, but it is unlikely that they have affected the validity of the study findings. Even though confounding may not be a major source of bias, lack of adjustment for potential confounding factors cannot preclude this bias; the Working Group did not consider as high quality studies those that did not take confounding into account.

Potential for selection bias has been identified in both cohort and case–control studies, although case–control studies are more prone to such bias than cohort studies. The studies considered as informative and of high quality have aimed to minimize potential selection bias by achieving high response and (for cohort studies) follow-up rates, high-quality contact and interviews with participants, and statistical adjustment by contextual variables such as socioeconomic status. However, response rates in several of the high-quality population-based case–control studies were below 70%; although

this is considered an acceptable response rate for population-based studies, it may have resulted in selection bias. The degree and even the direction of this bias is difficult to accurately quantify. Self-selection of workers out of night shift work has been found to be associated with age and health status. This concerns especially cohort studies with no update of exposure information during the follow-up, and studies with a long time difference between exposure assessment and cohort entry time. Including participants who had performed night shift work in the reference group may have biased estimates from cohort studies towards the null.

2.4.5 Cancer of the breast

Among the studies conducted within cohorts, the Working Group evaluated 11 cohort studies of night shift workers (Pronk et al., 2010; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016 (comprising three cohorts: the Million Women Study, EPIC-Oxford, and UK Biobank); Vistisen et al., 2017; Wegrzyn et al., 2017 (comprising two cohorts: NHS-I and NHS-II); Jones et al., 2019), 1 case–cohort study (Li et al., 2015), and 5 nested case–control studies (Tynes et al., 1996; Lie et al., 2006; Lie et al., 2011; Hansen & Lassen, 2012; Hansen & Stevens, 2012). Eight population-based case–control studies (Davis et al., 2001; O'Leary et al., 2006; Papantoniou et al., 2016; Yang et al., 2019; the GENICA study (Pesch et al., 2010; Rabstein et al., 2013, 2014); the Breast Cancer Environment and Employment Study (Fritschi et al., 2013, 2018); CECILE (Menegaux et al., 2013; Truong et al., 2014; Cordina-Duverger et al., 2016); the study described in Grundy et al. (2013a, b)) and one hospital-based case–control study (Wang et al., 2015a) evaluating night shift work, and a pooled analysis of five of these studies (Cordina-Duverger et al., 2018), were considered for inclusion in the evidence synthesis. Three cohort studies among airline cabin crew with information on transmeridian travel were also considered: Linnersjö et al. (2003), Pukkala et al. (2012), and the United States cabin crew study (Schubauer-Berigan et al., 2015; Pinkerton et al., 2016). All studies were evaluated on study quality and potential informativeness, emphasizing the quality and extent of exposure information in the overall evaluation.

Among cohort-based designs, 3 out of 11 assessing ever/never exposure to night shift work using varying definitions of night work found a positive association (Hansen & Lassen, 2012; Hansen & Stevens, 2012; Knutsson et al., 2013), and the other 8 showed no association with ever night work (Pronk et al., 2010; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016 (three cohorts); Vistisen et al., 2017; Jones et al., 2019). The 13 cohort, case–cohort, or nested case–control studies evaluated duration of exposure to night work in relation to cancer of the breast; 6 of these (Tynes et al., 1996; Lie et al., 2006; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Åkerstedt et al., 2015; Wegrzyn et al., 2017 (NHS-II)) found an increased risk of cancer of the breast with long duration of night work, although one study (Tynes et al., 1996) observed an increased risk only among women aged 50 years and older. Several studies examined other indices of exposure related to intensity of exposure (e.g. average hours of night work per week; Jones et al., 2019) or composite exposure scores, but these exposure indices were not comparable across many studies and results were not easily evaluated jointly. Of the 17 cohort-based studies, 6 (Tynes et al., 1996; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_EPIC; Travis et al., 2017_UK Biobank; Vistisen et al., 2017) were considered weakly informative because of concerns regarding exposure misclassification or limited (e.g. only "current") exposure assessment, while one study was considered uninformative because of its small size (Knutsson et al., 2013). Detailed exposure information was available for only a few (predominantly nested case–control) studies.

None of the most informative studies of airline cabin crew (Linnersjö et al., 2003; Pukkala et al., 2012; Schubauer-Berigan et al., 2015; Pinkerton et al., 2016) showed a positive association with cancer of the breast for any of the shift work metrics used (e.g. number of time zones crossed), with the exception of some substrata (e.g. high-parity women in the cohort studied by Schubauer-Berigan et al., 2015 and Pinkerton et al., 2016). There was substantial potential for exposure misclassification in two of the three studies (Linnersjö et al., 2003; Pukkala et al., 2012), and the positive results in the subset of higher-parity women have not been confirmed elsewhere (e.g. Jones et al., 2019).

In summary, of the informative studies within cohorts, the majority did not find a positive association by duration of night shift work. A comparison of findings between studies raises the possibility that studies of older women may not be able to detect an association if the effect was predominant in younger women or in recent time periods following the end of exposure. This pattern seems apparent when evaluating studies including women of a wide age range (such as the NHS-II cohort or the first follow-up of the NHS-I cohort when women were still active in the workforce) that identified an increased risk of cancer of the breast from exposure to night shift work, and those examining older women (such as the Million Women Study and the extended follow-up of the NHS-I cohort beyond retirement age) that did not identify an association.

Nine case–control studies and an additional large, pooled case–control study evaluated the association between night work and risk of cancer of the breast. The pooled case–control study, to which five individual case–control studies contributed, was considered the most informative. This pooled study harmonized the protocols of each of the five contributing case–control studies, particularly regarding exposure to night shift work and main confounders, and, with over 6000 cases of cancer of the breast, was the best-powered study to evaluate various metrics of exposure (including ever versus never shift work; shift work duration; time since last night work; and night shift length, frequency, and intensity) and to conduct analyses stratified by menopausal status.

In the pooled case–control study, among women of all ages combined there was a positive association between the risk of cancer of the breast and ever night shift work and number of night hours per week, but no clear association for duration of night shift work or any of the other night shift metrics. Among premenopausal women, results suggested positive associations for ever night shift work and with most night shift metrics, particularly for more intensive night schedules (i.e. a higher number of nights or more night hours per week) that are assumed to constitute biologically relevant exposures. The risk in premenopausal women was highest in those with current or recent (within 2 years) night shift work and was lowest for 20 years or more since exposure, suggesting that the risk of cancer of the breast decreases with time since last exposure. The use of detailed shift work exposure metrics and their positive associations with risk of cancer of the breast in this pooled case–control study were considered key in the overall evaluation.

Three of the remaining case–control studies that did not contribute to this pooled study were considered informative (Davis et al., 2001; Wang et al., 2015a; Yang et al., 2019). They all suggested an increased risk of cancer of the breast with ever working night shifts. One study (Davis et al., 2001) also investigated duration of night work, and results were suggestive of an increased risk of cancer of the breast.

Overall, findings from the case–control studies considered together provide evidence of a positive association between risk of cancer of the breast and ever, longer duration of, and higher intensity of night shift work. These associations may be stronger in premenopausal women.

Several studies examined the association between night shift work and different clinical and/or pathological characteristics of cancer of the breast, including ER and PR status, HER2 receptors, invasive versus in situ, differentiation grade, and histological type. Results among this small group of studies were inconsistent.

Recent meta-analyses are of varying (mostly poor) quality.

There is a large body of evidence to assess the potential association between night shift work and risk of cancer of the breast. The Working Group determined that a positive association has been observed between night shift work and risk of cancer of the breast. However, given the heterogeneity in findings between studies, the Working Group was unable to exclude with reasonable confidence bias as an explanation.

A small minority of Working Group members considered that a positive association was not observed in the body of evidence.[1]

2.4.6 Cancer of the prostate

Studies of cancer of the prostate included five general-population cohort studies, two industrial cohort studies, five population-based case–control studies, one hospital-based case–control study, and one cohort study among airline pilots. Seven studies were conducted in Europe, four in North America, and three in Asia.

In assessing the evidence, the Working Group considered two cohort (Pukkala et al., 2003; Behrens et al., 2017) and four case–control studies (Parent et al., 2012; Papantoniou et al., 2015; Wendeu-Foyet et al., 2018; Barul et al., 2019) as the most informative based on study size, study design aspects, and exposure assessment. Five of these six studies found positive associations between exposure indices for night shift work and risk of cancer of the prostate, particularly in association with longer duration of exposure (five studies), but in three studies there was no, or a very small, increased risk when examining the overall exposure index (ever vs never). The elevated risks observed with longer durations of exposure were moderate and, in some studies, high in magnitude. For other exposure indices (e.g. intensity-based measures or direction of rotation of the night shift), findings were not reported in all studies and it was therefore not easy to evaluate consistency between studies. One study identified higher risks for recent periods of exposure (less than 20 years since last exposure), although no differences were observed in a second study examining this association (Parent et al., 2012; Kogevinas et al., 2019).

Three studies examined aggressiveness of cancer of the prostate according to the Gleason score at diagnostic biopsy, which is strongly associated with prognosis. Cut-offs for the Gleason score to define low-grade (less aggressive) and high-grade (aggressive) cancers were similar but not identical. In two of the studies (Papantoniou et al., 2015; Wendeu-Foyet et al., 2018), risk associated with night shift work was higher among aggressive tumours compared with less-aggressive tumours, indicating that more intensive prostate-specific antigen screening of night shift workers is not likely to explain the observed increased risks. No differences by Gleason score

[1] Minority opinion of the Working Group: There is a large body of evidence to assess the potential association between night shift work and risk of cancer of the breast. The results from the many informative cohort studies, with only one exception, were consistent with no association between night shift work and breast cancer risk, including for long duration of night shift work. A pooled case–control study, considered to be strong because of relatively high power and detailed exposure metrics, overall found a modest association with ever night shift work, but no clear associations with other exposure metrics determined to be more informative, including night shift work duration. Other case–control and nested case–control studies provided some evidence of a positive association, but it was not possible to exclude, with reasonable confidence, bias due to differential participation and/or recall as an explanation for the positive associations observed between night shift work and breast cancer risk. The minority opinion is therefore that the evidence regarding a positive association between night shift work and cancer of the breast is inadequate. (This is in accordance with the Preamble to the *IARC Monographs*: "inadequate evidence regarding carcinogenicity" is determined if "there are studies of sufficient quality available in humans, but their results are inconsistent or otherwise inconclusive".)

were observed in the third study (Barul et al., 2019).

Overall, the Working Group found that there was evidence suggesting that risk of cancer of the prostate is positively associated with night shift work; however, because of the relatively small number of studies and lack of consistent results with the same exposure metrics, chance and bias could not be ruled out with reasonable confidence.

2.4.7 Cancer of the colon and rectum

There were a total of six studies of night shift work and cancer of the colon and rectum: four cohort (Papantoniou et al., 2018 and its predecessors, Jørgensen et al., 2017; Yong et al., 2014a, and two case–control (Parent et al., 2012; Papantoniou et al., 2017). Three out of four well-designed and informative studies found positive associations between exposure to night shift work and risk of cancer of the colon and rectum, particularly in association with longer durations of exposure (Parent et al., 2012; Papantoniou et al., 2017, 2018). However, the elevated risks observed with longer durations of exposure were moderate in magnitude, and some findings were not consistent between studies. Reports on the incidence of cancer of the colon and rectum from the NHS-I cohort, at 10 and 24 years of follow-up, found that the risk of cancer of the colon and rectum among female nurses with 15 years or more of rotating shift exposure diminished over time, although both reports found higher risks for cancer of the rectum compared with colon subsites (Schernhammer et al., 2003; Papantoniou et al., 2018). Analyses in the younger NHS-II cohort found no evidence for increased risk of cancer of the colon and rectum associated with 15 years or more of rotating shift exposure (Papantoniou et al., 2018). Potential reasons for inconsistencies between the first and second follow-up of the NHS-I cohort are that rotating night shift exposures in the first analysis of this older cohort were more recent, while results of the NHS-II cohort were limited by the relatively small number of exposed cases in the group exposed for 15 years or more. Taken together, these studies provide some, but not strong or consistent, evidence of an increased risk of cancer of the colon and rectum associated with rotating night shift exposure. Findings from the large MCC-Spain case–control study (Papantoniou et al., 2017) provided somewhat stronger evidence of an increased risk of cancer of the colon and rectum associated with ever and longer durations of rotating night shift exposure, but differed from the results of the NHS-I and NHS-II cohorts in not finding larger risks of cancer of the rectum relative to cancer of the colon. In addition, the increased overall risk associated with any night shift work exposure was not observed among women. With respect to permanent night shift exposure, the MCC-Spain study found inverse or null associations. The only other large case–control study, which was conducted in Montreal, Canada (Parent et al., 2012), found positive associations among men between cancers of the colon and rectum and ever working night shifts, but with no evidence of increasing risk with increasing duration of exposure. The set of studies considered informative for this evaluation were methodologically sound and had reasonable power; the observed trends with duration of exposure in several studies are unlikely to have occurred by chance.

Overall, the Working Group found that there is evidence suggesting that the risk of cancer of the colon and rectum is positively associated with night shift work; however, because of the small number of studies and lack of consistency in their results, chance and bias could not be ruled out with reasonable confidence.

2.4.8 Other cancers

For cancer of the lung, studies from Canada (Parent et al., 2012), China (Kwon et al., 2015), Germany (Yong et al., 2014a), and the USA

(Schernhammer et al., 2013; Gu et al., 2015) were considered. Although some positive associations were apparent, there were inconsistencies between studies and concerns about residual confounding by smoking in some studies.

For cancer of the ovary, the Working Group considered three high-quality studies of ovarian cancer incidence from Canada (Leung et al., 2019) and the USA (Poole et al., 2011; Bhatti et al., 2013), one high-quality study on ovarian cancer mortality in the USA (Gu et al., 2015), and an additional United States study with weaker exposure assessment and fatal cancer of the ovary (Carter et al., 2014). Although positive associations for some rotating shift or night work exposure parameters were apparent, these risks were not consistently seen across the body of evidence for this site, most studies lacked statistical power to investigate subgroups or interactions, and only one study considered chronotype (Leung et al., 2019).

For other cancer sites (oesophagus, stomach, pancreas, endometrium, kidney, bladder and urinary tract, skin, and haematopoietic and lymphoid tissues), available studies (between one and five studies per site) included: moderate- to high-quality studies from Canada (Parent et al., 2012), Spain (Costas et al., 2016; Gyarmati et al., 2016), and the USA (NHS: Viswanathan et al., 2007; Gu et al., 2015; Heckman et al., 2017; cockpit and cabin crew studies: Yong et al., 2014c; Pinkerton et al., 2018); a pooled cohort study of cockpit crew in Nordic countries (Pukkala et al., 2003); and other studies with weaker exposure assessment and/or small study populations. Although positive associations for some rotating shift or night work exposure or transmeridian air travel parameters were apparent, they were not consistently seen across studies within a cancer site. Several studies lacked the statistical power to detect risk, if it exists, for these less-common cancers. For each of these other cancer sites, human studies do not provide strong or consistent evidence for a positive association with night shift work.

The Working Group determined that no conclusions could be made for any of the other cancers because of the small number of studies reporting results, inconsistencies in the findings, lack of control for important cofounders (e.g. melanoma among flight crew), or the use of weak methods for assessing exposure to night shift work.

2.4.9 Effect modification

(a) Gene–environment interaction

Among the studies concerning the association between the risk of cancer and exposure to night shift work that were assessed as informative, five studies on cancer of the breast (Monsees et al., 2012; Grundy et al., 2013b; Zienolddiny et al., 2013; Rabstein et al., 2014; Truong et al., 2014) and one study on cancer of the prostate (Wendeu-Foyet et al., 2018) examined variants in clock or clock-related genes and their interactions with exposure to night shift work. Some studies reported statistically significant modification of the associations between exposure to night shift work and the risk of cancers of the breast and prostate by variants in clock genes after applying Bonferroni-type corrections for multiple comparisons. However, all studies were judged as being of limited power to evaluate gene–environment interactions and considered a limited number of clock-related candidate variants, and none replicated their findings. Overall, existing evidence did not allow an assessment of gene–environment interactions.

(b) Chronotype

Chronotype is an individual characteristic that describes the circadian phase and correlates with diurnal preference, that is, the individual preference for morning or evening activity (Horne & Ostberg, 1976). Chronotype has been associated with the capacity of night workers to

adapt to non-day work schedules, and it has been suggested that morning types working at night may have a higher risk of cancer than evening types (Erren, 2013). Four studies on cancer of the breast (Hansen & Lassen, 2012; Ramin et al., 2013; Papantoniou et al., 2016; Fritschi et al., 2018) and four on cancer of the prostate (Papantoniou et al., 2015; Dickerman et al., 2016; Behrens et al., 2017; Wendeu-Foyet et al., 2018) evaluated this hypothesis using different methods to define chronotype, but showed inconsistent results.

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3. CANCER IN EXPERIMENTAL ANIMALS

Experimental animal models in research facilities are generally kept in artificial light–dark (LD) schedules. The exposure of such animal models to alterations in the light–dark schedule can involve the following conditions: exposure to light for a variable period of time during the period of darkness or the natural night; repeated occurrences of exposure to light during the period of darkness or the natural night, and/or over multiple periods of darkness or natural nights, at any frequency; continuous light exposure; or shifts in the light–dark schedule, that is, the advance of light onset by 6–12 hours every 2–7 days. In rodent models of shifts in the light–dark schedule, exposure to light regularly occurs at the expected time of darkness.

In the studies of alterations in the light–dark schedule reviewed below, if circadian disruption was assessed and observed, it is briefly mentioned in the study description.

A few studies reviewed in the text that follows are not reported in Tables 3.1–3.5 because they were either inadequate for the evaluation of the carcinogenicity of alterations in the light–dark schedule in experimental animals (i.e. Bishehsari et al., 2016) or were described in insufficient detail to be tabulated (Jöchle, 1963; Joechle, 1964; van den Heiligenberg et al., 1999; Cos et al., 2006; Toth et al., 2017).

3.1 Shifts in the light–dark schedule

See also Table 3.1.

3.1.1 Mouse

Heterozygous PyMT oncogene female mice [FVB background, melatonin deficient] were exposed either to a constant schedule of 12 hours of light followed by 12 hours of darkness (LD12:12; $n = 12$ controls) or to shifts in the light–dark schedule ($n = 17$ exposed) from weaning (age, 3 weeks) until the age of 14 weeks. Exposed mice had their light–dark schedule inverted for three consecutive 24-hour periods every week. At the age of 14 weeks, 4–5 mice were killed by cervical dislocation every 4 hours over a 24-hour period. The mammary tumour mass was removed and weighed. The mammary tumour burden of exposed mice was significantly higher than that of controls (Kennaway, 2009). [The Working Group noted the limited experimental details.]

In a 70-week experiment to study chronic circadian rhythm disturbances, two groups of 25 female *Tp53*$^{R270H/+}$*WAPCre* mice prone to cancer of the breast [FVB background, melatonin deficient] (age, 8 weeks) were exposed either to a constant schedule of LD12:12 (control), or to a schedule of LD12:12 that was inverted at the end of every week by extending the light or dark phase to 24 hours (light exposure chamber, 141.5 lux, 345 μW/cm^2). The weekly 12-hour reversal of the light–dark schedule was not observed to disrupt the peripheral clock function in the liver. Mice were killed after tumour development, and the number of control and exposed mice bearing tumours was determined. In both groups, approximately 80% of the mice developed mammary

Table 3.1 Studies of carcinogenicity in experimental animals exposed to shifts in the light–dark schedule

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, latency, multiplicity, weight, or size of tumours	Significance	Comments
Full carcinogenicity Mouse, PyMT (F) 3 wk 11 wk Kennaway (2009)	Shifts in the LD schedule LD12:12 (control), LD12:12 schedule inverted for three consecutive 24-h periods per week (exposed) 12, 17 NR	*Mammary gland*: total tumours (gross examination) Weight (g): 6.0, 7.5*	*$P < 0.03$, one-tail test [not further specified]	Principal limitations: limited experimental details; no data on circadian disruption status Tumour weight read from graph
Full carcinogenicity Mouse, *p53*$^{R270H/+}$ *WAPCre* (F) 8 wk ~ 70 wk (read from graph) Van Dycke et al. (2015)	Shifts in the LD schedule LD12:12 (control), LD12:12 inverted 1×/wk by extending light or dark phase to 24 h (exposed) 25, 25 20, 21	*Mammary gland* All tumours Incidence: 18/20, 17/21 Latency (wk): 50.3, 42.6* Fibrosarcoma or carcinosarcoma Incidence: 12/20, 15/21 Carcinoma Incidence: 5/20, 1/21 Intraepithelial neoplasia Incidence: 1/20, 1/21 *Haematopoietic and lymphoid tissues*: lymphosarcoma Incidence: 3/20, 5/21	 NS *$P = 0.0127$, Kolmogorov–Smirnov NS NS NS NS	Mice were killed after tumour development or when moribund; strain with FVB background (melatonin deficient)
Full carcinogenicity Mouse, C57BL/6J (M, F) (combined) 4 wk 86 wk Kettner et al. (2015, 2016)	Shifts in the LD schedule LD12:12 (control) and weekly transfer between two rooms with LD12:12 conditions offset by 8 h (exposed) for each of wildtype; *Cry* mutant, *Per* mutant, *Alb*^{Cre}; *Bmal1*$^{fl/fl}$; *Car*$^{-/-}$; and *Fxr*$^{-/-}$ NR NR	*Liver*: hepatocellular carcinoma Incidence: 0/110, 7/80*; 7/60, 10/56; 10/80, 13/50**; 3/26, 5/43; 0/24, 0/25; 7/25, 19/31*** Multiplicity: 0, 2, 3, 6, 2.5, 6*, 23, 7, NR, NR, NR, NR Average size (cm): 0.00, 0.70, 0.59, 0.97*, 0.56, 1.08*, 0.12, 0.60*, NR, NR, NR, NR	 *$P = 0.007$ (Kaplan–Meier statistics), **[$P = 0.043$, Fisher one-tail exact test], ***[$P = 0.017$, Fisher two-tail exact test] *$P < 0.01$, Student *t*-test *$P < 0.001$, Student *t*-test	Percentage of survival, tumour multiplicity, and tumour size data were reported in graphic form; melatonin-deficient strain; approximately equal number of males and females of each genotype

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, latency, multiplicity, weight, or size of tumours	Significance	Comments
Full carcinogenicity Rat, inbred BN (F) 3 wk 147 wk Kort et al. (1986)	Shifts in the LD schedule LD12:12 (control), LD12:12 inverted 1×/wk by advancing by 12 h every Friday (exposed) 100, 100 30, 35	*Haematopoietic and lymphoid tissues*: histiocytic sarcoma Incidence: 1/100, 5/98	NS	Survival and body-weight data were reported in graphic form; melatonin-deficient strain

F, female; h, hour; LD, light–dark; LD12:12, 12 h of light followed by 12 h of darkness; M, male; NR, not reported; NS, not significant; wk, week.

tumours, including carcinomas and carcinosarcomas. The latency to mammary gland tumour development was reduced by 17% in the exposed mice compared with control mice (42.6 versus (vs) 50.3 weeks, respectively; Kolmogorov–Smirnov test, $P = 0.0127$). However, chronic weekly inversion of the light–dark schedule was not observed to affect the number of tumour-bearing mice or tumour type (mammary gland tumours, lymphosarcoma, or other tumours) (Van Dycke et al., 2015).

In the study by Kettner et al. (2015, 2016), groups of C57BL/6J (i) wildtype [melatonin deficient], (ii) *Cry1*$^{-/-}$;*Cry2*$^{-/-}$, (iii) *Per1*$^{-/-}$;*Per2*$^{-/-}$, (iv) *Alb*^{Cre};*Bmal1*$^{fl/fl}$, (v) *Car*$^{-/-}$, and (vi) *Fxr*$^{-/-}$ mice were fed standard mouse chow and water. From the age of 4 weeks until the age of 90 weeks, six groups of control mice were maintained at regular LD12:12 schedules, and six groups of mice were exposed to shifts in the light–dark schedule by being transferred once per week between two mouse rooms with LD12:12 schedules offset by 8 hours. Approximately equal numbers of male and female mice within each genotype were used. Mice were monitored twice per week, and moribund mice were killed for pathological analysis. At the end of the study, all tissues and organs were inspected, and abnormal tissues and tumours were processed for histological analysis. Circadian rhythm was disrupted in the exposed mice, and exposed wildtype and mutant mice showed significantly reduced survival compared with their respective control groups, with disease development including cancer. Compared with their respective controls, there was a significant increase in the incidence of hepatocellular carcinoma in exposed wildtype mice (7/80 exposed vs 0/110 controls, $P = 0.007$), in *Per1*$^{-/-}$;*Per2*$^{-/-}$ mice (13/50 exposed vs 10/80 controls [$P = 0.043$]), and in *Fxr*$^{-/-}$ mice (19/31 exposed vs 7/25 controls [$P = 0.017$]). Exposure to shifts in the light–dark schedule also increased the size of hepatocellular carcinomas in *Per* and *Cry* mutant mice and *Alb*^{cre}*Bmal1*$^{fl/fl}$ mice, and tumour multiplicity in *Per* mutant mice.

Toth et al. (2017) reported a study in which four groups of 38–40 male and female leukaemia-prone AKR/J mice [melatonin proficiency unclear] (age, 5 weeks) were exposed to a regular LD12:12 schedule or to shifts in the light–dark schedule throughout their lifespan. Mice were first stabilized for approximately 3 weeks on a regular LD12:12 schedule. Core temperature, locomotor activity, and running-wheel activity were monitored for 1 week during this period. Two groups of male and female mice were then switched to shifts in the light–dark schedule that were designed to mimic shift work. The dark (active) phase was extended by 8 hours on the first day of the simulated work week. This shift in the light–dark schedule was maintained for 5 days. On day 6 (the beginning of the simulated weekend), the onset of the dark (active) phase was advanced by 8 hours, thus returning to the control schedule. After 2 weekend-schedule days, the shift in the light–dark schedule began again. Mice remained on the shift in the light–dark schedule conditions for 4 weeks, and were then returned to a regular light–dark schedule for an additional 2 weeks. Room illumination conditions were 175 lux; within chambers at cage level with the chamber door closed, light intensity was approximately 5–10 lux during the dark phase (chamber internal lighting off) and 125–145 lux during the light phase (chamber internal lighting on). Median survival times for control females, exposed females, control males, and exposed males were 268, 251, 314.5, and 308 days, respectively. The combined analysis of all four groups revealed significant effects of sex, with male mice having a longer lifespan than female mice. The data were further analysed in subsets comprising mice that died before or after the median survival time for each group. [The Working Group noted that, although most AKR mice died from leukaemia or lymphoma, no data on tumour incidence or histopathological

verification of leukaemia or lymphoma were reported.]

3.1.2 Rat

In the study by Kort et al. (1986), a group of 100 inbred BN virgin female rats (age, 3 weeks) were exposed to shifts in the light–dark schedule over a long-term period. Every Friday, the automatic timer controlling the light for the exposed rats inverted the light–dark schedule by advancing the onset of the next light or dark period by 12 hours. Another group of 100 females exposed to a regular LD12:12 schedule served as controls. The experiment was terminated at age 150 weeks. There was no significant difference in survival between the exposed group and the control group. The mean body weight in the exposed group was significantly less than that in controls. Each organ system was examined in rats either found dead or moribund, or killed at age 150 weeks. Routine microscopic examination was performed on samples of more than 20 organs or tissues, and other organs were examined when suspected of neoplasms. The differences in tumour incidence were not significant for all organs or tissues (combined) or for any specific tissue or organ.

3.2 Shifts in the light–dark schedule with implant, transplant, graft, or modifying factors

See Table 3.2.

3.2.1 Shifts in the light–dark schedule with implant, transplant, or graft

(a) Mouse

The study by Li & Xu (1997) analysed the effect of shifts in the light–dark schedule on animal physiology and tumour progression using inbred male Kunming mice (age, 6 weeks) [assumed to be melatonin deficient]. Four groups of 10 mice were transplanted with either Ehrlich carcinoma or Sarcoma 180 and then maintained at regular LD12:12 schedules (control) or transferred between LD14:10 and LD10:14 schedules once every 3 days. Exposure to shifts in the light–dark schedule led to a significant increase in tumour growth rate by about 12% for the Sarcoma 180 model at 10 days, and to a significant reduction by 18% in survival time for the Ehrlich carcinoma model. The study also found that shifts in the light–dark schedule completely suppressed circadian rhythms of hypersensitivity reaction, neutrophil phagocytosis, leukocyte counts, and haemolysin. [The Working Group questioned the biological relevance of the small changes that were reported.]

In the study by Filipski et al. (2004), groups of B6D2F$_1$ male mice [melatonin proficient] (age, 6 weeks) were initially synchronized to a regular light–dark schedule (LD12:12) for 3 weeks. Mice were then maintained at LD12:12 (control), or else exposed to either an LD12:12 schedule that was advanced by 8 hours once every 2 days or to continuous light (LD24:0) (see also Table 3.5). Control mice displayed a coupled circadian rhythm of physical activity, body temperature, plasma corticosterone, and the expression of circadian genes *Per1* in the suprachiasmatic nuclei and *Per2* and *Nr1d1* in the liver. The circadian rhythm of these physiological parameters and gene expression patterns was completely abolished by the repeated advances in the light–dark schedule. Ten days after start of exposure, mice were inoculated with Glasgow osteosarcoma, and used to study the role of shifts in the light–dark schedule on tumour growth and survival in two experiments ("Experiment 2", n = 13 per group; "Experiment 3", n = 12–14 per group) and the effect of continuous light in a third experiment ("Experiment 4", n = 10 per group). Mice were killed 15 days after tumour inoculation. Compared with control mice, mice in the group exposed to shifts in the light–dark

Table 3.2 Studies of carcinogenicity in experimental animals exposed to shifts in the light–dark schedule, with implant, transplant, graft, or modifying factors

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, weight, or volume of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Mouse, Kunming (M) 6 wk > 15 d for mice transplanted with Ehrlich carcinoma, 10 d for mice transplanted with Sarcoma 180 Li & Xu (1997)	Shifts in the LD schedule LD12:12 (control), transferred between LD14:10 and LD10:14 every 3 d (exposed) Transplantation of Ehrlich carcinoma or Sarcoma 180, method unclear 10, 10 NR	Sarcoma 180: total tumours Weight (g): 1.45, 1.62*	*$P < 0.05$, Student *t*-test	Principal strengths: two tumour models were used Principal limitations: size of tumours at the time of transplantation was unclear Statistical analyses of the effects on tumour growth were not convincing; survival (lifespan) reduced in Ehrlich carcinoma model by 18% ($P < 0.05$) (15 d for controls and 12.3 d for exposed); survival in Sarcoma 180 model, unclear; melatonin proficiency of strain unknown (assumed to be deficient)
Co-carcinogenicity Mouse, B6D2F$_1$ (M) 6 wk ≤ 2 wk after inoculation Filipski et al. (2004)	Shifts in the LD schedule LD12:12 (control), LD12:12 advanced by 8 h every 2 d (exposed); mice were initially synchronized to LD12:12 for 3 wk All mice inoculated subcutaneously with 3 mm^3 fragments of mouse Glasgow osteosarcoma in each flank 10 d after start of LD advances 13, 13 NR	Glasgow osteosarcoma: total tumours Weight at day 11 (mg): 647, 1330*	*$P = 0.001$, Student *t*-test	"Experiment 2": mice killed 15 d after tumour inoculation; accelerated tumour growth ($P < 0.001$, ANOVA test) and decrease in survival in exposed mice; melatonin-proficient strain
Co-carcinogenicity Mouse, B6D2F$_1$ (M) 6 wk ≤ 2 wk after inoculation Filipski et al. (2004)	Shifts in the LD schedule LD12:12 (control), LD12:12 advanced by 8 h every 2 d (exposed); mice were initially synchronized to LD12:12 for 3 wk All mice inoculated subcutaneously with 3 mm^3 fragments of mouse Glasgow osteosarcoma in each flank 10 d after start of LD advances 12, 14 NR	Glasgow osteosarcoma: total tumours Weight at day 11 (mg): 847, 1376*	*$P = 0.005$, Student *t*-test	"Experiment 3": mice killed 15 d after tumour inoculation; accelerated tumour growth ($P = 0.002$, ANOVA test) and decrease in survival in exposed mice; melatonin-proficient strain

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, weight, or volume of tumours	Significance	Comments
Co-carcinogenicity Mouse, B6D2F$_1$ (M) NR 25 d Filipski et al. (2005)	Shifts in the LD schedule LD12:12 (control), LD12:12 advanced by 8 h every 2 d (exposed) Subcutaneous implantation of 3 mm^3 Glasgow osteosarcoma 10 d after start of LD advances 13, 14 NR	Glasgow osteosarcoma: total tumours Weight after 12 d (mg): 1317 (95% CI, 1067–1567); 1997 (95% CI, 1458–2356)	NR Tumours grew significantly more quickly ($P = 0.04$, ANOVA test) in exposed vs control mice	Light conditions: fluorescent tube (spectrum, 4100 °K; light efficiency, 58–80 lumen/W); mean light intensity of 318 lux in the middle of each compartment and 129 lux at each side Mice killed 15 d after tumour implantation; melatonin-competent strain
Co-carcinogenicity Mouse, BALB/c-Foxn1^{nu} (F) NR ≤ 4 wk Kennaway (2009)	Shifts in the LD schedule LD12:12 (control), LD12:12 schedule inverted for three consecutive 24-h periods 1×/wk (exposed) Subcutaneous injection of 5 × 10^6 human breast cancer MCF-7 cells (in Matrigel® Becton Dickinson) 4 wk after start of LD alterations NR NR	Human breast cancer MCF-7: total tumours Volume (mm^3): after 2 wk, 150 (control), 110* (exposed); after 3 wk, 225 (control), 200 (exposed); after 4 wk, 370 (control), 275 (exposed)	*$P < 0.05$ (decrease) [test unspecified] NS	Principal limitations: limited experimental details Tumour volume reported in graphic form; melatonin-deficient strain
Co-carcinogenicity Mouse, C57BL/6 (M) 6 wk 22 d Wu et al. (2012)	Shifts in the LD schedule LD12:12 (control), light onset advanced by 8 h every 48 h (exposed) Subcutaneous injection of Lewis lung carcinoma cells (0.2 mL, 5 × 10^6/mL) into both flanks 10 d after start of LD advances 24, 24 24, 24	Lewis lung carcinoma: total tumours Volume (mm^3): 777 , 1238* *Lung*: metastases Incidence: 3/24, 10/24*	*$P = 0.026$, two independent-samples *t*-test *$P = 0.023$, χ^2 test	Melatonin-deficient strain

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, weight, or volume of tumours	Significance	Comments
Co-carcinogenicity Rat, F344 (M) 50 d 6–8 wk Logan et al. (2012)	Shifts in the LD schedule LD12:12 (control), LD12:12 for 1–2 wk then advanced by 6 h every 2 d for a total of 10 advances (exposed) Injection of 1×10^5 MADB106 mammary tumour cells into jugular vein 20, 20 NR	*Lung*: tumours Incidence: 8/20, 16/20*	*$P < 0.0001$	Principal limitations: limited description of shifts in the LD schedule
Initiation–promotion (tested as promoter) Mouse, B6D2F$_1$ (M) 9–12 wk 10 mo Filipski et al. (2009)	Shifts in the LD schedule LD12:12 (control), period of light onset advanced by 8 h every 2 d for 10 mo (exposed) Daily intraperitoneal injection of 10 mg/kg bw DEN on days 1–11, then 7 mg/kg bw on days 21–33 and 41–46 (total dose, 243 mg/kg bw) NR NR	*Liver*: tumours Incidence: 11/13, 11/12 Multiplicity (range): 1–4, 1–6*	NS *$P = 0.028$ At least 2 tumours were observed in 77% of exposed mice ($P = 0.026$) compared with 33% of control mice	Principal limitations: small number of rats Liver tumours were hepatocellular carcinomas, cholangiocarcinomas, sarcomas, or mixed tumours with characteristics of both hepatocellular carcinoma and cholangiocarcinoma
Initiation–promotion (tested as promoter) Mouse, C57BL/6J (M) 2–3 mo 11 d Lee et al. (2019)	Shifts in the LD schedule LD12:12 (control), LD schedule advanced by 8 h every 2 d for 11 d (exposed) After LD12:12 conditions for 2 wk, all mice given subcutaneous injection in the right flank of 400 µg of 3-methylcholanthrene in peanut oil; after 30–60 d, mice separated into control and exposed groups 14, 14 14, 14	Total tumours [type unspecified] Relative tumour volume at 10 d: ~2.5 (control), ~4.8* (exposed) Relative tumour growth rate: ~0.15 (control), ~0.43** (exposed)	*$P < 0.001$, two-way ANOVA, and Bonferroni multiple comparisons test; normalized data derived from three independent experiments ** $P < 0.0001$, two-tail Student *t*-test	Tumour volume and tumour growth-rate data provided in graphic form; melatonin-deficient strain

bw, body weight; d, day; DEN, diethylnitrosamine; F, female; h, hour; LD, light–dark; LD10:14, 10 hours of light followed by 14 hours of darkness; LD12:12, 12 hours of light followed by 12 hours of darkness; LD14:10, 14 hours of light followed by 10 hours of darkness; M, male; mo, month; NR, not reported; NS, not significant; vs, versus; wk, week.

schedule displayed significantly accelerated tumour growth and decreased survival time in both experiments. Exposure to continuous light in the third experiment was not observed to have any effect on tumour growth or survival.

