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):			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)
		Never	925	1		
		1–14 yr	1324	1.08 (0.99–1.18)		
		15–29 yr	134	1.08 (0.90–1.30)		
		≥ 30 yr	58	1.36 (1.04–1.78)		
		Trend test *P* value, 0.02				
		Rotating night shift work history at baseline, premenopausal (RR):				
		Never	121	1		
		1–14 yr	174	1.23 (0.97–1.55)		
		≥ 15 yr	14	1.34 (0.77–2.33)		
		Trend test *P* value, 0.12				
		Rotating night shift work history at baseline, postmenopausal (RR):				
		Never	801	1		
		1–14 yr	1146	1.06 (0.97–1.16)		
		15–29 yr	120	1.05 (0.87–1.27)		
		≥ 30 yr	58	1.36 (1.04–1.78)		
		Trend test *P* value, 0.05				

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): Day shift only Shift without night Shift with night Type of work schedule, age < 60 yr (HR) Day shift only Shift without night Shift with night	 60 20 14 NR 17 12	 1 1.23 (0.70–2.17) 2.02 (1.03–3.95) 1 1.18 (0.67–2.07) 2.15 (1.1–4.21)	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

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): Never Ever Night/shift work, premenopausal (OR): Never Ever Night/shift work, postmenopausal (OR): Never Ever 1 hour-year increase of night/shift work (OR): 1 hour-year increase of night/shift work Trend test *P* value, 0.03	 360 41 128 19 232 22 NR	 1 1.38 (1.04–2.71) 1 1.33 (0.85–3.55) 1 1.4 (0.92–3.21) 1.15 (1.07–2.62)	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

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):			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
			Per 1000 h	125	1.08 (0.95–1.21)		
		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):			Age, race and/or ethnicity, HRT status, parity, age at first birth	
			Per 515 h	43	0.9 (0.79–1)		
		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.

References

Åkerstedt T, Knutsson A, Narusyte J, Svedberg P, Kecklund G, Alexanderson K (2015). Night work and breast cancer in women: a Swedish cohort study. *BMJ Open*, 5(4):e008127. doi:10.1136/bmjopen-2015-008127 PMID:25877283

Åkerstedt T, Narusyte J, Svedberg P, Kecklund G, Alexanderson K (2017). Night work and prostate cancer in men: a Swedish prospective cohort study. *BMJ Open*, 7(6):e015751. doi:10.1136/bmjopen-2016-015751 PMID:28600375

Alguacil J, Pollán M, Gustavsson P (2003). Occupations with increased risk of pancreatic cancer in the Swedish population. *Occup Environ Med*, 60(8):570–6. doi:10.1136/oem.60.8.570 PMID:12883017

Ballard T, Lagorio S, De Angelis G, Verdecchia A (2000). Cancer incidence and mortality among flight personnel: a meta-analysis. *Aviat Space Environ Med*, 71(3):216–24. PMID:10716165

Ballard TJ, Lagorio S, De Santis M, De Angelis G, Santaquilani M, Caldora M, et al. (2002). A retrospective cohort mortality study of Italian commercial airline cockpit crew and cabin attendants, 1965-96. *Int J Occup Environ Health*, 8(2):87–96. doi:10.1179/oeh.2002.8.2.87 PMID:12019685

Band PR, Le ND, Fang R, Deschamps M, Coldman AJ, Gallagher RP, et al. (1996). Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. *Am J Epidemiol*, 143(2):137–43. doi:10.1093/oxfordjournals.aje.a008722 PMID:8546114

Band PR, Spinelli JJ, Ng VT, Moody J, Gallagher RP (1990). Mortality and cancer incidence in a cohort of commercial airline pilots. *Aviat Space Environ Med*, 61(4):299–302. PMID:2339962

Barul C, Richard H, Parent M-E (2019). Night-shift work and risk of prostate cancer: results from a Canadian case-control study, the Prostate Cancer and Environment Study. *Am J Epidemiol*, 188(10):1801–11. doi:10.1093/aje/kwz167 PMID:31360990

Behrens T, Rabstein S, Wichert K, Erbel R, Eisele L, Arendt M, et al. (2017). Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. *Scand J Work Environ Health*, 43(6):560–8. doi:10.5271/sjweh.3666 PMID:28879368

Bhatti P, Cushing-Haugen KL, Wicklund KG, Doherty JA, Rossing MA (2013). Nightshift work and risk of ovarian cancer. *Occup Environ Med*, 70(4):231–7. doi:10.1136/oemed-2012-101146 PMID:23343856

Blettner M, Zeeb H, Auvinen A, Ballard TJ, Caldora M, Eliasch H, et al. (2003). Mortality from cancer and other causes among male airline cockpit crew in Europe. *Int J Cancer*, 106(6):946–52. doi:10.1002/ijc.11328 PMID:12918075

Blettner M, Zeeb H, Langner I, Hammer GP, Schafft T (2002). Mortality from cancer and other causes among airline cabin attendants in Germany, 1960-1997. *Am J Epidemiol*, 156(6):556–65. doi:10.1093/aje/kwf083 PMID:12226003

Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM (2014). Coronary artery disease and cancer mortality in a cohort of workers exposed to vinyl chloride, carbon disulfide, rotating shift work, and *o*-toluidine at a chemical manufacturing plant. *Am J Ind Med*, 57(4):398–411. doi:10.1002/ajim.22299 PMID:24464642

