IARC HANDBOOKS

ABSENCE OF EXCESS BODY FATNESS

VOLUME 16

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met in Lyon, 5–12 April 2016

LYON, FRANCE - 2018

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Introduction

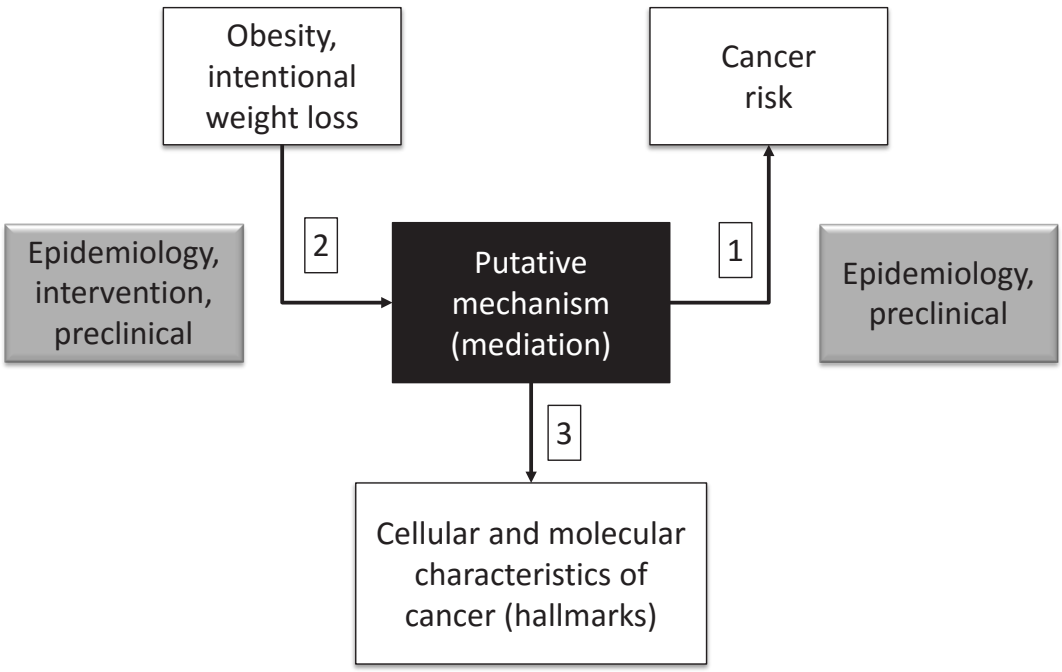
The goal of this section is to assess which cellular and molecular processes known to be dysregulated during the carcinogenesis process are causally linked with obesity and, when sufficient data are available, to identify the organ sites for which cancer risk is increased. This assessment, based primarily on data on obesity, was extended to consider whether the dysregulation observed in obesity was reversed by intentional weight loss (IWL). With evidence of resolution, the argument for a causal association was considered to be strengthened. There are two approaches to IWL with demonstrated efficacy in reducing body mass in obese individuals, i.e. dietary/energy restriction and bariatric surgery. For the purposes of this assessment, the term dietary restriction (DR) will be adopted to include both dietary and energy (calorie) restriction.

The framework for this evaluation resulted from the integration of the key characteristics of carcinogenic agents used for identifying and evaluating carcinogenic mechanisms in the IARC Monographs (Smith et al., 2016), the concepts arising from genome projects (Vogelstein et al., 2013), and the characteristics of cancer referred to as cancer hallmarks (Hanahan & Weinberg, 2000, 2011).

The approach used to evaluate the evidence that a particular factor mediates the effects of obesity on cancer development is shown in Fig. 4.1. Briefly, evidence must exist (i) that the factor plays a significant role in the carcinogenic process (arrow 1 in Fig. 4.1), (ii) that obesity exerts an effect on that factor (arrow 2), and (iii) that the factor affects the processes that regulate cell proliferation, cell death, and/or angiogenesis with an identifiable molecular basis for the observed changes in those processes (arrow 3). Although this approach is based on the traditional concept of mediation, it distinguishes itself by extending the assessment to hallmarks of cancer and their molecular underpinnings.

Factors were grouped as being operative within the target cell (i.e. intracellular factors) or as external factors to which target cells are exposed (i.e. host factors). Within the intracellular category, the key characteristics related to electrophilic and metabolically activated carcinogens of exogenous and endogenous origin, the damage they cause, and the mutations induced (Smith et al., 2016) are considered not individually but rather from the perspective of those mutations that confer a selective growth advantage to a cell (i.e. driver mutations) versus those that do not (i.e. passenger mutations) (Vogelstein et al., 2013); also considered within the intracellular category are other key characteristics (Smith et al., 2016) that contribute to the emergence of driver mutations and their expression, including oxidative stress, epigenetic alterations and various aspects of DNA repair. This assessment emphasized the cancer hallmarks related

Fig. 4.1 Diagram of the paradigm used to establish the mechanisms that mediate the effects of obesity on cancer risk



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to the dysregulation of the balance between cell proliferation and cell death, clonal expansion, and angiogenesis.

The host factors considered in this section are related to small molecules involved in energy metabolism and macromolecular synthesis, mediators involved in inflammation, and those factors that exert their effects via cell surface receptors (growth factors, sex hormones, and cytokines) (receptor-mediated effects). With regard to the small molecules, many of which can be considered as energy substrates, the approach was inclusive of the microbiome and of the intracellular energy sensors that integrate extracellular and intracellular signals by affecting the processes that drive clonal expansion and selection and disease progression. Most of the factors considered are shown in Fig. 4.2.