Filipski et al. (2005) conducted a study in which B6D2F$_1$ male mice [melatonin competent] (age, 6–8 weeks) were maintained in compartments lit with a fluorescent tube, with a light spectrum of 4100 °K and a light efficiency of 58–80 lumen/W (mean light intensity of 318 lux in the middle of each compartment and 129 lux at each side). The mice were synchronized to standard lighting conditions of LD12:12 for 2–3 weeks, and were then either maintained at this lighting regimen (n = 13, control group) or were exposed to shifts in the light–dark schedule by 8 hours every 2 days (n = 14, exposed group) for 10 days. All control and exposed mice were then given a subcutaneous implantation of a 3 mm^3 fragment of Glasgow osteosarcoma in both flanks, and tumour weight was measured daily. At 15 days after tumour implantation, all control and exposed mice were killed. The body weights of the control and exposed mice were observed to increase by similar amounts. Shifts in the light–dark schedule were observed to severely alter the circadian rhythms in the expression of clock genes in the liver and tumours of mice bearing Glasgow osteosarcoma. Tumours grew significantly more quickly in exposed mice than in control mice. On day 12, before tissue sampling mean tumour weight was 1317 mg (95% confidence interval, CI, 1067–1567) in control mice and 1997 mg (95% CI, 1458–2356) in exposed mice.

Kennaway (2009) reported a study in which BALB/c-Foxn1^{nu} mice [melatonin deficient, age and number not reported, assumed to be females] were exposed to shifts in the light–dark schedule for 4 weeks before being subcutaneously injected with human breast cancer MCF-7 cells (5×10^6; in Matrigel® Becton Dickinson). Exposed mice had their LD12:12 schedule inverted for three consecutive 24-hour periods by delaying the onset of the period of darkness by 12 hours once every week. Controls were kept at a regular LD12:12 schedule throughout the experimental period. Tumour volume was measured at 2, 3, and 4 weeks after the injection, during which time the exposed group were maintained under conditions of shifts in the light–dark schedule. There was a significant difference [statistical test unspecified] in tumour volume after 2 weeks, with a lower volume in the exposed mice. A trend towards lower tumour volumes persisted in the exposed mice, but no significant differences were observed throughout the remainder of the experiment. [The Working Group noted the limited experimental details.]

Wu et al. (2012) reported a study in which 48 male C57BL/6 [melatonin deficient] mice (age, 4 weeks) were initially synchronized to a regular light–dark schedule (LD12:12). After 2 weeks, the mice were either maintained at LD12:12 (controls, n = 24) or else exposed to advances in light onset by 8 hours every 48 hours (exposed, n = 24). After 10 days of exposure, all mice were subcutaneously injected with Lewis lung carcinoma cells (0.2 mL, 5×10^6 per mL) in both flanks. There was no significant difference in body weight between the control and exposed groups. Circadian rhythm was disrupted in the group exposed to shifts in the light–dark schedule. Tumours were palpable in 10 out of 24 control mice and 21 out of 24 exposed mice (significant increase; P = 0.0025, χ^2 test) 10 days after the injection. The tumours grew significantly faster (P = 0.004, ANOVA test) in the exposed group compared with the controls; mean tumour volume was significantly higher in the exposed group (1238 mm^3 vs 777 mm^3) 22 days after tumour inoculation. All of the samples, including the lung and tumour tissues, were examined histopathologically; it was reported that 10 out of 24 exposed mice had lung metastases compared with only 3 out of 24 control mice (P = 0.023).

(b) Rat

Logan et al. (2012) reported a study in which groups of 20 male Fischer 344 rats (age, 50 days) were either maintained at regular light–dark schedules of LD12:12 (control group) or exposed to LD12:12 for 1–2 weeks followed by a 6-hour advance in the light–dark schedule every 2 days for a total of 10 advances (exposed group). All rats were then injected with MADB106 mammary tumour cells (1×10^5 cells) into the jugular vein and kept for 6–8 weeks under a regular LD12:12 cycle to determine tumour frequency or prevalence. Circadian rhythm was disrupted in the exposed group, and it was observed that shifts in the light–dark schedule significantly ($P < 0.0001$) increased the incidence of lung tumours.

3.2.2 Shifts in the light–dark schedule with modifying factors

Mouse

Filipski et al. (2009) investigated the role of shifts in the light–dark schedule in the promotion of hepatocarcinogenesis induced by diethylnitrosamine (DEN) in 44 male B6D2F$_1$ mice [melatonin competent] (age, 6–8 weeks). The mice were initially synchronized to standard lighting conditions of 12 hours of light and 12 hours of darkness (LD12:12), with food and water ad libitum, for 3 weeks. The mice were then given daily intraperitoneal injections of DEN at 10 mg/kg body weight (bw) from day 1 to 11, and then at 7 mg/kg bw from day 21 to 33 and from day 41 to 46 (total dose, 243 mg/kg bw). They were then randomized to LD12:12 (control group) or to LD12:12 advanced by 8 hours every 2 days (exposed group) [the number of mice at the start per group was not reported]. DEN was observed to disrupt the circadian rhythm in both control and exposed groups of mice. Exposure to shifts in the light–dark schedule was also observed to disrupt the circadian rhythm, but partial recovery was observed after 5 months. Mice were killed after 10 months, and liver, lung, and kidneys were examined for macroscopic and microscopic neoplastic lesions. Microscopic examination showed that liver tumours were found in 11 out of 12 (92%) exposed mice compared with 11 out of 13 (85%) control mice. Liver tumour multiplicity was significantly ($P = 0.028$) higher in exposed mice (range, 1–6) than in control mice (range, 1–4). At least two liver tumours were observed in 77% of exposed mice ($P = 0.026$) compared with 33% of the control mice. In exposed mice, up to four different tumour types were observed in the same liver (i.e. hepatocellular carcinomas, cholangiocarcinomas, sarcomas, or mixed tumours with characteristics of both hepatocellular carcinoma and cholangiocarcinoma); four exposed mice had two different types of liver cancer and one had all four types of liver cancer. In control mice, a single histological type of tumour per liver [not further specified] was observed. [The Working Group noted the small number of mice, the lack of data on survival, and the fact that the carcinogen doses used in this study were very high, as indicated by the very high incidence of hepatocellular carcinoma in both groups.]

Bishehsari et al. (2016) reported a study to determine the effects of shifts in the light–dark schedule on alcohol-associated colon carcinogenesis in TS4Cre × APC^{lox468} mice (age, 4 weeks) [sex not reported]. Mice were given a diet initially supplemented by 3% ethanol, increased to 15% over 2 weeks, then maintained at 15% for another 2 weeks. Mice were then either maintained at a regular LD12:12 schedule (controls, $n = 3$) or exposed to weekly reversals of the light–dark schedule (exposed, $n = 5$). The study was terminated after 8 weeks of exposure to ethanol with or without exposure to shifts in the light–dark schedule. Mice exposed to both ethanol and shifts in the light–dark schedule developed a greater number of colon polyps and carcinoma in situ, and demonstrated an increased incidence of advanced adenoma, than control mice. [The Working Group noted that this model had not

been used previously to identify possible carcinogens. More importantly, group sizes used in the study (n = 3–5 mice per group) were far smaller than those required to support a statistically robust evaluation. The study was considered inadequate for the evaluation.]

In the experiment by Lee et al. (2019), male C57BL/6J mice [melatonin deficient] (age, 2–3 months) were kept under standard lighting conditions of LD12:12 with food and water available ad libitum. After acclimation for 2 weeks, mice were given subcutaneous injections of 400 µg of 3-methylcholanthrene in peanut oil along the right flank. After 30–60 days, mice were separated into two groups of 14 control mice and 14 mice exposed to shifts in the light–dark schedule. The control group was maintained at the LD12:12 lighting schedule, and the exposed group was subject to repeated 8-hour advances in the LD12:12 schedule every 2 days for 11 days. Circadian rhythm was disrupted in the exposed group. Tumour growth was measured with a digital calliper 3 times per week, and mice were killed when the tumour exceeded 20 mm in diameter. After 6, 8, and 10 days, the relative tumour volumes in the exposed group were significantly ($P < 0.001$) increased compared with those in the control group (data were obtained from three independent experiments). The relative tumour growth rate calculated from linear regression was also significantly ($P < 0.0001$) increased in the exposed mice compared with the controls. [The Working Group noted that no data were provided for tumour histopathology, and that tumour volume and tumour growth rate data were provided in graphic form.]

3.3 Extreme changes in photoperiod

See Table 3.3.

3.3.1 Excluded publication

One publication that was excluded from this review (Khan et al., 2018) studied the effects of artificial light at night on the circadian expression patterns of clock and clock-controlled genes, including several genes involved in ovarian carcinogenesis, in female zebrafish. The authors reported on the appearance of thecoma and granulosa cell tumours after exposure to continuous light for 1 year, but no quantitative data were provided (e.g. tumour incidence).

3.3.2 Main characteristics and review of the relevant studies

The aims of the long-term studies discussed here were to investigate the dynamics of tumour incidence and their histopathological characterization in mice and rats exposed to continuous light, compared with a regular light–dark schedule (LD12:12), a natural light–dark schedule involving large seasonal changes in photoperiod, or continuous darkness.

The experimental rodent models studied included known melatonin-proficient species and strains such as female CBA mice (Anisimov et al., 2004) and female Wistar rats (Bukalev et al., 2013), and melatonin-deficient mouse strains such as female FVB HER-2/neu mice (Baturin et al., 2001) or female 129/Sv mice (Popovich et al., 2013). Male and female LIO rats [Wistar-derived] have also been used, although their melatonin proficiency does not seem to be documented (Vinogradova et al., 2009, 2010). Age at the start of continuous illumination ranged from 25 days to 14 months, with most studies starting at age 1–5 months.

Light intensity in the groups exposed to continuous light ranged from 750 lux (Vinogradova et al., 2009, 2010; Bukalev et al., 2013) to about 2500 lux (Anisimov et al., 2004; Popovich et al., 2013). Light intensity was not always consistent between the continuous-light and the artificial

Table 3.3 Studies of carcinogenicity in experimental animals exposed to extreme changes in photoperiod

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, or number of tumours	Significance	Comments
Full carcinogenicity Mouse, CBA (F) 2 mo ≤ 971 d Anisimov et al. (2004)	Changes in photoperiod LD12:12 (control), LD24:0 50, 50 15, 0	*All sites*: tumours Incidence: 4/50, 15/50* Number: 5 (malignant, 3), 22 (malignant, 19) *Lung* Adenoma Incidence: 1/50, 1/50 Adenocarcinoma Incidence: 1/50, 7/50* *Liver*: hepatocellular carcinoma Incidence: 0/50, 4/50 *Haematopoietic and lymphoid tissues*: malignant lymphoma Incidence: 0/50, 6/50* *Mammary gland*: adenocarcinoma Incidence: 1/50, 2/50	 *$P < 0.001$, Fisher exact test NR NS *$P < 0.05$, Fisher exact test NS *$P < 0.02$, Fisher exact test NS	Principal strengths: melatonin-proficient strain; large groups (50 per group); full histopathology Light intensity: 300 lux in control group and 2500 lux in continuous-light group
Full carcinogenicity Mouse, FVB HER-2/neu (F) 2 mo ≤ 45 wk Baturin et al. (2001)	Changes in photoperiod LD12:12, LD24:0 30, 25 20% at 45 wk, 20% at 45 wk	*Mammary gland*: adenocarcinoma Incidence: 23/30 (76.7%), 19/25 (76.0%) Multiplicity: 3.3 (SD, 0.4), 5.0 (SD, 0.5)*	 NS * $P < 0.02$, Student *t*-test	Melatonin-deficient strain
Full carcinogenicity Mouse, 129/Sv (F) 5 mo Lifetime Popovich et al. (2013)	Changes in photoperiod LD12:12 (control), LD24:0 46, 46 22 (47.8%) at 800 d, 13 (28.3%) at 800 d*	*All organs*: all tumours Incidence: 39/45 (86.7%), 35/43 (81.4%) Number: 39, 38 *Uterus* Haemangioma Number: 6, 12 Sarcoma Number: 30, 20	 NS NS NS NS	Principal strengths: full histopathology Melatonin-deficient strain; cumulative incidence curves over time for LD24:0 vs LD12:12: $P = 0.0055$ for tumour-bearing mice and $P = 0.0183$ for fatal-tumour-bearing mice (χ^2 test); *survival: $P < 0.05$, Fisher exact test Light intensity: 70 lux in the LD12:12 group and 2600 lux in the LD24:0 group

Table 3.3 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, or number of tumours	Significance	Comments
Full carcinogenicity Rat, LIO (M) 25 d Lifetime Vinogradova et al. (2009); see also Bukalev et al. (2012)	Changes in photoperiod LD12:12, NL, LD24:0, LD0:24 57, 50, 50, 51 NR	*Testes*: leydigoma Number: 7, 6, 4, 6 *All organs* All tumours Incidence: 17/57 (29.8%), 11/50 (22.0%), 13/50 (26.0%), 11/51 (21.6%) Multiplicity: 1.35, 1.18, 1.08, 1.36 Number: 23, 13, 14, 15 Malignant tumours Incidence: 7/57 (12.3%), 6/50 (12.0%), 10/50 (20.0%), 5/51 (9.8%) Multiplicity: 1.35, 1.18, 1.08, 1.36 Number: 9, 6, 10, 5 *Haematopoietic and lymphoid tissues*: malignant lymphoma or leukaemia Number: 3, 4, 6, 3	 NS NS NR NR NS NR NR NR	Principal strengths: full histopathology Accelerated tumour development in LD24:0 group compared with LD12:12 group In the NL group, photoperiod ranged from 4.5 h of light in winter to 24 h in summer
Full carcinogenicity Rat, LIO (F) 25 d Lifetime Vinogradova et al. (2009)	Changes in photoperiod LD12:12, NL, LD24:0, LD0:24 40, 48, 54, 61 NR	*Testes*: leydigoma Number: 7, 6, 4, 6 *All organs* All tumours Incidence: 21/40 (52.5%), 34/48 (70.8%)*, 24/54 (44.4%), 15/61 (24.6%)** Multiplicity: 1.38, 1.41, 1.63, 1.07 Number: 29, 48, 39, 16	 NS *$P < 0.05$ (increase) vs LD12:12, Fisher exact test [presumably] **$P < 0.001$ (decrease) vs LD12:12, Fisher exact test [presumably] NR NR	Principal strengths: full histopathology Accelerated tumour development in LD24:0 group compared with LD12:12 group In the NL group, photoperiod ranged from 4.5 h of light in winter to 24 h in summer

Table 3.3 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, or number of tumours	Significance	Comments
Vinogradova et al. (2009) (cont.)		Malignant tumours		
		Incidence: 5/40 (12.5%), 7/48 (14.6%), 7/54 (13.0%), 3/61 (4.9%)	NS	
		Multiplicity: 1.35, 1.18, 1.08, 1.36	NR	
		Number: 5, 9, 7, 3	NR	
		Mammary gland		
		Benign tumours (fibroma or fibroadenoma)		
		Incidence: 14/40, 27/48*, 18/54, 5/61**	*$P < 0.05$ (increase) vs LD12:12 **$P < 0.01$ (decrease) vs LD12:12	
		Number: 15, 30, 21, 5	NR	
		Adenocarcinoma		
		Number: 0, 0, 1, 0	NR	
Full carcinogenicity Rat, LIO (M) 1 mo Lifetime Vinogradova et al. (2010); see also Lotosh et al. (2013)	Changes in photoperiod LD12:12, LD24:0 43, 34 Mean lifespan: 766 d (SD, 25.4), 744 d (SD, 28)	*All organs*		Principal strengths: full histopathology
		All tumours		
		Incidence: 15/43 (34.9%), 12/34 (35.3%)	NS	
		Multiplicity: 1.4, 1.08	NR	
		Number: 21, 13	NR	
		Malignant tumours		
		Incidence: 8/43 (18.6%), 10/34 (29.4%)	NS	
		Number: 8, 10	NR	
		Haematopoietic and lymphoid tissues: malignant lymphoma or leukaemia		
		Number: 3, 6	NR	

Table 3.3 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, or number of tumours	Significance	Comments
Full carcinogenicity Rat, LIO (M) 14 mo Lifetime Vinogradova et al. (2010); see also Lotosh et al. (2013)	Changes in photoperiod LD12:12, LD24:0 43, 90 Mean lifespan: 766 d (SD, 25.4), 818 d (SD, 18.1)	*All organs* All tumours Incidence: 15/43 (34.9%), 26/90 (28.9%) Multiplicity: 1.40, 1.31 Number: 21, 34 Malignant tumours Incidence: 8/43 (18.6%), 9/90 (10.0%) Number: 8, 9 *Testes*: leydigoma Number: 7, 16 *Soft tissue* Benign tumours (angiofibroma, fibroma, or chondroma) Number: 0, 3 Sarcoma Number: 0, 4	 NS NR NR NS NR NR NR NR	Principal strengths: full histopathology
Full carcinogenicity Rat, LIO (F) 1 mo Lifetime Vinogradova et al. (2010)	Changes in photoperiod LD12:12, LD24:0 30, 36 Mean lifespan: 844 d (SD, 33.6), 658 d (SD, 22.8)	*All organs* All tumours Incidence: 17/30 (56.7%), 20/36 (55.6%) Multiplicity: 1.47, 1.75 Number: 25, 35 Malignant tumours Incidence: 5/30 (16.7%), 5/36 (13.9%) Number: 5, 5 *Mammary gland* Benign tumours (fibroma or fibroadenoma) Incidence: 12/30, 16/36 Number: 13, 19	 NS NR NR NS NR NS NR	Principal strengths: full histopathology

Table 3.3 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, or number of tumours	Significance	Comments
Vinogradova et al. (2010) (cont.)		Adenocarcinoma		
		Number: 0, 1	NR	
		Uterus		
		Benign tumours (polyp, fibroma, or fibromyoma)		
		Number: 3, 6	NR	
		Adenocarcinoma		
		Number: 0, 1	NR	
Full carcinogenicity Rat, LIO (F) 14 mo Lifetime Vinogradova et al. (2010)	Changes in photoperiod LD12:12, LD24:0 30, 71 Mean lifespan: 844 d (SD, 33.6), 811 d (SD, 20.0)	*All organs*		Principal strengths: full histopathology
		All tumours		
		Incidence: 17/30 (56.7%), 30/71 (45.3%)	NS	
		Multiplicity: 1.47, 1.37	NR	
		Number: 25, 41	NR	
		Malignant tumours		
		Incidence: 5/30 (16.7%), 11/71 (15.5%)	NS	
		Number: 5, 11	NR	
		Mammary gland: benign tumours (fibroma or fibroadenoma)		
		Incidence: 12/30, 19/71	NS	
		Number: 13, 27	NR	
		Haematopoietic and lymphoid tissues: malignant lymphoma or leukaemia		
		Number: 3, 7	NR	

Table 3.3 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, or number of tumours	Significance	Comments
Full carcinogenicity Rat, Wistar (F) 25 d Lifetime Bukalev et al. (2013)	Changes in photoperiod LD12:12, LD24:0, LD0:24, NL 40, 54, 61, 48 At 24 mo: 25 (62.5%), 6 (11.1%), 23 (37.7%), 15 (31.2%)	*All organs* Benign tumours (mainly fibroma or fibroadenoma of mammary gland) Incidence: 24/40 (60.0%), 32/54 (59.3%), 13/61 (21.3%)*, 39/48 (81.3%)* Malignant tumours Incidence: 5/40 (12.5%), 7/54 (13.0%), 3/61 (4.9%)*, 9/48 (18.8%)	*$P < 0.05$ (χ^2 test), LD0:24 (decrease) or NL (increase) vs LD12:12 * $P < 0.05$ (χ^2 test), LD0:24 vs LD12:12 (decrease)	Principal strengths: large lifetime study with a 5.6-fold decrease in the 2-yr survival rate for LD0:24 vs LD12:12 Principal limitations: many other diseases, more frequent in LD24:0 and NL rats Benign or malignant tumour incidences similar for LD24:0 and LD12:12 groups; LD0:24 protective against all pathologies including benign or malignant tumours; in the natural light (NL) group, photoperiod ranged from 4.2 h of light in winter to 24 h in summer; L, 750 lux at cage level

d, day; F, female; h, hour; LD, light-dark; LD0:24, continuous darkness; LD12:12, 12 h of light followed by 12 h of darkness; LD24:0, continuous light; M, male; mo, month; NL, natural light; NR, not reported; NS, not significant; SD, standard deviation; vs, versus; wk, week; yr, year.

or natural light–dark schedules. Light intensity was not specified in three studies (Jöchle, 1963; Joechle, 1964; Baturin et al., 2001).

(a) Mouse

Groups of 30 female C3H/HeJ mice [melatonin proficient] (age, 100 days), which have an inherited autosomal recessive retinal degeneration, were exposed to either a regular light–dark schedule (LD12:12) or to continuous light (LD24:0) for 400 days (Jöchle, 1963). Exposure to continuous light (LD24:0) was observed to prolong estrus phase duration by 60–80% compared with exposure to a schedule of LD12:12. Exposure to continuous light also delayed the appearance of spontaneous mammary tumours compared with exposure to a regular light–dark schedule: at age 351–400, 401–450, and 451–499 days, 2 (LD24:0) versus 6 (LD12:12), 6 versus 7, and 0 versus 4 tumours appeared, respectively. At age 500 days, there was a cumulative incidence of 11 mammary tumours out of 30 mice in the group exposed to continuous light compared with 24 mammary tumours out of 30 mice in the group exposed to a schedule of LD12:12. The mice exposed to continuous light had a prolonged survival compared with the mice exposed to LD12:12 (Jöchle, 1963; see also Joechle, 1964). [The Working Group noted the very limited information given regarding the experimental methods, including the number of mice at the start. No histopathology or statistical comparisons were provided.]

In a subsequent article (Joechle, 1964), female C3H/A mice [melatonin proficient] were subject to the same experimental conditions as described above for Jöchle (1963). Those exposed to LD24:0 displayed minor disturbances of the estrus cycle, with a maximum of a 24 hour increase in the duration of estrus compared with the mice exposed to LD12:12. There was an earlier occurrence of mammary tumours in the group exposed to LD24:0 compared with the group exposed to LD12:12, with 16 (LD24:0) versus 4 (LD12:12) tumours observed on days 151–300, and a higher cumulative number of tumours of 21 versus 12 at the age of 450 days. Mice exposed to continuous light also had a shorter lifespan than mice exposed to LD12:12. [The Working Group noted that limited information was provided regarding the experimental methods, including the number of mice at start. No histopathology or statistical comparisons were reported.]

A well-designed study (Anisimov et al., 2004) clearly demonstrated large and statistically significant differences in tumour incidence between groups of female CBA mice [melatonin proficient] (age, 2 months) exposed to either LD12:12 (controls, $n = 50$) or LD24:0 ($n = 50$) for their lifetime. Light intensity at the bottom of the cages was 300 lux for the control group and 2500 lux for the group exposed to continuous light. An earlier first tumour was observed in the group exposed to LD24:0 (312 days) compared with the group exposed to LD12:12 (610 days). Compared with the group exposed to LD12:12, the group exposed to LD24:0 demonstrated an increased number of mice that developed tumours (15 out of 50 vs 4 out of 50, $P < 0.001$), an increased number of total tumours (22 vs 5), and an increased number of malignant tumours (19 vs 3). Tissue or organ sites with significant increases in tumour incidence in the group exposed to LD24:0 were the lung (adenocarcinoma, 7 out of 50 vs 1 out of 50) and haematopoietic and lymphoid tissues (malignant lymphoma, 6 out of 50 vs 0 out of 50). A non-statistically significant increase in the incidence of tumours was seen in the liver (4 out of 50 vs 0 out of 50). Mice exposed to LD24:0 had a faster mortality rate after the age of 900–1050 days compared with mice exposed to LD12:12. [The Working Group noted the adequate power and statistical significance of most comparisons, but also noted the fact that the light intensity exposure differed between the groups.]

Baturin et al. (2001) reported a study in which 104 homozygous FVB HER-2/neu female transgenic mice [melatonin deficient] (age, 2 months)

were randomly allocated to one of four groups; two groups were exposed to LD12:12 and two groups were exposed to LD24:0. For each exposure schedule, one group remained untreated and the other was given access (at night) to melatonin dissolved in tap water. Estrus cycle was reported to be unaltered in the mice from any group [data not shown]. In groups that did not receive melatonin, 23 out of 30 mice (76.7%) in the LD12:12 group and 19 out of 25 mice (76.0%) in the LD24:0 group developed one or more tumours of the mammary gland, all of which were classified as mammary adenocarcinomas. The number of mice that developed lung metastases was also similar between these two groups. However, the mammary tumour multiplicity was significantly increased in the LD24:0 group, and the percentage of mice with four or more mammary tumours increased to 60% compared with 33% for the LD12:12 group ($P < 0.05$). [The Working Group noted that no statistical comparison between survival curves was provided.]

Popovich et al. (2013) reported a lifetime study in which 92 female 129/Sv mice [melatonin deficient] (age, 2 months) were randomly allocated to two groups and exposed to either LD12:12 or LD24:0 up to age 20 months. Light exposure at the bottom of the cages was 70 lux for the group exposed to LD12:12 and 2600 lux for the group exposed to LD24:0. Estrus cycle length was significantly prolonged in the group exposed to LD24:0 and the proportion of mice with irregular estrus cycles reached 68.4% in this group compared with less than 20% in the group exposed to LD12:12. Survival at 800 days was significantly reduced in the group exposed to LD24:0 (28.3%) compared with the group exposed to LD12:12 (47.8%). All mice were autopsied, and all tumours found were examined microscopically. The first tumour in the LD24:0 group occurred 2 months earlier than in the LD12:12 group. There was no statistically significant difference in the incidence of total tumours (39 out of 45 in the LD12:12 group vs 35 out of 43 in the LD24:0 group). The uteri of the majority of the mice were enlarged at autopsy. There was a non-significant increase in the number of uterine haemangiomas in the group exposed to LD24:0, and a non-significant increase in the number of sarcomas of the uterus in the group exposed to LD12:12.

(b) Rat

Vinogradova et al. (2009) (see also Bukalev et al., 2012) reported a study in which 208 male and 203 female LIO rats [Wistar-derived, melatonin status not reported] (age, 25 days) were allocated to one of four groups exposed to light–dark schedules of either: LD12:12 (57 males, 40 females); natural light, in which photoperiod ranged from 4.5 hours of light in winter to 24 hours in summer (50 males, 48 females); LD24:0 (50 males, 54 females), that is, continuous light; or LD0:24 (51 males, 61 females), that is, continuous darkness. Light intensity was: 750 lux for the groups exposed to LD12:12 and LD24:0; varied over the range 50–1000 lux in the group exposed to conditions of natural light, according to the time of day and weather [equivalent to latitude ~62°]; and was less than 0.5 lux (with a dim red light for service) in the group exposed to LD0:24. Compared with the group exposed to LD12:12, the first tumours were detected 156 days earlier among males and 21 days earlier among females in the group exposed to LD24:0 (continuous light), and 324 days later among males and 21 days earlier among females in the group exposed to LD0:24 (continuous darkness). The accelerated tumour development in the group exposed to LD24:0 did not translate into an increased incidence of tumours. Over the 1200 days of the study, total tumour incidence in males was 13 out of 50 (26%) in the LD24:0 group versus 17 out of 57 (29.8%) in the LD12:12 group. In females, total tumour incidence was 24 of 54 (44.4%) in the LD24:0 group versus 21 out of 40 (52.5%) in the LD12:12 group. Differences in total tumour incidence and in the

incidence of tumours in specific organ or tissue sites were not statistically significant. The mean survival was shorter in female rats exposed to LD24:0 compared with those exposed to LD12:12. The mean survival of cancer-bearing female rats was significantly reduced in the LD24:0 group compared with the LD12:12 group. In males, exposure to either natural light or LD0:24 significantly influenced tumour incidence, tumour multiplicity, number of malignant tumours, and mean survival. However, in females, exposure to natural light significantly increased total tumour incidence compared with exposure to LD12:12 (70.8% vs 52.5%; $P < 0.05$) and significantly ($P < 0.01$) shortened the mean lifespan of both tumour-bearing and cancer-bearing rats. Exposure to continuous darkness (LD0:24) significantly reduced the incidence of total tumours compared with exposure to LD12:12 (24.6% vs 52.5%; $P < 0.001$) in female rats. Compared with exposure to LD12:12, the incidence of benign mammary tumours (fibroma or fibroadenoma) was significantly increased ($P < 0.05$) by exposure to natural light and significantly decreased ($P < 0.01$) by exposure to LD0:24. [The Working Group noted that the time of year when rats in the group exposed to natural light entered the study was not reported.]

Vinogradova et al. (2010) (see also Lotosh et al., 2013) reported a study in which 267 male and 135 female outbred LIO rats (age, 1 month) were randomly allocated to one of two groups and exposed to a light–dark schedule of either LD12:12 or LD24:0. At the age of 14 months, 34 male and 36 females remained alive in the group exposed to LD24:0. At this stage, 90 male rats and 71 female rats from the group exposed to LD12:12 were reallocated to the group exposed to LD24:0, leaving 43 male and 30 female rats exposed to LD12:12. Compared with rats exposed to LD12:12 from the age of 1 month, mean lifespan was significantly shortened in female rats (but not in male rats) exposed to continuous light from the age of 1 month ($P < 0.01$); no significant differences in mean lifespan were seen in male or female rats exposed to continuous light from the age of 14 months. No statistically significant differences were found in comparisons of total tumour incidence and organ- or tissue-specific tumour incidence by sex.

Bukalev et al. (2013) reported a lifetime study of a total of 203 female Wistar rats (age, 25 days) that were exposed to a light–dark schedule of either LD12:12 (control), LD24:0, LD0:24, or natural light. In the group exposed to natural light, photoperiod [equivalent to latitude ~62°] ranged from 4.2 hours of light in winter to 24 hours in summer. The 2-year survival was reduced in the groups exposed to LD24:0 (11.1%), LD0:24 (37.7%), and natural light (31.2%), compared with the group exposed to LD12:12 (62.5%); however, no statistical analysis was provided. Tumour incidence was similar among rats exposed to LD12:12 (benign, 60.0%; malignant, 12.5%) or LD24:0 (benign, 59.3%; malignant, 13.0%). Tumour incidence in the group exposed to LD0:24 (continuous darkness) was significantly lower (benign, 21.3%; malignant, 4.9%), and exposure to natural light significantly increased the incidence of benign tumours (benign, 81.3%; malignant, 18.8%). In all groups, benign tumours were mostly fibromas or fibroadenomas of the mammary gland; malignant tumours were all observed to have originated in the haematopoietic system, breast, uterus, or kidney. [The Working Group noted that the time of year when the group exposed to natural light entered the study was not reported.]

3.4 Extreme changes in photoperiod with modifying factors

See also Table 3.4.