Carter BD, Diver WR, Hildebrand JS, Patel AV, Gapstur SM (2014). Circadian disruption and fatal ovarian cancer. *Am J Prev Med*, 46(3 Suppl 1):S34–41. doi:10.1016/j.amepre.2013.10.032 PMID:24512929

Conlon M, Lightfoot N, Kreiger N (2007). Rotating shift work and risk of prostate cancer. *Epidemiology*, 18(1):182–3. doi:10.1097/01.ede.0000249519.33978.31 PMID:17179764

Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, et al. (2016). Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. *Chronobiol Int*, 33(6):783–7. doi:10.3109/07420528.2016.1167709 PMID:27078711

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

Costas L, Benavente Y, Olmedo-Requena R, Casabonne D, Robles C, Gonzalez-Barca EM, et al. (2016). Night shift work and chronic lymphocytic leukemia in the MCC-Spain case-control study. *Int J*

Cancer, 139(9):1994–2000. doi:10.1002/ijc.30272 PMID:27416551

Datta K, Roy A, Nanda D, Das I, Guha S, Ghosh D, et al. (2014). Association of breast cancer with sleep pattern–a pilot case control study in a regional cancer centre in South Asia. *Asian Pac J Cancer Prev*, 15(20):8641–5. doi:10.7314/APJCP.2014.15.20.8641 PMID:25374182

Davis S, Mirick DK, Stevens RG (2001). Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*, 93(20):1557–62. doi:10.1093/jnci/93.20.1557 PMID:11604479

De Stavola BL, Pizzi C, Clemens F, Evans SA, Evans AD, dos Santos Silva I (2012). Cause-specific mortality in professional flight crew and air traffic control officers: findings from two UK population-based cohorts of over 20,000 subjects. *Int Arch Occup Environ Health*, 85(3):283–93. doi:10.1007/s00420-011-0660-5 PMID:21674252

Devore EE, Massa J, Papantoniou K, Schernhammer ES, Wu K, Zhang X, et al. (2017). Rotating night shift work, sleep, and colorectal adenoma in women. *Int J Colorectal Dis*, 32(7):1013–8. doi:10.1007/s00384-017-2758-z PMID:28097381

Dickerman BA, Markt SC, Koskenvuo M, Hublin C, Pukkala E, Mucci LA, et al. (2016). Sleep disruption, chronotype, shift work, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. *Cancer Causes Control*, 27(11):1361–70. doi:10.1007/s10552-016-0815-5 PMID:27734240

dos Santos Silva I, De Stavola B, Pizzi C, Evans AD, Evans SA (2013). Cancer incidence in professional flight crew and air traffic control officers: disentangling the effect of occupational versus lifestyle exposures. *Int J Cancer*, 132(2):374–84. doi:10.1002/ijc.27612 PMID:22532267

Du HB, Bin KY, Liu WH, Yang FS (2017). Shift work, night work, and the risk of prostate cancer: A meta-analysis based on 9 cohort studies. *Medicine (Baltimore)*, 96(46):e8537. doi:10.1097/MD.0000000000008537 PMID:29145258

Erren TC (2013). Shift work and cancer research: can chronotype predict susceptibility in night-shift and rotating-shift workers? *Occup Environ Med*, 70(4):283–4. doi:10.1136/oemed-2012-100984 PMID:23343857

Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, et al. (2013). The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer*, 109(9):2472–80. doi:10.1038/bjc.2013.544 PMID:24022188

Fritschi L, Valérie Groß J, Wild U, Heyworth JS, Glass DC, Erren TC (2018). Shift work that involves circadian disruption and breast cancer: a first application of chronobiological theory and the consequent challenges. *Occup Environ Med*, 75(3):231–4. doi:10.1136/oemed-2017-104441 PMID:28775132

Gan Y, Li L, Zhang L, Yan S, Gao C, Hu S, et al. (2018). Association between shift work and risk of prostate cancer: a systematic review and meta-analysis of observational studies. *Carcinogenesis*, 39(2):87–97. doi:10.1093/carcin/bgx129 PMID:29126152

Gapstur SM, Diver WR, Stevens VL, Carter BD, Teras LR, Jacobs EJ (2014). Work schedule, sleep duration, insomnia, and risk of fatal prostate cancer. *Am J Prev Med*, 46(3 Suppl 1):S26–33. doi:10.1016/j.amepre.2013.10.033 PMID:24512928

Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, et al. (2018). Evaluating the Association between Artificial Light-at-Night Exposure and Breast and Prostate Cancer Risk in Spain (MCC-Spain Study). *Environ Health Perspect*, 126(4):047011 doi:10.1289/EHP1837 PMID:29687979

Grayson JK, Lyons TJ (1996a). Brain cancer, flying, and socioeconomic status: a nested case-control study of USAF aircrew. *Aviat Space Environ Med*, 67(12):1152–4. PMID:8968480

Grayson JK, Lyons TJ (1996b). Cancer incidence in United States Air Force aircrew, 1975-89. *Aviat Space Environ Med*, 67(2):101–4. PMID:8834932

Grundy A, Richardson H, Burstyn I, Lohrisch C, SenGupta SK, Lai AS, et al. (2013a). Increased risk of breast cancer associated with long-term shift work in Canada. *Occup Environ Med*, 70(12):831–8. doi:10.1136/oemed-2013-101482 PMID:23817841