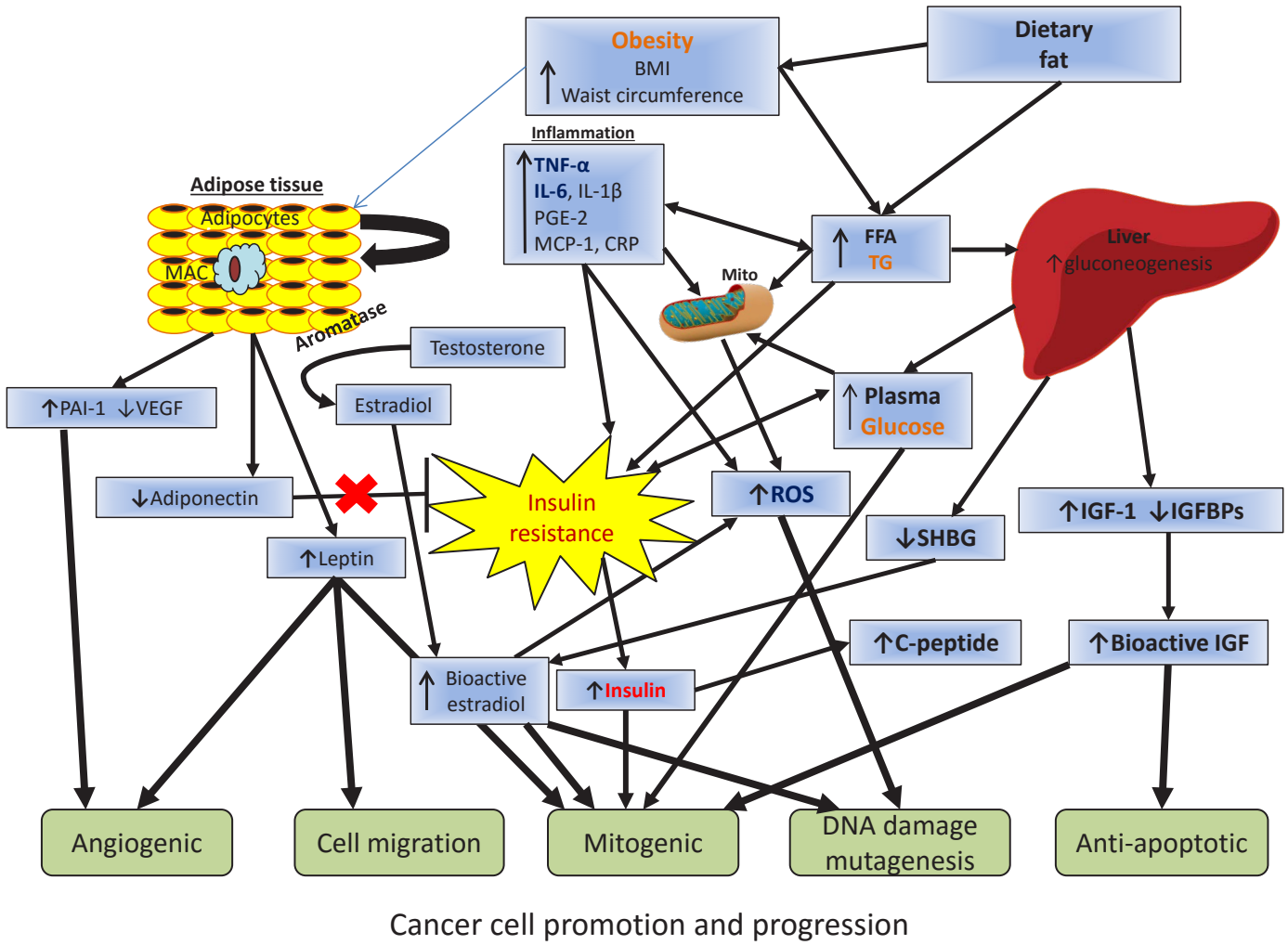
4.2 Intracellular factors

Within the approach outlined in Section 4.1, the findings are presented by the strength of the evidence of an effect of obesity or IWL on those factors.

4.2.1 Cell proliferation, apoptosis, and angiogenesis

Because the time frame for the development of obesity and cancer is long and the imbalance between cell proliferation and cell death is small at any snapshot in time (Bozic et al., 2010), evaluation of the impact of obesity on these factors is problematic, even though their involvement in obesity-induced carcinogenesis is obligatory. The impact of IWL, particularly via bariatric surgery, provides an opportunity to gain insight into how these processes are regulated in the situation of negative energy balance.

Fig. 4.2 Summary of mechanisms underlying the obesity–cancer link



Factors denoted in bold red text are established features of the obesity–cancer connection. Factors denoted in bold blue text are emerging features.
BMI, body mass index; CRP, C-reactive protein; FFA, free fatty acids; IGF, insulin-like growth factor; IGFBP, IGF binding protein; IL, interleukin; MAC, macrophage; MCP-1, monocyte chemoattractant protein 1; Mito, mitochondria; PAI-1, plasminogen activator inhibitor 1; PGE2, prostaglandin E2; ROS, reactive oxygen species; SHBG, sex hormone-binding globulin; TG, triglycerides; TNF-α, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.
Compiled by the Working Group.