Table 3.4 Studies of carcinogenicity in experimental animals exposed to extreme changes in photoperiod with modifying factors

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, number, or surface area of tumours	Significance	Comments
Co-carcinogenicity Rat, Outbred (F) 5–6 mo ≤ 23 wk Khaetski (1965)	Changes in photoperiod Natural illumination + DMBA (control), LD24:0 + DMBA Intravenous injections of DMBA (1.5 mg) 5× at 10-d intervals (for ~7 wk) beginning 7 wk after start of experiment NR NR	*Ovary*: granulosa cell tumour Incidence: 0/15, 4/17 *Mammary gland*: tumours Incidence: 6/15, 5/17	 [NS] [NS]	Principal limitations: limited details on exposure design; no data on the time of light switching on and off; small number of rats; only one sex; no statistics reported Continuous light from 300-W electric lamp fixed 1.5 m high; all surviving rats killed 16 wk after the last DMBA injection; earliest mammary tumours detected after the 4th and 13th week in the control and continuous-light groups, respectively
Initiation–promotion (tested as promoter) Rat, Outbred (F) 5–6 mo ≤ 12 wk Khaetski (1965)	Changes in photoperiod Natural illumination + DMBA (control), LD24:0 + DMBA Intravenous injections of DMBA (1.5 mg) 6× at 10-d intervals (for ~9 wk) NR NR	*Mammary gland*: all tumours Incidence: 10/14, 12/14 Multiplicity: 1.7, 3.1 Surface area (cm^2): 2.6, 8.7	 [NS] NR NR	Principal limitations: limited details on exposure design; no data on the time of light switching on and off; no statistics reported; small number of rats; only one sex Continuous light from 300-W electric lamp fixed 1.5 m high; rats exposed for additional 12 wk to either natural light or constant light 4 wk after the last DMBA injection, then killed
Co-carcinogenicity Rat, Sprague-Dawley (F) 43 d 8 mo Hamilton (1969)	Changes in photoperiod LD12:12, LD24:0 30 mg DMBA by gavage at age 50 d 26, 21 NR	*Mammary gland* All tumours Incidence: 15/26 (58%), 20/21 (95%)* Multiplicity: 1.39, 2.71 Number: 36, 57 Adenocarcinoma Multiplicity: 0.62, 0.19 Number: 16, 4* Fibroadenoma Multiplicity: 0.77, 2.52 Number: 20, 53*	 *[$P = 0.006$, two-tail Fisher exact test] NR NR NR *$P < 0.001$ (decrease) NR *$P < 0.001$ (increase)	Principal strengths: relatively long observation period

Table 3.4 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, number, or surface area of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Rat, Sprague-Dawley (F) 58 d ~20 wk Aubert et al. (1980)	Changes in photoperiod Sham LD12:12, sham LD24:0, PX LD12:12, PX LD24:0 25 mg DMBA by gavage 2 d after either sham surgery or PX 25, 25, 25, 25 NR	*Mammary gland*: all tumours No significant difference in tumour incidence		Principal limitations: no microscopic evaluation of tissues; no statistical analysis reported Continuous light increased mammary tumour latency in sham-operated rats (n = 21; 77.3 d, P < 0.02) compared with sham LD12:12 controls (n = 20, 64.8 d)
Co-carcinogenicity Rat, Holtzman (F) 1 d 6 mo Kothari et al. (1982)	Changes in photoperiod LD10:14 (control), LD24:0 20 mg DMBA by gavage at age 55 d 25, 47 NR	*Mammary gland* All tumours Incidence: 17/25 [68.0%], 45/47 (95.7%)* Multiplicity: 1.12, 2.18 Adenocarcinoma Incidence: 15/25 (60.0%), 45/47 (95.7%)* Multiplicity: [0.88], [2.16] Number: 15, 97 Fibroadenoma Incidence: 2/25, 1/47 Multiplicity: [0.12], [0.02] Number: 2, 1	 *[P = 0.0024, two-tail Fisher exact test] NR *[P = 0.0002, two-tail Fisher exact test] NR NR [NS] NR NR	Principal strengths: relatively long observation period Principal limitations: data were not clearly presented throughout the manuscript Statistical analysis was not reported
Co-carcinogenicity Rat, Holtzman (F) 1 d 6 mo Kothari et al. (1984)	Changes in photoperiod LD10:14 (control), LD24:0 20 mg DMBA by gavage at age 55 d 25, 60 NR	*Mammary gland* All tumours Incidence: 17/25 [68.0%], 58/60 (96.7%)* Multiplicity: 1.13, 2.26 Number: 19, 131 Adenocarcinoma Incidence: 15/25 (60.0%), 57/60 (95.0%)*	 *[P = 0.0007, two-tail Fisher exact test] NR NR *[P = 0.0002, two-tail Fisher exact test]	Principal strengths: relatively long observation period Principal limitations: data were not clearly presented throughout the manuscript Statistical analysis was not reported; controls appear to be as for Kothari et al. (1982) (same data) or else Kothari et al. (1984) is a follow-up study

Table 3.4 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, number, or surface area of tumours	Significance	Comments
Co-carcinogenicity Rat, Holtzman (F) 1 d 6 mo Kothari et al. (1984)	Changes in photoperiod LD10:14 (control), LD24:0 PX at birth and 20 mg DMBA by gavage at age 55 d 23, 29 NR	*Mammary gland* All tumours Incidence: 15/23 (65.2%), 26/29 (90.0%)* Multiplicity: 1.20, 2.65 Number: 18, 43 Adenocarcinoma Incidence: 14/23 (60.9%), 24/29 (82.8%)	 *[$P = 0.04$, two-tail Fisher exact test] NR NR [NS]	Principal strengths: relatively long observation period Principal limitations: data were not clearly presented throughout the manuscript Statistical analysis was not reported
Initiation–promotion (tested as initiator) Rat, Holtzman (F) 1 d 27 wk Subramanian & Kothari (1991)	Changes in photoperiod Intact + LD10:14 (control), intact + LD24:0, PX + LD10:14 (control), PX + LD24:0 10 mg DMBA by gavage 1× at age 55 d 20, 20, 20, 20 NR	*Mammary gland*: carcinoma Incidence: 70.0%, 80.0%, 87.5%, 90.0% Multiplicity: 1.4 ± 0.2, 1.4 ± 0.3, 1.4 ± 0.2, 1.4 ± 0.2	 NS NS	Principal strengths: relatively long observation period
Co-carcinogenicity Rat, Sprague-Dawley (F) 26 d 13 wk Anderson et al. (2000)	Changes in photoperiod LD8:16 (control), LD24:0 8 mg DMBA by gavage at age 52 d 50, 50 NR	*Mammary gland*: all tumours Incidence: 19/50, 8/50* Multiplicity: 2.6, 1.1	 *$P < 0.05$ (decrease) NR	Principal limitations: no histopathological examination
Co-carcinogenicity Rat, NR (F) 1 mo At least ≤ 390 d Anisimov et al. (1994)	Changes in photoperiod LD12:12, LD24:0, LD0:24 Intravenous injections of MNU at 50 mg/kg bw 1×/wk for 3 wk from age 6 wk 30, 50, 50 NR	*Mammary gland* All tumours Incidence: 12/22 (55%), 32/35 (91%)*, 6/38 (16%)** Adenocarcinoma Incidence: 7/22 (31%), 20/35 (57%)*, 1/38 (3%)**	 *$P < 0.05$ (increase) **$P < 0.05$ (decrease) *$P < 0.05$ (increase) **$P < 0.05$ (decrease)	Principal limitations: number of animals at start not reported; no information on survival or body weight; only one sex used; limited details on exposure design The effective number of animals (denominator) is the number of animals alive at appearance of first mammary gland tumour; see also Anisimov et al. (1996)

Table 3.4 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, number, or surface area of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Rat, F344/N (F) 50 d 26 wk Travlos et al. (2001)	Changes in photoperiod LD12:12, LD12:12 + intermittent light at night (5× 1-min exposures), LD12:12 + PX Intraperitoneal injection of MNU at 50 mg/kg bw at age 50 d 40, 40, 40 34, 34, 31	*Mammary gland* All tumours Incidence: 70%, 70%, 78% Multiplicity: 2.18, 1.89, 2.39 Number: 61, 53, 74	 NS NS NS	Principal limitations: the high dose of MNU may have precluded the identification of a carcinogenic response
Co-carcinogenicity Rat, Wistar (M+F) (combined) Gestation day 1 Lifetime Beniashvili et al. (2001)	Changes in photoperiod LD12:12 (control), LD24:0, LD0:24 Maternal exposure to ENU (80 mg/kg bw) on gestation day 18 or 19 61, 34, 40 NR	*All tumours* (in male offspring) Incidence: 26%, 85%*, 13%** *Peripheral nervous system* (in male offspring): all tumours Incidence: 20%, 62%*, 10% *Kidney* (in male offspring): all tumours (all mesenchymal) Incidence: 2%, 21%*, 3% *All tumours* (in female offspring) Incidence: 32%, 70%*, 11%** *Peripheral nervous system* (in female offspring): all tumours Incidence: 28%, 54%*, 7%** *Kidney* (in female offspring): all tumours (all mesenchymal) Incidence: 2%, 9%, 5%	 *$P < 0.01$ (increase) **$P < 0.01$ (decrease) *$P < 0.01$ (increase) *$P < 0.01$ (increase) *$P < 0.01$ (increase) **$P < 0.01$ (decrease) *$P < 0.01$ (increase) **$P < 0.01$ (decrease) NS	All groups of male and female offspring housed under LD12:12 schedule after weaning at age 1 mo

Table 3.4 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Incidence, multiplicity, number, or surface area of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Rat, Outbred (M) NR ≤ 20 wk Panchenko et al. (2008)	Changes in photoperiod LD12:12 + DMH (control), LD24:0 + DMH Subcutaneous injection of DMH (21 mg/kg bw) 5× at 1-wk intervals NR NR	*Colon*: carcinoma Incidence: 17/19, 17/19 Multiplicity: 1.5 ± 0.2, 1.8 ± 0.2 *Colon (ascending)*: carcinoma Incidence: 11/19, 16/19*	 [NS] NS *$P < 0.05$	Principal limitations: DMH doses may have been too high to permit identification of tumour-promoting effect; no data on circadian disruption status

bw, body weight; d, day; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, 1,2-dimethylhydrazine; ENU, *N*-ethyl-*N*-nitrosourea; F, female; LD, light-dark; LD0:24, continuous darkness; LD8:16, 8 hours of light followed by 16 hours of darkness; LD10:14, 10 hours of light followed by 14 hours of darkness; LD12:12, 12 hours of light followed by 12 hours of darkness; LD24:0, continuous light; M, male; min, minute; MNU, *N*-methyl-*N*-nitrosourea; mo, month; NR, not reported; NS, not significant; PX, pinealectomy/pinealectomized; wk, week.

Rat

(a) 7,12-Dimethylbenz[a]anthracene

In the first experiment of a study (Khaetski, 1965), groups of female outbred non-parous rats [number at start and strain not reported] (age, 5–6 months) were exposed to one of the following light–dark schedules: Group 1, constant light (LD24:0) using a 300 W electric lamp fixed 1.5 m high; Group 2, "natural" illumination [not further specified]; and Group 3, 2–3 hours of light followed by 21–22 hours of darkness. Beginning at 7 weeks from the start of the experiment, all rats were given five intravenous injections of 7,12-dimethylbenz[*a*]anthracene (DMBA) at 1.5 mg at 10-day intervals. The rats were killed when the tumours reached a diameter of 10 mm. Rats without tumours were killed 16 weeks after the last DMBA injection. In Group 1 (LD24:0), 4 out of 17 rats developed ovarian granulosa cell tumours, 2 out of 17 developed malignant mammary tumours, and 3 out of 17 developed benign mammary tumours [no significant increase in any incidence compared with Group 2]. In Group 2 ("natural" illumination), 6 out of 15 rats developed mammary tumours [histopathology not further specified] and no ovarian tumours were observed. In Group 3, 9 out of 19 rats developed malignant mammary tumours and 5 out of 19 developed benign mammary tumours. [The Working Group noted the inconsistency in data reported: in table 3 it was stated that 79% of rats of Group 3 had mammary tumours, that is, 15 out of 19 rats, but 14 out of 19 were reported.] The earliest mammary tumours were detected in groups 1, 2, and 3 at weeks 13, 4, and 4, respectively. [The Working Group noted that the number of rats per group was small.]

In a second experiment from the same study, female outbred rats [number at start and strain not reported] (age, 5–6 months) were given six intravenous injections of DMBA at 1.5 mg at 10-day intervals. At 4 weeks after the last injection, rats were subdivided into two groups: Group 1, exposed to continuous light (LD24:0); and Group 2, exposed to "natural" illumination [not further specified]. All surviving rats were killed 16 weeks after the last injection of the carcinogen. Mammary tumours [histopathology not further specified] developed in 12 out of 14 rats exposed to LD24:0 and in 10 out of 14 rats exposed to natural light [no significant difference]. In Groups 1 and 2 the multiplicity of mammary tumours was 3.1 and 1.7 per rat, and the surface area of tumours was 8.7 and 2.6 cm^2, respectively [no statistical analysis was reported] (Khaetski, 1965). [The Working Group noted that the number of rats per group was small.]

Hamilton (1969) reported a study in which 47 female Sprague-Dawley rats (age, 43 days) were exposed to either LD12:12 ($n = 26$, controls) or to LD24:0 ($n = 21$, continuous light), and were given a single oral dose of 30 mg DMBA by gavage at the age of 50 days and observed for 8 months. Compared with DMBA-treated control rats, DMBA-treated rats exposed to LD24:0 demonstrated a higher incidence and number of mammary tumours. Although the total incidence of mammary tumours was significantly increased in rats exposed to LD24:0 (20 out of 21 rats, 95%) compared with rats exposed to LD12:12 (15 out of 26 rats, 58%), rats exposed to LD12:12 developed significantly more mammary gland adenocarcinomas (16 vs 4, $P < 0.001$) than rats exposed to LD24:0. Most (53 out of 57) of the mammary tumours in the group exposed to LD24:0 were benign lesions (fibroadenomas); the large number of fibroadenomas seen in this group was responsible for the reported increase in the incidence of mammary tumours and total tumour number. [The Working Group noted that because rats exposed to continuous light developed significantly fewer mammary cancers than rats exposed to LD12:12, the implications of the results of this study are unclear.]

Aubert et al. (1980) reported a study in which two groups of 50 female Sprague-Dawley rats

(age, 58 days) were exposed to DMBA (25 mg) by gavage 2 days after either pinealectomy or sham surgery. Each group was then divided into another two groups, and exposed to either LD12:12 or LD24:0 (continuous light) and observed for approximately 20 weeks. In rats that had undergone sham surgery, mammary tumour latency was significantly increased in those exposed to LD24:0 compared with those exposed to LD12:12; this effect was abolished by pinealectomy. However, no significant difference in tumour incidence was seen between the groups.

Kothari et al. (1982) performed a study in which pregnant female Holtzman rats were exposed to continuous light, beginning on day 10–12 of gestation and continuing until parturition. At parturition, one group of dams and pups was maintained under continuous light (LD24:0), and the other group of dams and pups was transferred to a room maintained at a LD10:14 schedule. On day 21 after parturition, female offspring from both groups were weaned and dams were removed from the study. At the age of 55 days, 25 female rats exposed to LD10:14 and 47 female rats exposed to LD24:0 were given DMBA (20 mg) by gavage and observed for mammary tumour development for 6 months. Exposure to LD24:0 increased both mammary tumour incidence [$P = 0.0024$] and mammary tumour multiplicity [statistics not reported] compared with exposure to LD10:14. Almost all tumours were diagnosed as adenocarcinomas; there was therefore a significant increase in the incidence of mammary adenocarcinomas. The mean tumour latency period was significantly shorter in rats exposed to DMBA plus LD24:0 compared with rats exposed to DMBA plus LD10:14.

In a follow-on study, Kothari et al. (1984) reported a study in which pregnant female Holtzman rats were exposed to continuous light, beginning on day 10–12 of gestation and continuing until parturition. At 1–2 days after parturition, 52 female pups underwent pinealectomy and 85 female pups were left intact. Both intact and pinealectomized pups were then assigned to one of two groups exposed to either LD24:0 or LD10:14. At 21 days after parturition, female offspring from all groups were weaned and dams were removed from the study. At the age of 55 days, female rats were given DMBA (20 mg) by gavage and observed for mammary tumour development for 6 months. In intact female rats, exposure to LD24:0 increased both mammary tumour incidence [$P = 0.0007$] and mammary tumour multiplicity [statistics not reported] compared with rats exposed to LD10:14. Almost all mammary tumours identified in the study were diagnosed as adenocarcinomas; there was therefore a significant increase in the incidence of mammary adenocarcinomas. The mean tumour latency period was shorter in rats exposed to DMBA plus LD24:0 compared with rats exposed to DMBA plus LD10:14. [The Working Group noted that tumour responses in intact rats were virtually identical to those reported in Kothari et al. (1982). On this basis, it appears that the data reported in Kothari et al. (1982) may have been used again in Kothari et al. (1984).] In pinealectomized rats, exposure to LD24:0 increased both mammary tumour incidence [$P = 0.04$] and mammary tumour multiplicity [statistics not reported] compared with rats exposed to LD14:10. As was the case for intact rats, almost all mammary tumours were diagnosed as adenocarcinomas; however, the incidence of this tumour type was not significantly increased. As observed for intact rats, the mean tumour latency period was shorter in rats exposed to DMBA plus LD24:0 compared with rats exposed to DMBA plus LD10:14.

[The Working Group noted that mammary tumour data presented in an article by Shah et al. (1984) and recapitulated in Mhatre et al. (1984) are essentially identical to those presented in Kothari et al. (1982, 1984). Because the data

presented in these articles do not appear to be unique, they do not merit further discussion.]

The study by Subramanian & Kothari (1991) examined the role of continuous light on the incidence of DMBA-induced mammary tumours in intact or neonatally pinealectomized female Holtzman rats. Groups of 20 intact and pinealectomized rats were reared under light–dark schedules of either LD10:14 or LD24:0. Intact and pinealectomized female rats were given DMBA (10 mg) by gavage at the age of 55 days, and monitored for mammary tumour appearance and multiplicity for 27 weeks. Continuous light (LD24:0) did not significantly increase tumour incidence or multiplicity in either intact or pinealectomized rats compared with their respective LD10:14 control groups.

Anderson et al. (2000) performed a study in which groups of 50 virgin female Sprague-Dawley rats (age, 26 days) were exposed to either constant light (LD24:0) or a light–dark schedule of 8 hours of light followed by 16 hours of darkness (LD8:16) until termination of the study. At the age of 52 days, rats were given DMBA (8 mg) by gavage and monitored for mammary tumour development until terminal necropsy 13 weeks later. Rats exposed to constant light demonstrated a significant decrease in the incidence of mammary tumours compared with rats exposed to LD8:16. Mammary tumour incidence was 16% in rats in the constant light group versus 38% in rats in the LD8:16 group. Mean mammary tumour multiplicity was 1.1 tumour per rat in the group exposed to continuous light versus 2.6 tumours per rat in the group exposed to LD8:16. [The Working Group noted that a weakness of the study design was that tumour incidence was based on palpation and gross pathology only; tumours were not evaluated microscopically to confirm malignancy.]

(b) N-*methyl*-N-*nitrosourea*

Anisimov et al. (1994) (see also Anisimov et al., 1996) reported a study to determine the effects of light–dark schedules on the induction of mammary cancers in female rats [strain not reported] (age, 1 month). Rats were allocated to one of three groups, and exposed to either LD12:12 (n = 30), continuous light (LD24:0; n = 50), or continuous darkness (LD0:24, n = 50). After 2 weeks of exposure, all rats were given the first of three intravenous injections of *N*-methyl-*N*-nitrosourea (MNU) at 50 mg/kg bw at 1-week intervals. Compared with a mammary tumour incidence of 55% (12 out of 22) in the MNU-treated LD12:12 group, 91% (32 out of 35) of rats in the LD24:0 group developed mammary tumours. By contrast, mammary tumour incidence in the LD0:24 group was 16% (6 out of 38). The same pattern was observed if tumour data were limited to mammary gland adenocarcinoma: compared with a 31% mammary adenocarcinoma incidence (7 out of 22) in the LD12:12 group, rats in the LD24:0 group had a 57% incidence of mammary adenocarcinomas (20 out of 35) and rats in the LD0:24 group had a 3% incidence of mammary adenocarcinoma (1 out of 38). Each of these differences from the LD12:12 group was statistically significant ($P < 0.05$). [The Working Group noted the lack of details provided on the duration of the experiment (at least up to 390 days) and exposure design, and that the high dose of MNU may have had an impact on survival and tumour incidence.]

In a later study performed by Travlos et al. (2001) using the same carcinogen-induced mammary cancer model, intact or pinealectomized female Fischer 344/N rats (age, ~50 days) were given a single intraperitoneal injection of MNU at 50 mg/kg bw. Two groups of MNU-treated rats, one intact (n = 40) and the other pinealectomized (n = 40), were then exposed to a light–dark schedule of LD12:12. A third group of intact rats (n = 40) was also

exposed to LD12:12 with five intermittent exposures to 1 minute of light at 2 hour intervals, every night. All rats were observed for 26 weeks after treatment with MNU. A strong mammary cancer response was seen in all groups. Both exposure to intermittent light at night and pinealectomy did not have any statistically significant effect on mammary cancer incidence or multiplicity in this study. [The Working Group noted that the high dose of MNU may have precluded the identification of a carcinogenic response.]

(c) N-*ethyl*-N-*nitrosourea*

Beniashvili et al. (2001) performed a study in which groups of 24 pregnant female Wistar-derived outbred rats were exposed to either a daily schedule of 12 hours of light followed by 12 hours of darkness (LD12:12), constant light (LD24:0), or continuous darkness (LD0:24). The different light exposure regimens were initiated on the first day of gestation, and were continued throughout gestation and for 1 month after delivery. Each pregnant rat was given a single intravenous injection of *N*-ethyl-*N*-nitrosourea at 80 mg/kg bw on day 18 or 19 of gestation. At 1 month after delivery, offspring (males and females) from all groups were exposed to LD12:12 until their natural death. Compared with offspring exposed to LD12:12 during gestation and the early postpartum period, offspring exposed to LD24:0 demonstrated significant increases in the incidence of total tumours in males and females, in peripheral nervous system tumours in males and females, and in kidney tumours in males. All kidney tumours were mesenchymal tumours. In contrast, compared with offspring exposed to LD12:12 during these periods, offspring exposed to LD0:24 demonstrated a significantly lower total tumour incidence in males and females, and a significantly lower incidence of tumours in the peripheral nervous system in females.

(d) *Diethylnitrosamine*

To investigate the possible promoting activity of light at night on hepatocarcinogenesis induced in rats by DEN, a total of 65 male Wistar rats were given drinking-water containing DEN at a dose of 10 mg/kg bw every day for 6 weeks and then randomized into three experimental groups: DEN only (20 rats; negative control); DEN plus phenobarbital (30 mg per rat per day for 4 weeks; 22 rats, positive control), a promoter of tumours of the liver; or DEN plus continuous light (LD24:0) (23 rats). All rats were observed until death (≤ 5 months in all groups) (van den Heiligenberg et al., 1999). At 3 months after the start of the experiment, laparotomic evaluations demonstrated no [statistically significant] differences between groups in terms of total incidence of gross lesions on the surface of the liver (72% in rats treated with DEN only vs 89% in rats treated with DEN plus phenobarbital and 95% in rats treated with DEN plus continuous light). In contrast, when compared with the DEN-only group, groups treated with either DEN plus phenobarbital or DEN plus continuous light demonstrated statistically significant increases in the percentage of rats with six or more grossly visible nodules on the surface of the liver and in the percentage of rats with a largest nodule of size at least 3 mm. [The Working Group noted that these data were presented only as bar graphs and not as precise numerical data for lesion incidence.] At the time of death, all rats demonstrated grossly detectable nodules on the surface of the liver (van den Heiligenberg et al., 1999). [The Working Group noted that this study was weakened by the high dose of DEN that may have precluded the identification of the carcinogenic response, and by the fact that the total number of lesions throughout the hepatic parenchyma was not quantified in each rat.]

(e) 1,2-Dimethylhydrazine

Male outbred LIO Wistar-derived rats (white rats from the Rappolovo breeding nursery, Russian Federation) were subdivided into five groups (Panchenko et al., 2008). Four groups were given five subcutaneous injections of 1,2-dimethylhydrazine (DMH) at a dose of 21 mg/kg bw at 1 week intervals from the first day of the experiment, and exposed to: Group 1, LD12:12 (L, 250 lux; D, 0.5 lux); Group 2, LD24:0; Group 3, LD24:0 plus melatonin at a concentration of 20 mg/L in the drinking-water during "nighttime", 6 times per week, from the first injection of DMH and for 20 weeks after the last DMH injection; and Group 4, LD0:24, with the exception of a 15-minute exposure to red light to clean the rats' cages (5 lux, 3 times per week). Group 5 consisted of 5 intact rats that were not given DMH (control) and were exposed to a light–dark schedule of LD12:12 (L, 250 lux). Rats were killed 20 weeks after the last DMH injection. The incidence of colon carcinoma was 17 out of 19 (89%), 17 out of 19 (89%), 11 out of 19 (58%; $P < 0.01$, decrease), and 12 out of 19 (63%) in Groups 1–4, respectively. However, the incidence of ascending colon carcinoma was 11 out of 19 (58%), 16 out of 19 (84%; $P < 0.05$, increase), 9 out of 19 (47%), and 9 out of 19 (47%) in groups 1–4, respectively. In conclusion, exposure to constant light may have promoted DMH-induced colon carcinogenesis in rats (Panchenko et al., 2008). [The Working Group noted that histopathology was performed on the ascending and descending colon and the rectum. The Working Group also noted the absence of data on circadian disruption, and that the DMH dose may have been too high to permit identification of a tumour-promoting effect.]

(f) Supporting studies

Cos et al. (2006) reported that light at night increased the growth rate of DMBA-induced mammary tumours, although the effect on the incidence or multiplicity of DMBA-induced mammary tumours in rats was not evaluated. In this study, alteration in the light–dark schedule was initiated when palpable mammary tumours were present. Female Sprague-Dawley rats that had been treated with 20 mg DMBA were assigned to groups when their first palpable mammary tumour reached 1 cm in diameter. Groups of 16 tumour-bearing rats were exposed to either: LD12:12 (L, 300 lux); constant light (300 lux); LD12:12 with a 30-minute period of normal light (300 lux) at the midpoint of the dark cycle; or LD12:12 with normal light (300 lux) during the period of light and dim light (0.21 lux) during the period of darkness. After 12 weeks, compared with rats in the first group (LD12:12), mean tumour surface area was increased ($P < 0.05$) in all three groups exposed to light at night. [The Working Group noted that mean tumour surface areas were provided in graphic form.]

3.5 Extreme changes in photoperiod with implant, transplant, or graft

See also Table 3.5.

3.5.1 Mouse

In the study by Otálora et al. (2008), groups of 10–21 C57BL/6 male mice [age, not reported; body weight, ~22 g; melatonin deficient] were given a subcutaneous injection of murine B16 melanoma cells to study the effects of exposure to continuous light (LD24:0) on tumour growth and circadian rhythm of core body temperature. Exposure to LD24:0 accelerated tumour progression (malignancy scored semiquantitatively; ANOVA test, $P < 0.05$) and abolished the circadian rhythm of core body temperature. [The Working Group noted that statistical analyses were inappropriate, reducing the suitability of the study for further evaluation.]

Table 3.5 Studies of carcinogenicity in experimental animals exposed to extreme changes in photoperiod with implant, transplant, or graft

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Growth rates, malignancy, weight, or volume of tumours	Significance	Comments
Co-carcinogenicity Mouse, B6D2F$_1$ (M) 6 wk ≤ 2 wk after inoculation Filipski et al. (2004)	Changes in photoperiod LD12:12 (control), LD24:0; mice were initially synchronized to LD12:12 for 3 wk Subcutaneous inoculation with 3 mm^3 fragments of mouse Glasgow osteosarcoma in each flank at age 9 wk 10, 10 NR	*Glasgow osteosarcoma*: total tumours Weight at 13 d (mg): 1700, 1550	NS	Principal limitations: tumour weight read from graph "Experiment 4": no effect on tumour growth and survival; melatonin-proficient strain
Co-carcinogenicity Mouse, C57BL/6 (M) NR 21 d after inoculation Otálora et al. (2008)	Changes in photoperiod LD12:12 (control with loggers), LD24:0 (with loggers) Subcutaneous inoculation with 0.5 × 10^6 murine B16 melanoma cells in left flank 10 d after exposure 12, 21 9, 11	*B16 murine melanoma*: total tumours Malignancy score: 3.25, 3.62*	*Light at night significantly increased rate of tumour progression (malignancy score: $P < 0.05$, ANOVA test)	Principal strengths: studied the role of light at night on tumour growth Principal limitations: statistical analyses considered inappropriate by the Working Group Melatonin-deficient strain
Initiation–promotion (tested as promoter) Mouse, BALB/c (M) 8 wk ≤ 21 d (PC3) or ≤ 17 d (HeLa) after inoculation Yasuniwa et al. (2010)	Changes in photoperiod HeLa + LD12:12 (control), HeLa + LD24:0, PC3 + LD12:12 (control), PC3 + LD24:0 Subcutaneous injection of 1 × 10^6 HeLa (human cervical cancer) or 1 × 10^6 PC3 (human prostate cancer) cells at two dorsal sites per mouse 16, 16, 8, 8 NR	*Human cervical adenocarcinoma (HeLa cells) or prostatic small cell carcinoma (PC3 cells)*: total tumours Volume (mm^3): at 17 d, 1100, 1600*; at 21 d, 350, 700*	*Tumours displayed increased volume in mice exposed to LD24:0 compared with mice exposed to LD12:12 ($P < 0.01$ for both models)	Melatonin-deficient strain; tumour volume read from graph

Table 3.5 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Growth rates, malignancy, weight, or volume of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Rat, RNU (F) NR ≤ 72 d after inoculation Blask et al. (2003)	Changes in photoperiod LD12:12 (control), LD24:0 Subcutaneous inoculation with 3 mm^3 tumour tissue (MCF-7 human breast cancer tissue xenograft, 10^7 cells) blocks to inguinal region 3, 4 NR	*Human MCF-7 breast carcinoma*: total tumours Weight at 55 d (g): 2.8, 6.1*	MCF-7 tumour xenografts grew twice as fast in rats exposed to LD24:0 than in those exposed to LD12:12 ($P < 0.05$); *tumour volume significantly increased by more than 2-fold	Principal strengths: measured endogenous melatonin level under both LD24:0 and LD12:12 cycles Principal limitations: very small number of animals per group Rats were exposed to either LD12:12 or LD24:0 for 40 d after inoculation; tumour volume read from graph
Co-carcinogenicity Rat, Buffalo (M) NR ≤ 25 d after inoculation Blask et al. (2005)	Changes in photoperiod Six groups all exposed to light for 12-h period, then light at either 0.0 (i.e. LD12:12), 0.02, 0.05, 0.06, 0.08, or 345 (i.e. LD24:0) μW/cm^2 for 12-h period Subcutaneous inoculation with 3 mm^3 tumour block 2 wk after exposure 6, 6 NR	*Rat hepatocarcinoma 7288CTC*: total tumours Weight (g): LD12:12, 1.5 at 13 d; LD24:0, 8 at 8 d	Tumour grafts displayed increased rate of growth in rats exposed to light at night at 0.05, 0.06, 0.08, or 345 μW/cm^2 ($P < 0.05$) compared with those in rats exposed to 0.0 (i.e. LD12:12) and 0.02 μW/cm^2	Principal strengths: tested the impact of multiple types of light-at-night conditions on tumour growth; used two graft models Principal limitations: small number of animals per group Tumour weight read from graph
Co-carcinogenicity Rat, RNU (F) NR ≤ 35 d after inoculation Blask et al. (2005)	Changes in photoperiod Six groups exposed to light for 12-h period then light at either 0.0 (i.e. LD12:12), 0.02, 0.05, 0.06, 0.08, or 345 (i.e. LD24:0) μW/cm^2 for 12-h period Subcutaneous inoculation with 3 mm^3 tumour xenograft block 2 wk after exposure 6, 6 NR	*Human MCF-7 breast carcinoma*: total tumours Weight at 17 d (g): LD12:12, 1.8; LD24:0, 5.8	Tumour xenografts displayed increased rate of growth in rats exposed to light at night at 0.05, 0.06, 0.08, or 345 μW/cm^2 ($P < 0.05$) compared with those in rats exposed to 0.00 (i.e. LD12:12) and 0.02 μW/cm^2	Principal strengths: tested the impact of multiple types of light-at-night conditions on tumour growth; used two graft models Principal limitations: small number of animals per group Tumour weight read from graph

Table 3.5 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Growth rates, malignancy, weight, or volume of tumours	Significance	Comments
Co-carcinogenicity Rat, RNU (F) NR 30 d after inoculation Blask et al. (2014)	Changes in photoperiod LD12:12 (control), LD12:12 with dim light during the dark phase (0.08 μW/cm²) Subcutaneous inoculation with 3 mm³ human MCF-7 breast cancer 6 wk after exposure 6, 6 NR	*Human MCF-7 breast carcinoma*: total tumours Weight at 19 d (g): 2.4, 6.0	Tumours in rats exposed to light at night (0.08 μW/cm²) displayed a significant accelerated growth rate compared with those in rats exposed to LD12:12 (control) ($P < 0.01$)	Principal limitations: no survival or body-weight data; short duration of exposure; small number of animals used in tumour growth analysis Tumour weight read from graph
Co-carcinogenicity Rat, Buffalo (M) 5 wk ≤ 25 d after inoculation Dauchy et al. (1997)	Changes in photoperiod LD12:12 (control), LD12:12 with 0.08 μW/cm² light contamination during the dark phase, LD24:0 (345 μW/cm²) Subcutaneous injection of 3 mm³ rat hepatocarcinoma 7288CTC at age 12 wk 6, 6, 6 NR	*Morris hepatoma (rat hepatocarcinoma) 7288CTC*: total tumours Weight at 15 d (g): 2.2, 5, 10.4 Growth rate (g/d): 0.72 ± 0.09, 1.30 ± 0.15*, 1.48 ± 0.17*	Tumour growth rate displayed a positive relationship with the intensity of light at night; rats exposed to LD24:0 displayed the fastest rate (*$P < 0.001$) of tumour growth, followed by rats exposed to LD12:12 with light contamination (*$P < 0.001$); rats exposed to LD12:12 (control) demonstrated the lowest tumour growth rate	Principal strengths: compared the effect of two types of light-at-night conditions on the rate of tumour growth Principal limitations: small number of animals per group Tumour weight read from graph
Co-carcinogenicity Rat, RNU (F) NR NR, > 15 d Wu et al. (2011)	Changes in photoperiod LD12:12 (control), LD12:12 with light contamination (0.08 μW/cm²) Subcutaneous inoculation of 3 mm³ tumour tissue block after 2 wk of exposure 36, 36 NR	*Human MCF-7 SR⁻ breast cancer xenograft*: total tumours Latency to onset (d): 15, 11 Growth rate (g/d): 0.26 ± 0.04, 0.56 ± 0.03*	*$P < 0.05$, ANOVA test	Principal strengths: adequate number of animals used in the study Principal limitations: the approach of euthanizing animals for tumour isolation was unclear

Table 3.5 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Agent tested Exposure schedule No. of animals at start No. of surviving animals	Growth rates, malignancy, weight, or volume of tumours	Significance	Comments
Full carcinogenicity Rat, Wistar (M) NR 13 d after inoculation Guerrero-Vargas et al. (2017)	Changes in photoperiod LD12:12 (control), LD24:0 Subcutaneous inoculation with 5×10^6 rat C6 glioma cells after 5 wk of exposure 7, 7 NR	*Rat glioma C6 cell line*: total tumours Volume at 11 d (mm^3): 400, 750 Volume at 13 d (mm^3): 250, 650 Weight at 13 d (g): 0.5, 1.2*	*Tumours in rats exposed to LD24:0 grew faster ($P = 0.0240$) and larger in terms of weight ($P < 0.05$) and volume ($P < 0.01$) compared with those in rats exposed to LD12:12 (control)	Tumour volume and weight read from graph

d, day; F, female; h, hour; LD, light-dark; LD12:12, 12 h of light followed by 12 h of darkness; LD24:0, continuous light; M, male; NR, not reported; NS, not significant; wk, week.

Yasuniwa et al. (2010) studied HeLa (human cervical cancer cell) and PC3 (human prostate cancer cell) xenograft models using four groups of male BALB/c nude mice [melatonin deficient] (age, 8 weeks). Mice were given a subcutaneous injection of 1×10^6 HeLa (two groups, $n = 16$ per group) or PC3 (two groups, $n = 8$ per group) cells and then exposed to light–dark schedules of either LD12:12 (control) or LD24:0. Compared with the groups exposed to LD12:12, tumours in the LD24:0 groups (after 21 days for PC3 cells and after 17 days for HeLa cells) demonstrated a significantly increased volume ($P < 0.01$) and also significantly increased tumour micro-vessels and stroma.

3.5.2 Rat

Blask et al. (2003) studied the effects of exposure to continuous light on the growth of MCF-7 human breast cancer xenografts (10^7 cells) and plasma melatonin in immunodeficient female Rowett nude (RNU) rats [age, not reported]. Beginning 40 days after inoculation, rats were exposed to light–dark schedules of either LD12:12 or LD24:0 (continuous light). Compared with rats exposed to LD12:12 ($n = 3$), tumour growth rate was significantly increased ($P < 0.05$) and tumour weight at 55 days was significantly increased ($P < 0.05$) by more than 2-fold in rats exposed to LD24:0 ($n = 4$). Exposure to LD24:0 also completely suppressed the circadian rhythm of plasma melatonin. [The Working Group noted the very small group sizes.]

In the study by Blask et al. (2005), the effects of various intensities of light at night were investigated in groups of male Buffalo rats [age not reported, adult] bearing the rat hepatocarcinoma 7288CTC syngeneic graft and in groups of female RNU rats [age not reported, adult] bearing the MCF-7 breast cancer xenograft. Starting 2 weeks before tumour implantation, and continuing for up to 35 days after implantation, rats were exposed to a schedule of 12 hours of light and 12 hours of darkness, with six different intensities of light during the 12-hour period of darkness ($n = 6$ per group per light intensity): 0.00 (i.e. LD12:12, controls), 0.02, 0.05, 0.06, 0.08, or 345 (i.e. LD24:0 or constant light) μW/cm^2. In both models, rats exposed to light at 0.05, 0.06, 0.08, or 345 μW/cm^2 demonstrated significantly ($P < 0.05$) faster tumour growth rates compared with those exposed to light at 0.00 (controls) and 0.02 μW/cm^2. In male Buffalo rats, mean tumour weights were about 1.5 g at 13 days in those exposed to LD12:12 and about 8 g at 8 days in those exposed to LD24:0 [estimated by the Working Group from graphical data]. In female RNU rats, mean tumour weights at 17 days were about 1.8 g in those exposed to LD12:12 and about 5.8 g in those exposed to LD24:0 [estimated by the Working Group from graphical data]. There was also a dose-dependent suppression of plasma nocturnal melatonin levels in both rat models. [The Working Group noted the small number of rats.]

The study by Blask et al. (2014) used the same female RNU rat [age not reported, adult] MCF-7 human breast cancer xenograft model and approaches as described in the previous studies (Blask et al., 2003, 2005) to investigate the effect of exposure to dim light (0.08 μW/cm^2) during the period of darkness on tumour growth. Exposure to LD12:12 (controls) or to a schedule of 12 hours of light and 12 hours of dim light during the period of darkness was started 6 weeks before tumour implantation and continued for up to 30 days after implantation. Compared with rats maintained at LD12:12, rats exposed to dim light during the period of darkness ($n = 6$ rats per group) demonstrated a dramatically accelerated rate of tumour growth ($P < 0.01$) during the 30-day observation period. Dim light during the period of darkness also completely suppressed host serum melatonin and disrupted the circadian-regulated rhythm of the host–cancer balance. [The Working Group noted the small number of rats.]