Grundy A, Schuetz JM, Lai AS, Janoo-Gilani R, Leach S, Burstyn I, et al. (2013b). Shift work, circadian gene variants and risk of breast cancer. *Cancer Epidemiol*, 37(5):606–12. doi:10.1016/j.canep.2013.04.006 PMID:23725643

Gu F, Han J, Laden F, Pan A, Caporaso NE, Stampfer MJ, et al. (2015). Total and cause-specific mortality of U.S. nurses working rotating night shifts. *Am J Prev Med*, 48(3):241–52. doi:10.1016/j.amepre.2014.10.018 PMID:25576495

Gudmundsdottir EM, Hrafnkelsson J, Rafnsson V (2017). Incidence of cancer among licenced commercial pilots flying North Atlantic routes. *Environ Health*, 16(1):86. doi:10.1186/s12940-017-0295-4 PMID:28814301

Gundestrup M, Storm HH (1999). Radiation-induced acute myeloid leukaemia and other cancers in commercial jet cockpit crew: a population-based cohort study. *Lancet*, 354(9195):2029–31. doi:10.1016/S0140-6736(99)05093-X PMID:10636367

Gyarmati G, Turner MC, Castaño-Vinyals G, Espinosa A, Papantoniou K, Alguacil J, et al. (2016). Night shift work and stomach cancer risk in the MCC-Spain study. *Occup Environ Med*, 73(8):520–7. doi:10.1136/oemed-2016-103597 PMID:27312400

Haldorsen T, Reitan JB, Tveten U (2000). Cancer incidence among Norwegian airline pilots. *Scand J Work Environ Health*, 26(2):106–11. doi:10.5271/sjweh.519 PMID:10817375

Haldorsen T, Reitan JB, Tveten U (2001). Cancer incidence among Norwegian airline cabin attendants. *Int J Epidemiol*, 30(4):825–30. doi:10.1093/ije/30.4.825 PMID:11511611

Haldorsen T, Reitan JB, Tveten U (2002). Aircraft accidents and other causes of death among Norwegian commercial pilots. *Aviat Space Environ Med*, 73(6):587–92. PMID:12056676

Hammar N, Linnersjö A, Alfredsson L, Dammström BG, Johansson M, Eliasch H (2002). Cancer incidence in airline and military pilots in Sweden 1961-1996. *Aviat Space Environ Med*, 73(1):2–7. PMID:11817615

Hammer GP, Auvinen A, De Stavola BL, Grajewski B, Gundestrup M, Haldorsen T, et al. (2014). Mortality from cancer and other causes in commercial airline crews: a joint analysis of cohorts from 10 countries. *Occup Environ Med*, 71(5):313–22. doi:10.1136/oemed-2013-101395 PMID:24389960

Hammer GP, Blettner M, Langner I, Zeeb H (2012). Cosmic radiation and mortality from cancer among male German airline pilots: extended cohort follow-up. *Eur J Epidemiol*, 27(6):419–29. doi:10.1007/s10654-012-9698-2 PMID:22678613

Hammer GP, Emrich K, Nasterlack M, Blettner M, Yong M (2015). Shift work and prostate cancer incidence in industrial workers: a historical cohort study in a German chemical company. *Dtsch Arztebl Int*, 112(27–28):463–70. PMID:26214232

Hansen J (2001). Increased breast cancer risk among women who work predominantly at night. *Epidemiology*, 12(1):74–7. doi:10.1097/00001648-200101000-00013 PMID:11138824

Hansen J, Lassen CF (2012). Nested case-control study of night shift work and breast cancer risk among women in the Danish military. *Occup Environ Med*, 69(8):551–6. doi:10.1136/oemed-2011-100240 PMID:22645325

Hansen J, Stevens RG (2012). Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer*, 48(11):1722–9. doi:10.1016/j.ejca.2011.07.005 PMID:21852111

He C, Anand ST, Ebell MH, Vena JE, Robb SW (2015). Circadian disrupting exposures and breast cancer risk: a meta-analysis. *Int Arch Occup Environ Health*, 88(5):533–47. doi:10.1007/s00420-014-0986-x PMID:25261318

Heckman CJ, Kloss JD, Feskanich D, Culnan E, Schernhammer ES (2017). Associations among rotating night shift work, sleep and skin cancer in Nurses' Health Study II participants. *Occup Environ Med*, 74(3):169–75. doi:10.1136/oemed-2016-103783 PMID:27663986

Horne JA, Ostberg O (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*, 4(2):97–110. PMID:1027738

Horne JA, Ostberg O (1977). Individual differences in human circadian rhythms. *Biol Psychol*, 5(3):179–90. doi:10.1016/0301-0511(77)90001-1 PMID:922076

IARC (2010). Painting, firefighting, and shiftwork. *IARC Monogr Eval Carcinog Risks Hum*, 98:1–804. Available from: http://publications.iarc.fr/116 PMID:21381544

Ijaz S, Verbeek J, Seidler A, Lindbohm ML, Ojajärvi A, Orsini N, et al. (2013). Night-shift work and breast cancer–a systematic review and meta-analysis. *Scand J Work Environ Health*, 39(5):431–47. doi:10.5271/sjweh.3371 PMID:23804277