(a) Cell proliferation

The effect of IWL on neoplasia-associated cell proliferation has received little attention in intervention studies, and the evidence is limited to effects of bariatric surgery. Whereas IWL via bariatric surgery, including the Roux-en-Y gastric bypass, resulted in a reduction in endometrial hyperplasia (Argenta et al., 2013; Modesitt et al., 2015), proliferation was reported to be increased after Roux-en-Y gastric bypass or jejunoileal bypass surgery in the rectum (Appleton et al., 1988; Sainsbury et al., 2008; Kant et al., 2011); however, when a sleeve gastrectomy was used, hyperproliferation was not observed in the rectal mucosa (Kant et al., 2014). Although the reduction in endometrial hyperplasia is consistent with reduced risk of endometrial cancer, the question of how the hyperproliferative state would affect the risk of cancer of the colon and rectum has been identified as a concern (Appleton et al., 1988; Sainsbury et al., 2008; Kant et al., 2011).

Another question of interest is how the regulation of cell cycle machinery, which ultimately accounts for effects on the magnitude of cell proliferation observed in a tissue, is affected by IWL; however, that specific question has not been addressed in IWL intervention studies in humans or rodents. What has been done in experiments in rodents is to investigate the effects of DR, which is protective against cancer (see Section 3) and has been reported to decrease cell proliferation in mammary tumours (Zhu et al., 1999b; Jiang et al., 2003). Briefly, the studies focused on factors that regulate the G1/S transition, which appears to be a target when energy availability is limited by DR (Jiang et al., 2003). Observed effects included reductions in levels of phosphorylated retinoblastoma protein and the transcription factor E2F1, decreased activity of cyclin-dependent kinase 2 (CDK2) and CDK4, increased concentrations of the CDK inhibitors Cip1/p21 and Kip1/p27, increased levels of these proteins complexed with CDK2, and increased binding of p16 and p19 to CDK4 (Zhu et al., 1999a; Jiang et al., 2003). In addition, DR reduced epidermal proliferation during tumour promotion in mice (Azrad et al., 2011), and endometrial cancer cells grown in sera obtained from women randomized to calorie restriction were less mitogenic than cells grown in sera obtained from overweight women (Moore et al., 2012).

(b) Apoptosis

Intervention studies of IWL that evaluated apoptosis end-points in cancer were not identified. Therefore, studies in rat and mouse models with cancer-related end-points were reviewed. A dose-dependent relationship between DR and elevated rates of apoptosis has been reported (Zhu et al., 1999b; Thompson et al., 2004a; Tomita, 2012; Olivo-Marston et al., 2014). DR induced a pro-apoptotic state via the coordinated regulation of pro- and anti-apoptotic factors involved in the mitochondrial pathway of caspase activation (Thompson et al., 2004a). Specifically, complementary DNA (cDNA) microarray analysis identified the *Bcl-2*, *CARD*, and *IAP* functional gene groupings as being involved in induction of apoptosis. Consistent with the microarray data, the activities of caspases 9 and 3 were observed to be 2-fold higher in carcinomas from DR rats, whereas the activity of caspase 8 was similar in carcinomas from DR animals and those fed ad libitum. Collectively, this evidence indicated that DR-induced apoptosis is mediated by the mitochondrial pathway.

(c) Angiogenesis

Studies of the effects of IWL on angiogenesis in the context of cancer in humans were not identified. However, studies have reported the effects of IWL via DR (Rizkalla et al., 2012; Cullberg et al., 2013) or bariatric surgery (Lemoine et al., 2012; Moreno-Castellanos et al., 2015) on circulating factors that reflect angiogenic drive and on gene and protein expression profiles in adipose tissue sampled before and after weight

loss. For either intervention approach, levels of circulating factors associated with angiogenesis, for example vascular endothelial growth factor A (VEGF-A) and angiopoietin 1 (ANG-1), are reduced by IWL, whereas the level of angiopoietin-like 4 (ANGPTL-4) is increased and the pattern of gene or protein expression in adipose tissue in response to IWL has been characterized as anti-angiogenic (Cullberg et al., 2013).

Reduction in tumour vascularization in response to DR has been reported in rodent models of cancer (Mukherjee et al., 2004; Thompson et al., 2004a; Higami et al., 2006; Powolny et al., 2008; Zhu et al., 2009; De Lorenzo et al., 2011; Kurki et al., 2012), and this has been shown to involve many of the same factors identified in the clinical studies. These factors play roles at different stages of the angiogenic process, which can be divided into endothelial proliferation and migration, blood coagulation, fibrinolysis, and the degradation of basement membranes and the extracellular matrix.

(d) Synthesis

Alteration of cell proliferation, apoptosis, and angiogenesis are key characteristics of carcinogenesis, and their necessary involvement in the development of cancer is established. Available studies of IWL in humans and rodents, although limited in number, support the view that obesity dysregulates one or more of these processes, and that IWL can reverse these changes.

4.2.2 The mTOR network and other energy-sensor networks

Blood levels of amino acids, carbohydrates, and lipids – the primary substrates that are interconverted and metabolized to produce energy – are generally altered in obesity, and are reduced during IWL, whether it is achieved via bariatric surgery or DR (Thompson et al., 2012; Fabian et al., 2013; Modesitt et al., 2015). In addition, IWL exerts systemic effects by altering circulating concentrations of growth factors and hormones that affect cell function as well as the mechanisms that drive the carcinogenic process. These IWL-mediated intracellular and systemic effects are transduced to signalling pathways that regulate tissue growth and endothelial homeostasis via intracellular nutrient and energy sensors. Prominent among these pathways are those regulated by adenosine monophosphate (AMP)-activated protein kinase (AMPK)–mammalian target of rapamycin (mTOR)–protein kinase B (AKT), sirtuins, peroxisome proliferator-activated receptors (PPARs), and soluble guanylyl cyclase (sGC). Most of this discussion focuses on AMPK–mTOR–AKT (i.e. the mTOR network); the other pathways are briefly discussed, recognizing their likely involvement in mediating the effects of IWL.