The study by Dauchy et al. (1997) used the male Buffalo rat hepatocarcinoma 7288CTC syngeneic graft model to study the effect of dim light during the period of darkness on tumour growth. In this study, rats (age, 5 weeks) were exposed to either LD12:12 (controls), 12 hours of light and 12 hours of light contamination at 0.2 lux or 0.08 μW/cm², or LD24:0 schedules (n = 6 per group). Tumour growth rate displayed a positive relationship with the intensity of light at night. Compared with LD12:12 controls, rats exposed to LD24:0 displayed the fastest rate of tumour growth followed by rats exposed to light contamination during the period of darkness ($P < 0.001$). In addition, exposure to either LD24:0 or light contamination during the period of darkness was observed to completely suppress the plasma level of melatonin, and exposure to LD24:0 (but not to light contamination during the period of darkness) was observed to disrupt the circadian rhythm of plasma lipids in the hosts. [The Working Group noted the small number of rats.]

The study by Wu et al. (2011) used the same female RNU rat MCF-7 human breast cancer xenograft model described in Blask et al. (2005, 2014) to study the effects of dim light contamination (0.8 μW/cm²) on tumour growth and latency to onset; rats [age not reported, adult] were divided into two groups (n = 36 per group) and exposed to either LD12:12 (control) or to light contamination during the 12-hour period of darkness, starting 2 weeks before implantation. Tumour growth in rats exposed to light contamination during the period of darkness was significantly increased ($P < 0.05$) compared with LD12:12 controls (0.56 g per day vs 0.26 g per day) (Wu et al., 2011). [The Working Group noted that the duration of the study was not reported.]

Guerrero-Vargas et al. (2017) studied the effect of exposure to continuous light on the growth of rat C6 glioma grafts implanted in two groups of seven male Wistar rats. Exposure to continuous light (LD24:0) was observed to significantly accelerate tumour growth and significantly increase tumour volume and weight compared with exposure to LD12:12. Continuous light also abolished the circadian rhythm of body temperature, immune function, energy homeostasis, and metabolism. [The Working Group noted the small number of rats.]

3.6 Evidence synthesis for cancer in experimental animals

The evaluation of the carcinogenicity of alterations in the light–dark schedule in experimental animals was primarily based on the well-designed lifetime carcinogenicity studies reported by Anisimov et al. (2004) and Kettner et al. (2016). The Kettner et al. (2016) article reported a series of independent studies in which male and female mice of three strains (one wildtype and two genetically engineered) were exposed to shifts in the light–dark schedule in the form of repeated 8-hour advances until age 90 weeks. Compared with control mice of each strain exposed to a regular light–dark schedule of LD12:12, exposure to shifts in the light–dark schedule was observed to significantly increase the incidence of hepatocellular carcinoma in all three strains. The study by Anisimov et al. (2004) compared tumour incidence and latency in wildtype female mice exposed for life to either a light–dark schedule of LD12:12 (control) or to continuous light (LD24:0). Statistically significant increases in the incidence of lung adenocarcinoma, malignant lymphoma, and total tumours were observed in mice exposed to LD24:0. The positive results reported in a few other studies in rodents exposed to shifts in the light–dark schedule or to continuous light, and in many studies using carcinogen-induced or transplantable tumour models, support the carcinogenicity of alterations in the light–dark schedule demonstrated in the lifetime carcinogenicity

evaluations of Kettner et al. (2016) and Anisimov et al. (2004).

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4. MECHANISTIC EVIDENCE

4.1 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether night shift work induces oxidative stress; is immunosuppressive; induces chronic inflammation; is genotoxic; induces epigenetic alterations; modulates receptor-mediated effects; alters cell proliferation, cell death or nutrient supply; and causes immortalization (i.e. induces changes in telomere length). For the evaluation of the other key characteristics of carcinogens, data were not available or considered insufficient.

4.1.1 Induces oxidative stress

(a) Humans

See Table 4.1.

In one study, levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in urine excreted by night shift workers during their day sleep were statistically significantly lower than those in urine excreted during their night sleep (Bhatti et al., 2016). Urinary 8-OHdG levels were not statistically significantly different between night shift workers and day shift workers. The study stipulated that participants were required to work at least 20 hours per week and 8 hours per shift, and that the night shift workers could not finish their shift earlier than 06:00. [The Working Group noted that in the reported comparison group, 8-OHdG levels were high.] In another study within the same population, the urinary 8-OHdG levels excreted by night shift workers were significantly lower during night work than during night sleep (Bhatti et al., 2017). In both studies, the results were adjusted for most of the relevant confounding covariates, such as age, sex, and alcohol consumption. Ishihara et al. (2008) reported that urinary 8-OHdG levels were significantly higher for female shift workers than for female part-time workers. [The Working Group noted that the comparison group was small and that the work schedules were ill defined. Also, the time-points for urine collection were not given.] Day–night (rotating) shift work in healthy men was correlated with increased urinary 8-OHdG levels ($P = 0.044$), but after adjustment for other lifestyle factors, this effect was borderline statistically significant (Kasai et al., 2001). An 11-fold inter-subject variation in 8-OHdG levels was observed, and detailed information on shift work schedules was lacking. [The Working Group noted that the findings on 8-OHdG were inconsistent across the four studies with regard to direction of effect.]

Manzella et al. (2015) reported lower expression of the 8-oxoguanine DNA glycosylase-1 (*OGG1*) gene, which is responsible for excising oxidized guanine, in night shift workers than in day shift workers. However, the shift work conditions of the comparison group (factory workers) were unclear. In a cross-sectional study of 49 full-time doctors, participants who worked on call,

Table 4.1 Oxidative stress in night shift workers

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Reference
8-OHdG	Urine	USA Health-care industry workers Cross-sectional study	440 (217 DS, 223 NS)	8-OHdG in NS group during day sleep period < night sleep period ($P = 0.03$)	Age, sex, alcohol consumption in the 24 h preceding the urine collection period	Bhatti et al. (2016)
8-OHdG	Urine	USA Health-care industry workers Short-term follow-up study	50 (NS)	8-OHdG in night work period < night sleep period ($P < 0.001$)	Age, sex	Bhatti et al. (2017)
8-OHdG	Urine	Japan Nurses, office workers, etc. Cross-sectional study	77 (65 F NS, 12 F part-time DS)	NS > part-time DS ($P < 0.004$)	None	Ishihara et al. (2008)
8-OHdG	Urine	Japan Steel-manufacturing company Cross-sectional study	318 (169 day-night shift, 149 DS)	Day-night shift > DS ($P = 0.055$)	Age, BMI, smoking, meat consumption (number of times per week), exercise	Kasai et al. (2001)
OGG1 gene expression	Lymphocytes	Italy Nurses Cross-sectional study	116 (60 NS, 56 DS)	NS < DS ($P < 0.05$)	None	Manzella et al. (2015)
DNA strand breaks (FPG+ comet assay); DNA repair gene expression (*OGG1*, *ERCC1*, *XRCC1*)	Blood	Hong Kong Special Administrative Region Medical doctors Cross-sectional study	49 (24 on-call on-site working overnight, 25 with no overnight work)	DNA breaks (+ and – FPG) in NS > DS ($P < 0.0001$) DNA repair in NS < DS ($P < 0.01$)	None Multiple eligibility criteria	Cheung et al. (2019)
SOD, CAT, MDA	Blood	Spain Intensive-care nurses Cross-sectional	32 nurses (7 M, 25 F) and 35 age-matched workers (12 M, 23 F). SW: MS, ES, NS	SOD and MDA for ES and NS > DS ($P < 0.01$)	Multiple eligibility criteria	Casado et al. (2008)

Table 4.1 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Reference
SOD, CAT, MDA	Blood	Spain Palliative-care workers Cross-sectional	52 nurses (23 M, 29 F) and 50 age-matched workers (24 M, 26 F). SW: MS, ES, NS	SOD and MDA for ES and NS > DS ($P < 0.01$)	Multiple eligibility criteria	Casado et al. (2011)
d-ROM, BAP	Blood	Japan Local government prison officers Cross-sectional	55 F SW, 63 F DS	BAP for SW > DS ($P < 0.0001$) d-ROM/BAP for SW < DS ($P = 0.001$)	Age, BMI, communication time, duration of sleep, alcohol consumption, smoking, VDT time	Ebata et al. (2017)
TOS, OSI, TAS	Blood	Turkey Medical residents, nurses, non-health-care staff Cross-sectional	71 medical residents (55 M, 16 F) on 24-h shift, and 45 nurses (F) and 30 (15 M, 15 F) non-health-care staff working 8-h shift	TOS and OSI were increased and TAS decreased ($P < 0.001$) after 24-h continuous shifts compared with 8-h shift	Within-person analysis	Buyukhatipoglu et al. (2010)
8-Isoprostane	Urine	Japan Breast-cancer screening survey Cross-sectional	F NS ($n = 10$) and non-shift workers ($n = 532$)	NS > non-shift ($P = 0.03$)	Age, BMI, smoking status, physical activity, use of dietary supplements, history of hypertension and diabetes	Nagata et al. (2017)
TAC	Blood	Islamic Republic of Iran Industrial catering staff Cross-sectional	44 RS (day–night–off–off)	DS < NS ($P < 0.001$)	Age, BMI Multiple eligibility criteria	Sharifian et al. (2005)
GSH-Px	Blood	Poland Nurses Cross-sectional	349 rotating NS, 359 DS only	Rotating NS > DS ($P = 0.009$)	Age, oral contraceptive hormone use, smoking, alcohol consumption during last 24 h	Gromadzińska et al. (2013)
TOS, TAS, OSI	Blood collected before and after shift	Turkey Nurses Cross-sectional	60 NS, 60 DS	Significant increase at the end of the shift (in both NS and DS)	None Multiple eligibility criteria	Ulas et al. (2012)
TOS, TAS, OSI	Blood collected before and after shift	Turkey Nurses Cross-sectional	70 NS, 70 DS	Significant increase at the end of the shift (in both NS and DS)	None Multiple eligibility criteria	Ulas et al. (2013)

Table 4.1 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Reference
CAT, TTG, TAC	Saliva	Islamic Republic of Iran Control room operators (petrochemical complex) Cross-sectional	30 RS	– (for various light conditions)	Multiple eligibility criteria	Kazemi et al. (2018)
TAC, MDA	Blood	Islamic Republic of Iran Refinery workers Cross-sectional	189 RS	– (for SW)	SW history Multiple eligibility criteria	Khajehnasiri et al. (2014)
TAC, TOS, OSI	Blood	Turkey Health-care workers Cross-sectional	45 rotating NS, 45 DS	OSI, NS > DS (P = 0.051) – (TOS, TAC)	None Multiple eligibility criteria	Özdemir et al. (2013)

–, not significant; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; BAP, biological antioxidant potential; BMI, body mass index; CAT, catalase; d-ROM, reactive oxygen metabolites-derived compound; DS, day shift; ERCC1, excision repair 1, endonuclease non-catalytic subunit; ES, evening shift; F, female; FPG, formamidopyrimidine-DNA glycosylase; GSH-Px, glutathione peroxidase; h, hour; M, male; MDA, malondialdehyde; MS, morning shift; NS, night shift; OGG1, 8-oxoguanine DNA glycosylase 1; OSI, oxidative stress index (TOS/TAC); RS, rotating shift; SOD, superoxide dismutase; SW, shift work; TAC, total antioxidant capacity; TAS, total antioxidant status; TOS, total oxidant status; TTG, total thiol molecules; VDT, video display terminal; XRCC1, X-ray repair cross complementing 1.

overnight, and on site with acute sleep deprivation, defined as sleeping less than two sleep cycles (3 hours) during their shift, had lower baseline expression of DNA repair genes and more oxidative damage to DNA than participants who did not work overnight (Cheung et al., 2019).

More than 10 studies have evaluated oxidative stress biomarkers other than 8-OHdG in blood, serum, saliva, or urine (see Table 4.1). These biomarkers included superoxide dismutase (SOD), catalase (CAT), oxidized low-density lipoprotein, malondialdehyde (MDA), neutrophil gelatinase lipocalin-2, glutathione peroxidase (GSH-Px), serum prolidase, reactive oxygen metabolite-derived compounds (d-ROMs), biological antioxidant potential (BAP), total thiol molecules, glycosaminoglycans, and 8-isoprostane. The studies also measured total oxidative status (TOS), total antioxidant status (TAS), total antioxidant capacity (TAC), and total oxidative stress index (OSI). [The Working Group noted that few studies measured more than one of these markers, and replicated results were not always available for the same end-point across studies.]

Seven studies reported positive associations. In two studies, significantly increased levels of the oxidative stress biomarkers SOD and MDA were found in shift workers working night and evening shifts compared with those working day shifts (Casado et al., 2008, 2011). There was no effect of sex, but the oxidative stress levels increased with age. In another study, BAP levels were significantly increased, and the ratio of d-ROMs to BAP was reduced, in female night shift workers compared with female daytime workers (Ebata et al., 2017). The results were corrected for multiple covariates, including age, body mass index (BMI), sleep duration, smoking, and alcohol consumption. These studies had a small sample size and no detailed exposure information, and time of blood collection was not reported. In another small study, 24-hour work shifts resulted in increased TOS levels and decreased TAS in blood compared with 8-hour work shifts (Buyukhatipoglu et al., 2010). Furthermore, women currently working night shifts had significantly higher levels of the oxidative stress biomarker 8-isoprostane in urine compared with women not working night shifts (Nagata et al., 2017). [The Working Group noted that the number of current night shift workers included was small (n = 10).] In a small group of shift workers in industrial catering, rotating from day shift work to night shift work was associated with a significant reduction in total plasma antioxidant capacity, in a study that assessed the impact of age and BMI (Sharifian et al., 2005). In a cross-sectional study of rotating shift workers, the GSH-Px activity measured in erythrocytes of premenopausal nurses was significantly higher in those working rotating night shifts than in those working only day shifts (Gromadzińska et al., 2013). This increase in the levels of GSH-Px activity was associated with working more night shifts per month. High GSH-Px activity may be indicative of a higher oxidative stress level. Data were corrected for age, use of hormonal oral contraceptives, smoking, and alcohol consumption during the previous 24 hours.

Five studies reported no significant associations between night shift work and oxidative stress markers. Ulas et al. (2012, 2013) compared oxidative stress levels measured at two time-points (08:00 and 16:00) and found that the levels were significantly increased in all nurses at the end of both the day shift and the night shift. However, no comparisons were made between day shift workers and night shift workers. Kazemi et al. (2018) found no associations between oxidative stress and various light intensities, but the intensity and duration of night shift work were not described. Khajehnasiri et al. (2014) reported no significant association between shift work experience and levels of TAC and MDA in rotating shift workers in an oil refinery. Özdemir et al. (2013) reported no differences in the oxidative stress status (TOS and TAC) between day shift workers and night shift workers, but an increased

OSI was found in night shift workers, which was borderline statistically significant.

[The Working Group noted that the majority of the studies were cross-sectional in design and some had insufficient details on shift work schedules, some were lacking specific information on the intensity and duration of night shift work, some had small sample sizes, and in some the biosamples were collected at only one time-point.]

(b) Experimental systems

Data from studies investigating whether oxidative stress is induced after alterations in the light–dark schedule are compiled in Table 4.2. A short-term advance in the light–dark schedule in male stroke-prone spontaneously hypertensive rats (SHRSP) and in male Wistar-Kyoto (WKY) rats was associated with increased levels of thiobarbituric acid-reactive substances in the rostral ventrolateral medulla (Kishi & Sunagawa, 2011). Levels of oxidative stress markers (e.g. lipid peroxidation) were also elevated in male Wistar rats exposed to continuous (23.5 hours) dark conditions for 30 days (Kuchukashvili et al., 2012). Increased expression of antioxidant systems (Cu,Zn-SOD; MnSOD; and extracellular SOD) was also reported in male Wistar rats housed under continuous light for 6 weeks (Temneanu et al., 2012). In mice that underwent shifts in the light–dark schedule for 10 days, glutathione levels decreased and nicotinamide adenine dinucleotide levels increased in the brain (LeVault et al., 2016). Nocturnal adult female tammar wallabies housed for 10 weeks under either amber light or white light at night had no change in plasma lipid peroxidation levels (for both light types) and decreased plasma antioxidant capacity (for both light types) when compared with animals housed under continuous dark conditions at night (Dimovski & Robert, 2018; see also Section 4.2.1(b)).

Alterations in the light–dark schedule in young diurnal Sudanian grass rats (*Arvicanthis ansorgei*) for 3 months did not alter either plasma antioxidant capacity or hepatic 8-OHdG levels (Grosbellet et al., 2015; see also Section 4.1.8(b)).

4.1.2 Is immunosuppressive

(a) Humans

Several studies have evaluated the occurrence of infectious disease in association with shift work (Mohren et al., 2002; Boden et al., 2014; Vijayalaxmi et al., 2014; Loef et al., 2019). While all were based on self-report of infection status, each of the studies has demonstrated an increased occurrence of infection in association with shift work. For example, in a study of 501 rotating and/or night shift workers and 88 non-shift workers, the incidence of self-reported influenza-like illness and acute respiratory infection in shift workers was 1.2-fold (95% confidence interval (CI), 1.01–1.43) that in non-shift workers (Loef et al., 2019). [The Working Group noted that suppression of immune function is a potential mechanism that may underlie these observed associations.]

Multiple studies evaluating markers of immune function in association with shift work were identified and are summarized in Table 4.3 and Table 4.4. Most of the studies were cross-sectional in nature and compared various measures of immune function between day shift workers and either permanent night shift workers or rotating shift workers (see Table 4.3). The largest study involved participants in the National Health and Nutrition Examination Survey (NHANES) (Buss et al., 2018). No statistically significant differences in lymphocyte count were observed when comparing day shift workers with night shift or rotating shift workers. Details with regard to frequency, intensity, and duration of shift work were not captured. In addition, only blood samples collected at a single time-point were compared and the timing of blood collection was not specified. Measures of immunity, such as lymphocyte count, vary diurnally (Fan et al., 1977; Cove-Smith et al., 1978; Bertouch

Table 4.2 Oxidative stress after alterations in the light–dark schedule in experimental systems

Experimental system	Exposure	Relevant findings	Reference
Adult SHRSP and WKY rat (M)	Control: LD14:10 Treatment: 12-h advance in the light–dark schedule for 5 d	WKY: ↑ TBARS in the RVLM (day 2) SHRSP: ↑ TBARS in the RVLM (days 2 and 5)	Kishi & Sunagawa (2011)
Wistar rat (M)	Control: LD10:14 Treatment: continuous (23.5 h) darkness for 30 d	In brain, ↑ lipid peroxidation and oxidative stress (NO, Ca^{2+}, MDA, diene conjugates) and ↓ mitochondrial SOD and catalase activity	Kuchukashvili et al. (2012)
Wistar rat (M)	Control: LD12:12 Treatment: continuous light for 6 wk	↑ Lung Cu,Zn-SOD, Mn-SOD, and extracellular SOD expression	Temneanu et al. (2012)
APPSwDI *NOS2*$^{-/-}$ mouse (M, F) Non-transgenic mouse on C57BL/6 109 background (M, F)	Control: LD12:12 Treatment: 8-h advance in the light–dark schedule every 3 d for 10 d	↓ Brain GSH and ↑ NADH levels in both genotypes	LeVault et al. (2016)
Adult tammar wallaby (*Macropus eugenii*) (F)	Control: no light during the period of darkness (0.37×10^{-3} W/m^2) Treatment: amber LED (605 nm, 2.00 W/m^2), or white LED (448 nm, 2.87 W/m^2) during the period of darkness for up to 10 wk	White LED during the period of darkness: ↓ plasma melatonin concentration White or amber light during the period of darkness: no change in plasma lipid peroxidation levels; ↓ plasma Trolox equivalent antioxidant capacity at 10 wk	Dimovski & Robert (2018) (see also Section 4.2.1(b))
Sudanian grass rat (M) (diurnal)	Control: LD12:12 for 3 mo Treatment: advance in the light–dark schedule by 10 h every week for first 4 d of the week for 3 mo	No difference in oxidative damage to DNA (8-OHdG levels, ELISA) in liver or plasma antioxidant capacity (OXY) Shorter telomeres (qPCR) in the liver, not only in old rat liver cells (–18%) but also at an intermediate level in shifted young rats (–9%)	Grosbellet et al. (2015) (see also Section 4.1.8(b))

↑, increase; ↓, decrease; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; d, day; ELISA, enzyme-linked immunosorbent assay; F, female; GSH, glutathione; h, hour; LD, light–dark schedule, light(h):darkness(h); LED, light-emitting diode; M, male; MDA, malondialdehyde; mo, month; NADH, nicotinamide adenine dinucleotide; NO, nitric oxide; NOS2$^{-/-}$, nitric oxide synthase 2$^{-/-}$; qPCR, quantitative polymerase chain reaction; RVLM, rostral ventrolateral medulla; SOD, superoxide dismutase; SHRSP, stroke-prone spontaneously hypertensive; TBARS, thiobarbituric acid-reactive substances; wk, week; WKY, Wistar-Kyoto.

Table 4.3 End-points relevant to immune function in cross-sectional studies in shift workers

End-point	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Lymphocyte count	USA NHANES	6667 DS, 970 NS/ES, 809 RS	–	Age, race, education, marital status, diabetes, smoking status, cold illness, waist circumference, HDL, total cholesterol, systolic blood pressure, BMI	Buss et al. (2018)
Lymphocyte count	Japan Male and female physicians at critical-care emergency centres and hospitals	27 RS (8–12 h including NS), 39 traditional shift (includes NS), 8 DS	–	None	Okamoto et al. (2008)
Lymphocyte count	Germany Male and female industrial workers	137 DS, 225 shift workers (91% in 3-shift RS with NS; 9% in other including permanent NS)	–	None	van Mark et al. (2010)
Lymphocyte count	Italy Hospital nurses	28 DS, 68 RS (1 DS 06:00–14:00; 1 AS 14:00–22:00; 1 NS 22:00–06:00), ≥ 2 yr in current schedule	–	Job seniority, and presence of offspring	Copertaro et al. (2011)
Lymphocyte proliferative response	Italy Hospital nurses	28 DS, 68 RS (1 DS 06:00–14:00; 1 AS 14:00–22:00; 1 NS 22:00–06:00), ≥ 2 yr in current schedule	–	Job seniority, and presence of offspring	Copertaro et al. (2011)
Lymphocyte proliferative response	Italy Male pressmen in newspaper industry	12 AS, 12 RS (weekly rotation: DS 06:00–13:00; NS 23:00–06:00; AS, 13:00–20:00)	RS < AS ($P < 0.025$)	Multiple eligibility criteria	Curti et al. (1982)
T-cell proliferative response	Japan Wholesale market	20 NS, 19 DS	NS < DS ($P < 0.05$)	None	Nakano et al. (1982)
T-cell proliferative response	Japan Iron-manufacturing company	20 RS (DS 07:00–15:00; AS 15:00–22:00; NS 22:00–07:00), 20 DS	RS < DS at 17:00 after DS ($P < 0.05$) and at 19:00 at start of NS ($P < 0.05$)	None	Nakano et al. (1982)

Table 4.3 (continued)

End-point	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
NK cell activity	Japan Male and female physicians at critical-care emergency centres and hospitals	27 RS (8–12 h, including NS), 39 traditional shift (includes NS), 8 DS	RS< DS ($P < 0.01$)	None	Okamoto et al. (2008)
NK cytotoxicity	Italy Hospital nurses	28 DS, 68 RS (1 DS 06:00–14:00; 1 AS 14:00–22:00; 1 NS 22:00–06:00), ≥ 2 yr in current schedule	–	Job seniority, and presence of offspring	Copertaro et al. (2011)

–, not significant; AS, afternoon shift; BMI, body mass index; DS, day shift; ES, evening shift; h, hour; HDL, high-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; NK, natural killer; NS, night shift; RS, rotating shift; yr, year.

Table 4.4 End-points relevant to immune function in non-cross-sectional studies in shift workers

End-point[a]	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Lymphocyte count	Islamic Republic of Iran NR	25 randomized to 3 DS, 1 rest day, and 3 NS; 25 randomized to 3 NS, 1 rest day, and 3 DS	NS > DS ($P = 0.008$)	Multiple eligibility criteria; within-person analysis	Khosro et al. (2011)
Lymphocyte count	Japan Female nurses at hospital	57 RS (DS 08:30–17:15; NS 00:30–09:15; ES 16:30–01:15), mean 19 yr duration	NS > DS for CD3 and CD4 ($P < 0.01$); NS < DS CD16/CD56 ($P < 0.01$)	Within-person analysis	Nagai et al. (2011)
NK cell activity	Japan Female nurses at hospital	57 RS (DS 08:30–17:15; NS 00:30–09:15; ES 16:30–01:15), mean 19 yr duration	NS < DS for NK cell activity ($P < 0.01$)	Within-person analysis	Nagai et al. (2011)
Cytokine secretion/ T-lymphocyte	Canada Healthy men and women in laboratory study	8 participants transitioned from DS to NS	Phase advance in IFNγ and IL2 ($P < 0.001$)	Multiple eligibility criteria; within-person analysis	Cuesta et al. (2016)
PBMC transcriptome	Canada Healthy men and women in laboratory study	8 participants transitioned from DS to NS	Phase shift and/or reduced amplitude of NK immune response transcripts	Multiple eligibility criteria; within-person analysis	Kervezee et al. (2018)
Proteome	USA Men in laboratory study	6 participants transitioned from DS to NS	NS < DS for antigen presentation and IFN signalling proteins ($P < 0.05$)	Multiple eligibility criteria; within-person analysis	Depner et al. (2018)

DS, day shift; ES, evening shift; IL, interleukin; IFN, interferon; NK, natural killer; NR, not reported; NS, night shift; PBMC, peripheral blood mononuclear cell; RS, rotating shift.

[a] End-points measured in blood.

et al., 1983) [the Working Group noted that single time-points of comparison could miss effects that occur at other times of the day, and systematic differences in blood collection timing could lead to spurious associations or even mask significant associations]. No significant associations with lymphocyte count were observed in any of the other cross-sectional studies that evaluated this marker (Okamoto et al., 2008; van Mark et al., 2010; Copertaro et al., 2011). A few cross-sectional studies evaluated other markers, including lymphocyte or T-cell proliferative response and natural killer (NK) activity and/or cytotoxicity, and findings were mixed (Curti et al., 1982; Nakano et al., 1982; Okamoto et al., 2008; Copertaro et al., 2011).

Although most of the cross-sectional studies included well-defined timings of blood sample collection, they had various other limitations, including small sample sizes, minimal to no adjustment for covariates, different blood collection times for day shift workers versus and night or rotating shift workers, a lack of data on duration of work for the various shift schedules, and unspecified temporal proximity or no temporal proximity to night shift work (Curti et al., 1982; Nakano et al., 1982; Okamoto et al., 2008; van Mark et al., 2010; Copertaro et al., 2011). [The Working Group noted that the latter is unlikely to be an issue for detecting longer-term (i.e. chronic) effects of night shift work.] For example, in their study of 68 rotating shift workers and 28 day shift workers who had worked their respective shifts for at least 2 years, Copertaro et al. (2011) observed no significant differences in lymphocyte count, lymphocyte proliferative response, or NK cell cytotoxicity between the two groups. However, blood samples for the rotating shift workers were collected on a day off with no night shift work on the preceding day. [The Working Group noted that acute effects of night shift work may have been missed because of the recovery of immune function over multiple days without night shift work.]

Of the remaining studies, summarized in Table 4.4, one was a randomized crossover trial (Khosro et al., 2011), another was a short-term longitudinal study (Nagai et al., 2011), and two were small but highly controlled studies conducted in sleep laboratories (Cuesta et al., 2016; Depner et al., 2018). All evaluated very short periods of exposure to shift work, meaning that the studies were more likely to detect acute as opposed to chronic effects. In the crossover trial, lymphocyte counts were evaluated in 50 participants who were randomized to either start with 3 day shifts and then transition to 3 night shifts, or start with 3 night shifts and then transition to 3 day shifts (Khosro et al., 2011). Blood samples were collected in the morning during both day shift and night shift periods. Night shift work was associated with an elevated lymphocyte count. In the short-term longitudinal study, immune system measures were compared in a group of rotating shift workers using blood samples collected on consecutive days (in the morning on a day shift and in the morning after completing a night shift) (Nagai et al., 2011); no other time-points were captured. Statistically significantly increased counts of CD3 and CD4 and decreased counts of CD16/56 lymphocytes were observed after night shift work. In one of the laboratory-based studies, eight healthy participants were transitioned from a day shift to a night shift schedule (maintained for only 4 days), with multiple blood samples collected during the simulated day shift and night shift periods (Cuesta et al., 2016). Transitioning to a night shift schedule resulted in statistically significant phase advances in the per-cell secretion of interferon-gamma (IFNγ) and interleukin 2 (IL2) in stimulated T lymphocytes. Using samples from the same study, the impact of a night shift schedule on the blood transcriptome was investigated (Kervezee et al., 2018). A phase shift and reduced amplitude of transcripts related to NK cell-mediated immune response was observed during the night shift. In a separate laboratory-based study

of proteomics in six healthy participants who were transitioned from a day shift to a night shift schedule (maintained for only 2 days), a decrease in proteins associated with antigen presentation and processing and interferon signalling was observed (Depner et al., 2018).

(b) Experimental systems

See Table 4.5.

Multiple studies have demonstrated suppression of the immune response in rodents exposed to alterations in the light–dark schedule. Logan et al. (2012) investigated the effects of shifts in the light–dark schedule on NK cell function in male Fischer 344 rats. NK cytotoxicity was reduced in the group exposed to shifts in the light–dark schedule, and the suppressed circadian expression of NK cell cytolytic activity was associated with increased growth of tumours after intravenous injection of mammary adenocarcinoma cells. Shifts in the light–dark schedule affected the circadian expression of the cytolytic factors perforin and granzyme B, and IFNγ, all critical factors in the cytotoxicity of NK cells. In a study of immune function in male Sprague-Dawley rats, Li & Xu (1997) showed that alteration of the light–dark schedule modulated the circadian pattern of the delayed-type hypersensitivity (DTH) response to sheep red blood cells (SRBCs) and suppressed the response at multiple timepoints. Phagocytosis was also suppressed in rats exposed to shifts in the light–dark schedule (Li & Xu, 1997). Valdés-Tovar et al. (2015) demonstrated suppression of the primary antibody response to SRBC in male Wistar rats exposed to continuous light for 15 days. A 38% decrease in the number of IL2-secreting splenocytes was also observed, and corresponded to decreased secretion of IL2 when splenocytes taken from continuous light exposed rats were stimulated with SRBC in vitro. Secretion of immunoactive Met-enkephalin-containing peptides, which modulate macrophage activation and cytokine production, was also reduced in these cells. In contrast, in diurnal Nile grass rats, dim light during the period of darkness enhanced innate, cell-mediated, and humoral immunity (Fonken et al., 2012). DTH responses after sensitization with 2,4-dinitro-1-fluorobenzene (DNFB), antigen-specific immunoglobulin-G in the plasma 10 and 15 days after immunization with keyhole limpet haemocyanin in male rats, and bactericidal activity against *Escherichia coli* were all elevated in rats exposed to dim light during the period of darkness compared with controls (Fonken et al., 2012). Deprés-Brummer et al. (1997) reported that in male Sprague-Dawley rats, leukocytes and certain lymphocyte subpopulations showed circadian patterns, which could be modulated by prolonged exposure to continuous light or continuous darkness. Exposure to continuous darkness increased the absolute number of circulating T and B lymphocytes in male Wistar rats (Mikolajczak et al., 2000).

Viral clearance after intranasal infection with a murine gammaherpesvirus and response to a secondary inflammatory challenge with lipopolysaccharide (LPS) was investigated in male and female BALB/cByJ and *IFNγ*-deficient BALB/cByJ mice exposed to shifts in the light–dark schedule (Trammell & Toth, 2016). Although there was no difference in viral clearance in multiple tissues after the initial infection, viral load was significantly increased in the lungs of in BALB/cByJ mice exposed to shifts in the light–dark schedule, 7 days after LPS treatment. *IFNγ* knock-out mice exposed to shifts in the light–dark schedule had lower levels of pulmonary cytokines than control mice (Trammell & Toth, 2016). Alteration in the daily light–dark schedule modulated plasma cytokine levels in response to LPS injection (Phillips et al., 2015). Basal levels of plasma cytokines were similar; however, 3 hours after LPS injection, alteration of the light-dark schedule resulted in a significant increase in plasma IL17, a suppression of plasma IL6, IL12, monocyte chemoattractant protein-1, and keratinocyte chemoattractant, as well as a significant

Table 4.5 Immune suppression in response to alterations in the light–dark schedule in experimental systems

Experimental system (sex)	Exposure	Relevant finding(s)	Reference
Fischer 344 rat (M)	Control: LD12:12 Treatment: repeated 6-h advance in the light–dark schedule every 2 d for 10 d, followed by continuous darkness for 5–7 d; injection with MADB106 mammary adenocarcinoma cells at CT 19 during the period of continuous darkness	↓ NK cell cytotoxicity Altered expression of cytolytic factors (perforin, IFNγ, granzyme B) ↑ Lung tumour growth (MADB106 mammary adenocarcinoma)	Logan et al. (2012) (see also Section 4.2.2)
Sprague-Dawley rat (M)	Control: LD12:12 Treatment: LD14:10 for 3 d then LD10:14 for 3 d, for a total of 28 d	↓ DTH response ↓ Phagocytosis	Li & Xu 1997
Wistar rat (M)	Control: LD12:12 Treatment: continuous light (50 lux) for 15 d	↓ Humoral immune response after immunization with sheep red blood cells ↓ Number of IL2 secreting splenocytes ↓ IL2 secretion after antigen stimulation ex vivo	Valdés-Tovar et al. (2015)
Nile grass rat (*Arvicanthis niloticus*) (M) (diurnal)	Control: LD14:10 Treatment: LD14:10, with dim light (5 lux) during the period of darkness for 3 wk	↑ Anti KLH IgG in plasma ↑ DTH after DNFB ↑ Plasma bactericidal activity against *Escherichia coli* in vitro	Fonken et al. (2012)
Sprague-Dawley rat (M)	Control: LD12:12 Treatment: continuous light for 8 wk, then continuous darkness for 2 wk Treatment: continuous light or continuous darkness for 17 wk, then return to LD12:12 for 16 wk	Mean counts of circulating leukocytes were similar in all groups at 8 wk Leukocyte circadian rhythm suppressed after continuous light for 11 or 16 wk, with persistent loss of synchronization after return to LD12:12 Leukocyte circadian rhythm suppressed after 16 wk of continuous darkness, with reversion to normal synchronization after return to LD12:12 ↓ NK cells after continuous light for 11 or 16 wk, which persisted after return to LD12:12	Deprés-Brummer et al. (1997)
Wistar rat (M)	Control: LD12:12 Treatment: continuous darkness for 12 wk	↑ Number of circulating T lymphocytes (both $CD4^+$ and $CD8^+$) ↑ Number of circulating B lymphocytes	Mikolajczak et al. (2000)
BALB/cByJ mouse (M, F) *IFNγ*-deficient BALB/cByJ mouse	Control: LD12:12 Treatments: 8-h extension of period of darkness for 5 d for study duration, then 2-d rest period with LD12:12 for 10 wk Intranasal infection with murine gammaherpes virus	No significant difference in viral clearance after initial infection ↑ Viral load in lungs of BALB/cByJ mice after LPS ↓ Pulmonary cytokines in *IFNγ*-deficient mice	Trammell & Toth (2016)
C57BL/6 mouse (M)	Control: LD12:12 Treatment: LD10:10 for 4 wk	Altered plasma cytokine in response to LPS (400 µg/kg bw) challenge Altered cytokine mRNA expression in hypothalamus	Phillips et al. (2015)

Table 4.5 (continued)

Experimental system (sex)	Exposure	Relevant finding(s)	Reference
C57BL/6 mouse (M)	Control: LD12:12 Treatments: 6-h advance in the light–dark schedule for 4 wk or continuous darkness for 2 d 3.5-mm punch biopsy wound	↑ Peripheral blood levels of IL6 after ex vivo culture with LPS	Adams et al. (2013)
C57BL/6 mouse (M)	Control: LD12:12 Treatment: advance in the period of light by 8 h every 48 h for 2 wk	↑ Plasma IL6	Wu et al. (2010)
Kunming mouse (M)	Control: LD12:12 Treatment: LD14:10 for 3 d, then LD10:14 for 3 d, and injection of Ehrlich carcinoma cells at onset of altered light–dark schedule	↓ Total leukocytes ↓ Lymphocytes ↓ Survival after tumour transplantation	Li & Xu 1997
C57BL/6 mouse (F)	Control: LD14:10 Treatment: dim light (5 lux) during period of darkness for 3 wk	Exposure to dim light before wounding delayed healing and time to wound closure	Walker et al. (2019)
Siberian hamster (*Phodopus sungorus*) (M)	Control: LD16:8 Treatment: dim light (5 lux) during period of darkness for 4 wk	↓ Cell-mediated immune responses to DNFB ↓ Bactericidal activity in plasma after LPS (400 µg/kg bw) challenge	Bedrosian et al. (2011)
Siberian hamster (*Phodopus sungorus*) (M)	Control: LD16:8 Treatment: LD8:16 for approximately 20 wk	Altered febrile response after LPS (400 µg/kg bw) challenge No significant difference in cell-mediated immunity	Ikeno et al. (2014)
Siberian hamster (*Phodopus sungorus*) (F)	Control: LD16:8 Treatment: single 2-h light pulse, then 3-h alteration in the light–dark schedule by extending the period of light	↓ Febrile response to LPS (625 µg/kg bw) after a 30-d recovery period	Prendergast et al. (2015)
Siberian hamster (*Phodopus sungorus*) (F)	Control: LD16:8 Sham control: LD16:8 then 3-h alteration in the light–dark schedule by extending the period of light (no single 2-h light pulse) Treatment: single 2-h light pulse, then 3-h alteration in the light–dark schedule by extending the period of light 3.5-mm punch biopsy wound	Delayed wound healing	Cable et al. (2017)
Siberian hamster (*Phodopus sungorus*) (M)	Treatments: long day, LD16:8; short day, LD8:16; long day, LD16:8 with dim light (5 lux) during period of darkness; short day, LD8:16 with dim light (5 lux) during period of darkness for 8 wk Restraint stress: 2 wk at the end of the alteration in the light–dark schedule	Dim light during the period of darkness: ↓ cell-mediated immune responses to DNFB ↓ Cell-mediated immunity, exacerbated by restraint stress	Aubrecht et al. (2014)

↑, increase; ↓, decrease; bw, body weight; CT, circadian time; d, day; DNFB, 2,4-dinitro-1-fluorobenzene; DTH, delayed-type hypersensitivity; F, female; h, hour; IFN, interferon; IgG, immunoglobulin-G; IL, interleukin; KLH, keyhole limpet haemocyanin; LD, light-dark schedule, light(h):darkness(h); LPS, lipopolysaccharide; M, male; mRNA, messenger RNA; NK, natural killer; wk, week.

elevation of mRNA expression of *IL6* and tumour necrosis factor alpha (*TNFα*) in the hypothalamus. Adams et al. (2013) evaluated the response to an inflammatory challenge in male C57BL/6 mice exposed to continuous darkness for 2 days. LPS-induced IL6 secretion was elevated at most time-points examined, although it followed a release pattern similar to that of controls. In the same study, serum IL6 was elevated in mice exposed to an altered light–dark schedule for 4 weeks. Advancing the onset of the period of light changed the circadian profiles of peripheral lymphocytes and T-helper cells in the spleen, and increased plasma IL6 levels in male C57BL/6 mice (Wu et al., 2010). In male Kunming mice, alteration of the light-dark schedule reduced total leukocyte and lymphocyte counts in the peripheral blood, as well as survival after transplantation with Ehrlich carcinoma cells (Li & Xu, 1997). In C57BL/6 mice, exposure to dim light during the period of darkness before wounding impaired healing and significantly delayed the time to wound closure compared with control mice and with mice housed under dim light conditions only after wounding (Walker et al., 2019).