Irvine D, Davies DM (1992). The mortality of British Airways pilots, 1966-1989: a proportional mortality study. *Aviat Space Environ Med*, 63(4):276–9. PMID:1610337

Irvine D, Davies DM (1999). British Airways flightdeck mortality study, 1950-1992. *Aviat Space Environ Med*, 70(6):548–55. PMID:10373044

Jia Y, Lu Y, Wu K, Lin Q, Shen W, Zhu M, et al. (2013). Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol*, 37(3):197–206. doi:10.1016/j.canep.2013.01.005 PMID:23403128

Jones ME, Schoemaker MJ, McFadden EC, Wright LB, Johns LE, Swerdlow AJ (2019). Night shift work and risk of breast cancer in women: the Generations Study cohort. *Br J Cancer*, 121(2):172–9. doi:10.1038/s41416-019-0485-7 PMID:31138896

Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ (2017). Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health*, 43(2):117–26. doi:10.5271/sjweh.3612 PMID:28245504

Kaji M, Tango T, Asukata I, Tajima N, Yamamoto K, Yamamoto Y, et al. (1993). Mortality experience of cockpit crewmembers from Japan Airlines. *Aviat Space Environ Med*, 64(8):748–50. PMID:8368989

Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J (2013). Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*, 138(1):291–301. doi:10.1007/s10549-013-2433-1 PMID:23400581

Kjaer TK, Hansen J (2009). Cancer incidence among large cohort of female Danish registered nurses. *Scand J Work Environ Health*, 35(6):446–53. doi:10.5271/sjweh.1358 PMID:19806273

Knutsson A, Alfredsson L, Karlsson B, Akerstedt T, Fransson EI, Westerholm P, et al. (2013). Breast cancer among shift workers: results of the WOLF longitudinal cohort study. *Scand J Work Environ Health*, 39(2):170–7. doi:10.5271/sjweh.3323 PMID:23007867

Kogevinas M, Espinosa A, Papantoniou K, Aragonés N, Pérez-Gómez B, Burgos J, et al. (2019). Prostate cancer risk decreases following cessation of night shift work. *Int J Cancer*, 145(9):2597–9. doi:10.1002/ijc.32528 PMID:31232468

Kojo K, Pukkala E, Auvinen A (2005). Breast cancer risk among Finnish cabin attendants: a nested case-control study. *Occup Environ Med*, 62(7):488–93. doi:10.1136/oem.2004.014738 PMID:15961626

Koppes LL, Geuskens GA, Pronk A, Vermeulen RC, de Vroome EM (2014). Night work and breast cancer risk in a general population prospective cohort study in The Netherlands. *Eur J Epidemiol*, 29(8):577–84. doi:10.1007/s10654-014-9938-8 PMID:25012051

Kubo T, Oyama I, Nakamura T, Kunimoto M, Kadowaki K, Otomo H, et al. (2011). Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. *Int J Urol*, 18(3):206–11. doi:10.1111/j.1442-2042.2010.02714.x PMID:21332815

Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, et al. (2006). Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol*, 164(6):549–55. doi:10.1093/aje/kwj232 PMID:16829554

Kwon P, Lundin J, Li W, Ray R, Littell C, Gao D, et al. (2015). Night shift work and lung cancer risk among female textile workers in Shanghai, China. *J Occup Environ Hyg*, 12(5):334–41. doi:10.1080/15459624.2014.993472 PMID:25616851

Lahti TA, Partonen T, Kyyrönen P, Kauppinen T, Pukkala E (2008). Night-time work predisposes to non-Hodgkin lymphoma. *Int J Cancer*, 123(9):2148–51. doi:10.1002/ijc.23566 PMID:18697199

Langner I, Blettner M, Gundestrup M, Storm H, Aspholm R, Auvinen A, et al. (2004). Cosmic radiation and cancer mortality among airline pilots: results from a European cohort study (ESCAPE). *Radiat Environ Biophys*, 42(4):247–56. doi:10.1007/s00411-003-0214-7 PMID:14648170

Lee T, Taubman SB, Williams VF (2016). Incident diagnoses of non-melanoma skin cancer, active component, U.S. Armed Forces, 2005-2014. *MSMR*, 23(12):2–6. PMID:28055220

Leung L, Grundy A, Siemiatycki J, Arseneau J, Gilbert L, Gotlieb WH, et al. (2019). Shift work patterns, chronotype, and epithelial ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev*, 28(5):987–95. doi:10.1158/1055-9965.EPI-18-1112 PMID:30842128

Li W, Ray RM, Thomas DB, Davis S, Yost M, Breslow N, et al. (2015). Shift work and breast cancer among women textile workers in Shanghai, China. *Cancer Causes Control*, 26(1):143–50. doi:10.1007/s10552-014-0493-0 PMID:25421377

Lie JA, Kjuus H, Zienolddiny S, Haugen A, Kjærheim K (2013). Breast cancer among nurses: is the intensity of night work related to hormone receptor status? *Am J Epidemiol*, 178(1):110–7. doi:10.1093/aje/kws428 PMID:23788666

Lie JA, Kjuus H, Zienolddiny S, Haugen A, Stevens RG, Kjærheim K (2011). Night work and breast cancer risk among Norwegian nurses: assessment by different exposure metrics. *Am J Epidemiol*, 173(11):1272–9. doi:10.1093/aje/kwr014 PMID:21454824