(a) The mTOR network

IWL can inhibit tumour growth by suppressing the activation of the mTOR signalling network. In this network, mTOR plays a key role in integrating information received from the extracellular environment via the binding of growth factors and hormones with their cognate receptor tyrosine kinases (Gwinn et al., 2008). Suppression is mediated through the effects of restricted energy availability on concentrations of the circulating growth factors and hormones and of the substrates used in intermediary metabolism to synthesize high-energy phosphates and reducing equivalents. As a consequence, the drive for cell proliferation is reduced (Zhu et al., 1999a; Jiang et al., 2003; Moore et al., 2008; Lashinger et al., 2011; De Angel et al., 2013), a pro-apoptotic environment is maintained (Zhu et al., 1999b; Thompson et al., 2004a), and the stimulus for formation of new blood vessels is suppressed (Thompson et al., 2004b). One or more elements of the mTOR network are dysregulated in the majority of human cancers (Wood et al., 2007).

AMPK serves as a metabolic checkpoint, downregulating cell growth and cell division

in the absence of an adequate supply of biosynthetic and energy substrates (Gwinn et al., 2008). AMPK has been shown to be an exquisitely sensitive detector of small changes in the intracellular ratio of AMP to adenosine triphosphate (ATP), and some investigators have even proposed that AMPK plays a central role in homeostatic regulation of whole-body energy metabolism (Hardie, 2004).

IWL by bariatric surgery (Peng et al., 2010) and DR (Jiang et al., 2008, 2009) results in AMPK activation. This suggests that either energy availability alters substrate availability (the fuel mixture presented to tissues throughout the body) or activation is being induced via a mechanism independent of the AMP-to-ATP ratio. In this regard, it is clear that additional factors control the activation of AMPK, including various cytokines such as adiponectin (Kahn et al., 2005).

Limiting energy availability, for example by DR, has been reported to decrease circulating levels of insulin and insulin-like growth factor 1 (IGF-1) (Zhu et al., 2005; Jiang et al., 2008; Nogueira et al., 2012; Ford et al., 2013; Lashinger et al., 2013; Harvey et al., 2014; Olivo-Marston et al., 2014). Lower levels of these growth factors downregulate signalling via the pathway of which IGF-1 receptor (IGF-1R), phosphoinositide 3-kinase (PI3K), and AKT are components. Of these proteins, activated Akt, a serine/threonine kinase, is the critical effector molecule (Hursting et al., 2003).

(b) Sirtuins

Studies of the effects of IWL on histone deacetylase activity in the context of cancer in humans have not been identified. However, it is widely recognized that the activity of SIRT1 is lower in obesity and that sirtuins are activated by IWL in liver and adipose tissue (Moschen et al., 2013; Xu et al., 2013; Jukarainen et al., 2016; Rappou et al., 2016). Sirtuins play a significant role in altering gene expression, and recent studies have shown that activation or inhibition of histone deacetylases can alter the carcinogenic process (Ahmad et al., 2012; Guo & Zhang, 2012; Jiang et al., 2013; Ravillah et al., 2014; Busch et al., 2015).

(c) Peroxisome proliferator-activated receptors

PPARs are transcription factors that are activated by long-chain fatty acids and their oxidized metabolites, the oxylipins. There are three isoforms of PPARs (α, β/δ, and γ), each of which has tissue-specific distribution and activity (Georgiadi & Kersten, 2012; Janani & Ranjitha Kumari, 2015). Because the intracellular concentrations of PPARs are affected by obesity and IWL, they are considered to be energy sensors, and their activation or lack thereof regulates not only energy metabolism (lipid metabolism as well as glucose homeostasis) but also cell growth and differentiation (Cantó et al., 2015; Cetrullo et al., 2015; Cao et al., 2016).

Studies of the effects of IWL on PPAR expression in the context of cancer in humans were not identified. The expression of PPARγ1, which has been reported to be suppressed in subcutaneous adipose tissue in obesity, is restored by IWL induced by bariatric surgery (Leyvraz et al., 2012). Many reports in humans and rodents indicate that suppression of PPAR-related signalling constitutes a link between obesity and cancer and that pharmacological activation of PPARs is protective against cancer (Georgiadi & Kersten, 2012; Laplante & Sabatini, 2013; Janani & Ranjitha Kumari, 2015; Kim et al., 2015; Mishra et al., 2016; Polvani et al., 2016).