In a study of cell-mediated and innate immune responses in male Siberian hamsters, exposure to dim light during the period of darkness reduced cell-mediated immune responses after sensitization and challenge with DNFB (Bedrosian et al., 2011). After challenge with LPS, bactericidal activity in plasma was also suppressed in hamsters exposed to dim light during the period of darkness compared with controls. Ikeno et al. (2014) also observed differences in response to LPS associated with an altered light–dark schedule in male Siberian hamsters. There was a significant increase in body temperature in all animals 1 hour after LPS injection; however, compared with controls, the febrile spike was significantly higher in animals housed under a shortened period of light. In contrast, Prendergast et al. (2015) reported that alterations in the light–dark schedule significantly reduced febrile responses in female Siberian hamsters after LPS treatment. Using a similar study design, Cable et al. (2017) found that punch biopsy wounds healed more slowly in female Siberian hamsters exposed to alterations in the light–dark schedule however, the timing of wounding did not affect healing.

Similar to the Bedrosian et al. (2011) study, Aubrecht et al. (2014) found that dim light during the period of darkness impaired DTH response to DNFB in combination with a shortened period of light in male Siberian hamsters. When the hamsters underwent 2 weeks of restraint stress in addition to alterations in the light–dark schedule, suppression was exacerbated compared with animals undergoing either restraint stress or dim light during the period of darkness alone.

4.1.3 Induces chronic inflammation

(a) Humans

Several studies evaluating the potential inflammatory effects of shift work were identified and are summarized in Table 4.6 and Table 4.7. Leukocyte count was the most commonly evaluated marker across studies (nine studies), followed by various cytokines, including IL6, C-reactive protein (CRP), and TNFα. [The Working Group noted that results were mixed across studies evaluating leukocyte count.] The largest of the studies was a cross-sectional evaluation of NHANES participants (Buss et al., 2018). No statistically significant differences in leukocyte count were observed when comparing day shift workers with night shift or rotating shift workers. [The Working Group noted that the limitations of the study included a lack of detail on shift schedules, single time-point of blood collection and a lack of specificity with regard to the time of day the blood samples were collected. The timing of blood sample collection is an important consideration as certain markers of inflammation exhibit diurnal variation, and

Table 4.6 End-points relevant to chronic inflammation in cross-sectional studies in shift workers

End-point[a]	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Leukocyte count	USA NHANES	6667 DS 970 NS/ES; 809 RS	–	Age, race, education, marital status, diabetes, smoking status, cold illness, waist circumference, HDL, total cholesterol, systolic blood pressure, BMI	Buss et al. (2018)
Leukocyte count	Japan Wholesale market	20 NS, 19 DS	–	None	Nakano et al. (1982)
Leukocyte count	Japan Iron-manufacturing company	20 RS (DS 07:00–15:00; AS 15:00–22:00; NS 22:00–07:00), 20 DS	–	None	Nakano et al. (1982)
Leukocyte count	Japan Male workers in synthetic-fibre manufacturing	107 DS, 101 RS (DS 07:00–14:00; AS 14:00–22:00; NS 22:00–07:00)	RS > DS ($P = 0.003$)	None	Nishitani & Sakakibara (2007)
Leukocyte count	Argentina Male factory workers	877 DS, 474 RS (28-day rotation: 4 DS 06:00 start; 3 rest days; 2 NS 18:00 start; 3 rest days; 4 NS 3 rest days; 2 DS; 3 rest days; 4 DS)	RS > DS ($P = 0.008$)	Age, metabolic syndrome	Sookoian et al. (2007)
Leukocyte count	Japan Male and female physicians at critical-care emergency centres and hospitals	27 RS (8–12 h including NS), 39 traditional shift (includes NS), 8 DS	–	None	Okamoto et al. (2008)
Leukocyte count	Finland Male and female airline workers	300 DS, 334 FS; 443 2-shift RS (DS and ES), 270 3-shift RS (DS, ES and NS), 530 in-flight[b]	Male 2-shift > DS ($P = 0.005$); male 3-shift > DS ($P = 0.021$); female in-flight < DS ($P = 0.005$)	Age, recent infectious disease, CRP levels, alcohol consumption, physical activity, education, smoking, obesity (BMI > 30), insomnia, sleep depth (h), perceived stress; co-exposure to ionizing radiation not considered	Puttonen et al. (2011)
Leukocyte count	Finland Male maintenance-unit airline workers	319 RS (2-shift DS and ES; 3-shift fast rotation with 1 DS, 1 ES and 1 NS; 3-shift slow rotation with 3 ES, 3 DS and 3 NS; flexible 3-shift with varied durations and consecutive numbers of shifts), 453 DS	–	Age, interaction between age and shift system	Viitasalo et al. (2015)

Table 4.6 (continued)

End-point[a]	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Leukocyte count	Republic of Korea Male workers in display manufacturing company	86 RS (6 NS, 2 rest days, 6 ES, 2 rest days, 6 DS, 2 rest days; mean duration, 10 yr), 46 former RS (mean duration, 2.79 yr), 112 DS	RS > DS ($P < 0.001$); former RS > DS ($P = 0.004$)	Age, BMI, alcohol consumption, smoking, regular exercise, sleep duration, sleep depth, sleep insufficiency, education, weekly work hours Multiple eligibility criteria	Kim et al. (2016)
Leukocyte count	Italy Female and male hospital nurses	84 DS, 71 NS	Monocyte count: NS > DS ($P < 0.001$)	Age, sex, BMI, WC, pack-years, binge drinking, CVD history, CRP, eosinophils, basophils, monocytes	Pavanello et al. (2017)
Cytokines	Japan Males and females nested in occupational cohort	3660 DS, 181 SW without NS, 1276 SW with NS, 142 NS	IL6: NS > DS ($P < 0.01$)	Age, sex, years of education, hours worked per week, annual household income, BMI, laboratory data (LDL-C and HbA1c), job stress Multiple eligibility criteria	Amano et al. (2018)
Cytokines	USA Males and females	11 DS (07:00–19:00, ≥ 3 shifts/wk for > 3 mo), 11 NS (19:00–07:00, ≥ 3 shifts/wk for > 3 mo)	NS > DS IL6 mesor ($P < 0.02$) and amplitude ($P < 0.02$)	Multiple eligibility criteria	Swanson et al. (2016)
Cytokines	Brazil Male workers in sanitary metals industry	21 DS (07:00–17:00) for median 4 yr, 17 NS (21:00–06:00) for median 3 yr	–	None	Reinhardt et al. (2019)
Cytokines	Brazil Male steel industry workers	9 NS (22:00–06:00), 6 EMS (06:00–14:00), and 7 DS (08:00–17:00); all schedules fixed for 2 yr	TNFα: EMS and NS > DS ($P < 0.0001$)	Multiple eligibility criteria	Crispim et al. (2012)
Cytokines	Germany Male and female industrial workers	137 DS, 225 SW (91% in 3-shift RS with NS, 9% in other including permanent NS)	–	None	van Mark et al. (2010)
Cytokines	Italy Hospital nurses	28 DS, 68 RS (1 day shift, 06:00–14:00; 1 AS 14:00–22:00; 1 NS 22:00–06:00); ≥ 2 yr in current schedule	TNFα and IL1β: RS < DS ($P \leq 0.03$)	Job seniority, and presence of offspring	Copertaro et al. (2011)
Cytokines	Finland Male and female airline workers	300 DS, 334 FS, 443 2-shift RS (DS and ES), 270 3-shift RS (MS, ES and NS), 530 in-flight[b]	CRP: male 3-shift > DS ($P = 0.002$); female 2-shift > DS ($P = 0.03$)	Age, recent infection or disease, CRP levels, alcohol consumption, physical activity, education, smoking, obesity (BMI > 30), insomnia, sleep depth (h), perceived stress	Puttonen et al. (2011)

Table 4.6 (continued)

End-point[a]	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Cytokines	Belgium Male steel workers	9 DS (mean, 13 yr), 16 fast clockwise RS (mean, 14 yr), 18 slow counter-clockwise RS (mean, 16 yr) (RS: DS 06:00–14:00; AS 14:00–22:00; NS 22:00–06:00)	–	None	Kantermann et al. (2014)
Cytokines	Finland Male maintenance-unit airline workers	319 RS (2-shift DS and ES; 3-shift fast rotation with 1 DS, 1 ES and 1 NS; 3-shift slow rotation with 3 ES, 3 DS and 3 NS; flexible 3-shift rotation with varied durations and consecutive numbers of shifts), 453 DS	–	Minimal adjustment for covariates	Viitasalo et al. (2015)
Cytokines	Republic of Korea Male workers in display manufacturing company	86 RS (6 NS, 2 rest days, 6 ES, 2 rest days, 6 DS, 2 rest days; mean duration, 10 yr), 46 former RS (mean duration, 2.79 yr), 112 DS	CRP: RS > DS ($P = 0.002$)	Age, BMI, alcohol consumption, smoking, regular exercise, sleep duration, sleep depth, sleep insufficiency, education, weekly work hours Multiple eligibility criteria	Kim et al. (2016)
Cytokines	Italy Female and male hospital nurses	84 DS, 71 NS	CRP: NS > DS ($P < 0.001$)	Age, sex, BMI, WC, pack-years, binge drinking, CVD history, CRP, eosinophils, basophils, monocytes	Pavanello et al. (2017)
LPS-binding protein	USA Males and females	11 DS (07:00–19:00, ≥ 3 shifts/wk for > 3 mo); 11 NS (19:00–07:00, ≥ 3 shifts/wk for > 3 mo)	LPS mesor: NS > DS ($P < 0.01$)	Multiple eligibility criteria	Swanson et al. (2016)

–, not significant; AS, afternoon shift; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DS, day shift; EMS, early morning shift; ES, evening shift; FS, former shift worker; h, hour; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; IL, interleukin; LDL-C, low-density lipoprotein-cholesterol; LPS, lipopolysaccharide; mo, month; MS, morning shift; NHANES, National Health and Nutrition Examination Survey; NS, night shift; RS, rotating shift; SW, shift work; TNFα, tumour necrosis factor alpha; WC, waist circumference; wk, week; yr, year.

[a] End-points measured in blood, except Reinhardt et al. (2019) (measured in saliva).

[b] Irregular working hours with MS, ES, and NS of different length, and with or without time lag.

Table 4.7 End-points relevant to inflammation in non-cross-sectional studies of shift work

End-point[a]	Location, setting	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Leukocyte count	Islamic Republic of Iran NR	25 randomized to 3 DS, 1 rest day, and 3 NS; 25 randomized to 3 NS, 1 rest day, and 3 DS	NS > DS ($P < 0.01$)	Multiple eligibility criteria; within-person analysis	Khosro et al. (2011)
Platelets	Islamic Republic of Iran NR	25 randomized to 3 DS, 1 rest day, and 3 NS; 25 randomized to 3 NS, 1 rest day, and 3 DS	NS > DS ($P < 0.01$)	Multiple eligibility criteria; within-person analysis	Khosro et al. (2011)
Cytokines	Islamic Republic of Iran NR	25 randomized to 3 DS, 1 rest day, and 3 NS; 25 randomized to 3 NS, 1 rest day, and 3 DS	NS > DS for IL6 and CRP ($P < 0.01$)	Multiple eligibility criteria; within-person analysis	Khosro et al. (2011)
Cytokines	Canada Healthy men and women in laboratory study	8 participants transitioned from DS to NS	NS vs DS phase advance in IL6, TNFα, and IL1β secretion/monocyte ($P < 0.01$)	Multiple eligibility criteria; within-person analysis	Cuesta et al. (2016)

CRP, C-reactive protein; DS, day shift; IL, interleukin; NR, not reported; NS, night shift; RS, rotating shift; TNFα, tumour necrosis factor alpha; vs, versus.

[a] All end-points measured in blood.

leukocyte count has been shown to vary diurnally (Sennels et al., 2011).] Other cross-sectional studies were reviewed (Nakano et al., 1982; Nishitani & Sakakibara, 2007; Sookoian et al., 2007; Okamoto et al., 2008; Puttonen et al., 2011; Viitasalo et al., 2015; Kim et al., 2016; Pavanello et al., 2017). [The Working Group noted that limitations across these studies included small sample sizes, single time-points of blood collection, limited or no adjustment for covariates, and poorly defined shift schedules, including a lack of data on the duration that participants worked in the various shift schedules.] Two of the studies did not collect blood samples during or immediately after night shift work (Puttonen et al., 2011; Viitasalo et al., 2015), and two of the studies did not specify when samples were collected relative to completion of night shift work (Nishitani & Sakakibara, 2007; Sookoian et al., 2007).

In the only study of leukocyte count that was not of cross-sectional design, 50 participants were randomized to either start with 3 day shifts and then transition to 3 night shifts, or start with 3 night shifts and then transition to 3 day shifts. Blood samples were collected in the morning during both day shift and night shift periods. Night shift work was associated with an elevated leukocyte count (Khosro et al., 2011).

Results of the studies evaluating IL6, CRP, and TNFα were mixed. The majority of studies were cross-sectional in design, the largest of which included over 5000 participants from an occupational cohort in Japan (Amano et al., 2018). Night shift workers were found to have statistically significantly higher circulating levels of IL6 compared with day shift workers. No significant differences in CRP were observed. In addition to a lack of detail with regard to shift schedules, blood samples were collected at single time-points that were not specified. [The Working Group noted that this is a concern for IL6, which has been observed to vary rhythmically over a 24-hour day (Bogaty et al., 2013; Nilsonne et al., 2016); however, it may not be a limitation when considering CRP, for which levels in blood seem to be fairly stable over time (Meier-Ewert et al., 2001, 2004).] Although a few studies did capture cytokine measurements at multiple specified time-points, two of the studies were small in size and did not adjust for potential confounding factors (Swanson et al., 2016; Reinhardt et al., 2019). Also, in one of the studies that restricted enrolment to healthy, non-obese men who did not use medications, alcohol, or tobacco, the levels for each cytokine were simply averaged over the multiple time periods, meaning that time period-specific effects were not considered (Crispim et al., 2012). Many of the cross-sectional studies evaluating cytokines did not collect blood samples during or immediately after night shift work (or blood sample timing relative to night shift work was unspecified) (van Mark et al., 2010; Copertaro et al., 2011; Puttonen et al., 2011; Kantermann et al., 2014; Viitasalo et al., 2015; Kim et al., 2016). [The Working Group noted that, of these studies, those reporting null associations may have failed to capture the more acute inflammatory effects of night shift work that might have dissipated over subsequent days during which night shift work was not conducted.]

Only two non-cross-sectional studies of cytokines were identified, and both evaluated relatively short periods of exposure to night shift work (see Table 4.7). In the randomized trial of night shift work (either starting with 3 day shifts and then transitioning to 3 night shifts, or starting with 3 night shifts and then transitioning to 3 day shifts), statistically significantly elevated circulating levels of IL6 ($P < 0.01$) and CRP ($P = 0.01$), but not TNFα, were observed in association with night shift work (Khosro et al., 2011). In a laboratory-based study of eight healthy participants, it was found that transitioning from a day shift schedule to a night shift schedule resulted in statistically significant phase advances in the per-cell secretion of IL1β,

IL6, and TNFα, in stimulated monocytes (Cuesta et al., 2016).

(b) Experimental systems

See Table 4.8.

Alteration in the light–dark schedule has been shown to enhance inflammation in rodent studies and models of inflammatory disease. Polidarová et al. (2017) examined the expression levels of pro-inflammatory cytokine genes in colonic mucosa obtained from Wistar rats exposed to shifts in the light–dark schedule. In rats for which the light–dark schedule was advanced and then delayed, there were minimal changes in expression of pro-inflammatory genes; however, expression of regulator of G protein signalling 16 (*Rsg16*), which regulates the inflammatory response, was suppressed. Exposure to continuous light significantly upregulated the expression of *IL1α*, IL17 receptor α, and signal transducer and activator of transcription 3 (*Stat3*), but had no effect on *TNFα* or *Rsg16* gene expression in the colon (Polidarová et al., 2017). Guerrero-Vargas et al. (2017) investigated the influence of alteration in the light-dark schedule on tumour growth (see Table 3.5) and inflammation in male Wistar rats. Plasma TNFα levels were significantly higher in rats exposed to continuous light at both 40 and 80 minutes after a single injection of LPS.

In a study of the impact of alteration of the light–dark schedule on the development and progression of colitis, extensive tissue destruction and mucosal ulceration was seen in C57BL/6 mice given 2% dextran sodium sulfate (DSS) in drinking-water and exposed to advances in the light-dark schedule (Preuss et al., 2008). In mice given DSS without alteration of the light-dark schedule, only a mild infiltration of inflammatory cells and reduction in the number of goblet cells in the mucosa were observed. Myeloperoxidase activity was also significantly higher with alteration of the light-dark schedule in mice given DSS (Preuss et al., 2008). Summa et al. (2013) examined the effects of alteration of the light–dark schedule on alcohol-induced liver and gastrointestinal tract inflammation in C57BL/6J mice. Advances in the light–dark schedule resulted in a significant increase in alcohol-induced intestinal permeability, an elevation of serum LPS, and hepatic steatosis compared with mice on the same diet that were not subject to alteration of the light-dark schedule. Alteration of the light–dark schedule alone increased intestinal permeability to a similar degree as observed in mice fed alcohol in the absence of light–dark schedule alterations. Increased levels of mRNA for the inflammatory mediators *IL1β* and *IL6* were observed in liver tissue from male C57BL/6 mice exposed to an altered light–dark schedule, which could be modulated by a nutrient-rich dietary supplement in the form of essence of chicken (Wu et al., 2015). Khalyfa et al. (2017) examined the inflammatory status of visceral white adipose tissue in male C57BL/6 mice. Total macrophage numbers, as well as the number of pro-inflammatory M1 macrophages, were significantly increased, while the number of FoxP3+ cells (regulatory T lymphocytes) was decreased, in mice exposed to an inverted light–dark schedule. Hand et al. (2016) showed that continuous light disrupted the night-time repression of inflammatory pathways in male DBA/1 mice immunized with collagen in an established model of inflammatory arthritis. Serum cytokine levels and joint swelling demonstrated diurnal variation in arthritic mice, with serum levels of several pro-inflammatory cytokines showing significant elevation during the period of light and a time-dependent fluctuation in disease severity. In arthritic mice exposed to continuous light, diurnal variation in paw size was absent and pro-inflammatory cytokine expression remained elevated in inflamed joints throughout a 24-hour period, although there were no differences in overall disease incidence or severity. Male CD1 mice exposed to continuous light demonstrated elevated levels of granulocytic and monocytic

Table 4.8 Inflammation in response to alterations in the light–dark schedule in experimental systems

Experimental system	Exposure	Relevant finding(s)	Reference
Wistar rat (M, F)	Control: LD12:12 Treatment: continuous light for 4 wk, or shift in the light-dark schedule (6-h advance for 2 d followed by 6-h delay for 2 d, with 4 advances and 4 delays over 16 d)	Continuous light: ↑ expression of pro-inflammatory cytokine genes (*IL1α*, *IL17rα*, *Stat3*) Shift in the light-dark schedule: suppression of the immunoregulatory gene *Rgs16* in colonic tissue	Polidarová et al. (2017)
Wistar rat (M)	Control: LD12:12 Treatment: continuous light for 5 wk Intravenous injection of LPS at 2 µg/kg bw 1 wk after removal from continuous light	↑ Plasma TNFα (40 and 80 min) after LPS injection	Guerrero-Vargas et al. (2017)
C57BL/6 mouse (M)	Control: LD12:12 Treatment: advance in the light-dark schedule by 12 h every 5 d for 3 mo 2% dextran sodium sulfate beginning after the 19th advance in the light-dark schedule	↑ Inflammation, tissue damage, and myeloperoxidase activity in the colon	Preuss et al. (2008)
C57BL/6 mouse (M)	Control: LD12:12 Treatment: 12-h advance in the light-dark schedule 1×/wk for 22 wk Chronic alcohol diet beginning 3 mo after the onset of shifts in the light-dark schedule	↑ Intestinal permeability (advance in the light-dark schedule without alcohol) ↑ Alcohol-induced intestinal permeability, elevation of serum LPS, and hepatic steatosis	Summa et al. (2013)
C57BL/6 mouse (M)	Control: LD12:12 Treatment: reversed the light-dark schedule every 4 d for 12 wk	↑ mRNA for *IL-1β* and *IL-6* in liver	Wu et al. (2015)
C57BL/6 mouse (M)	Control: NR Treatment: reversed the light-dark schedule every 2 wk for 8 wk	↑ Numbers of M1 macrophages in adipose tissue ↓ Number of FoxP3+ cells (regulatory T lymphocytes)	Khalyfa et al. (2017)
DBA/1 mouse (M)	Control: LD12:12 Treatment: continuous light 1 mg/mL bovine type II collagen emulsified in CFA injected intradermally at the base of the tail after 2 wk of exposure to continuous light	Altered diurnal variation in paw size and expression of pro-inflammatory cytokines	Hand et al. (2016)
CD1 mouse (M)	Control: LD12:12 Treatment: continuous light Heat-inactivated *Mycobacterium tuberculosis* emulsified in CFA injected into the footpad before exposure to continuous light	↑ Numbers of MDSC ↓ Number of circulating T lymphocytes (both $CD4^+$ and $CD8^+$)	Perfilyeva et al. (2017)
Swiss Webster mouse (M)	Control: LD14:10 Treatment: LD14:10 with dim light (5 lux) during the period of darkness for approximately 4 wk Injection of LPS (0.5 mg/kg bw) after 4 wk of alteration in the light-dark schedule	↑ Expression of pro-inflammatory genes (*TNFα*, *IL1β*, and *IL6*) in microglial cells	Fonken et al. (2013)

Table 4.8 (continued)

Experimental system	Exposure	Relevant finding(s)	Reference
Per2^{Luc} knock-in mouse	Control: LD12:12 Treatments: advance in the light-dark schedule (18:6, 1×/wk for 4 wk)	Hypothermia and reduced survival after injection of LPS (12.5 mg/kg bw) ↑ Serum levels of IL1β, GM-CSF, IL12, and IL13	Castanon-Cervantes et al. (2010) (see also Section 4.2.2)
Per2^{Luc} knock-in mouse	Control: LD12:12 Treatments: advances in the light-dark schedule (18:6, 1×/wk for 4 wk) Intraperitoneal injection of LPS (5 mg/kg bw) 7 d after final advance in the light–dark schedule	↑ Serum levels of IL6, IL18, MIP-2, and LIF-2	
Per2^{Luc} knock-in mouse	Control: LD12:12 Treatments: advances in the light-dark schedule (18:6, 1×/wk for 4 wk)	↑ Secretion of IL6 from peritoneal macrophages cultured with LPS (10 μg/mL) ex vivo	
Per2^{Luc} knock-in mouse	Control: LD12:12 Treatments: advances in the light-dark schedule (18:6, 1×/wk for 12 wk)	↑ Peripheral blood levels of IL6 after culture with LPS (50 μg/mL) ex vivo	Brager et al. (2013)

↑, increase; ↓, decrease; bw, body weight; CFA, complete Freund adjuvant; d, day; F, female; GM-CSF, granulocyte macrophage colony-stimulating factor; h, hour; IL, interleukin; LD, light–dark schedule, light(h):darkness(h); LIF-2, leukaemia inhibitory factor-2; LPS, lipopolysaccharide; M, male; MDSC, monocytic myeloid-derived suppressor cells; MIP-2, macrophage inflammatory protein-2; mo, month; NR, not reported; Rgs16, regulator of G protein signalling 16; Stat3, signal transducer and activator of transcription 3; TNFα, tumour necrosis factor alpha; wk, week.

myeloid-derived suppressor cells (MDSCs) (Perfilyeva et al., 2017). The increase was greater in the presence of adjuvant-induced arthritis; however, there was no change in inflammatory measures of disease such as paw thickness. At 4 weeks, the changes in the number of MDSCs were accompanied by a corresponding significant decrease in the numbers of CD4+ and CD8+ T lymphocytes. Continuous exposure to dim light increased the expression of pro-inflammatory genes in microglial cells obtained from male Swiss Webster mice after LPS administration (Fonken et al., 2013). In *Per2*^{Luc} mice maintained on a high-fat diet (60% fat calories, 20% protein calories, 20% carbohydrate calories), multiple shifts in the light–dark schedule resulted in an elevation of the total number of mature macrophages and the overall percentage of pro-inflammatory M1 macrophages in adipose tissue (Kim et al., 2018) (see Section 4.2.2(b)). A corresponding significant decrease in the percentage of anti-inflammatory M2 macrophages was also noted. Bone marrow-derived macrophages cultured from cells obtained from mice exposed to shifts in the light–dark schedule showed similar elevations in the percentage of M1 macrophages to that from cells of control mice. mRNA expression of the pro-inflammatory cytokines *IL1β*, *IL6*, and *TNFα* was elevated 2–3-fold in cultured adipose tissues from mice exposed to an altered light–dark schedule relative to controls, and was elevated 3–5-fold in bone marrow-derived macrophages after in vitro stimulation with LPS relative to cells from control mice (Kim et al., 2018; see Section 4.2.2(b)). Castanon-Cervantes et al. (2010) examined the immune response to LPS in *Per2*^{Luc} knock-in mice. Mice exposed to an altered light–dark schedule showed significant and persistent hypothermia after intraperitoneal challenge with LPS, and survival was significantly reduced in mice exposed to 4 weeks of advances in the light–dark schedule. Serum levels of pro-inflammatory mediators were significantly elevated in mice that were exposed to light–dark schedule shifts and challenged with LPS. Peritoneal macrophages obtained from mice exposed to advances in the light–dark schedule also demonstrated elevated IL6 secretion when cultured in vitro with LPS (Castanon-Cervantes et al., 2010) (see also Section 4.2.2(b)). IL6 levels were also significantly elevated after ex vivo LPS challenge in peripheral blood collected from *Per2*^{Luc} knock-in mice that had been exposed to advances in the light–dark schedule (Brager et al., 2013).

4.1.4 Is genotoxic

(a) Humans

No data were available to the Working Group on genotoxicity, other than in aircrews. Aircrews that engage in transmeridian travel have jobs with considerable circadian disruption. Studies on the key characteristics of carcinogens in aircrews have been conducted, but the focus of these studies was on associations with ionizing radiation exposure, with little to no consideration of the potential contribution of circadian disruption. For example, multiple studies in aircrews have reported on chromosomal damage (Romano et al., 1997; Cavallo et al., 2002a; Bolzán et al., 2008), sister-chromatid exchanges (Silva et al., 1999), gaps, breaks, and translocations (Cavallo et al., 2002b), dicentric formation (De Luca et al., 2009), and translocations (in pilots with flight years, Yong et al., 2009; with commercial flight cosmic radiation exposure, Grajewski et al., 2018). Only the study by Grajewski et al. (2018) considered the role of circadian disruption on the occurrence of chromosomal damage. However, because of the high degree of correlation between the measures of ionizing radiation exposure and cumulative time zones crossed (Pearson correlation coefficient, 0.89), independent associations could not be assessed. [In light of the well-established effects of ionizing radiation on many of the key characteristics of carcinogens, and the lack of data on the independent effects

of circadian disruption in aircrews, the Working Group concluded that mechanistic studies in aircrews were uninformative.]

(b) Experimental systems

No data were available to the Working Group on genotoxicity in experimental systems.

4.1.5 Induces epigenetic alterations

(a) Humans

See Table 4.9.

Methylation of clock genes is discussed in Section 4.2.2.

Alterations in DNA methylation patterns have been studied in night shift workers, with no effect of shift work on DNA methylation at Alu and long interspersed nuclear element-1 repetitive elements or on promoter methylation of glucocorticoid receptor, *IFNγ*, or *TNFα* genes (Bollati et al., 2010). [The Working Group noted that there was only one time-point at which blood was collected, and the timing of this collection was not specified.]

Four reports from the same group evaluated the effects of long-term night shift work (> 10 years) (Zhu et al., 2011; Jacobs et al., 2013; Shi et al., 2013; Liu et al., 2015). A genome-wide methylation analysis revealed widespread methylation alterations in night shift workers at many methylation- and cancer-relevant genes (Zhu et al., 2011). Forty-eight CpG loci, corresponding to 29 microRNAs (miRNAs), were methylated differently in night shift workers (categorized into three groups according to duration of night shift work) than in day shift workers, including the circadian-relevant miR219, with expression implicated in several cancers (Shi et al., 2013). Long-term night shift work altered the methylation patterns at imprinted genes, such as *DLX5*, *IGF2-AS*, and *TP73* (Jacobs et al., 2013). Long-term night shift work (> 10 years) was associated with the methylation-based suppression of *miR34b*, which is a known tumour suppressor (Liu et al., 2015). [The Working Group noted that the limitations of these studies included the small sample of long-term shift workers, the lack of detail on intensity and frequency of shift work, and the lack of specificity of timing of the blood sample collection. Diurnal variation of lymphocyte subsets may lead to biased DNA methylation measurements. Adjusting for lymphocyte cell profile, which the studies did not do, could have addressed this issue.]

Assays for genome-wide DNA methylation in blood samples revealed that different loci were affected between night and day shift workers, and the average methylation was decreased in night shift workers (working ≥ 24 hours per week and ending no earlier than 06:00 for 6 months) across 16 135 CpG loci (Bhatti et al., 2015). Adams et al. (2017) reported no statistically significant associations at the genome-wide level with shift work or chronotype; the timing of the single sample collection was not specified, but adjustment for leukocyte cell profile was performed.

A cross-sectional study in Lodz, Poland, reported that current rotating shift work was not associated with methylation status of promoter sites within the *BRCA1* and *BRCA2* genes (Peplonska et al., 2017).

(b) Experimental systems

See Table 4.10.

Several studies have reported that DNA methylation may be influenced by induction or repression of DNA methylation enzymes caused by alterations in the light–dark schedule. In particular, DNA methyl transferase-1 protein levels increased by more than 2-fold in the liver of female Sprague-Dawley rats exposed to repeated advances of the light–dark schedule (Kochan et al., 2015). In ovariectomized athymic, inbred nude Crl:NIH-*Foxn1*^{rnu} rats, dim light during the period of darkness increased *Stat3* expression via an epigenetic mechanism, of Aplasia Ras homologue member I (ARHI) promoter methylation (Xiang et al., 2019).

Table 4.9 DNA methylation in the blood of night shift workers

Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Italy Chemical plants Cross-sectional study	150: 100 RS (MS, 06:00–14:00; AS, 14:00–22:00; NS, 22:00–06:00; worked 4 d followed by 2 rest days), 50 DS	– (Alu and LINE-1 elements; *GCR*, *TNFα*, *IFNγ* genes)	Age, BMI, job seniority	Bollati et al. (2010)
Denmark[a]	29: 19 long-term NS (≥ 10 yr of work starting at 19:00 or later and ending before 09:00), 10 DS	+ (Genome-wide methylation; Illumina Infinium Methylation Chip)	Age, folate intake	Zhu et al. (2011)
Denmark[a]	20: 10 long-term NS (≥ 10 yr of work starting at 19:00 or later and ending before 09:00), 10 DS	48 CpG of 29 miRNAs: hypermethylation, NS > DS 2 CpG of 2 miRNAs: hypomethylation, NS > DS (Genome-wide methylation; Illumina Infinium Methylation Chip)	Age, folate intake	Shi et al. (2013)
Denmark[a]	20: 10 long-term NS (≥ 10 yr of work starting at 19:00 or later and ending before 09:00), 10 DS	397 CpG in 56 imprinted genes: 20 hypermethylation ($P < 0.05$), 30 hypomethylation ($P < 0.001$) in NS (Genome-wide methylation; Illumina Infinium Methylation Chip)	Age, folate intake	Jacobs et al. (2013)
Denmark[a]	20: 10 long-term NS (≥ 10 yr of work starting at 19:00 or later and ending before 09:00), 10 DS	*miR34b* hypermethylation: NS > DS ($P = 0.016$) (Genome-wide methylation; Illumina Infinium Methylation Chip)	Age, folate intake	Liu et al. (2015)
USA Health-care workers Cross-sectional study	124: 59 NS, 65 DS Blood collected within 2 h of completing the work shift on the 3rd day (07:00–09:00 for NS and 17:00–19:00 for DS)	NS < DS (FDR: $q < 0.05$) (Genome-wide methylation; Illumina Infinium Methylation Chip)	Age, sex, BMI, race, smoking status, leukocyte cell profile (by flow cytometry)	Bhatti et al. (2015)
USA Health-care workers Cross-sectional study	111 NS, 86 DS (female) 110 female NS, 131 male NS	– (Genome-wide alteration; Illumina Infinium Methylation Chip)	Age, BMI, race, alcohol consumption, smoking, leukocyte cell mixture	Adams et al. (2017)

Table 4.9 (continued)

Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Poland Nurses and midwives Cross-sectional study	710: 347 rotating NS (night, 19:00–07:00; day, 07:00–19:00) and 363 DS (07:00–16:00) Blood collected 06:00–10:00	– *BRCA1* and *BRCA2* gene promoters	Night work status, smoking, obesity, physical activity, alcohol consumption	Peplonska et al. (2017)

–, not significant; +, significant; AS, afternoon shift; BMI, body mass index; CpG, cytosine–phosphate–guanine; d, day; DS, day shift; FDR, false discovery rate; GCR, glucocorticoid receptor; h, hour; IFN, interferon; LINE-1, long interspersed nuclear element-1; MS, morning shift; NS, night shift; RS, rotating shift; TNFα, tumour necrosis factor alpha.