Lie JA, Roessink J, Kjaerheim K (2006). Breast cancer and night work among Norwegian nurses. *Cancer Causes Control*, 17(1):39–44. doi:10.1007/s10552-005-3639-2 PMID:16411051

Lin X, Chen W, Wei F, Ying M, Wei W, Xie X (2015b). Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. *Sleep Med*, 16(11):1381–7. doi:10.1016/j.sleep.2015.02.543 PMID:26498240

Lin Y, Nishiyama T, Kurosawa M, Tamakoshi A, Kubo T, Fujino Y, et al.; JACC Study Group (2015a). Association between shift work and the risk of death from biliary tract cancer in Japanese men. *BMC Cancer*, 15(1):757 doi:10.1186/s12885-015-1722-y PMID:26490349

Lin Y, Ueda J, Yagyu K, Kurosawa M, Tamakoshi A, Kikuchi S (2013). A prospective cohort study of shift work and the risk of death from pancreatic cancer in Japanese men. *Cancer Causes Control*, 24(7):1357–61. doi:10.1007/s10552-013-0214-0 PMID:23619608

Linnersjö A, Hammar N, Dammström BG, Johansson M, Eliasch H (2003). Cancer incidence in airline cabin crew: experience from Sweden. *Occup Environ Med*, 60(11):810–4. doi:10.1136/oem.60.11.810 PMID:14573710

Liu T, Zhang C, Liu C (2016). The incidence of breast cancer among female flight attendants: an updated meta-analysis. *J Travel Med*, 23(6):taw055. doi:10.1093/jtm/taw055 PMID:27601531

Liu W, Zhou Z, Dong D, Sun L, Zhang G (2018). Sex differences in the association between night shift work and the risk of cancers: a meta-analysis of 57 articles. *Dis Markers*, 2018:7925219. doi:10.1155/2018/7925219 PMID:30598709

Lizama N, Heyworth J, Thomson A, Slevin T, Fritschi L (2017). Self-reported shift work, recall bias, and belief about disease causation in a case-control study of breast cancer. *Cancer Epidemiol*, 50(Pt A):9–15. doi:10.1016/j.canep.2017.07.007 PMID:28756308

Mancio J, Leal C, Ferreira M, Norton P, Lunet N (2018). Does the association of prostate cancer with night-shift work differ according to rotating vs. fixed schedule? A systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*, 21(3):337–44. doi:10.1038/s41391-018-0040-2 PMID:29700389

McElroy JA, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton JM, Egan KM (2006). Duration of sleep and breast cancer risk in a large population-based case-control study. *J Sleep Res*, 15(3):241–9. doi:10.1111/j.1365-2869.2006.00523.x PMID:16911025

Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES (2005). Night work and breast cancer risk: a systematic review and meta-analysis. *Eur J Cancer*, 41(13):2023–32. doi:10.1016/j.ejca.2005.05.010 PMID:16084719

Menegaux F, Guénel P (2012). Night work and breast cancer: the CECILE study. *Arch Mal Prof Environ*, 73(3):547–8. doi:10.1016/j.admp.2012.03.009 PMID:22689255

Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. (2013). Night work and breast cancer: a population-based case-control study in France (the CECILE study). *Int J Cancer*, 132(4):924–31. doi:10.1002/ijc.27669 PMID:22689255

Menegaux F, Truong T, Anger A, Kerbrat P, Arveux P, Lamkarkarch F, et al. (2011). Night work and breast cancer risk: CECILE study. *Cancer Res*, 71(8 Supplement):3728. doi:10.1158/1538-7445.AM2011-3728

Milanov L, Dimitrov D, Danon S (1999). Cancer incidence in Republic of Bulgaria aircrew, 1964-1994. *Aviat Space Environ Med*, 70(7):681–5. PMID:10417004

Monsees GM, Kraft P, Hankinson SE, Hunter DJ, Schernhammer ES (2012). Circadian genes and breast cancer susceptibility in rotating shift workers. *Int J Cancer*, 131(11):2547–52. doi:10.1002/ijc.27564 PMID:22473669

Nicholas JS, Lackland DT, Dosemeci M, Mohr LC Jr, Dunbar JB, Grosche B, et al. (1998). Mortality among US commercial pilots and navigators. *J Occup Environ Med*, 40(11):980–5. doi:10.1097/00043764-199811000-00008 PMID:9830605

O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, et al.; Electromagnetic Fields and Breast Cancer on Long Island Study Group (2006). Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol*, 164(4):358–66. doi:10.1093/aje/kwj211 PMID:16777931

Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Ardanaz E, et al. (2016). Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol*, 31(9):867–78. doi:10.1007/s10654-015-0073-y PMID:26205167

Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Burgos J, et al. (2015). Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. *Int J Cancer*, 137(5):1147–57. doi:10.1002/ijc.29400 PMID:25530021

Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Martin V, et al. (2017). Shift work and colorectal cancer risk in the MCC-Spain case-control study. *Scand J Work Environ Health*, 43(3):250–9. doi:10.5271/sjweh.3626 PMID:28251241

Papantoniou K, Devore EE, Massa J, Strohmaier S, Vetter C, Yang L, et al. (2018). Rotating night shift work and colorectal cancer risk in the nurses' health studies. *Int J Cancer*, 143(11):2709–17. doi:10.1002/ijc.31655 PMID:29978466