(d) Soluble guanylyl cyclase

sGC is the receptor for nitric oxide, which is synthesized and released by various cell types as a paracrine–autocrine mechanism that coordinates energy production with consumption, in part by improving the delivery of substrates and oxygen via the vascular system (Bellamy et al., 2002; Nossaman et al., 2012). Nitric oxide-mediated

signalling has been reported to be suppressed in obesity and restored by IWL induced by bariatric surgery (Felipo et al., 2013; Blum et al., 2015). Although the activation of sGC by nitric oxide induces tissue-specific responses, its link with energy metabolism and cancer is attributed to endothelial homeostasis, to induction of angiogenesis, and to the downstream effects of cyclic guanosine monophosphate (cGMP), the product of sGC; cGMP activates protein kinase GI, which in turn inhibits RhoA, resulting in the release of the RhoA/Rho-associated protein kinase (ROCK)-dependent inhibition of the insulin–insulin receptor substrate 1 (IRS-1)–PI3K–Akt pathway (Furukawa et al., 2005; Huang et al., 2013). Of additional interest is a recent report that sGC agonists induce brown adipose tissue differentiation and the browning of white adipose tissue in obese mice, effects that result in increased energy expenditure and weight loss (Hoffmann et al., 2015). Therefore, this little-studied energy-sensing cascade provides direct links between energy metabolism, vascular supply, and tumour progression.

(e) Synthesis

The role of the mTOR network in obesity and cancer is well established and illustrates the complex nature of the regulatory cascades that underlie this relationship. There are suggestions that other energy-sensing networks, such as sirtuins, PPARs, and sGC, are involved in the association between obesity and cancer; however, direct evidence of an effect of IWL is lacking.

4.2.3 Epigenetics, oxidative stress, DNA repair, and telomeres

(a) Epigenetics

(i) Epigenetics and obesity

Unlike in cancer research, epigenetic investigations are relatively new in the field of obesity research (van Dijk et al., 2015). In the general population, the more than 100 identified loci associated with body mass index (BMI) account for only 3% of the inter-individual variation of BMI, and genome-wide estimates suggest that common variation accounts for more than 20% of BMI variation (Speliotes et al., 2010; Locke et al., 2015; Shungin et al., 2015). It is hypothesized that epigenetic mechanisms may be a missing link between the obesity-associated genes and the phenotype, and evidence is beginning to emerge in this area. Despite the different types of epigenetic alterations, studies in humans have largely been limited to examining DNA methylation. In a few small genome-wide studies, associations between DNA methylation and BMI or other indices of obesity were investigated, but the findings were generally inconclusive (Feinberg et al., 2010; Wang et al., 2010; Almén et al., 2012; Relton et al., 2012).

An epigenome-wide association study investigated associations between methylation patterns in whole blood from 459 European individuals and BMI. Samples were typed using the Infinium HumanMethylation450 array. BMI was associated with differential methylation at sites cg22891070, cg27146050, and cg16672562 located in the intron 1 region of *HIF3A* (Dick et al., 2014). A subanalysis of methylation patterns in adipose tissue found a similar association, thus suggesting that this is a BMI-related modification of the epigenome. In a subsequent investigation conducted in 991 individuals in the USA, with replication sets from other cohorts in the USA, associations between DNA methylation and BMI and waist circumference were assessed (Aslibekyan et al., 2015). Differentially methylated loci in *CPT1A* and *PHGDH* (genes involved in energy metabolism) and *CD38* were found to be associated with BMI and waist circumference.

(ii) Epigenetics and intentional weight loss

Emerging evidence in humans suggests that IWL is associated with changes in DNA methylation patterns. A small study showed that DNA

methylation in adipose tissue after a 6-month DR were higher in 7 women who lost 3% or more of their body fat than in 7 women who lost less than 3% of their body fat (Bouchard et al., 2010). Results from other studies using shorter-term dietary interventions also suggest that diet-induced weight loss causes differential DNA methylation patterns (Milagro et al., 2011; Mansego et al., 2015).

(iii) Epidemiological evidence of the epigenetic mediation between obesity and cancer risk

Evidence supporting an epigenetic mediation in the link between obesity and cancer risk is sparse and fragmented, and was identified only for breast cancer and colorectal cancer (CRC).

In a study of 803 premenopausal and postmenopausal women with breast cancer, associations between BMI and waist-to-hip ratio (WHR) with methylation at the *E-cadherin*, *p16*, and *RAR-β2* genes were examined in breast tumour tissue (Tao et al., 2011). Promoter methylation was assessed by using real-time methylation-specific polymerase chain reaction (PCR). Compared with women in the lowest quartile of WHR, those in the highest quartile were more likely to have methylation at one or more of the promoter regions that were assessed (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.10–3.11). No significant differences were found in similar case–case comparisons of BMI, or weight change (from age 20 years to 1 year before study enrolment), nor were significant trends detected for these indicators of body size and body size history.

In another study of 532 postmenopausal women with breast cancer in the USA, one arm of the investigation examined whether BMI was associated with promoter methylation status in 13 breast cancer-related genes (*APC*, *BRCA1*, *CCND2*, *CDH1*, *DAPK1*, *ESR1*, *GSTP1*, *HIN1*, *CDKN2A*, *PGR*, *RARβ*, *RASSF1A*, and *TWIST1*) (McCullough et al., 2015). Promoter methylation status was assessed by methylation-specific PCR or the MethyLight assay. Compared with 209 normal-weight women (BMI, 18.5–24.9 kg/m^2), 167 overweight women (BMI ≥ 25.0 kg/m^2) were more likely to have methylated promoter regions for *HIN1* (OR, 1.57; 95% CI, 1.03–2.39). No significant associations were detected for the 12 other genes that were investigated.

A subsequent study examined methylation at 1505 genes with known relevance to cancer using breast tumour tissue from women with breast cancer (Hair et al., 2015). Methylation status of the tissue was assessed using the Cancer Panel 1 platform. Although 30 CpG sites were differentially methylated among 195 normal-weight women with breast cancer compared with 150 obese women with breast cancer in unadjusted analyses, only two sites (on the *SH3BP2* and *XIST* genes) remained statistically significant in the final adjusted models (false discovery rate $q < 0.05$). In analyses limited to estrogen receptor (ER)-positive tumours, differential methylation at CpG sites was statistically significant on the *SH3BP2*, *IGFBP6*, *DNMT3B*, and *ERCC6* genes.