[a] Study participants had previously participated in the Danish Diet, Cancer and Health prospective cohort.

Table 4.10 Epigenetic alterations in response to alterations in the light–dark schedule in experimental systems

Experimental system	Exposure	Relevant finding(s)	Reference
Sprague-Dawley rat (F)	Control: LD12:12 Treatments: advance in the light–dark schedule by 3 h each day for 6 d; advance in the light–dark schedule by 3 h each day for 6 d followed by a 10-d regular LD12:12 for a total of 54 d (6–10–6–10–6–10–6)	↑ (by > 2-fold) in DNMT1 protein levels in the liver samples (6–10–6–10–6–10–6) ↓ miR127 and miR146b levels and activity in mammary tissues (both treatments)	Kochan et al. (2015)
Ovariectomized athymic, inbred nude Crl:NIH-*Foxn1*^{rnu} rat (F)	Control: LD12:12 Treatment: LD12:12, with dim light during period of darkness; human MCF-7 tumour implantation 1 wk after start of exposure to dim light	↑ *Stat3* expression via ARHI promotor methylation	Xiang et al. (2019)
Adult C57BL/6J mouse (M)	Mice were housed in two different light–dark schedules with light during 06:00–18:00 or 18:00–06:00 Treatments: advance in the light–dark schedule by 6 h by turning on the lights at ZT18; advance in the light–dark schedule by 6 h by turning on the lights at ZT18 1×/wk for 8 wk Analysis 1 wk after the final advance; livers collected around the clock	Rapid H3K4me3 histone modification (trimethylation of lysine 4 on histone 3) in livers at four time-points (ZT3, ZT8, ZT15, and ZT20) (both treatments)	Grygoryev et al. (2018)
C3H/HePas mouse (M)	Control: LD12:12 Treatment: continuous light for 8 wk	↑ Expression of *Rev-erbα*-targeting *miR140–5p*, *185–5p*, *326–5p*, and *328–5p* in liver	Borck et al. (2018)
Golden Syrian hamster (M)	Control: LD12:12 Treatments: abrupt shift to LD8:16 or to LD16:8 for 3 wk; continuous dim light (30 lux) for 3 wk, followed by continuous bright light (100 lux) for 3 wk	Altered expression of *miR132*, *miR212*, and their direct target, methyl CpG-binding protein *MeCP2*, in SCN tissues (both treatments)	Mendoza-Viveros et al. (2017)

↑, increase; ↓, decrease; ARHI, aplasia Ras homologue member I; d, day; DNMT1, DNA methyltransferase-1; F female; h, hour; H3K4me3, trimethylation of lysine 4 on histone 3; LD, light–dark schedule, light(h):darkness(h); miR, microRNA; *Rev-erb,* circadian nuclear receptor gene; SCN, suprachiasmatic nucleus; STAT3, signal transducer and activator of transcription-3; wk, week; ZT, Zeitgeber time.

Epigenetic regulation via histone modifications was associated with both single and repeated advances in the light–dark schedule (Grygoryev et al., 2018). In particular, trimethylation of lysine 4 on histone 3 (H3K4me3) circadian histone modification in the liver of mice responded rapidly to an altered light–dark schedule. Epigenetic regulation via miRNA mechanism was also influenced by alteration in the light-dark schedule. For example, the expression of *Rev-erbα*-targeting miRNAs, *miR140–5p*, *185–5p*, *326–5p*, and *328–5p*, was increased in liver cells of C3H/HePas mice exposed to continuous light (Borck et al., 2018). Changes in *miR127* and *miR146b* levels in mammary tissues of female Sprague-Dawley rats were induced by both short-term and repeated shifts in the light–dark schedule (Kochan et al., 2015). In the suprachiasmatic nucleus tissues of male golden Syrian hamsters, advances in the light–dark schedule influenced expression of *miR132* and *miR212*, and of their direct target, methyl CpG-binding protein (*MeCP2*) (Mendoza-Viveros et al., 2017).

Studies on telomere shortening in experimental systems are addressed in Section 4.1.8(b).

4.1.6 *Modulates receptor-mediated effects: endocrine hormones*

(a) Humans

See Table 4.11.

(i) Estrogens and progesterone

In a cross-sectional analysis, there was an increase in plasma estradiol (but not estrone) with duration of shift work in postmenopausal women who participated in the Nurses' Health Studies (NHS-I and NHS-II) (Schernhammer et al., 2004). In another cross-sectional study of 177 Japanese postmenopausal women who were not using hormone replacement therapy, ever working at night was associated with elevated estrone serum levels, and estradiol levels were modestly elevated (Nagata et al., 2008). In the second Nurses' Health Study (NHS-II) cohort, there was a modest inverse association of 6-sulfatoxymelatonin (aMT6s) levels and follicular estradiol ($P = 0.07$) in 459 largely premenopausal women; no significant association was seen with estradiol, progesterone, estrone or estrone sulfate (or with dehydroepiandrostenedione, dehydroepiandrostenedione sulfate, testosterone, or androstenedione) measured either in the luteal or the follicular phase of the menstrual cycle (Schernhammer et al., 2006). In a study of 31 premenopausal Italian nurses engaged in a rapid forward rotating shift schedule (1 morning, 1 afternoon, 1 night, followed by 2 days off) maintained for at least the last 2 months, serum levels of 17-β-estradiol measured in the follicular phase of the menstrual cycle were elevated in shift work nurses compared with daytime nurses, particularly in those who did not take a nap during their shift relative to those who did (Bracci et al., 2013, 2014). [The Working Group noted that these findings suggest that circadian disruption from night shift work would affect estrogen level independently of melatonin suppression.] In a study of 94 premenopausal shift-working nurses, 82 of whom completed follow-up, an inverse relationship between aMTS6 and serum estradiol in winter was suggested, but the association lacked statistical significance when adjusted for multiple covariates including menstrual cycle stage (Langley et al., 2012). Similarly, covariate adjustment attenuated observed associations in increased levels of estradiol, estrone, and progesterone with increasing years of night shift work history. Sixty-three women engaged in a rapidly forward rotating night shift work schedule (2 or 4 mornings, 2 afternoons, 2 nights, and 2 days off) had higher serum estradiol and progesterone levels, especially in the follicular phase of the menstrual cycle, compared with 73 day shift workers (Gómez-Acebo et al., 2015). In another study in Spain in 75 workers on either a rapidly or slowly rotating night shift schedule and 42 daytime workers, levels of total progestagens

Table 4.11 Endocrine receptor-mediated effects in shift workers

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Estrogen	USA Nurses' Health Studies (NHS-I and NHS-II) Cross-sectional	> 3 yr rotating NS in 644 postmenopausal women (hormone replacement therapy not used within 3 mo of blood draw); number of NS worked in the last 2 wk in 79 premenopausal women (hormones or oral contraceptives not used in prior 6 mo)	Increase in estradiol ($P = 0.03$), but not estrone ($P = 0.34$), with duration of rotating NS in postmenopausal women; no association with recent NS in premenopausal women	Age, BMI, time of blood draw, laboratory batch	Schernhammer et al. (2004); see also Table 4.15
Estrogen, testosterone	Japan Breast cancer screening Cross-sectional	7 ever vs 170 never worked at night; postmenopausal women not using hormone replacement therapy	Ever > never, estrone ($P = 0.006$); modest increase in estradiol ($P = 0.11$), no effect on testosterone	Age, BMI, smoking status, alcohol consumption, group of participants, day length before urine collection	Nagata et al. (2008); see also Table 4.15
Estrogen, testosterone, progesterone, androstenedione, DHEA, DHEAS	USA Nurses' Health Study II (NHS-II) Cross-sectional	459 women (384 controls from a nested case–control study of urinary melatonin levels and breast cancer risk, 80 premenopausal women from a validation study), of whom 44 had ≥ 1 NS in the last 2 wk and 310 had ≥ 1 yr of rotating NS	Modest inverse association of follicular estradiol and aMT6s levels ($P = 0.07$) in premenopausal women – (for sex hormones measured either in the luteal or the follicular phase of the menstrual cycle)	Age, BMI, weight change from age 18 yr, alcohol consumption, month of urine collection, antidepressant use, aspirin use, physical exercise, smoking history and pack-years smoked, height, first spot morning urine, sleep duration	Schernhammer et al. (2006)
Estrogen	Italy Hospital nurses Cross-sectional	31 healthy premenopausal nurses (not using drug treatments) on rapid forward rotating NS in the last ≥ 2 mo; 31 DS nurses	NS who did not take naps during their shift > NS who did take naps or in DS workers (estradiol levels, $P < 0.05$)	Age, BMI, physical exercise, smoking	Bracci et al. (2013); see also Table 4.1
Estrogen	Italy Nurses Cross-sectional study	116 F nurses: 60 with ≥ 2 yr of SW, 56 permanent DS	NS > DS (17-β-estradiol levels, $P = 0.040$)	Age, physical activity, number of offspring	Bracci et al. (2014); see also Table 4.1
Estradiol, estrone, progesterone	Canada Shift-working nurses, F Cross-sectional	Years of NS work in 94 premenopausal nurses working a full-time RS schedule	–	Age, BMI, menstrual cycle stage, OC use, recent alcohol consumption, recent caffeine consumption, smoking status, recent physical activity	Langley et al. (2012)

Table 4.11 (continued)

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Estrogen, progesterone, testosterone	Spain Health-care workers and teachers Cross-sectional	63 F rotating NS, 73 F DS (no hormone replacement therapy, no OC use in last 6 mo)	Rotating NS > DS for all women (estradiol, $P = 0.041$; progesterone, $P = 0.008$) Rotating NS < DS for women in the luteal phase (testosterone, $P = 0.024$)	Menopausal status, season, age, BMI, number of cigarettes the day before	Gómez-Acebo et al. (2015)
Estrogen, progesterone, androgens	Spain Hospital, car industry, railway company Cross-sectional	75 rotating NS (rapid and slow), 42 DS, both sexes; 53 women, not using hormone therapy or OCs (16 each of NS and DS who were premenopausal; 4 DS and 17 NS who were postmenopausal)	NS > DS (progestagens, $P < 0.05$; androgen, $P < 0.05$) – (estrogen)	Age, sex, BMI, menopausal status, menstrual phase, education, smoking, physical activity, caffeine, sleep, parity, age at first full-term birth, chronic symptoms, drug use, hours of sunlight	Papantoniou et al. (2015)
Estrogen	Poland Hospital nurses and midwives Cross-sectional	263 F NS workers and 269 DS not using OCs or hormone replacement therapy (345 premenopausal, 187 postmenopausal); every NS was followed by a day off	– (for premenopausal women) Association in postmenopausal modified by chronotype with a significant increase with years of NS in morning chronotypes (P for trend, < 0.001) but not in evening chronotypes (P for trend, 0.60)	Age, age at menopause, BMI, physical activity, smoking status	Peplonska et al. (2016)
Estrogen	Japan Hospital nurses Repeated measures study design	Rapid backward RS including DS, ES, and NS; 3 pregnant and 6 non-pregnant nurses	– (for time of the day and type of shift)	None	Yamauchi (2004)

Table 4.11 (continued)

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Estrogen, LH, FSH	USA Nurses, F Cross-sectional	323 nurses (172 NS and 151 DS) with regular menstrual cycles (no hormone use in 30 d before screening)	Results within NS nurses: Day sleep > night sleep for estrogen ($P < 0.01$), LH ($P < 0.001$), and FSH ($P < 0.001$) Night work > night sleep for estrogen ($P < 0.05$), LH ($P < 0.05$), and FSH ($P < 0.05$) Results comparing NS to DS nurses: NS (during day sleep) > DS (during night sleep) for LH and FSH levels ($P < 0.01$); no difference in estrogen level – (night sleep estrogen, LH, or FSH levels) NS (working) > DS (sleeping) for night LH and night FSH ($P < 0.01$); no change in night estrogen levels	Age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, use of psychotherapeutics	Davis et al. (2012)
Prolactin, LH, FSH	Japan Multiple workplaces 1-d trial	Rest day vs night work shift; 5 NS nurses and 6 resting nurses	Decreased prolactin level in NS workers at 02:00 ($P < 0.05$) but not at 22:00; no difference in LH and FSH	None specified	Miyauchi et al. (1992)
Prolactin	France Healthy volunteers 24-h observation	8 permanent NS workers (observed in laboratory for 24-h period after a NS under usual day sleep conditions), 10 day-active participants (observed in laboratory for 24-h period with an 8-h shift in their usual sleep time)	–	None	Spiegel et al. (1996)
Prolactin	Poland Hospital nurses and midwives Cross-sectional	327 women working in irregularly rotating NS, 330 working in DS only (no hormone replacement therapy)	– (for current shift work status, duration of NS, or NS characteristics)	Time of blood sampling, recent cigarette smoking, season of blood sampling, parity with breastfeeding, age, age at menopause	Bukowska et al. (2015)

Table 4.11 (continued)

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Prolactin, growth hormone, cortisol, urinary catecholamines	Italy Hospital intensive-care unit 4-d trial	10 F nurses in rapid forward RS observed on 4 consecutive days of work (MS, AS, NS, NS)	Prolactin and growth hormone rapidly responded to the RS; cortisol at 07:00, end of the NS < beginning of the MS ($P < 0.05$); catecholamines, first half of NS > second half of NS ($P < 0.05$)	None	Costa et al. (1997)
Prolactin, cortisol, testosterone	France Oil refinery workers 8-h monitoring (midnight to 08:00)	4 male oil-refinery workers in a fast rotating NS schedule, 6 healthy men synchronized to daytime schedule	NS < DS in overall and night "trough" testosterone levels ($P < 0.001$, $P < 0.05$) and overall prolactin ($P < 0.001$); NS > DS in night "trough" cortisol ($P < 0.01$)	None	Touitou et al. (1990)
Cortisol, testosterone, LH	USA Resident physicians, M Repeated measures collected on 4 d (during initial 2 wk of residency, immediately after vacation, after a 36-h shift including on-call NS in obstetrics, and during a DS in gynaecology)	6 resident physicians (M) after a 36-h shift including night	Vacation > initiation of residency ($P = 0.008$) or after NS in obstetrics ($P = 0.0005$) for testosterone; vacation > after NS in obstetrics for LH ($P = 0.039$); no differences in cortisol except that morning < afternoon after NS in obstetrics; no significant differences for gynaecology	None	Chatterton & Dooley (1999)
Growth hormone	France Volunteers from general population 24-h observation	11 M volunteer permanent NS workers (observed in laboratory for 24-h period after a NS under usual day sleep conditions), 10 male day-active participants (observed in laboratory for 24-h period under usual night sleep conditions) performing polysomnography	–	None	Brandenberger & Weibel (2004)
Cortisol	Ontario, Canada Hospital employees, F Cross-sectional	160 DS, 168 RS	RS on NS < DS (for total diurnal cortisol production, $P < 0.01$) – (for RS on DS vs DS, $P = 0.14$)	Age, education, chronotype	Hung et al. (2016)

Table 4.11 (continued)

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Cortisol	Sweden Pulp and paper factory Cross-sectional	42 backward rotating NS workers, divided into two groups of satisfaction in the shift schedule; serum level (collected during 07:00–09:00 during a morning shift in the first work period of a cycle and during a morning shift in the seventh work period of the cycle)	– (morning cortisol by shift satisfaction) Decreased morning cortisol level at end of shift cycle in evening chronotypes ($P < 0.01$)	Work period and sleep sufficiency before morning shift	Axelsson et al. (2003)
Cortisol	Denmark Hospital Repeated measures	29 surgeons over 4 consecutive days (pre-call; on-call, 15:30–08:30; post-call day 1; post-call day 2); level in saliva	On-call < pre-call ($P < 0.001$)	None	Amirian et al. (2015)
Cortisol	Finland Media workers Cross-sectional	66 irregular SW, 66 regular DS	In irregular SW, decrease in cortisol/melatonin ratio 8 h after awakening for those with vs without prolonged daytime sleepiness ($P = 0.035$)	None	Lindholm et al. (2012)
Cortisol	Italy Hospital Cross-sectional	23 F nurses in a clockwise rapidly RS schedule, 25 DS nurses; (5 saliva samples collected during a MS after a day off in both groups)	RS < DS for morning (06:00 and 08:00) collection times ($P < 0.05$), but not for subsequent collection times (15:00, 20:00, and 04:00 next day)	None	Bracci et al. (2016)
Cortisol	USA Civil aviation employees Experiment	28 workers (12 M, 16 F) randomly assigned to 2 wk of RS: clockwise (2 EMS, 2 AS, 1 midnight) or counter-clockwise (2 AS, 2 EMS, 1 midnight)	– (cortisol rhythm)	None (randomization)	Boquet et al. (2004)
Cortisol	Italy Hospital intensive-care unit Repeated measurements over 4 consecutive shifts	15 F nurses in rapid forward RS; plasma level measured at the beginning, middle, and end of 4 consecutive shifts (MS, AS, NS, NS)	– (cortisol rhythm); cortisol at 07:00, end of NS < beginning of MS ($P < 0.05$)	None	Costa et al. (1994)

Table 4.11 (continued)

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Cortisol, testosterone	Denmark Male police officers Crossover intervention study	73 participants ("2+2": 2 consecutive NS followed by 2 consecutive recovery days; "4+4": 4 consecutive NS followed by 4 consecutive recovery days; "7+7": 7 consecutive NS followed by 7 consecutive recovery days)	Delay in phase of the cortisol rhythm by 33 min/d – (testosterone)	None	Jensen et al., 2016
Thyroid hormones	Republic of Korea University hospital employees Repeated measures over 5 yr (2011–2015)	546 F NS (≥ 4 NS/mo), 421 F DS; serum level	NS > DS, TSH level ($P = 0.006$) and risk of subclinical hypothyroidism ($P = 0.022$)	Age, department	Moon et al. (2016)
Thyroid hormones	Italy Hospital employees Cross-sectional	220 rotating NS, 422 DS; M and F	Rotating NS > DS, abnormal anti-TPO antibodies ($P = 0.05$)	Age, sex, smoking, drinking, family history of autoimmune thyroid disease, radiation exposure	Magrini et al. (2006)

–, not significant; aMT6s, 6-sulfatoxymelatonin; AS, afternoon shift; BMI, body mass index; d, day; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DS, day shift; F, female; FSH, follicle-stimulating hormone; h, hour; LH, luteinizing hormone; M, male; min, minute; mo, month; MS, morning shift; NHS-I, Nurses' Health Study cohort; NHS-II, Nurses' Health Study II cohort; NS, night shift; OC, oral contraceptive; RS, rotating shift; SW, shift work; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; vs, versus; wk, week; yr, year.

and androgens, but not estrogens, were higher in night shift workers than in daytime workers after adjusting for potential confounders including menstrual phase; the peak level of androgens was also delayed (Papantoniou et al., 2015). In a study of 263 women working irregular rotating night shifts and 269 women working during days, after adjusting for multiple confounders postmenopausal women engaged in night shift work for more than 15 years had higher estradiol levels than those who had worked night shifts for less than 5 years. Current night shift work status, frequency of night duties, and duration of working night shifts were also positively associated with serum estradiol levels in postmenopausal women with a morning chronotype (Peplonska et al., 2016). In a small trial, including three pregnant and six non-pregnant volunteering nurses engaged in a rapidly backward rotating three-shift schedule (morning, afternoon, night, day off) in Japan, estriol level did not vary with time of urine collection (i.e. during the day shift or the night shift) in within-worker comparisons, or with pregnancy status (Yamauchi et al., 2001; Yamauchi, 2004). In an evaluation of early to mid-luteal phase work and levels of sleep estrone conjugate in urine collected throughout work and sleep periods in 323 premenopausal female nurses (172 night shift and 151 day shift), significantly elevated levels in night shift nurses in daytime sleep (vs in night time sleep) and in night time work among night shift nurses (vs in night time sleep) were observed; however, there were no significant differences in work or sleep estrone conjugate levels between night shift nurses and day shift nurses (Davis et al., 2012) (see also Section 4.1.6(a)(ii) below).

(ii) Prolactin, luteinizing hormone, follicle-stimulating hormone, and androgens

In a study of five female nurses during their night shift and six female nurses on their resting day in Japan, nurses working night shifts had significantly lower plasma concentrations of prolactin (PRL) at 02:00 (but not at 22:00), although plasma concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) did not differ between the two groups (Miyauchi et al., 1992). There was also a significantly higher incidence of irregular menstrual cycle in women working at night in a comparison of surveyed teachers, office workers, nurses, factory workers, and barmaids in the same report. [The Working Group noted that the study size was too small for any reliable inference to be drawn.] In a trial of volunteering workers, 8 engaged in permanent night work and 10 in day work, no differences in the plasma PRL profile were observed over two 24-hour sleep–wake cycles (Spiegel et al., 1996). In a study of 327 hospital nurses and midwives working irregularly rotating night shift schedules compared with 330 nurses and midwives working day shifts only, there was no significant association between type of night shift or sleep characteristics and serum PRL level (Bukowska et al., 2015). Plasma PRL immediately responded to alterations to sleep-activity cycle in 10 young female nurses of an intensive care unit engaged in an 8-day rapid forward rotating shift schedule (1 afternoon, 2 mornings, 1 afternoon, 2 nights, 2 rest days) including 1 or 2 nights, but did not differ between measurements taken at the same time on different days (Costa et al., 1997). On the contrary, a significant decrease in PRL level was observed in four male oil refinery workers monitored every 2 hours during their night shift (Touitou et al., 1990). [The Working Group noted that the role of pituitary hormones, such as PRL and growth hormone (discussed below), in cancer of the breast has been investigated less extensively. PRL is released by the anterior lobe of the pituitary gland, but also by the mammary gland, lymphocytes, uterus, prostate, and placenta. By interacting with specific receptors, PRL induces a protein (prolactin-induced protein or PIP) that stimulates DNA synthesis, epithelial cell proliferation, and milk production in the breast (Froes Brandao et al., 2016). In turn,

PIP promotes the growth of breast cancer cells and has a role in facilitating metastasis (Naderi, 2015; Shemanko, 2016).]

Compared with measurements during a period on vacation, plasma LH was decreased in six male resident physicians after a 36-hour work shift, including the night, in an obstetrics ward. No significant changes were observed when the same physicians worked at a gynaecology ward (Chatterton & Dooley, 1999).

Testosterone levels were also monitored in the above study of six male resident physicians. In these men, plasma testosterone levels were suppressed after a night on call at the obstetrics ward and during the first 2 weeks of residency compared with during a vacation period. No significant variations were observed while on-call at the gynaecology ward (Chatterton & Dooley, 1999). In the study of 172 premenopausal night shift nurses and 151 premenopausal day shift nurses (see also Section 4.1.6(a)(i) above), there were significantly elevated urinary LH and FSH in night shift workers in daytime sleep (vs night sleep) and in night work (vs night sleep), when comparing levels during day sleep (for night shift workers) with those in night sleep (for day shift workers), and when comparing levels in night work (for night shift workers) with those in night sleep (for day shift workers) (Davis et al., 2012). In the study of four male oil refinery workers who were engaged in fast rotating shift work, testosterone rhythm was erratic and, at the times of peaks and trough, the serum levels were significantly lower in shift workers than in controls (Touitou et al., 1990). No effect on serum testosterone was observed in the Japanese study of 177 postmenopausal women who ever worked night shifts (Nagata et al., 2008); however, serum testosterone was higher in both men and women working rapid and slow rotating night shifts in the Spanish study covering different trades (Papantoniou et al., 2015), and it was reduced independently of menopausal status, significantly so in the luteal phase, in the study by Gómez-Acebo et al. (2015). [The Working Group noted that the role of testosterone in carcinogenesis is controversial (Klap et al., 2015). Further, whether FSH and LH play a role in modulating the risk of cancer is unclear (Nagamani et al., 1992).]

(iii) Growth hormone

Growth hormone (GH) has been indicated as a contributor to the development, progression, and metastasis of cancer of the breast (Subramani et al., 2017). One study explored the relationship between night shift work that resulted in disruption of the circadian rhythm and changes in the daily rhythm of GH release. GH was monitored every 10 minutes while performing polysomnography in supine posture and receiving enteral nutrition in 11 male workers with at least 2 years of permanent engagement in night shift work at a frequency of 4–5 times per week, and in 10 day workers. The total amount of GH secreted over 24 hours, as well as the mean plasma GH levels, did not vary between the day-active and the night-active workers. In addition, in permanent night shift workers the sleep-related decrease in GH release was compensated for by its increase at varying, unpredictable moments during the waking hours, without any correlation with plasma melatonin levels (Brandenberger & Weibel, 2004). In 10 young female nurses of an intensive care unit, plasma GH rapidly responded to changes in sleep–activity cycle, although its peak at night was less pronounced (Costa et al., 1997).

(iv) Cortisol

Plasma cortisol was suppressed after a night on call, and became normal or elevated in the afternoon in resident doctors in the USA (Chatterton & Dooley, 1999). Cortisol rhythm also had a lesser amplitude, but serum levels at midnight were more elevated in oil refinery night shift workers than in daytime workers (Touitou et al., 1990). Similarly, in a study of female hospital employees

(160 day workers and 168 rotating shift workers) from Ontario, Canada, diurnal cortisol curves were flatter in shift workers on the night shift. In addition, cortisol was decreased in shift workers on the night shift, but cortisol production in shift workers on their day shift was similar to that of day workers (Hung et al., 2016). In a study of 42 shift workers at a paper and pulp factory engaged in rapid backward rotating shift work schedule (1 night, 1 afternoon, and 1 morning, repeated 7 times; then 1 week of rest), participants with an evening chronotype had lower morning cortisol levels at the end of a shift cycle than participants with a morning chronotype (Axelsson et al., 2003). Thirty surgeons who rotated rapidly over two shifts (08:30–15:30, 15:30–08:00, day off) were monitored for 4 days starting at 07:00 on the day shift. In the 29 participants from whom data were collected, cortisol levels manifested a regular rhythm with reduced levels at night and increased levels in the morning hours, although reduced compared with pre-call values (Amirian et al., 2015). Some type of shift rotation was also relevant in influencing adaptation of and levels of cortisol and other hormones. For instance, irregular work shifts in 70 media workers resulted in insufficient recovery and an associated decrease in the salivary cortisol:melatonin ratio (Lindholm et al., 2012). In addition, salivary cortisol levels in the morning hours were lower in 23 nurses employed in clockwise rapidly rotating shift work schedule (1 day, 1 afternoon, 1 night, 2 rest days) compared with 25 nurses working day shifts (Bracci et al., 2016). However, cortisol rhythm was unaffected by rotating shifts, whether clockwise or counter-clockwise, in 28 men and women evenly distributed at random between the two groups (Boquet et al., 2004), or by regular rapidly rotating shifts (2 afternoon, 2 morning, 1 afternoon, 2 nights, 2 rest days) in 15 young female nurses working in an intensive care unit (Costa et al., 1994). In a study of 73 police officers, an increasing number of night shifts altered the diurnal rhythm of cortisol but not testosterone (Jensen et al., 2016). [The Working Group noted that cortisol activates DNA-damaging free radical production, and impairs apoptosis and DNA repair processes, which prevent the progression of abnormal cells towards cancer development (Spiers et al., 2015).]

(v) Thyroid hormones

In a study in the Republic of Korea (n = 967), female night shift workers (4 night shifts/month at a university hospital) demonstrated significantly (P = 0.006) higher levels of thyroid-stimulating hormone (TSH) than those of non-night shift workers, and a 1.4-fold excess risk (P = 0.022) of subclinical hypothyroidism after adjusting for age and hospital department (Moon et al., 2016). The hypothesis of an autoimmune response predisposing to hypothyroidism was investigated by examining anti-peroxidase thyroid antibodies in 220 shift workers engaged in a rotating shift schedule including nights, and 422 daytime workers. After taking into account age, sex, smoking habits, alcohol intake, familial history of autoimmune thyroid disease, and exposure to radiation as possible confounders, shift workers had an increase of more than 2-fold in subclinical autoimmune hypothyroidism (Magrini et al., 2006). [The Working Group noted that in addition to regulating metabolism, development, and growth, thyroid hormones can also stimulate cancer cell proliferation (Lin et al., 2016).]

(b) Experimental systems

Data from studies that evaluated changes in endocrine function in response to alterations in the light–dark schedule in experimental systems are compiled in Table 4.12.

Several studies evaluated serum hormone levels in nonhuman primates exposed to alterations in the light-dark schedule. Capuchin monkeys exposed to continuous light for approximately the last 50 days of gestation had decreased maternal plasma melatonin concentration, and no significant change in either

maternal plasma estradiol or cortisol concentration (Torres-Farfan et al., 2004; Torres-Farfan et al., 2006; Richter et al., 2018). In contrast, increased cortisol concentration in the offspring was observed when the dam was exposed to continuous light during part of the pregnancy. Rhesus macaques maintained on a schedule of 12 hours of light and 12 hours of darkness (LD12:12) had elevated plasma melatonin and progesterone concentrations at night, whereas estradiol, estrone, and cortisol reached peak concentrations in the early morning. Lights were then left on for 12 days, resulting in decreased plasma melatonin concentration but no effect on other steroids (Matsumoto et al., 1991). [The Working Group noted that these studies using capuchin monkeys were of small sample sizes, and that some studies duplicated previously reported data.]

Female Sprague-Dawley rats with mammary adenocarcinomas induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) were exposed to either LD12:12, continuous light, or partial or dim light during the period of darkness (Cos et al., 2006). Rats exposed to light during the period of darkness, especially those under dim light during the period of darkness, had higher tumour growth rates, increased serum estradiol concentration, and lower nocturnal excretion of aMT6s (Cos et al., 2006). Mendez et al. (2012) examined rat maternal and fetal endocrine status as a result of exposure to continuous light during the second half of gestation. Exposure of pregnant dams to continuous light during the second half of gestation had no effect on maternal corticosterone production, despite suppressing maternal melatonin rhythm (Mendez et al., 2012). This maternal exposure to continuous light also retarded intrauterine growth and affected fetal adrenal function in several ways, including changing adrenal clock gene expression and corticosteroid rhythm. Altered corticosteroid rhythm was also observed in mice undergoing shifts in the light–dark schedule (Filipski et al., 2004). Fantie et al. (1984) reported that male Long-Evans rats exposed to either continuous light or continuous dim red light for 60–90 days had higher serum prolactin concentrations or higher serum androgen levels, respectively, compared with controls maintained at LD12:12.

Alterations in the light–dark schedule can also alter other receptor-mediated processes (Table 4.13). For instance, Kettner et al. (2016) demonstrated that advances in the light–dark schedule deregulate nuclear receptor-controlled cholesterol/bile acid and xenobiotic metabolism. Transgenic mice lacking the farnesoid X receptor have increased hepatic bile acid concentrations and, when exposed to shifts in the light–dark schedule, an increased incidence of hepatocellular carcinoma. A reduction in hepatocarcinogenesis was seen in transgenic mice with reduced expression of the constitutive androstane receptor (Kettner et al., 2016). Data relevant to key characteristics of carcinogens from studies that evaluated other receptor-mediated effects after alterations in the light–dark schedule (e.g. Szántóová et al., 2011; Van Dycke et al., 2015; Kochan et al., 2016; Marti et al., 2017) are compiled in Table 4.13.

Aryl hydrocarbon receptor activation affected the expression of clock genes and their response to alterations in the light–dark schedule (Jaeger & Tischkau, 2016). Disruption of *Per1* gene expression in the mammary gland, liver, and haematopoietic cells increased 2,3,7,8-tetrachlorodibenzo-*para*-dioxin-induced CYP1A1 and CYP1B1 expression (Garrett & Gasiewicz, 2006; Qu et al., 2007, 2009).

4.1.7 Alters cell proliferation, cell death, or nutrient supply

(a) Humans

No data were available to the Working Group.

Table 4.12 Effects on endocrine function in response to alterations in the light–dark schedule in experimental systems

Experimental system	Exposure	Relevant finding(s)	Reference
Pregnant capuchin monkey (*Cebus apella*)	Control: LD14:10 Treatment: continuous light from gestation day 100–150 (approximately)	↓ Maternal plasma melatonin No effect on maternal plasma estradiol or cortisol concentration ↑ Plasma cortisol concentration in the offspring	Torres-Farfan et al. (2004)
Pregnant capuchin monkey (*Cebus capucinus*)	Control: LD14:10 Treatment: continuous light from gestation day 100–140 (approximately)	↓ Maternal plasma melatonin ↑ Fetal adrenal 3β-HSD mRNA and progesterone No effect on fetal plasma cortisol or cortisone concentration	Torres-Farfan et al. (2006)
Pregnant capuchin monkey (*Cebus capucinus*)	Control: LD14:10 Treatment: continuous light from gestation day 100 to delivery (approximately 57 d)	↑ Maternal plasma melatonin No effect on maternal plasma cortisol concentration ↑ Newborn plasma cortisol and ↓ DHEAS concentrations; ↓ StAR, 3β-HSD mRNA, and protein expression in adrenal explants of offspring at age 10 mo	Richter et al. (2018)
Rhesus monkey (*Macaca mulatta*) (F)	Control: LD12:12 Treatment: continuous light for 12 d	↓ Plasma melatonin No effect on progesterone, estradiol, estrone, or cortisol concentrations	Matsumoto et al. (1991)
Sprague-Dawley rat (F)	Control: LD12:12 Treatment: continuous light, with dim light during the entire 12-h period of darkness	Light during period of darkness: ↓ nocturnal excretion of aMT6s; changes in the light–dark schedule altered estrous cyclicity Continuous light: ↑ serum estradiol levels ↑ Tumour growth in all groups versus control	Cos et al. (2006)
Sprague-Dawley rat (F)	Control: LD12:12 Treatment: continuous light during second half of gestation	Maternal responses: ↓ maternal plasma melatonin; no effect on maternal plasma corticosterone concentration Fetal responses: ↓ fetal weight, adrenal gland corticosterone, corticosterone response to ACTH, and adrenal gland expression of both MT_1 and *Egr1*	Mendez et al. (2012)
Adult Long-Evans rat (M)	Control: LD12:12 Treatment: continuous white light or continuous darkness (red dim light) for 60–90 d	Both groups: ↓ intromission and ejaculation Continuous darkness: ↑ serum androgen levels Continuous light: ↑ serum prolactin levels	Fantie et al. (1984)
B6D2F$_1$ mouse inoculated with Glasgow osteosarcoma	Control: LD12:12 Treatment: advance in the light–dark schedule by 8 h for 10 d	Disrupted, biphasic corticosterone profile ↓ Hepatic and tumour expression of both *Per2* and *Rev-erb* Enhanced tumour growth	Filipski et al. (2004) (see also Section 4.2.2)

↑, increase; ↓, decrease; 3β-HSD, 3β-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropic hormone; aMT6s, 6-sulfatoxymelatonin; d, day; DHEAS, dehydroepiandrosterone sulfate; *Egr1*, early growth response protein-1; F, female; h, hour; LD, light–dark schedule, light(h):darkness(h); M, male; mo, month; mRNA, messenger RNA; MT_1, melatonin receptor-1; *Per2*, period 2 clock gene; *Rev-erb,* circadian nuclear receptor gene; StAR, steroidogenic acute regulatory protein.