Parent M-É, El-Zein M, Rousseau M-C, Pintos J, Siemiatycki J (2012). Night work and the risk of cancer among men. *Am J Epidemiol*, 176(9):751–9. doi:10.1093/aje/kws318 PMID:23035019

Paridou A, Velonakis E, Langner I, Zeeb H, Blettner M, Tzonou A (2003). Mortality among pilots and cabin crew in Greece, 1960-1997. *Int J Epidemiol*, 32(2):244–7. doi:10.1093/ije/dyg056 PMID:12714544

Perez-Gomez B, Pollán M, Gustavsson P, Plato N, Aragonés N, López-Abente G (2004). Cutaneous melanoma: hints from occupational risks by anatomic site in Swedish men. *Occup Environ Med*, 61(2):117–26. doi:10.1136/oem.2002.006320 PMID:14739377

Pesch B, Harth V, Rabstein S, Baisch C, Schiffermann M, Pallapies D, et al. (2010). Night work and breast cancer - results from the German GENICA study. *Scand J Work Environ Health*, 36(2):134–41. doi:10.5271/sjweh.2890 PMID:20039012

Pinkerton LE, Hein MJ, Anderson JL, Christianson A, Little MP, Sigurdson AJ, et al. (2018). Melanoma, thyroid cancer, and gynecologic cancers in a cohort of female flight attendants. *Am J Ind Med*, 61(7):572–81. doi:10.1002/ajim.22854 PMID:29687925

Pinkerton LE, Hein MJ, Anderson JL, Little MP, Sigurdson AJ, Schubauer-Berigan MK (2016). Breast cancer incidence among female flight attendants: exposure-response analyses. *Scand J Work Environ Health*, 42(6):538–46. doi:10.5271/sjweh.3586 PMID:27551752

Pinkerton LE, Waters MA, Hein MJ, Zivkovich Z, Schubauer-Berigan MK, Grajewski B (2012). Cause-specific mortality among a cohort of U.S. flight attendants. *Am J Ind Med*, 55(1):25–36. doi:10.1002/ajim.21011 PMID:21987391

Poole EM, Schernhammer ES, Tworoger SS (2011). Rotating night shift work and risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*, 20(5):934–8. doi:10.1158/1055-9965.EPI-11-0138 PMID:21467237

Pronk A, Ji BT, Shu XO, Xue S, Yang G, Li HL, et al. (2010). Night-shift work and breast cancer risk in a cohort of Chinese women. *Am J Epidemiol*, 171(9):953–9. doi:10.1093/aje/kwq029 PMID:20375193

Pukkala E, Aspholm R, Auvinen A, Eliasch H, Gundestrup M, Haldorsen T, et al. (2003). Cancer incidence among 10,211 airline pilots: a Nordic study. *Aviat Space Environ Med*, 74(7):699–706. PMID:12862322

Pukkala E, Auvinen A, Wahlberg G (1995). Incidence of cancer among Finnish airline cabin attendants, 1967-92. *BMJ*, 311(7006):649–52. doi:10.1136/bmj.311.7006.649 PMID:7549630

Pukkala E, Helminen M, Haldorsen T, Hammar N, Kojo K, Linnersjö A, et al. (2012). Cancer incidence among Nordic airline cabin crew. *Int J Cancer*, 131(12):2886–97. doi:10.1002/ijc.27551 PMID:22447246

Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggvadottir L, et al. (2014). Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med*, 71(6):398–404. doi:10.1136/oemed-2013-101803 PMID:24510539

Qiu J, Yang R, Rao Y, Du Y, Kalembo FW (2012). Risk factors for breast cancer and expression of insulin-like growth factor-2 (IGF-2) in women with breast cancer in Wuhan City, China. *PLoS One*, 7(5):e36497. doi:10.1371/journal.pone.0036497 PMID:22662119

Rabstein S, Harth V, Justenhoven C, Pesch B, Plöttner S, Heinze E, et al.; GENICA Consortium (2014). Polymorphisms in circadian genes, night work and breast cancer: results from the GENICA study. *Chronobiol Int*, 31(10):1115–22. doi:10.3109/07420528.2014.957301 PMID:25229211

Rabstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, et al.; GENICA Consortium (2013). Night work and breast cancer estrogen receptor status–results from the German GENICA study. *Scand J Work Environ Health*, 39(5):448–55. doi:10.5271/sjweh.3360 PMID:23543199

Rafnsson V, Hrafnkelsson J, Tulinius H (2000). Incidence of cancer among commercial airline pilots. *Occup Environ Med*, 57(3):175–9. doi:10.1136/oem.57.3.175 PMID:10810099

Rafnsson V, Sulem P, Tulinius H, Hrafnkelsson J (2003). Breast cancer risk in airline cabin attendants: a nested case-control study in Iceland. *Occup Environ Med*, 60(11):807–9. doi:10.1136/oem.60.11.807 PMID:14573709

Rafnsson V, Tulinius H, Jónasson JG, Hrafnkelsson J (2001). Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes Control*, 12(2):95–101. doi:10.1023/A:1008983416836 PMID:11246849

Ramin C, Devore EE, Pierre-Paul J, Duffy JF, Hankinson SE, Schernhammer ES (2013). Chronotype and breast cancer risk in a cohort of US nurses. *Chronobiol Int*, 30(9):1181–6. doi:10.3109/07420528.2013.809359 PMID:23961712