In a case–case study, associations between BMI and the CpG island methylator phenotype (CIMP) in CRC were investigated using data from 3119 patients from the Colon Cancer Family Registry (Weisenberger et al., 2015). CIMP CRC was more common in women (16.8%) than in men (9.3%) ($P = 0.0001$). However, only among women were positive associations between BMI and CIMP CRC observed. Compared with normal-weight women, overweight and obese women were more likely to have CIMP CRC (OR, 1.42; 95% CI, 1.09–1.86 for overweight women and OR, 1.93; 95% CI, 1.09–2.56 for obese women).

Evidence on IWL is limited to experimental studies. One study used a diet-induced obesity (DIO) rodent model followed by DR to investigate the epigenetic effects of DIO and DR on mammary tissue (Rossi et al., 2016). C57BL/6 mice were fed a control diet or a DIO regimen, and mice on the DIO regimen were then randomized

to continue the DIO diet or switch to the control diet, resulting in formerly obese mice with weights comparable to those of the control mice. Comparisons among control, DIO mice, and formerly obese mice both showed that there was a persistent effect of obesity on hypermethylation patterns in mammary tumours, even after DR.

(iv) Synthesis

Data on the epigenetics of obesity are emerging. Although epigenetic links between obesity and cancer risk are biologically plausible, to date the evidence in support of them is sparse and fragmented, and most of the studies have investigated only DNA methylation. Epidemiological studies of breast cancer (Tao et al., 2011; Hair et al., 2015; McCullough et al., 2015) and CRC (Weisenberger et al., 2015) have used DNA methylation at known cancer-related genes to investigate associations of BMI with epigenetic tumour characteristics. Taken together, these studies suggest that obesity may contribute to carcinogenesis via epigenetic mechanisms, but to date few associations have been detected and there has been almost no replication of findings among the different investigations.

(b) Oxidative stress

Oxidative stress is a well-established mechanism of the carcinogenic process and is one of the key characteristics as defined by Smith et al. (2016). To date, multiple biomarkers have been developed that measure oxidative damage. A commonly measured marker for whole-body oxidative stress is the isoprostane 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), which can be measured in blood and/or urine (Morrow & Roberts, 1997; Czerska et al., 2015). The activity of antioxidant enzymes and their products (e.g. glutathione peroxidase, catalase) and 8-hydroxydeoxyguanosine (8-oxo-dG) can also provide some information about oxidative stress processes in humans (Roszkowski, 2014).

(i) Oxidative stress and obesity

In obesity, adipose tissue is characterized by chronic, low-grade inflammation, which promotes oxidative stress. Adipokines can also induce the production of reactive oxygen species (ROS), resulting in oxidative stress and, in turn, causing production of other adipokines (Marseglia et al., 2015). Many activated immune cells generate free radicals, and the synthesis of ROS further promotes inflammation (Marseglia et al., 2015). Obesity-induced oxidative stress may elicit or exacerbate insulin resistance (Marseglia et al., 2015). In addition, increased ROS production may promote calcium mishandling by affecting the redox state of key proteins implicated in this process. Levels of ROS are frequently increased in obesity, and obesity induced by a high-fat diet has been shown to increase oxidative stress in animal models (e.g. Dobrian et al., 2001; Vincent et al., 2007; Matsuda & Shimomura, 2013; Cerdá et al., 2014).

(ii) Oxidative stress and dietary restriction/ weight loss

One important and consistent effect of DR is the ability to reduce oxidative stress and its resulting damage to macromolecules. Three possible mechanisms have been identified for the antioxidant effects of DR: DR may (i) reduce the production of ROS, (ii) directly increase the activity of antioxidant enzymes, or (iii) increase the turnover of oxidized macromolecules, such as oxidized lipids or DNA, which are commonly measured as biomarkers. These effects are complicated and are thought to be influenced by several factors, including sex, species, or tissue studied, types of ROS or biomarkers and antioxidant enzymes examined, and duration of DR (Merry, 2000; Skrha, 2009).

Five recent studies were identified that investigated the effect of weight-loss interventions on an individual's oxidative stress level: three randomized controlled trials (RCTs) (Meydani et al., 2011; Buchowski et al., 2012; Wegman et

al., 2015) and two non-randomized intervention studies (Gutierrez-Lopez et al., 2012; Chae et al., 2013). All of these studies measured oxidative stress by identifying markers (e.g. activity of enzymes, 8-epi-$PGF_{2\alpha}$, 8-oxo-dG) in blood (plasma or serum) or urine samples.

Buchowski et al. (2012) conducted an RCT comparing a 25% calorie-restricted diet and a control (habitual) diet in 40 overweight or obese women, with direct observation for 28 days and follow-up for the next 90 days. The initial (baseline) serum F_2-isoprostane concentration in the calorie-restricted group (median, 57.0 pg/mL; interquartile range, 40.5–79.5 pg/mL) was 1.75 times the average concentration in normal-weight women (32.5 pg/mL). During calorie restriction (which resulted in a 3.2% reduction in body weight after 29 days), F_2-isoprostane levels fell rapidly, resulting in statistically significant differences from the control group by day 5 (median, 33.5 pg/mL; interquartile range, 26.0–48.0 pg/mL; $P < 0.001$). F_2-isoprostane levels remained low while the study participants continued on the calorie-restricted diet, but returned to the higher baseline concentrations in about 80% of the women after 3 months on a habitual diet.