Table 4.13 Other effects on receptor function seen in response to alterations in the light–dark schedule in experimental systems, mapped to selected key characteristics of carcinogens

Key characteristic	Experimental system	Exposure	Relevant finding(s)	Reference
Alters cell proliferation, cell death, or nutrient supply Modulates receptor-mediated effects	C57BL/6J inbred wildtype, *Per1–/–;Per2–/–*, *Cry1–/–;Cry2–/–*, *Albcre;Bmal fl/fl*, *Car–/–*, and *Fxr–/–* mice	Control: LD12:12 Treatment: advances in the light–dark schedule by 8 h (up to 90 wk)	↓ Lifespan with ↑ incidence and earlier onset of NAFLD ↑ Both numbers and sizes of tumours in *Per* and *Cry* mutants, and also the size of tumour in HCC-bearing *Albcre;Bmal fl/fl* mice Deregulation of nuclear receptor-controlled cholesterol, bile acid, and xenobiotic metabolism in the livers of exposed wildtype mice at all ages studied; suppression of FXR and induction of CAR in HCCs; upregulation of transcription factors stimulating cell proliferation and steatosis including β-catenin, c-Myc, Srebp1, Pparγ, Cyp2B10, and Cyp7A1	Kettner et al. (2016)
Alters DNA repair or causes genomic instability	Sprague-Dawley rat (F)	Control: LD12:12 Treatments: advance in the light–dark schedule by 3 h each day for 6 d; advance in the light–dark schedule by 3 h each day for 6 days followed by a 10-d regular LD12:12 for a total of 54 d (6–10–6–10–6–10–6)	After 2 wk (tissues collected 19 h after lights on): base-excision repair, homologous recombination, mismatch repair, and nucleotide-excision repair suggest ↓ DNA repair; ↓ Tp53 signalling and ↓ apoptosis	Kochan et al. (2016)
Modulates receptor-mediated effects	Wistar and Sprague-Dawley rat (M)	Control: LD12:12 Treatment: forced activity for 8 h/d during either normal active or rest periods, for 3 d	Forced activity during normal rest period: ↓ phosphorylation of cap-bound Bmal1 and S6K1 reduced in the PFC; ↓ PFC synaptic ARC protein	Marti et al. (2017)
Modulates receptor-mediated effects	Wistar rats (M)	Control: LD12:12 Treatment: shift (delay) in the light–dark schedule by 8 h every 2 d, for 10 wk	Change in clock gene expression and phase shift in metabolic genes (e.g. *Rev-erbα*, *Pparα*, and *Pdk4*) in the liver and heart	Szántóová et al. (2011)
Modulates receptor-mediated effects	FVB mouse (F)	Control: LD12:12 Treatment: shift (advance or delay) in the light–dark schedule by 8 h every 5 d; samples collected after 1 shift and 5 d recovery, or 6 shifts and 14 d recovery	Corticosterone serum levels affected by both treatments Multiple genes were differentially expressed in the liver from mice from both treatment groups, including: *Cyp2c29*, *Cyp2b10*, *Ntrk2* (kinase signalling), *Tusc3*, *Armcx3* (tumour suppression), and *Gspt2* (cell-cycle progression), among others	Van Dycke et al. (2015)

↑, increase; ↓, decrease; ARC, activity-regulated cytoskeleton-associated protein; Armcx3, armadillo repeat-containing X-linked 3; Bmal1, brain-and-muscle aryl hydrocarbon nuclear translocator (arnt)-like protein-1; CAR, constitutive androstane receptor; Cyp, cytochrome P450; d, day; F, female; FXR, farnesoid X receptor; Gspt2, G1 to S phase transition 2; h, hour; HCC, hepatocellular carcinoma; h, hour; LD, light–dark schedule, light(h):darkness(h); M, male; NAFLD, non-alcoholic fatty liver disease; Ntrk, neurotrophic tyrosine receptor kinase; pdk4, pyruvate dehydrogenase kinase 4; PFC, prefrontal cortex; Ppar, peroxisome proliferator-activated receptor; *Rev-erb*, circadian nuclear receptor; S6K1, S6 kinase β-1; SREBP1, sterol regulatory element-binding protein-1; Tusc3, tumour suppressor candidate-3; wk, week.

(b) Experimental systems

Several studies directly evaluated tumour growth after alteration in the light–dark schedule; these studies are discussed below and in Section 4.2. Additional information can also be found in Section 3 of the present monograph.

Altering the light–dark schedule in mice can result in hepatic pathology, elevated liver enzymes, and increased hepatocyte and bile duct proliferation as assessed using histochemical markers of cell proliferation (e.g. cytokeratin 19, Ki67) (Kettner et al., 2016) (see Section 3.1 and Table 4.13). Blask et al. (2014) showed that DNA synthesis was increased in MCF-7 breast cancer xenografts implanted in rats exposed to light during the period of darkness (see Section 3.5). Tumour growth and cell proliferation (measured using proliferating cell nuclear antigen, PCNA) was increased in rats exposed to light during the period of darkness (Wu et al., 2011) (see Section 3.5). Tumour PCNA levels remained high throughout the entire 24-hour period in rats exposed to light during the period of darkness. Male outbred rats given five subcutaneous injections of 1,2-dimethylhydrazine and kept under continuous light had increased tumour cell proliferation (assessed by PCNA) compared with rats kept at LD12:12 (Panchenko et al., 2008) (see Section 3.4 for additional details).

A single study evaluated the Warburg effect in rats undergoing alterations in the light–dark schedule (Blask et al., 2014). In this study, female nude rats (Hsd:RH-*Foxn1[rnu]*) were exposed to either LD12:12 (control) or to dim light during the period of darkness and, after 6 weeks of exposure, implanted with MCF-7 human breast cancer xenografts (Blask et al., 2014) (see Section 3.5). Exposure continued until tumours reached approximately 5–6 g. The Warburg effect was assessed by evaluating tumour uptake of arterial blood glucose coupled with the release of lactate into the tumour venous blood. Exposure to light during the period of darkness disrupted the rhythms seen in tumour cyclic adenosine monophosphate levels, total fatty acid uptake, linoleic acid uptake, and 13-hydroxyoctadecadienoic acid. Levels of each of these parameters remained significantly elevated over the 24-hour period. [The Working Group noted that there were concerns related to the evaluation of a xenograft tumour model.] Kettner et al. (2016) evaluated changes in glucose metabolite (e.g. glucose 6-phosphate) concentrations in the serum and liver of mice that had been exposed to prolonged alterations in the light–dark schedule, observing the occurrence of accelerated cytoplasmic glycolysis in response. Altered glucose (and glutamine) metabolism was also reported in K-$ras^{LSL\text{-}G12D/+}$;$p53^{flox/flox}$ mice. *Per2* mutant cells had increased rates of glucose consumption and increased levels of lactate excretion compared with $Per2^{+/+}$ cells (Papagiannakopoulos et al., 2016) (see also Section 4.2.2(b)). [The Working Group noted that the circadian clock is critical to metabolism (reviewed by Eckel-Mahan & Sassone-Corsi, 2013; Dibner & Schibler, 2015; Panda, 2016; Maury, 2019). Changes in glucose metabolism are seen in tumour cells, a reliance on glycolysis known as the Warburg effect (Xu et al., 2015). The Working Group's review focused on changes in tumour cell glucose metabolism in response to alterations in the light–dark schedule of experimental systems.]

Blask et al. (2005) performed several studies in situ where tumours were perfused with blood collected from human volunteers exposed to different intensities of light, resulting in different melatonin levels. Human breast cancer xenografts and rat hepatomas perfused in situ with melatonin-rich blood had decreased cell proliferation and linoleic acid uptake and/or metabolism. Tumours perfused with melatonin-deficient blood had higher tumour cell proliferation (Blask et al., 2005) (see also Section 4.2.1(b)). [The Working Group noted that other factors may also have been present in the blood of the human volunteers.]

Fewer studies have used the measurement of PCNA, DNA synthesis, or [^{3}H]thymidine incorporation or a similar approach to directly measure cell proliferation after changes in clock gene expression (e.g. Yang et al., 2009; Lee et al., 2010) (see also Section 4.2.2(b)) or alterations in the light–dark schedule in experimental systems. Shah et al. (1984) showed that exposure of female Holtzman rats to continuous light (24 hours per day) immediately after birth significantly increased DMBA-induced mammary gland cell proliferation as measured using incorporation of [^{3}H]thymidine.

4.1.8 Causes immortalization: changes in telomere length

(a) Humans

See Table 4.14.

Human telomerase reverse transcriptase (*TERT*) mRNA expression, and therefore telomerase activity, oscillates with circadian rhythm under the control of the CLOCK-BMAL1 heterodimer; on the other hand, CLOCK deficiency causes loss of rhythmic telomerase activity, TERT mRNA oscillation, and shortened telomere length (Chen et al., 2014). In a study of 27 physicians, 14 working in emergency departments with night shifts and 13 working in non-emergency departments without night shifts, leukocytes of emergency physicians had a similar low telomerase activity at 10:00 and 17:00. This result indicates loss of the circadian rhythm of telomerase activity (Chen et al., 2014). [The Working Group noted that the authors did not specify the type of shift roster or the sex of the participating physicians.] In a study of 608 employed women and 240 unemployed or part-time working women in the USA, 15 years or more of rotating shifts or night work was not significantly related to relative leukocyte telomere length shortening (Parks et al., 2011). Telomere length in peripheral blood leukocytes was reduced, but not significantly so, after adjustment for age, BMI, and cigarette smoking in female nurses participating in the Nurses' Health Study (NHS-I) with a longer history of night shift work (Liang et al., 2011). Such an effect was seen in women aged 50 years or younger, but not in those older than 50 years. In a nested case–control study of Norwegian nurses including 563 cases of cancer of the breast and 619 controls, telomere length was reduced (–3.18; 95% CI, –6.46 to –0.58; $P = 0.016$) in those working 6 consecutive nights or more for 5 years or more compared with those who only worked day shifts (Samulin Erdem et al., 2017a). Telomere shortening was associated with an increased risk of cancer of the breast in nurses with a long duration of intense night shift work, in terms of number of consecutive nights. Conversely, nurses with longer telomere lengths working 4–5 consecutive nights for 5 years or more had a lower risk of cancer of the breast (Samulin Erdem et al., 2017a).

(b) Experimental systems

One study in young Sudanian diurnal grass rats (*Arvicanthis ansorgei*) showed that alterations in the light–dark schedule were associated with telomere shortening (Grosbellet et al., 2015); see also Section 4.1.1(b) and Table 4.2.

4.1.9 Studies of multiple key characteristics

(a) Humans

[The Working Group noted that metabolism and circadian rhythms are linked at a transcriptional level, although it is unclear whether such effects are under direct CLOCK control, or are mediated by the rest–activity cycle and the timing of food intake.] In a trial in 10 healthy unmedicated male volunteers conducted under controlled conditions of enforced posture, continuous dim light, hourly isocaloric meals, and sleep deprivation for 40 hours, about 15% of all identified metabolites, notably fatty acids in plasma and amino acids in saliva, were under direct circadian control (Dallmann et al., 2012).

Table 4.14 Effects on telomere length in shift workers

End-point	Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Telomerase activity	Taiwan, China Volunteering physicians Cross-sectional	14 physicians from emergency department, 13 physicians from non-emergency departments (sex not specified)	Loss of circadian oscillation of telomerase activity in emergency physicians; mean telomerase activity at 10:00 > at 17:00 ($P < 0.001$) in non-emergency but not in emergency physicians after a NS ($P > 0.05$)	None	Chen et al. (2014)
Telomere length	USA Sister study Cross-sectional	608 women, currently employed or with a moderate and/or substantial past employment history, 94 with ≥ 1 yr of RS and 152 with ≥ 1 yr of NS	– (for duration of RS or NS employment)	Age, race, current smoking status, perceived stress, BMI, sleep, physical activity, health status, cardiovascular disease, diabetes, marital status, education, number of children, child in household, total number of years worked	Parks et al. (2011)
Telomere length	USA Nurses' Health Study (NHS-I) Cross-sectional	2409 female nurses with a history of rotating NS (≥ 1 yr), 1583 female DS nurses	– (for duration of rotating NS, $P = 0.36$)	Age, BMI, cigarette smoking	Liang et al. (2011)
Telomere length	Norway Hospital nurses Nested case–control study	563 breast cancer cases and 619 controls; 96 nurses worked ≥ 6 consecutive nights for ≥ 5 yr and 166 DS nurses	Telomere shortening ($P = 0.016$) with NS	Not reported	Samulin Erdem et al. (2017a)

–, not significant; BMI, body mass index; DS, day shift; NHS-I, Nurses' Health Study cohort; NS, night shift; RS, rotating shift.

Patterns of human plasma proteins were assessed in six healthy male participants during daytime food intake and night sleep while in accordance with the circadian rhythm, versus daytime sleep and night food intake under conditions of simulated night shift work. A total of 127 proteins were altered during simulated night shift work, associated with immune function, metabolism, and cancer. Of these, 30 proteins were observed to be strongly regulated by the circadian cycle; these were associated with pathways involved in extracellular matrix organization, tyrosine kinase signalling, and signalling by receptor-tyrosine protein kinase erbB-2 (Depner et al., 2018).

(b) Experimental systems

Kettner et al. (2016) performed microarrays on total liver RNA from control mice (LD12:12), and mice exposed to shifts in the light–dark schedule, at age 12 and 30 weeks (see Table 4.13 for a partial description of the results; see also Table 3.1). This study also included a circadian metabolomics study of serum and hepatic carnitines, lipids and prostaglandins, coenzyme A, and tricarboxylic acid cycle metabolites in wildtype mice at age 12 and 30 weeks. Kochan et al. (2016) investigated the effect of various alterations in the light–dark schedule on mammary gene expression in Sprague-Dawley rats (see Table 4.13). In this study, control rats were exposed to LD12:12 for 6 or 54 days after an initial acclimation period. In the first treatment group, the period of light was initiated 3 hours earlier each day for 6 days (only). In the second treatment group, the 6 days of 3-hour advances in the light–dark schedule were followed by 10 days of LD12:12, followed by another 6 days of 3-hour advances in the light–dark schedule, for a total of 54 days (6, 10, 6, 10, 6, 10, 6). Their analysis revealed significant changes in gene expression at a single time-point (at 2 weeks and 19 hours after the initiation of the period of light). Gene expression changes observed at this time were associated with disturbances in base-excision repair, homologous recombination, mismatch repair, and nucleotide-excision repair processes. Gene expression patterns correlating with decreased Tp53 signalling, decreased DNA repair, and decreased apoptosis were also observed. [The Working Group noted that these results should be interpreted with caution because changes in gene expression occurred in only a single group, sample sizes were small, and no exposure duration-response relationship was observed.] Livers from female FVB mice exposed to six shifts in the light–dark schedule in both clockwise and counter-clockwise directions were evaluated using microarray approaches (Van Dycke et al., 2015; see also Table 4.13 and Table 3.1). Shifts in the light–dark schedule led to changes in hepatic expression of *Cd36*, *Ntrk2*, *Igh-VJ558*, *Srgap3*, *Tram1*, *Snrpn*, *Rbp1*, *Cyp2b10*, and *Cyp2c29*. Several of these genes (e.g. *Cd36*, *Ntrk2*) were postulated as being associated with cancer of the breast. Wu et al. (2012) investigated the effect of advances in the light–dark schedule on tumour growth and metastasis in male C57BL/6 mice (see also Table 3.2). In this study, Lewis lung carcinoma cells were inoculated into mice exposed for 10 days to either LD12:12 (control) or to advances in the light–dark schedule by 8 hours every 48 hours for 37 days (inoculation on day 10). cDNA microarrays and real-time quantitative reverse transcription polymerase chain reaction on liver and tumour cells were used to assess gene expression. Tumours grew faster in the mice exposed to advances in the light–dark schedule than in control mice. Microarray data showed that, in both liver and tumours, there was altered expression of genes related to the cell cycle, apoptosis, immune response, and metastasis suppressor genes. The expression of the *Ndrg1* gene was suppressed by advances in the light–dark schedule. Continuous gestational light in rats has also been reported to induce modification of the fetal liver transcriptome representing a diverse set of pathways,

including haematopoiesis, coagulation cascade, complement system, and carbohydrate and lipid metabolism (Spichiger et al., 2015).

4.2 Other relevant evidence

4.2.1 Melatonin

(a) Humans

This section focuses on studies with a sample size of more than 10 that assessed melatonin levels and had stronger design features (including the timing and multiplicity of biosample collection, appropriateness of control group, and characterization of the night shift work exposure). [The Working Group also noted that definitions of shift work varied across the studies. Although most studies collected urine samples for melatonin measurement, the timing and times of sample collection also varied across studies.]

The studies included in this section measured melatonin in the urine or saliva to determine whether shift work can reduce melatonin production (Table 4.15). For example, Schernhammer et al. (2004) measured aMT6s, a major metabolite of melatonin, from morning-void urine samples over a 3-year period in 79 premenopausal women who participated in the Nurses' Health Study cohorts to evaluate potential associations between night work and hormone levels. A significant inverse association was observed between an increasing number of nights worked within the 2 weeks preceding morning-void urine collection and aMT6s levels ($r = -0.30$; $P = 0.008$). A later publication from the same group also reported that melatonin concentrations calculated across 24 hours were similar for different shift work categories, with a variation of these concentrations over the course of the day. In a study set within the NHS-II cohort, rotating shift workers on night shifts had lower levels of urinary melatonin during the night compared with day workers, as well as smaller peaks and later peak onset (Razavi et al., 2019). There was also a significant interaction between rotating shift work and chronotype, with better alignment between rotating shift work and chronotype with less disruption of melatonin rhythms.

Burch et al. (2005) also measured and compared melatonin production, light exposure, and physical activity levels in 165 manufacturing workers on three non-rotating shifts (first, 06:00–14:00; second, 14:00–22:00; and third, 22:00–06:00). Concentrations of 6-hydroxymelatonin sulfate (6-OHMS), another major urinary metabolite of melatonin, were measured as adjusted mean sleep–work ratios of 6-OHMS concentration normalized to urinary creatinine levels (6-OHMS/cr) in post-shift and post-sleep urine samples. Levels of 6-OHMS were very similar between the first (ratio, 4.2) and the second (ratio, 4.5) shifts, but lower for the third shift (ratio, 2.3).

Davis et al. (2012) conducted the largest study of female nurses, comprising 172 night shift and 151 day shift nurses, to investigate whether night shift work is associated with decreased levels of melatonin. Their results showed that aMT6s levels were 62% lower during the daytime sleep of night shift workers than during the night sleep of day shift workers.

Mirick et al. (2013) performed the largest study in men, including 185 night shift and 158 day shift health-care workers, to investigate whether night shift work affects levels of melatonin. The study found that night shift workers had significantly lower aMT6s levels during daytime sleep (57% lower) than the day shift workers during night sleep.

Findings from 10 other studies also support the association between night shift work and a significantly decreased melatonin level (Hansen et al., 2006; Grundy et al., 2009; Bracci et al., 2013; Dumont & Paquet, 2014; Papantoniou et al., 2014; Amirian et al., 2015; Gómez-Acebo et al., 2015; Jensen et al., 2016; Leung et al., 2016; Daugaard et al., 2017). Studies that examined

Table 4.15 Effects on levels of melatonin in urine or saliva of shift workers

Melatonin or metabolite	Biosample type	Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
aMT6s	Post-sleep urine	USA Nurses' Health Studies (NHS-I and NHS-II) (three sample collections over 3 yr) Cross-sectional analysis	79 premenopausal women, number of NS in the last 2 wk (0, 1–4, > 4)	Melatonin decreased with increasing number of NS ($P = 0.008$)	None	Schernhammer et al. (2004)
aMT6s	72-h urinary collection after ≥ 3 d without night shift work	USA Nurses' Health Study II (NHS-II) Cross-sectional analysis	130 female nurses (84 RS and 46 DS)	RS on NS < DS; interaction between RS and chronotype ($P < 0.05$)	Age, BMI, melatonin batch, region (time zone), month of melatonin collection	Razavi et al. (2019)
6-OHMS	Post-sleep urine (creatinine-adjusted)	USA Medical device-manufacturing facility Cross-sectional study	165 workers on non-rotating shifts (71 first shift, 06:00–14:00; 62 second shift, 14:00–22:00; and 32 third shift, 22:00–06:00)	Third < first or second shift ($P < 0.01$)	Month, second-hand smoke, EMF concerns, eye colour, BMI	Burch et al. (2005)
aMT6s	24-h urinary collection	USA Hospital nurses Cross-sectional study	323 female nurses (172 NS and 151 DS)	NS < DS for: day sleep vs night sleep ($P < 0.0001$), night sleep vs night sleep ($P < 0.0001$), and night work vs night sleep ($P < 0.0001$) For NS, day < night sleep ($P < 0.001$) and night work < night sleep ($P < 0.0001$)	Age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, use of psychotherapeutics	Davis et al. (2012)
aMT6s	24-h urinary collection	USA Health-care providers Cross-sectional study	343 male health-care workers (185 NS and 158 DS)	NS < DS ($P < 0.0001$)	Age, hours of darkness, BMI, number of alcoholic beverages consumed, nicotine/tobacco use, medication use	Mirick et al. (2013)
aMT6s	24-h urinary collection on a work day and on a day off	Denmark Female nurses Cross-sectional study	89 fixed shift nurses (27 DS, 07:00–15:00; 12 ES, 15:00–23:00; 50 NS, 23:00–07:00)	NS < days off ($P < 0.001$); NS < DS on work days ($P < 0.01$)	Age, BMI, smoking, number of children, age at birth of first child, menopausal status	Hansen et al. (2006)

Table 4.15 (continued)

Melatonin or metabolite	Biosample type	Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
aMT6s	One post-sleep urine and four saliva samples over a 24-h period	Canada Female nurses Cross-sectional study	61 RS nurses (29 sampled on DS, 07:00–19:00; 32 sampled on NS, 19:00–07:00)	NS < DS (urinary melatonin, $P = 0.0003$) – (salivary melatonin)	None	Grundy et al. (2009)
aMT6s	Urine collected during 23:00–07:00	Italy Hospital nurses Cross-sectional study	31 healthy premenopausal (not using drug treatments) rapid forward rotating NS in the last 2 mo or longer; 31 DS	NS < DS ($P < 0.05$)	Age, BMI, physical exercise, smoking	Bracci et al. (2013)
aMT6s	24-h urinary collection	Spain Workers from two public hospitals, a car manufacturer, and a railway company Cross-sectional study	113 workers (72 NS and 41 DS)	NS < DS ($P < 0.001$), particularly in NS workers with a morning chronotype	Age, chronotype, education level, sex, menopausal status, parity, age at first full-term birth	Papantoniou et al. (2014)
aMT6s	24-h urinary collection	Canada Simulated NS work in healthy young participants Laboratory study	38 participants (simulated DS, 09:00–17:00; followed by 3 consecutive days of simulated NS, midnight to 08:00)	NS < DS ($P < 0.05$)	Within-person design	Dumont & Paquet (2014)
aMT6s	12-h urinary collection (21:00–09:00) over 4 consecutive days (pre-call; on-call, 15:30–08:30; post-call day 1; post-call day 2)	Denmark Physicians Cross-sectional study	21 surgeons	On-call < pre-call ($P = 0.004$)	None	Amirian et al. (2015)
aMT6s	24-h urinary collection	Spain Health-care workers and teachers Cross-sectional study	136 female workers (73 DS and 63 rotating NS)	NS < DS (significance not reported)	None	Gómez-Acebo et al. (2015)

Table 4.15 (continued)

Melatonin or metabolite	Biosample type	Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
aMT6s	Saliva samples collected every 4 h when awake on the last day with NS, and on the last recovery day, for each intervention	Denmark Male police officers Crossover intervention study	73 participants ("2+2": 2 NS followed by 2 recovery days; "4+4": 4 NS followed by 4 recovery days; "7+7": 7 NS followed by 7 recovery days)	Melatonin decreased with increasing number of NS ($P = 0.006$)	None	Jensen et al. (2016)
aMT6s	48-h urinary collection	Canada Female health-care workers Cross-sectional study	261 workers (147 fixed DS and 114 on RS including NS)	NS < DS ($P < 0.05$), particularly in NS workers with a later chronotype	Cumulative shift work, age, education, parity, age at first birth, use of sleep aid	Leung et al. (2016)
aMT6s	Saliva samples collected every 4 h on both a work day and a day off	Denmark Indoor, outdoor, and night workers Cross-sectional study	341 workers (254 DS and 87 NS, 19 of which regular and 68 RS)	NS < DS on work days ($P < 0.05$) but not on days off	Time of day, age, sex, BMI, current smoking, diurnal preference, use of antidepressant medication	Daugaard et al. (2017)
aMT6s	First morning urine void	Japan Breast cancer screening Cross-sectional study	7 Ever vs 170 never worked at night; all postmenopausal women not using hormone replacement therapy	–	Age, BMI, smoking status, alcohol consumption, group of participants, day length before urine collection	Nagata et al. (2008)
aMT6s	Morning urine	USA Nurses' Health Study Cross-sectional analysis	464 women (384 controls from a nested case–control study on urinary melatonin and breast cancer and 80 premenopausal participants from a validation study), of whom 44 had worked ≥ 1 night in the most recent 2 wk and 310 had worked ≥ 1 yr of rotating NS	– (for number of NS worked in the 2 wk before urine collection or years of rotating NS)	Age, BMI, weight change from age 18 yr, alcohol consumption, month of urine collection, antidepressant use, aspirin use, physical exercise, smoking history and pack-years smoked, height, first spot morning urine, sleep duration	Schernhammer et al. (2006)

Table 4.15 (continued)

Melatonin or metabolite	Biosample type	Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
aMT6s	24-h urinary collection	UK Oil rig workers Cross-sectional study	34 participants with 2 wk of DS (06:00–18:00) followed by 2 wk of NS (18:00–06:00): 5 drill crew in winter, 6 maintenance crew in winter, 23 maintenance crew in summer	–	None	Barnes et al. (1998a)
aMT6s	24-h urinary collection	Canada Telecommunications workers Cross-sectional study	13 full-time RS (sampled for two 24-hour periods, one including a NS and one including a DS/ES)	–	None	Dumont et al. (2012)
aMT6s	Urine collection at the beginning of a morning shift after a regular night's sleep on a day off	Italy Nurses Cross-sectional study	116 female nurses (60 with ≥ 2 yr of SW and 56 permanent DS)	–	Age, physical activity, number of offspring	Bracci et al. (2014)
aMT6s	24-h urinary collection	UK Oil rig workers Cross-sectional study	18 participants with 1 wk of DS (12:00 to midnight) followed by 1 wk of NS (midnight – 12:00): 11 in November, 7 in March	Mixed results by season	None	Barnes et al. (1998b)

–, not significant; 6-OHMS, 6-hydroxymelatonin sulfate; aMT6s, 6-sulfatoxymelatonin; BMI, body mass index; d, day; DS, day shift; EMF, electromagnetic field; ES, evening shift; h, hour; mo, month; NHS-I, Nurses' Health Study cohort; NHS-II, Nurses' Health Study II cohort; NS, night shift; RS, rotating shift; vs, versus; wk, week; yr, year.

levels of melatonin by chronotype reported inconsistent findings (Papantoniou et al., 2014; Leung et al., 2016).

However, in a study by Nagata et al. (2008), no significant difference was observed in urinary levels of aMT6s between postmenopausal women who had ever and never worked at night. Schernhammer et al. (2006) found no association between short- or long-term rotating night shift work and urinary levels of aMT6s in women in the NHS-II cohort. Several other studies also found no significant difference in total 24-hour aMT6s production between night shift and day shift work periods (Barnes et al., 1998a; Dumont et al., 2012; Bracci et al., 2014); an additional study reported mixed results (Barnes et al.,1998b). [The Working Group noted that the sample sizes of these four studies were relatively small (n = 34, 13, 60, and 18, respectively).]

(b) Experimental systems

Data relevant to key characteristics of carcinogens from studies that evaluated melatonin in experimental systems exposed to alterations in the light–dark schedule are compiled in Table 4.16. Blask et al. (2003) (see Section 3.5.2) demonstrated that rats maintained on LD12:12 exhibited a robust circadian melatonin rhythm that was abolished by exposure to continuous light. Rats inoculated with human MCF-7 breast cancer xenografts and exposed to continuous light had increased tumour growth, increased linoleic acid and its metabolism to the mitogenic molecule 13-hydroxyoctadecadienoic acid (13-HODE), and higher tumour growth rate, suggesting increased cell proliferation. In a series of follow-up studies, Blask et al. (2005) (see Section 3.5.2) showed that exposure of rats bearing rat hepatomas or human breast cancer xenografts to increasing intensities of light during each 12-hour dark phase (0–345 μW/cm^2) resulted in a dose-dependent suppression of nocturnal melatonin blood levels and a stimulation of tumour growth and linoleic acid uptake/metabolism to 13-HODE. Blask et al. (2005) also performed several in situ studies in which tumours were perfused with blood collected from human volunteers exposed to different levels of light. These exposures resulted in different melatonin levels in the blood. In these tumour perfusion studies, human breast cancer xenografts and rat hepatomas perfused in situ with blood high in melatonin (derived from humans exposed to a normal light–dark schedule) had decreased cell proliferation and linoleic acid uptake/metabolism. In contrast, tumours perfused with melatonin-deficient blood (collected from people exposed to light at night) had higher tumour cell proliferation. Nude rats inoculated with MCF-7 human breast cancer xenografts and exposed to dim light during the period of darkness had almost-undetectable blood melatonin levels, more rapid onset of tumour growth, and significantly increased tumour cell proliferation (Dauchy et al., 2014). Female Sprague-Dawley rats given a single oral dose of DMBA at 20 mg and exposed to continuous dim light during the period of darkness had significantly lower melatonin production, as assessed by urinary excretion of aMT6s, and elevated rates of mammary tumour growth (Cos et al., 2006; see Section 4.1.6(b)). A study performed by van den Heiligenberg et al. (1999), which involved the exposure to continuous light of Wistar rats given diethylnitrosamine, reported similar effects on melatonin production and tumour growth rates. In contrast, Travlos et al. (2001) reported that light during the period of darkness also impaired melatonin production in female Fischer 344 rats; however, tumour growth rates (induced by injection of *N*-nitroso-*N*-methylurea) were unaffected by decreased melatonin production.

Dimovski & Robert (2018) reported decreased plasma melatonin in adult tammar wallabies housed under either amber or white light at night (see also Section 4.1.1(b)).

Table 4.16 Melatonin disruption in response to alterations in the light–dark schedule, mapped to selected key characteristics of carcinogens

Key characteristic	Experimental system	Exposure	Relevant finding(s)	Reference
Alters cell proliferation, cell death, or nutrient supply	RNU nude rats (F) implanted with MCF-7 breast cancer xenografts grown in BALB/c nude mice	Control: LD12:12 Treatment: continuous light Melatonin measured after 5 wk; all rats continued on LD12:12 after implantation until day 40, when some tumour-bearing rats were changed to continuous light	↑ Tumour growth ($P < 0.05$), ↑ Tumour LA uptake and its metabolism to 13-HODE (mitogen)	Blask et al. (2003)
Alters cell proliferation, cell death, or nutrient supply	Buffalo (BUF(BUF/Ncr)) rats (M) implanted with rat hepatocarcinoma Nude rats (HSD:RH-rnu) (F) implanted with MCF-7 human breast cancer xenografts	Control: LD12:12 Treatment: variable light intensity during each 12-h period of darkness: 0 (continuous darkness), 0.02, 0.05, 0.06, 0.08, and 345 (continuous light) μW/cm^2; exposure began 2 wk before tumour implantation, and continued until the end of each tumour growth period ± Tumours perfused in vitro with human blood collected from women exposed to various different lighting conditions: daytime; night after 2 h of complete darkness; and night after 90 min of white light exposure	Rat hepatoma expressed both MT_1 and MT_2; tumours expressing MT_1 were responsive to melatonin (e.g. ↓ tumour cAMP levels) Male rats exposed to variable light showed a dose-dependent ↓ in serum melatonin levels Tumour perfusion with blood collected during night: ↓ [^{3}H]thymidine incorporation compared with blood collected during the day; the addition of S20928, a non-selective MT_1/MT_2 antagonist, blocked the tumour-suppressive effects of melatonin-rich blood collected at night	Blask et al. (2005)
Alters cell proliferation, cell death, or nutrient supply	Nude rats (HSD:RH-*Foxn1*^{rnu}) (F) implanted with MCF-7 human breast cancer xenografts; some rats treated with tamoxifen when tumours were ~ 2.5 g	Control: LD12:12 Treatment: dim light during the period of darkness Tumours implanted 1 wk after change in the light–dark schedule; exposure continued until study termination when tumours became larger	↓ Blood melatonin levels ↑ Tumour incorporation of [^{3}H]thymidine Breast tumour xenografts from rats housed in dim light during the period of darkness had ↓ latency-to-onset ($P < 0.001$) and a faster growth rate ($P < 0.001$)	Dauchy et al. (2014)
Alters cell proliferation, cell death, or nutrient supply	Wistar rats (M) Rats given DEN orally at ~ 10 mg/kg bw per d for 6 wk, then either DEN only, DEN + phenobarbital (at 30 mg/d), or continuous light for up to 77 d	Control: LD12:12 Treatment: continuous light	↓ Urinary aMT6s, ↑ hepatic tumour frequency and size ($P < 0.05$)	van den Heiligenberg et al. (1999)
Alters cell proliferation, cell death, or nutrient supply	F344/N rats (F) pineal-intact and pinealectomized Single intraperitoneal injection of NMU at 50 mg/kg bw	Control: LD12:12 Treatment: light during the period of darkness for 1-min intervals at 14:00, 16:00, 18:00, 20:00, and 22:00 Up to 26 wk	↓ Serum melatonin, no effect on the incidence or development of NMU-induced mammary tumours	Travlos et al. (2001)

↓, decrease; ↑, increase; 13-HODE, 13-hydroxyoctadecadienoic acid; aMT6s, 6-sulfatoxymelatonin; bw, body weight; cAMP, cyclic adenosine monophosphate; d, day; DEN, diethylnitrosamine; F, female; h, hour; LA, linoleic acid; LD, light–dark schedule, light(h):darkness(h); M, male; min, minute; MT_1 or MT_2, melatonin receptor 1 or 2; NMU, *N*-nitroso-*N*-methylurea; wk, week.

4.2.2 Disruption of clock genes

(a) Humans

See Table 4.17.

Ten studies in humans, mostly of cross-sectional design, have examined the association between shift work and alterations in the expression of clock genes (i.e. core circadian genes). None of these studies provided data on dysfunction metrics of the molecular circadian clock or any measure of its phase shift or amplitude modification.

Of the 10 studies, 5 measured mRNA expression of clock genes and 5 measured methylation of those genes, which may modulate their expression (Rauch et al., 2009; Bell et al., 2011). The studies varied considerably in terms of eligibility criteria, number of participants, shift schedules evaluated, and control of covariates.

In the studies of clock gene expression, there was a general lack of consistency between studies in terms of the specific clock genes identified and the direction of effects. Limitations of the studies included the small numbers of participants and/or only single time-points being considered (Reszka et al., 2013; Bracci et al., 2014; Fang et al., 2015; Kervezee et al., 2018; Koshy et al., 2019). Expression of clock genes is known to vary over a 24-hour day (Zhang et al., 2014), but multiple measurements throughout a day were not always captured. [The Working Group noted that differences in study design may explain some differences in results.] For example, Bracci et al. (2014) compared clock gene expression in blood between rotating shift workers (≥ 2 years on shift) and day shift workers (see also Section 4.1.6(a)). Since blood samples were collected from the rotating shift workers during a day shift that followed a day off (i.e. not during or immediately after completing a night shift), short-term effects on gene expression were likely to be missed. On the other hand, Kervezee et al. (2018) conducted a laboratory-based study of healthy volunteers that evaluated changes in gene expression over 4 days of simulated night shift work (see also Section 4.1.2(a)). This study highlighted rapid acute disruption of the circadian coordination by simulated night work, but it was unable to address the issue of chronic impacts of long-term shift work on gene expression.

Results of the methylation studies were also mixed in terms of specific clock genes identified and the direction of effects (Zhu et al., 2011; Bhatti et al., 2015; Adams et al., 2017; Samulin Erdem et al., 2017b). Compared with gene expression, DNA methylation is thought to be more stable over shorter periods of time. Thus, capturing multiple measurements over the course of a single day is likely to be unnecessary. [However, DNA methylation is cell specific, so an important consideration of the Working Group was the potential for systematic differences in the composition of tissue samples between comparison groups.] Diurnal variation in blood cell composition, for example, could contribute to observed differences in clock gene methylation. This issue can be addressed through adjustment for cellular composition (Houseman et al., 2012), which was not performed in two of the studies (Zhu et al., 2011; Reszka et al., 2018). In two of the studies, participants may have last performed shift work many years before blood sample collection (Zhu et al., 2011; Samulin Erdem et al., 2017b); [the Working Group noted that it is uncertain how this may have impacted the ability to observe relevant changes in methylation related to shift work].