Rana S, Munawar M, Shahid A, Malik M, Ullah H, Fatima W, et al. (2014b). Deregulated expression of circadian clock and clock-controlled cell cycle genes in chronic lymphocytic leukemia. *Mol Biol Rep*, 41(1):95–103. doi:10.1007/s11033-013-2841-7 PMID:24190490

Rana S, Shahid A, Ullah H, Mahmood S (2014a). Lack of association of the NPAS2 gene Ala394Thr polymorphism (rs2305160:G>A) with risk of chronic lymphocytic leukemia. *Asian Pac J Cancer Prev*, 15(17):7169–74. doi:10.7314/APJCP.2014.15.17.7169 PMID:25227809

Rao D, Yu H, Bai Y, Zheng X, Xie L (2015). Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. *Onco Targets Ther*, 8:2817–26. PMID:26491356

Ren ZF (2014). Association of sleep duration, daytime napping, and night shift work with breast cancer risk. *Cancer Res*, 74(19 Supplement):2181. doi:10.1158/1538-7445.AM2014-2181

Reynolds P, Cone J, Layefsky M, Goldberg DE, Hurley S (2002). Cancer incidence in California flight attendants (United States). *Cancer Causes Control*, 13(4):317–24. doi:10.1023/A:1015284014563 PMID:12074501

Rogers D, Boyd DD, Fox EE, Cooper S, Goldhagen M, Shen Y, et al. (2011). Prostate cancer incidence in U.S. Air Force aviators compared with non-aviators. *Aviat Space Environ Med*, 82(11):1067–70. doi:10.3357/ASEM.3090.2011 PMID:22097644

Ronckers CM, Erdmann CA, Land CE (2005). Radiation and breast cancer: a review of current evidence. *Breast Cancer Res*, 7(1):21–32. doi:10.1186/bcr970 PMID:15642178

Salisbury DA, Band PR, Threlfall WJ, Gallagher RP (1991). Mortality among British Columbia pilots. *Aviat Space Environ Med*, 62(4):351–2. PMID:2031640

Schernhammer E (2014). Nightshift work and breast cancer risk - good news, bad news? *Occup Environ Med*, 71(Suppl 1):A121. doi:10.1136/oemed-2014-102362.381

Schernhammer ES, Feskanich D, Liang G, Han J (2013). Rotating night-shift work and lung cancer risk among female nurses in the United States. *Am J Epidemiol*, 178(9):1434–41. doi:10.1093/aje/kwt155 PMID:24049158

Schernhammer ES, Kroenke CH, Laden F, Hankinson SE (2006). Night work and risk of breast cancer. *Epidemiology*, 17(1):108–11. doi:10.1097/01.ede.0000190539.03500.c1 PMID:16357603

Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, et al. (2001). Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst*, 93(20):1563–8. doi:10.1093/jnci/93.20.1563 PMID:11604480

Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, et al. (2003). Night-shift work and risk of colorectal cancer in the nurses' health study. *J Natl Cancer Inst*, 95(11):825–8. doi:10.1093/jnci/95.11.825 PMID:12783938

Schernhammer ES, Razavi P, Li TY, Qureshi AA, Han J (2011). Rotating night shifts and risk of skin cancer in the nurses' health study. *J Natl Cancer Inst*, 103(7):602–6. doi:10.1093/jnci/djr044 PMID:21335547

Schubauer-Berigan MK, Anderson JL, Hein MJ, Little MP, Sigurdson AJ, Pinkerton LE (2015). Breast cancer incidence in a cohort of U.S. flight attendants. *Am J Ind Med*, 58(3):252–66. doi:10.1002/ajim.22419 PMID:25678455

Schwartzbaum J, Ahlbom A, Feychting M (2007). Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health*, 33(5):336–43. doi:10.5271/sjweh.1150 PMID:17973059

Sigurdardottir LG, Valdimarsdottir UA, Fall K, Rider JR, Lockley SW, Schernhammer E, et al. (2012). Circadian disruption, sleep loss, and prostate cancer risk: a systematic review of epidemiologic studies. *Cancer Epidemiol Biomarkers Prev*, 21(7):1002–11. doi:10.1158/1055-9965.EPI-12-0116 PMID:22564869

Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al.; WHO International Agency For Research on Cancer Monograph Working Group (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*, 8(12):1065–6. doi:10.1016/S1470-2045(07)70373-X PMID:19271347

Talibov M, Pukkala E, Martinsen JI, Tryggvadottir L, Weiderpass E, Hansen J (2018). Night-shift work and hematological cancers: a population based case-control study in three Nordic countries. *Scand J Work Environ Health*, 44(3):258–64. doi:10.5271/sjweh.3705 PMID:29323398

Travis RC, Balkwill A, Fensom GK, Appleby PN, Reeves GK, Wang XS, et al. (2016). Night shift work and breast cancer incidence: three prospective studies and meta-analysis of published studies. *J Natl Cancer Inst*, 108(12):108 doi:10.1093/jnci/djw169 PMID:27758828

Travis RC, Reeves GK, Peto R, Key TJ, Beral V (2017). Response. *J Natl Cancer Inst*, 109(4). doi:10.1093/jnci/djx008 PMID:28376172