In an intervention study of 16 normal-weight and 32 obese individuals (BMI, 30–34.9 kg/m^2), Gutierrez-Lopez et al. (2012) studied the effects of a hypocaloric diet and a hypocaloric diet plus regular moderate aerobic exercise on oxidative stress. Over 90 days, an average weight loss of 7.6% was achieved. Higher levels of oxidative stress markers and increased molecular damage and polymerization of insulin were observed in the blood from obese individuals at baseline. Treatment with a hypocaloric diet significantly decreased oxidative stress and molecular damage to values similar to those of normal-weight individuals.

As part of a controlled feeding study, Meydani et al. (2011) studied 46 moderately overweight volunteers (BMI, 25–30 kg/m^2) aged 20–42 years who were randomized to either a high glycaemic load or a low glycaemic load regimen with either 10% ($n = 12$) or 30% ($n = 34$) reduction in calorie intake for 6 months. Overall, independently of the type of calorie-restriction regimen, body weight decreased, plasma glutathione peroxidase activity increased ($P = 0.04$), and plasma protein carbonyl levels decreased ($P = 0.02$), with a concurrent nonsignificant decrease in plasma 8-epi-$PGF_{2\alpha}$ levels ($P = 0.09$) and no changes in superoxide dismutase and catalase activity.

Wegman et al. (2015) recruited a cohort of 24 healthy individuals in a double-crossover, double-blinded RCT of intermittent fasting. Study participants underwent two 3-week treatment periods: intermittent fasting and intermittent fasting with antioxidant (vitamins C and E) supplementation. Despite strict adherence to study-provided diets, no change in expression of oxidative stress markers was observed. Body weight remained stable over the entire trial period.

Chae et al. (2013) investigated overweight or obese participants (BMI, 25–34 kg/m^2, $n = 122$, aged 30–59 years) who joined a clinical intervention lasting 3 years and involving daily calorie deficits of 100 kcal. Body weight changed by 5.4% (−4.16 ± 0.31 kg) in the group with successful mild weight loss ($n = 50$) compared with 0.05 ± 0.14 kg in the unsuccessful group ($n = 49$). Successful mild weight loss was coupled with significantly reduced serum levels of insulin, IL-6 (30% decrease; $P = 0.031$), IL-1β (45% decrease; $P < 0.001$), and tumour necrosis factor alpha (TNF-α) ($P < 0.001$), as well as urinary 8-epi-$PGF_{2\alpha}$ (14% decrease; $P = 0.036$). A positive correlation was reported between IL-1β and urinary 8-epi-$PGF_{2\alpha}$ ($r = 0.435$, $P < 0.001$) and between the corresponding changes in IL-6 and urinary 8-epi-$PGF_{2\alpha}$ ($r = 0.393$, $P < 0.001$).

(iii) Synthesis

Oxidative stress is well established as a cellular mechanism that can affect DNA integrity and has been linked to cancer, metabolic syndrome, and obesity. Evidence of the involvement of oxidative stress in obesity-induced cancer in humans is limited by methodological issues. Results from weight-loss intervention trials indicate that oxidative stress can be rapidly reduced and the lower level sustained through a modest reduction in calorie intake.

(c) DNA repair

(i) DNA repair mediation in obesity and cancer

Elevated BMI is consistently associated with CRC (see Section 2.2.1). To assess the role of DNA repair in this association, several studies have investigated associations between BMI and CRC stratified by tumour microsatellite status (Campbell et al., 2010; Hoffmeister et al., 2013). In a population-based study, CRC cases were divided into those with high-level microsatellite instability (MSI-high) tumours and microsatellite-stable (MSS) tumours (Hoffmeister et al., 2013). Among the 1215 cases, 67% were overweight or obese, and 115 (9.5%) had MSI-high tumours. BMI was weakly associated with MSS tumours in women (OR, 1.15; 95% CI, 0.97–1.35 per 5 kg/m^2) and in men (OR, 1.25; 95% CI, 1.08–1.45 per 5 kg/m^2); in contrast, the association between BMI and MSI-high CRC was significant only in women (OR, 2.04; 95% CI, 1.50–2.77 per 5 kg/m^2). When the analysis was limited to case–case comparisons, BMI was more strongly associated with MSI-high than with MSS tumours in women (OR, 1.84; 95% CI, 1.34–2.52 per 5 kg/m^2), but not in men.

Elevated BMI is consistently associated with increased risk of endometrial cancer (see Section 2.2.9). Endometrial cancer is also commonly observed in women with Lynch syndrome (hereditary non-polyposis CRC due to a defect in the DNA mismatch repair system), and in about 30% of endometrial cancer cases, sporadic MSI occurs (Mills & Longacre, 2016). Furthermore, the positive associations observed between BMI and endometrial cancer are significantly stronger among carriers of germline mutations in the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2* than among non-carriers (Win et al., 2011).

In a clinical study of 446 women with endometrial cancer (McCourt et al., 2007), women with MSS tumours were significantly heavier (median BMI, 32.7 kg/m^2) than those with MSI tumours (median BMI, 30.3 kg/m^2) ($P = 0.02$). A larger, population-based case–control study of 524 cases and 1032 controls investigated associations between obesity and endometrial cancer by microsatellite status (Amankwah et al., 2013). Unlike in the previous study, the association between BMI and MSI tumours was stronger than that between BMI and MSS tumours ($P_{heterogeneity} = 0.05$ for overweight and 0.02 for obesity).