(b) Experimental systems

Circadian clock genes have been shown to alter cell proliferation and tumour growth. For example, transgenic mice deficient in the circadian clock gene, period homologue 2 (*Per2*), had increased tumour development after gamma radiation (Fu et al., 2002; Fu & Lee, 2003; Lee et al., 2010) and accelerated $Apc^{Min/+}$ tumorigenesis (Wood et al., 2008) compared with wildtype mice. Castanon-Cervantes et al. (2010) (Table

Table 4.17 Clock gene expression and methylation in shift workers

End-point	Biosample type	Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Clock gene expression	Blood	Poland Nurses and midwives Cross-sectional study	92 RS (mean duration NS 24.2 yr), 92 DS (mean duration NS12.0 yr)	RS > DS for *PER1* ($P = 0.03$) NS for ≥ 15 yr > DS for *PER1* ($P = 0.01$)	Hour and season of the year of blood collection	Reszka et al. (2013)
Clock gene expression	Blood	Italy Nurses Cross-sectional study	60 RS (day 1, 07:00–14:00; day 2, 14:00–22:00; day 3, 22:00–07:00) for ≥ 2 yr, 56 DS	RS > DS for *BMAL1* ($P = 0.04$), *CLOCK* ($P = 0.008$), *NPAS2* ($P = 0.012$), *PER1* ($P = 0.008$), *PER2* ($P = 0.047$), *REV-ERBα* ($P = 0.045$) RS < DS for *PER3* ($P = 0.012$), *CRY1* ($P = 0.002$), *CRY2* ($P = 0.005$)	Age, chronotype score, physical activity, number of offspring Multiple eligibility criteria	Bracci et al. (2014)
Clock gene expression	Blood	USA Hospital residents and/or interns Short-term follow-up study	15 participants on 7-d floating NS	NS > DS for *PER2* ($P = 0.03$)	Multiple eligibility criteria; within-person design	Fang et al. (2015)
Clock gene expression	Blood	Canada Healthy men and women in laboratory study	8 participants transitioned from DS to NS	NS < DS for *PER1* amplitude ($P < 0.001$)	Within-person design	Kervezee et al. (2018)
Clock gene expression	Blood and oral mucosa	Location, NR Male and female police officers Short-term follow-up study	11 participants observed over 1 wk of DS and ES and over 1 wk of NS (5 consecutive 9-h nights and 2 12-h nights)	DS or ES (but not NS) demonstrated significantly increased *PER1–2* and *REV-ERBα* acrophase ($P < 0.05$), and significantly decreased *PER1* acrophase ($P < 0.01$) NS vs DS/ES, *PER1* phase shift ($P < 0.0001$)	None	Koshy et al. (2019)
Clock gene methylation	Blood	Denmark Female participants nested in cohort study Cross-sectional study	19 NS (≥ 10 yr), 98 DS (no history of NS)	NS < DS for *CLOCK* ($P = 0.05$); NS > DS for *CRY2* ($P = 0.04$)	Age, total folate intake	Zhu et al. 2011

Table 4.17 (continued)

End-point	Biosample type	Location, setting, study design	Exposure level, and number of exposed and controls	Response (significance)	Covariates controlled	Reference
Clock gene methylation	Blood	USA Female and male health-care workers Cross-sectional study	59 NS (24 h/wk for ≥ 6 mo), 65 DS	NS < DS (FDR ≤ 0.05) for *CLOCK*, *CSNK1D*, *CSNK1E*, *NPAS2*, *NR1D1*, *PER1*, *PER2*, *PER3*, *RORA*	Age, sex, BMI, race, smoking status, leukocyte cell proliferation Multiple eligibility criteria	Bhatti et al. (2015)
Clock gene methylation	Saliva	Norway Female nurses Case–control study	278 breast cancer cases: 70 never NS, 209 ever NS (28 never ≥ 3 consecutive NS; 41 ≥ 3 consecutive NS for < 5 yr; 140 with ≥ 3 consecutive NS for ≥ 5 yr)	Among cases, ≥ 3 consecutive NS < 5 yr > *BMAL1* methylation ($P = 0.003$); ever NS, never ≥ 3 NS and ≥ 3 consecutive NS ≥ 5 yr < *CRY1* methylation ($P = 0.040$); ≥ 3 NS < 5 yr > *PER1* methylation ($P = 0.035$)	Alcohol (BMAL1), familiar breast cancer (CRY1), years since cancer, alcohol consumption (PER1)	Samulin Erdem et al. (2017b)
Clock gene methylation	Blood	USA Female health-care workers Cross-sectional study	111 NS (≥ 20 h/wk, 8 h per shift for ≥ 6 mo), 86 DS	–	Age, BMI, race, alcohol consumption, smoking, leukocyte cell mixture (FDR ≤ 0.05) Multiple eligibility criteria	Adams et al. (2017)
Clock gene methylation	Blood	Poland Nurses and midwives Cross-sectional study	347 RS (including NS 19:00–07:00), 363 DS	RS < DS for *PER2* ($P = 0.004$); more NS per month < fewer NS per month for *PER2* ($P = 0.012$)	Age, current smoking status, folate intake, blood collection time	Reszka et al. (2018)

–, not significant; BMI, body mass index; d, day; DS, day shift; ES, evening shift; FDR, false discovery rate; h, hour; mo, month; NR, not reported; NS, night shift; RS, rotating shift; vs, versus; wk, week; yr, year.

4.18) reported altered immune response to LPS in *Per2*^{Luc} knock-in mice after alteration in the light–dark schedule (see also Section 4.1.3 (b)). *Per2*$^{m/m}$ mice also have increased small intestinal mucosa β-catenin and cyclin D protein levels and increased numbers of colonic polyps compared with wildtype mice (Wood et al., 2008). Mice deficient in *Bmal1* (*Bmal1*$^{+/-}$), *Cry1* and *Cry2* (*Cry1*$^{-/-}$; *Cry2*$^{-/-}$), *Per1* and *Per2* (*Per1*$^{-/-}$; *Per2*$^{m/m}$), or *Per2* alone (*Per2*$^{-/-}$), kept under alternating light–dark conditions (24-hour light-dark cycles) and irradiated had an increased incidence of cancer (Lee et al., 2010) (see also Section 4.1.7(b)).

Relevant studies evaluating clock genes in experimental systems use different environmental light–dark schedules including: (i) 24-hour light–dark conditions; (ii) continuous exposure to either light or darkness; and (iii) other alterations in the light–dark schedule. Collectively, these studies have shown that changes in the light–dark schedule that result in altered clock gene expression have effects on the immune system, cell proliferation including increased tumour growth, and some changes in receptor-mediated function (Table 4.18). Repeated advances in the light–dark schedule in rats can: alter clock gene expression cytokine cyclicity and function (Castanon-Cervantes et al., 2010; Logan et al., 2012); impair natural NK cytolytic activity (Logan et al., 2012); and, in rats inoculated with mammary adenocarcinoma MADB106 tumour cells, have functional consequences expressed as increased tumour growth (Logan et al., 2012). Advances in the light–dark schedule altered neuropeptide, lipid metabolism, inflammation, and endoplasmic reticulum gene profiles in multiple tissues (Herrero et al., 2015). Increased inflammation also occurred in transgenic mice with altered clock gene expression exposed to alterations in their light–dark schedule (Kim et al., 2018). Effects such as decreased expression of Tp53, increased c-Myc expression, and enhanced growth of transplanted tumours in animals undergoing shifts in the light–dark schedules have also been reported (Filipski et al., 2004, see Table 4.12; Filipski et al., 2005, 2006; Papagiannakopoulos et al., 2016).

4.2.3 Vitamin D

See Table 4.19.

Serum 25-hydroxyvitamin D concentrations lower than 50 nmol/L (20 ng/mL) are usually considered to be insufficient for osteogenesis (Coppeta et al., 2018); such a condition has been reported in shift workers and indoor workers (Coppeta et al., 2018). For instance, Itoh et al. (2011) reported that 9% and 13% of 83 female premenopausal nurses working full-time rotating shifts had a deficient or inadequate vitamin D status after summer/autumn and winter/spring, respectively. Important determinants of vitamin D levels were vitamin D supplement use, use of tanning beds, and season. A rapid, forward rotating work shift roster, including 2–9 nights per month, had little effect on serum vitamin D levels in 67 German nurses (Lehnert et al., 2018). The same result was reported in a smaller Japanese study comparing 14 male workers on a rotating shift schedule including nights (1 morning, 1 afternoon, 1 night, 2 rest days), a rotating shift schedule not including nights, or day shift (Itoh et al., 2011). In a Jordanian study of 140 employees, the mean level of 25-hydroxyvitamin D was 23.8 ng/mL. [The Working Group noted that this would suggest that a substantial portion of this population sample had a level below that affecting bone metabolism, despite living in a middle-eastern country at a temperate latitude.] Levels were lower in female, but not male, night shift workers working at least 4 nights (16:00–07:00) per month for 3 years or more (Alefishat & Abu Farha, 2016). In an Italian study of 96 night shift factory workers engaged in a rapid forward rotating shift schedule (1 morning, 1 afternoon, 1 night, 2 rest days) including 2–3 night shifts per week, mean vitamin D levels were lower than

Table 4.18 Clock gene disruption in response to alterations in the light–dark schedule, mapped to selected key characteristics of carcinogens in experimental systems

Key characteristic	Experimental system	Exposure	Clock gene(s) affected	Relevant finding(s)	Reference
Is immunosuppressive	F344 rat (M) Injected at CT 19 with MADB106 tumour cells	Control: LD12:12 Treatments: 6-h advances in the light–dark schedule every 2 d for a total of 10 advances Other rats, used to assess alteration of circadian expression of cytolytic factors, cytokines, and cytolytic capabilities in NK cells, were killed at six time-points 5–7 d into total darkness, corresponding to CT 3, 7, 11, 19, and 23	Total darkness: ↓ *Per2* and *Bmal1* expression and altered cyclicity in NK cells	Advances in the light–dark schedule altered circadian expression and/or ↓ peak expression of *IFNγ*, perforin, and granzyme B in enriched NK cells, with similar changes in NK cell cytotoxicity and ↓ cytolytic activity; ↑ frequency and prevalence of lung tumours at 6–8 wk; no change in plasma corticosterone levels when measured at CT 7 and CT 19	Logan et al. (2012); see also Table 4.5
Is immunosuppressive	Wistar rat (M)	Control: LD12:12 Treatments: 6-h advance in the light–dark schedule alternated with 6-h delay in the light–dark schedule; one advance or delay every 5 d	Advance in the light–dark schedule: WAT expression of *Bmal1* ↑ and *Per2* ↓	↑ WAT expression of the inflammatory marker Inos; ↑ ER marker Pdi	Herrero et al. (2015)
Induces chronic inflammation	*Per2*^{Luc} knock-in mice (M, F)	Control: LD12:12 Treatments: shift to LD18:6, 1×/wk for 4 wk Intraperitoneal injection of LPS at 12.5 mg/kg bw	*Per2* knock-in	Hypothermia and reduced survival after treatment with LPS with 4 wk of treatment; ↑ serum levels of IL1β, GM-CSF, IL12, and IL13	Castanon-Cervantes et al. (2010); see also Table 4.8
Induces chronic inflammation	*Per2*^{Luc} knock-in mice (M, F)	Control: LD12:12 Treatments: advance in the light–dark schedule by 12 h every 5 d for up to 10 wk	*Per2* knock-in	Altered Per2 cyclicity; ↑ mature macrophages (F4/80^{+} CD11b^{+} cells) and pro-inflammatory M1 macrophages (F4/80^{+} CD11b^{+} CD11c^{+} CD206^{-} cells) in adipose tissue; ↓ anti-inflammatory M2 macrophages in adipose tissue; ↑ *IL1β*, *IL6*, and *TNFα* mRNA levels in adipose tissues	Kim et al. (2018); see also Section 4.1.3(b)

Table 4.18 (continued)

Key characteristic	Experimental system	Exposure	Clock gene(s) affected	Relevant finding(s)	Reference
Modulates receptor-mediated effects	Wistar rat (M)	Control: LD12:12 Treatments: 6-h advance in the light–dark schedule alternated with 6-h delay in the light–dark schedule; one advance or delay every 5 d	Advance in the light–dark schedule: hepatic expression of *Bmal1* ↑ and *Per2* and *Rev-erbα* ↓	↓ Hepatic expression of *Pparα* and *Pparγ*	Herrero et al. (2015)
Alters cell proliferation, cell death, or nutrient supply	*K-ras*$^{LSL-G12D/+}$;*p53*$^{flox/flox}$ or *K-ras*$^{LSL-G12D/+}$ mice Induced lung tumour model	Control: LD12:12 Treatment: advance in the light–dark schedule by 8 h for 13 wk	*Per2* or *Bmal1* knockout	Promoted lung tumour growth and progression, ↑ c-Myc expression, enhanced cell proliferation	Papagiannakopoulos et al. (2016)
Alters cell proliferation, cell death, or nutrient supply	B6D2F$_1$ mice (M) inoculated with Glasgow osteosarcoma	Control: LD12:12 Treatment: advance in the light–dark schedule by 8 h for 10 d	Hepatic expression of *Cry1*, *Bmal1*, *Per2*, and *Rev-erb* ↓	Expression of ↓ p53 and ↑ c-Myc; promoted hepatic tumour growth	Filipski et al. (2005)
Alters cell proliferation, cell death, or nutrient supply	B6D2F$_1$ mice with ablated SCN inoculated with Glasgow osteosarcoma	Control: LD12:12 Treatment: advance in the light–dark schedule by 8 h for 10 d	Hepatic and tumour expression of *Per2* and *Rev-erbα* ↓	Promoted hepatic tumour growth	Filipski et al. (2006)

↑, increase; ↓, decrease; bw, body weight; CT, circadian time; d, day; ER, endoplasmic reticulum; F, female; GM-CSF, granulocyte macrophage colony stimulating factor; h, hour; IL, interleukin; Inos, inducible nitric oxide synthase; LD, light–dark schedule, light(h):darkness(h); LPS, lipopolysaccharide; M, male; MADB, mammary adenocarcinoma B cells; mo, month; mRNA, messenger RNA; NK, natural killer; Pdi, protein disulfide isomerase; *Ppar*; peroxisome proliferator activated receptor; *Rev-erb,* circadian nuclear receptor gene; SCN, suprachiasmatic nuclei; TNFα, tumour necrosis factor alpha; WAT, white adipose tissue; wk, week.

Table 4.19 Serum vitamin D levels in shift workers

Location, setting, study design	Exposure level, and number of exposed cases	Response (significance)	Covariates controlled	Reference
Germany Health-care workers Cross-sectional	47 female forward RS (early, late, NS, including 2–9 nights/mo), 20 female DS	–	Age, season, BMI, smoking status, physical activity	Lehnert et al. (2018)
Japan Metal tool factory workers Cross-sectional	14 male workers: 4 in rapid forward RS, 4 in RS not including nights, and 6 DS	–	Age	Itoh et al. (2011)
Jordan University hospital and non-medical staff Cross-sectional	82 NS (≥ 4 nights/mo for ≥ 3 yr), 58 DS, both sexes	NS < DS ($P = 0.003$)	None	Alefishat & Abu Farha (2016)
Italy Aluminium product-manufacturing plant Cross-sectional	96 NS (working nocturnal hours at least 2×/wk), 100 DS	NS < DS ($P < 0.001$)	Age, smoking status, BMI, waist circumference	Romano et al. (2015)

–, not significant; BMI, body mass index; DS, day shift; mo, month; NS, night shift; RS, rotating shift; wk, week; yr, year.

in those of 100 day workers (13.4 ± 5.3 ng/mL vs 21.9 ± 10.7 ng/mL; $P < 0.001$) (Romano et al., 2015). [The Working Group noted that vitamin D has demonstrated protective effects against cancer development in laboratory animal studies, but findings have been inconsistent in studies in humans; a reduced risk of cancer of the colon or rectum and cancer of the bladder, a higher risk of cancer of the prostate and possibly cancer of the pancreas, and no clear association for most other organ sites have been reported (Mondul et al., 2017).]

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5. SUMMARY OF DATA REPORTED

5.1 Exposure characterization

"Night shift work" involves work, including transmeridian travel, during the regular sleeping hours of the general population. The disruption of circadian rhythms of body functions as a result of alterations in the environmental light–dark schedule is the most pronounced effect of night shift work.

Night shift work is essential for guaranteeing round-the-clock production and activities. In the modern "24/7 society" (24 hours per day, 7 days per week) the nature of night shift work is changing as a result of the diversification of working time patterns. Its prevalence differs between sectors, and occurs most commonly in health care, manufacturing, transport, retail, and services. It is estimated that 1 out of 5 workers worldwide are engaged in night shift work, although definitions, quality, and extent of statistical data vary. Globalization of the labour market has led to increasing use of night shift work in low- and middle-income countries. Regulatory approaches for night shift work and their degree of implementation vary widely across regions and sectors.

Night shift workers may be occupationally co-exposed to biological, chemical, and physical carcinogens (e.g. cosmic radiation exposure in aircrew). In addition, several individual, lifestyle, and environmental factors may mediate, confound, or moderate the potential risk of cancer in night shift workers.

Exposure to night shift work and flying over time zones may be assessed in epidemiological studies with questionnaires, interviews, or diary methods, as well as registry (e.g. payroll) or work schedule data of actual working hours (e.g. flight history records of aircrew). The amount of detail and quality of exposure information on night shift work in epidemiological studies varies considerably between individual studies.

5.2 Cancer in humans

There have been several informative cohort, case–cohort, nested case–control, and case–control studies conducted in specific occupational groups (most predominantly, nurses, and also including aircrew) exposed to night shift work, as well as in the general population. Since the publication of the previous monograph on the subject of night shift work (*IARC Monographs* Volume 98), the number of such studies has grown considerably. The most important development within the body of research has been the refinement and expansion of exposure assessment metrics.

Many of the available studies were of high quality. The largest number of studies examined cancer of the breast, several examined cancer of the prostate and cancer of the colon and rectum, while fewer were conducted on most other cancers, including common cancers such as of the lung or hormone-related cancers such as of the ovary and endometrium.

For cancer of the breast, the majority of the informative cohort studies did not find a positive association with duration of night shift work. The informative nested case–control studies provided support for a positive association between night shift work and risk of cancer of the breast. Findings from the informative case–control studies, including a large, pooled case–control study that incorporated many of the more detailed exposure metrics, provided evidence for positive associations between various exposure metrics of night shift work and risk of cancer of the breast.

The variation in findings between studies could be attributed to differences in exposure assessment or to the inclusion of only older women in some studies, such that they may not be able to determine an effect in younger women.

In summary, there is now a large body of evidence to assess the potential association between night shift work and risk of cancer of the breast. A small minority of the Working Group held the viewpoint that a positive association has not been observed in this body of evidence. The Working Group consensus was that a positive association between night shift work and cancer of the breast has been observed in the body of evidence; however, given the variability in findings between studies, the Working Group were unable to exclude with reasonable confidence bias as an explanation.

Studies on cancer of the prostate include several studies in the general population, industrial cohort studies, population-based case–control studies, and one study in airplane cockpit crew. Several of these studies found positive associations between exposure to night shift work and the risk of cancer of the prostate, particularly in association with longer durations of exposure; however, other studies reported no, or a very small, increased risk when examining ever versus never exposure to night shift work. Overall, the Working Group found that there is suggestive evidence that risk of cancer of the prostate is positively associated with night shift work; however, because of the relatively small number of studies and lack of consistent results with the same exposure metrics, chance and bias could not be ruled out with reasonable confidence.

Several cohort and case–control studies of night shift work and cancer of the colon and rectum have been conducted. The majority of the well-designed and informative studies found positive associations between exposure to night shift work and risk of cancer of the colon and rectum, particularly in association with longer durations of exposure. However, the elevated risks observed with longer durations of exposure were moderate in magnitude, and some findings were not consistent between studies. Overall, the Working Group found that there is some evidence suggesting that the risk of cancer of the colon and rectum is positively associated with exposure to shift work involving night work; however, because of the small number of studies and lack of consistency in their results, chance and bias could not be ruled out with reasonable confidence.

The Working Group determined that no conclusions could be made for any of the other cancers, because of either the small number of studies reporting results, inconsistencies in the findings, or the use of weak methods for assessing exposure to night shift work.

5.3 Cancer in experimental animals

In one article reporting on a series of well-designed lifetime studies using both male and female mice (and considered key to the evaluation of alteration in the light–dark schedule), shifts in the light–dark schedule significantly increased the incidence of hepatocellular carcinoma in wildtype and two different knockout mouse models. In one well-designed lifetime study in female mice exposed to continuous light (and considered key to the evaluation of

alteration in the light–dark schedule), significant increases in the incidence of malignant lymphoma, lung adenocarcinoma, and total tumours were observed.

Shifts in the light–dark schedule increased mammary tumour weight in one study and decreased tumour latency in another study in cancer-prone transgenic mice. A lifetime study in female rats exposed to shifts in the light–dark schedule gave negative results.

In a lifetime study in female transgenic mice prone to cancer of the mammary gland and exposed to continuous light, the multiplicity of adenocarcinoma of the mammary gland was significantly increased.

In two lifetime studies, one in male and female rats and one in female rats, the animals were exposed to natural light–dark alterations, with light durations ranging from 4 hours in winter to 24 hours (continuous light) in summer. In the study in male and female rats, significant increases in the incidence of benign mammary gland tumours and of total tumours were observed in female rats exposed to natural light–dark alterations. A significant increase in the incidence of benign tumours (mainly mammary gland tumours) was observed in the study in female rats exposed to natural light–dark alterations.

In one of two studies with limited experimental details, female mice exposed for life to continuous light demonstrated an increase in the incidence of tumours of the mammary gland. No increase was observed in the second study in another mouse strain. One lifetime study in female mice and one lifetime study in male and female rats exposed to continuous light gave negative results.

Studies have been reported in which the effects of continuous light were evaluated in rats or mice exposed to a chemical carcinogen. In most studies, tumour incidence and/or multiplicity were compared in carcinogen-treated groups exposed to either continuous light or to a normal light–dark schedule. Studies reported in nine publications were performed to investigate the effects of continuous light on the induction of mammary tumours in carcinogen-treated female rats. Exposure to continuous light increased the incidence and/or multiplicity of mammary tumours in four out of nine studies; the other five studies gave negative results, and one reported decreased incidence of mammary tumours in rats exposed to continuous light. The effects of continuous light on carcinogen-induced tumorigenesis in other organs were evaluated in a total of three studies. In a two-generation study in rats, continuous light enhanced the induction of tumours of the peripheral nervous system and of the kidney. In two studies in male rats, effects on hepatocarcinogenesis and colon carcinogenesis were less convincing; no significant differences in tumour incidence were observed in either study.

Seven of eight studies in transplantable or carcinogen-induced tumour models provide evidence that shifts in the light–dark schedule increase the rate of tumour growth in mice and rats. In a first study, shifts in the light–dark schedule significantly increased the growth rate of 3-methylcholanthrene-induced tumours in male mice. In a second study, significantly increased multiplicity of diethylnitrosamine-induced liver tumours was observed in male mice. In a third study, a significantly increased rate of syngeneic sarcoma growth was observed in male mice. In two other studies, significantly increased osteosarcoma growth rates were observed in male mice. In a sixth study, significantly increased growth rates of syngeneic lung carcinoma were observed in male mice; a significant increase in lung metastases was also observed. In a seventh study, significantly increased incidence of lung metastases of a syngeneic mammary tumour was observed in male rats.

Studies have been reported in which the effects of continuous light were evaluated in mice

or rats injected with tumour cells. In one study in mice injected subcutaneously with tumour cells, continuous light accelerated tumour progression. In two studies in male mice subcutaneously injected with human cervical adenocarcinoma cells or human prostatic carcinoma cells, and exposed to continuous light, there was a significant increase in tumour growth. In a study in immunodeficient female rats inoculated with human breast cancer cells and in a study in male rats inoculated with rat glioma cells, there were significant increases in tumour growth rate, tumour volume, and tumour weight in rats exposed to continuous light. In a study in male rats transplanted with syngeneic hepatocarcinoma and in a study in immunodeficient female rats inoculated with human breast cancer cells, significant increases in tumour growth were observed in rats exposed to continuous light. In two studies in immunodeficient female rats exposed to dim light during the dark phase and inoculated with human breast cancer cells, there were significant increases in tumour growth. In a study in male rats transplanted with syngeneic hepatocarcinoma and exposed to standard light regimen, dim light during the dark phase, or constant light, a significant positive linear relationship was observed between light intensity and tumour growth.

5.4 Mechanistic evidence

With respect to the key characteristics of carcinogens, available evidence comprised end-points relevant to whether night shift work induces oxidative stress; is immunosuppressive; induces chronic inflammation; is genotoxic; induces epigenetic effects (including on clock genes); modulates receptor-mediated effects (i.e. relevant to endocrine hormones); alters cell proliferation, cell death, and nutrient supply; and causes immortalization. Considerations included the consistency of results across studies of similar end-points and designs, and coherence across studies of similar end-points. Some studies of night shift work reported elevated levels of oxidative stress markers or decreased antioxidant capacity, while some reported null findings, and positive results were not always replicated for the same end-points across studies. Many of the available studies had limitations, including small sample sizes and insufficient descriptions of exposure. Studies in experimental systems also had mixed findings, which may be due in part to the use of different exposure scenarios and experimental end-points. Many of these studies evaluated short-term responses and relied on the measurement of outcomes at single time-points.

Several studies demonstrated an increased occurrence of self-reported infectious disease in shift workers, suggestive of immunosuppression. Results for markers of immune function and inflammation were mixed, and the studies had several limitations, including small sample sizes, lack of adjustment for potential confounding factors, and issues around timing of biospecimen collection. Multiple studies in rodents exposed to alterations in the light–dark schedule demonstrated immune suppression in nocturnal rats, mice, and hamsters, and immune enhancement in a diurnal rodent. Experimentally induced alteration in the light–dark schedule has been shown to enhance inflammation in studies in rodents and in models of inflammatory disease. Overall, these studies provide consistent and coherent evidence that alteration of the light–dark schedule modulates the immune response in experimental systems.

Studies of genotoxicity in night shift workers, including those providing positive findings, were available only for aircrew, and these studies were uninformative due to confounding by exposure to ionizing radiation. No studies were available in experimental systems. A few studies in humans and several in experimental animals showed epigenetic effects; however, they covered a narrow range of end-points and the results were inconsistent.

A number of studies evaluated the effect of night shift work on blood levels of estrogens, providing suggestive evidence. There was a set of five studies with positive results, including two large studies nested in cohorts of nurses. There were also studies with negative results, one of which was from a large and well-controlled study of nurses. In a few studies, night shift workers showed an increased risk of hypothyroidism. For hormones other than melatonin, estrogen, and thyroid, the studies were few in number and the results were inconsistent. In experimental systems, estrogen levels were evaluated in multiple species in response to alteration in the light–dark schedule, but the results were inconsistent.

No data on alterations in cell proliferation, cell death, or nutrient supply were available from studies in humans. In experimental animals, a few studies that directly measured cell proliferation showed that it increased in transplanted tumours after alterations in the light–dark schedule. Additional studies using inoculated tumour cells or exposures to carcinogens in rodents exposed to changes in the light–dark schedule showed increased tumour growth consistent with cell proliferation. One study in female nude rats showed an impact of alteration in the light–dark schedule on tumour glucose metabolism (Warburg effect in tumours).

Studies in night shift workers were mostly consistent in showing telomere shortening, but they were few in number. One study in a diurnal rodent model showed telomere shortening in response to an alteration in the light–dark schedule.

With regard to other relevant evidence, melatonin is an important regulator of circadian rhythms and a biomarker of circadian disruption in both humans and animals. There is consistent evidence that night shift work suppresses melatonin levels in humans, from multiple cross-sectional studies across different occupations. This is consistent with evidence that light at night decreases melatonin production in most of the studies in experimental animals.

Few studies in humans of night shift work and clock gene expression and methylation were identified, and results varied across the studies. This may be attributable, at least in part, to differences in study design, including genes evaluated, sample sizes, eligibility criteria, and the shift work schedules under consideration. Studies in experimental systems show that the expression of clock genes is altered in response to shifts in the light–dark schedule, and are associated with cell proliferation or tumour growth.

To summarize, the mechanistic evidence is consistent and coherent with respect to the key characteristics of carcinogens on the basis of effects consistent with immunosuppression, chronic inflammation, and cell proliferation in experimental systems. In exposed humans, there is suggestive evidence for effects on estrogen levels in female night shift workers. In humans and in experimental systems, there is robust and consistent evidence of changes in melatonin in response to alterations in the light–dark schedule.

6. EVALUATION AND RATIONALE

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of night shift work. Positive associations have been observed between night shift work and cancers of the breast, prostate, colon, and rectum.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of alteration in the light–dark schedule.

6.3 Mechanistic evidence

There is *strong evidence* in experimental systems that alteration in the light–dark schedule exhibits key characteristics of carcinogens, based on evidence of effects consistent with immunosuppression, chronic inflammation, and cell proliferation.

6.4 Overall evaluation

Night shift work is *probably carcinogenic to humans* (Group 2A).

6.5 Rationale

In reaching the Group 2A evaluation, the Working Group considered the bodies of evidence related to exposure characterization, cancer in humans, cancer in experimental animals, and mechanistic evidence.

A large number of informative studies on cancer in humans were evaluated. A key aspect of the informativeness of the studies was the quality of the exposure assessment methods, which varied considerably, particularly across studies of different designs. In general, the case–control studies were given greater prominence in the overall evaluation due to their stronger exposure assessments. The largest and highest-quality case–control studies observed positive associations between night shift work and cancers of breast, prostate, colon, and rectum. However, results were inconsistent among cohort studies for these cancer types. Thus, the Working Group evaluated the evidence as *limited* for these cancers.

Based on reports of lifetime carcinogenicity bioassays from two laboratories, the Working Group concluded that there is *sufficient evidence* in experimental animals for the carcinogenicity of alteration in the light–dark schedule. In a first report, three mouse strains – including one wild-type strain – exposed to shifts in the light–dark schedule demonstrated significant increases in the incidence of hepatocellular carcinoma compared with strain-specific control groups exposed to a 12 hour light–12 hour dark cycle. In the second report, mice from a second wild-type strain exposed to continuous light demonstrated significant increases in the incidence of malignant lymphoma, lung adenocarcinoma,

and total tumours compared with a control group exposed to a 12 hour light–12 hour dark cycle. Several other studies supported the carcinogenicity of alterations in the light–dark schedule seen in the lifetime bioassays.

Studies of night shift work in humans and alteration in the light–dark schedule in experimental animals provided evidence relevant to key characteristics of carcinogens. Experimental designs and selection of end-points as they relate to each of these key characteristics varied for both streams of evidence. Findings for certain key characteristics were sometimes discordant, and this lack of coherence could not always be explained in both streams of evidence. The Working Group did find support for a conclusion of *strong evidence* in experimental systems, based on findings consistent with immunosuppression, chronic inflammation, and cell proliferation. There was suggestive evidence of alterations in estrogen homeostasis in female night shift workers.

LIST OF ABBREVIATIONS

6-OHMS	6-hydroxymelatonin sulfate
8-OHdG	8-hydroxy-2′-deoxyguanosine
13-HODE	13-hydroxyoctadecadienoic acid
24/7	24 hours per day, 7 days per week
aMT6s	6-sulfatoxymelatonin
BAP	biological antioxidant potential
BMI	body mass index
bw	body weight
C171	(ILO) Night Work Convention, 1990 (No. 171)
CAT	catalase
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CMR	carcinogenic, mutagenic, and reprotoxic
CNS	central nervous system
CRP	C-reactive protein
CYP	cytochrome P450
DEN	diethylnitrosamine
DMBA	7,12-dimethylbenz[*a*]anthracene
DNFB	2,4-dinitro-1-fluorobenzene
d-ROM	reactive oxygen metabolite-derived compound
DSS	dextran sodium sulfate
DTH	delayed-type hypersensitivity
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
ERR	excess relative risk
EU	European Union
FSH	follicle-stimulating hormone
GH	growth hormone
GSH-Px	glutathione peroxidase
h	hour
HeLa	human cervical cancer cell
HER2	human epidermal growth factor 2
HR	hazard ratio
ICAO	International Civil Aviation Organization

IFN	interferon
IL	interleukin
ILO	International Labour Organization
JEM	job-exposure matrix
LD	light–dark schedule
LD0:24	continuous darkness
LD10:14	10 hours of light followed by 14 hours of darkness
LD12:12	12 hours of light followed by 12 hours of darkness
LD24:0	continuous light
LH	luteinizing hormone
LPS	lipopolysaccharide
MCC-Spain	multicase–control Spain study
MDA	malondialdehyde
MDSC	myeloid-derived suppressor cell
miRNA	microRNA
MNU	*N*-methyl-*N*-nitrosourea
mRNA	messenger RNA
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NHS	Nurses' Health Study
NK	natural killer
NL	natural light
OR	odds ratio
OSI	total oxidative stress index
PC3	human prostate cancer cell
PCNA	proliferating cell nuclear antigen
PIP	prolactin-induced protein
PR	progesterone receptor
PRL	prolactin
R178	(ILO) Night Work Recommendation, 1990 (No. 178)
RNU	Rowett nude
RR	relative risk or rate ratio
Rsg16	regulator of G protein signalling-16
SCN	suprachiasmatic nucleus
SIR	standardized incidence ratio
SNP	single-nucleotide polymorphism
SOD	superoxide dismutase
SRBCs	sheep red blood cells
SRR	standardized rate ratio
TAC	total antioxidant capacity
TAS	total antioxidant status
TERT	telomerase reverse transcriptase
TNFα	tumour necrosis factor alpha
TOS	total oxidative status
vs	versus
wk	week
WTD	European Working Time Directive No. 2003/88/EC
yr	year

ANNEX 1. SUPPLEMENTARY MATERIAL FOR SECTION 1, EXPOSURE DATA

The supplementary web-only tables presented in Annex 1 (available from: http://publications.iarc.fr/593, and listed below) were produced in draft form by the Working Group and were subsequently fact-checked but not edited. Please report any errors to imo@iarc.fr.

Table S1.4 Legislation on night work by country

Table S1.7 Exposure assessment quality in cohort and nested case–control studies of cancer of the breast among night shift workers other than aircrew

Table S1.8 Exposure assessment quality in case–control studies of cancer of the breast among night shift workers other than aircrew

Table S1.9 Exposure assessment quality in studies of cancer of the prostate among night shift workers other than aircrew

Table S1.10 Exposure assessment quality in studies of cancer of the colon and rectum among night shift workers other than aircrew

Table S1.11 Exposure assessment quality in studies of cancer at other organ sites among night shift workers other than aircrew

Table S1.12 Exposure assessment quality in studies of cancer among aircraft cockpit crew

Table S1.13 Exposure assessment quality in studies of cancer among aircraft cabin crew

ANNEX 2. SUPPLEMENTARY MATERIAL FOR SECTION 2, CANCER IN HUMANS

The supplementary web-only text and table presented in Annex 2 (available from: http://publications.iarc.fr/593, and listed below) were produced in draft form by the Working Group and were subsequently fact-checked but not edited. Please report any errors to imo@iarc.fr.

Descriptions of individual studies contributing to the pooled case–control study by Cordina-Duverger et al. (2018)

Table S2.1 Case–control studies of cancer of the breast included in the pooled case–control study by Cordina-Duverger et al. (2018)

Reference

Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, et al. (2018). Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol.* 33(4):369–79. doi:10.1007/s10654-018-0368-x PMID:29464445

IARC MONOGRAPHS

This volume of the *IARC Monographs* provides an evaluation of the carcinogenicity of night shift work, that is, work occurring during the regular sleeping hours of the general population. Globally, an estimated one out of five workers is engaged in regular night shift work, with percentages increasing over time in some countries. Night shift work is most common in the following industry sectors: transportation (for example, aircrew and truck drivers on long-haul trips), health care, manufacturing, and services (for example, social assistance, accommodation and food services, information and communications, travel and tourism).

An *IARC Monographs* Working Group reviewed studies of cancer in people exposed to night shift work (including transmeridian air travel), studies of cancer in experimental animals exposed to shifts in the light–dark schedule, and mechanistic evidence in both exposed humans and experimental systems. The review of the present Working Group was the first to be guided by the amended Preamble to the *IARC Monographs*, which was substantially updated in 2019.