Truong T, Liquet B, Menegaux F, Plancoulaine S, Laurent-Puig P, Mulot C, et al. (2014). Breast cancer risk, night-work, and circadian clock gene polymorphisms. *Endocr Relat Cancer*, 21(4):629–38. doi:10.1530/ERC-14-0121 PMID:24919398

Tse LA, Lee PMY, Ho WM, Lam AT, Lee MK, Ng SSM, et al. (2017). Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. *Environ Int*, 107:1–7. doi:10.1016/j.envint.2017.06.012 PMID:28644961

Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T (1996). Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control*, 7(2):197–204. doi:10.1007/BF00051295 PMID:8740732

Vistisen HT, Garde AH, Frydenberg M, Christiansen P, Hansen AM, Andersen J, et al. (2017). Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data. *Scand J Work Environ Health*, 43(1):59–67. doi:10.5271/sjweh.3603 PMID:27841916

Viswanathan AN, Hankinson SE, Schernhammer ES (2007). Night shift work and the risk of endometrial cancer. *Cancer Res*, 67(21):10618–22. doi:10.1158/0008-5472.CAN-07-2485 PMID:17975006

Walasa WM, Carey RN, Si S, Fritschi L, Heyworth JS, Fernandez RC, et al. (2018). Association between shift-work and the risk of colorectal cancer in females: a population-based case-control study. *Occup Environ Med*, 75(5):344–50. doi:10.1136/oemed-2017-104657 PMID:29438001

Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, et al. (2013). A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. *Ann Oncol*, 24(11):2724–32. doi:10.1093/annonc/mdt283 PMID:23975662

Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, et al. (2015a). Night-shift work, sleep duration, daytime napping, and breast cancer risk. *Sleep Med*, 16(4):462–8. doi:10.1016/j.sleep.2014.11.017 PMID:25794454

Wang X, Ji A, Zhu Y, Liang Z, Wu J, Li S, et al. (2015b). A meta-analysis including dose-response relationship between night shift work and the risk of colorectal cancer. *Oncotarget*, 6(28):25046–60. doi:10.18632/oncotarget.4502 PMID:26208480

Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, et al. (2017). Rotating night-shift work and the risk of breast cancer in the nurses' health studies. *Am J Epidemiol*, 186(5):532–40. doi:10.1093/aje/kwx140 PMID:28541391

Wendeu-Foyet MG, Bayon V, Cénée S, Trétarre B, Rébillard X, Cancel-Tassin G, et al. (2018). Night work and prostate cancer risk: results from the EPICAP Study. *Occup Environ Med*, 75(8):573–81. doi:10.1136/oemed-2018-105009 PMID:29921728

Wendeu-Foyet MG, Menegaux F (2017). Circadian disruption and prostate cancer risk: an updated review of epidemiological evidences. *Cancer Epidemiol Biomarkers Prev*, 26(7):985–91. doi:10.1158/1055-9965.EPI-16-1030 PMID:28377415

WHO (2004). ICD-10: international statistical classification of diseases and related health problems. 10th revision, 2nd ed. Geneva, Switzerland: World Health Organization.

Wickremaratne K, Strand H, Zhao I (2017). Rotating shift work and colorectal cancer among nurses and midwives: a cross-sectional study. *Aust J Adv Nurs*, 34(4):6–15.

Yang W, Shi Y, Ke X, Sun H, Guo J, Wang X (2019). Long-term sleep habits and the risk of breast cancer among Chinese women: a case-control study. *Eur J Cancer Prev*, 28(4):323–9. doi:10.1097/CEJ.0000000000000458 PMID:30188375

Yong LC, Pinkerton LE, Yiin JH, Anderson JL, Deddens JA (2014c). Mortality among a cohort of U.S. commercial airline cockpit crew. *Am J Ind Med*, 57(8):906–14. doi:10.1002/ajim.22318 PMID:24700478

Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C, Hammer GP (2014a). A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health*, 40(5):502–10. doi:10.5271/sjweh.3438 PMID:24892305

Yong M, Nasterlack M, Messerer P, Oberlinner C, Lang S (2014b). A retrospective cohort study of shift work and risk of cancer-specific mortality in German male chemical workers. *Int Arch Occup Environ Health*, 87(2):175–83. doi:10.1007/s00420-013-0843-3 PMID:23377535

Zeeb H, Blettner M, Hammer GP, Langner I (2002). Cohort mortality study of German cockpit crew, 1960-1997. *Epidemiology*, 13(6):693–9. doi:10.1097/00001648-200211000-00014 PMID:12410011

Zeeb H, Blettner M, Langner I, Hammer GP, Ballard TJ, Santaquilani M, et al. (2003). Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. *Am J Epidemiol*, 158(1):35–46. doi:10.1093/aje/kwg107 PMID:12835285

Zeeb H, Hammer GP, Langner I, Schafft T, Bennack S, Blettner M (2010). Cancer mortality among German aircrew: second follow-up. *Radiat Environ Biophys*, 49(2):187–94. doi:10.1007/s00411-009-0248-6 PMID:19841929

Zienolddiny S, Haugen A, Lie JA, Kjuus H, Anmarkrud KH, Kjærheim K (2013). Analysis of polymorphisms in the circadian-related genes and breast cancer risk in Norwegian nurses working night shifts. *Breast Cancer Res*, 15(4):R53 doi:10.1186/bcr3445 PMID:23822714