(ii) DNA repair and dietary restriction/weight loss

One recent RCT investigated the effect of weight loss on DNA repair capacity. The Nutrition and Exercise for Women RCT recruited 439 women, who were randomized to one of four groups: (i) dietary intervention, (ii) aerobic exercise, (iii) diet plus exercise, or (iv) control (Habermann et al., 2015). The diet intervention was a group-based programme with a goal of 10% weight loss. The exercise intervention consisted of moderate to vigorous aerobic activity for 45 minutes per day, 5 days per week. DNA repair capacity was measured in fasting blood samples taken at baseline and after 12 months in a subset of 226 women, using a modified comet assay conducted in pre- and post-intervention cryopreserved lymphocytes, analysed within the same batch. DNA repair capacity did not change significantly with any of

the diet or exercise interventions compared with the control group. Similarly, there were no significant changes when the analysis was stratified by changes in body composition or aerobic fitness (maximal oxygen consumption, VO_{2max}).

(iii) Synthesis

The role of DNA repair function in cancer risk is unequivocal and is particularly well established for cancers of the colorectum, breast, endometrium, and skin. However, there have been few studies investigating functional assays of DNA repair in the context of obesity or weight reduction. One well-designed RCT showed no effects, but assay limitations were present. Several studies point towards a link between BMI and DNA mismatch repair deficiencies. Overall, a causal link of obesity and weight control with DNA repair is still lacking.

(d) Telomeres

Multiple studies have reported that obesity is associated with shorter telomere length in different cell types. A recent systematic review and meta-analysis comprising 119 439 individuals reported that 39 studies showed weak to moderate correlations between obesity and telomere length (Mundstock et al., 2015). However, there was significant heterogeneity, which suggests that this relationship is still incompletely understood.

In the Nutrition and Exercise for Women RCT of 439 postmenopausal women randomized to diet, exercise, diet plus exercise, or control groups for 1 year (see Section 4.2.3c(ii)), DNA was extracted from isolated leukocytes, and telomere length was measured by quantitative PCR (Mason et al., 2013a). Baseline telomere length was correlated inversely with age ($r = -0.12$, $P < 0.01$) and positively with VO_{2max} ($r = 0.11$, $P = 0.03$), but was not correlated with BMI or body fat percentage. The change in telomere length was inversely associated with the telomere length at baseline ($r = -0.47$, $P < 0.0001$). None of the interventions resulted in any significant group differences in leukocyte telomere length compared with controls, and there were no differences in telomere length by the degree of weight loss.

García-Calzón et al. (2014) reported that a 2-month energy-restricted diet (30% of energy from fat, 15% from proteins, and 55% from carbohydrates) among overweight or obese adolescents aged 12–16 years resulted in increased telomere length, with a greater effect in those who had the shortest telomeres at baseline ($r = 0.96$, $P < 0.001$).

4.3 Receptor-mediated effects

Adiposity and overweight/obesity are associated with significant metabolic and endocrinological changes that are included as key characteristics of the carcinogenesis process, in particular (i) alterations in sex hormone metabolism, (ii) changes in insulin levels and IGF signalling, and (iii) chronic inflammation (see Table 4.1; for a review, see Pischon & Nimptsch, 2016). A large and growing number of epidemiological and experimental studies have measured biomarkers of these pathways in relation to cancer at different sites. Data in the tables are presented by type of cancer (Tables 4.2–4.11), whereas the text summarizes the studies by mechanistic pathway.

4.3.1 Sex hormones

Sex hormones are involved in specific cancers, exemplified by the implications of estrogen in breast and endometrial cancers and of androgen in prostate cancer. In postmenopausal women, estrogens are synthesized almost exclusively in adipose tissue stromal cells, and consequently obese postmenopausal women have elevated levels of estrogens compared with leaner postmenopausal women (Key et al., 2003).

(a) Cancer of the breast

See Table 4.2.

Estrogens stimulate the proliferation of normal breast tissue and neoplastic breast epithelial cells directly and can promote the development of ER-positive, estrogen-dependent breast cancer by both endocrine and paracrine mechanisms (Vona-Davis & Rose, 2007; Bulun et al., 2012).

Elevated levels of circulating estrogens have been linked to breast cancer risk in numerous epidemiological studies (Hankinson et al., 1998a; Kaaks et al., 2005; Tworoger et al., 2011; Zhang et al., 2013). The Endogenous Hormones and Breast Cancer Collaborative Group, which pooled data from nine prospective investigations of sex hormone levels and breast cancer comprising individual data from 663 incident breast cancer cases and 1765 controls, reported that risk of postmenopausal breast cancer is 2-fold higher among women in the highest versus the lowest quintile of estradiol and testosterone levels, as well as for other related sex hormones such as estrone, dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione (Key et al., 2002). Furthermore, in a subsequent analysis, the positive association between BMI and risk of postmenopausal breast cancer was almost entirely explained by levels of estradiol (Key et al., 2003). For premenopausal breast cancer, the risk of breast cancer was 40% higher among women in the highest versus the lowest quintile of estradiol level. Levels of androstenedione, DHEA sulfate, and testosterone were also significantly positively associated with risk of breast cancer in multivariate models that included established breast cancer risk factors (Key et al., 2013).

(b) Cancer of the endometrium

See Table 4.3.

Estrogens play a critical role in the normal proliferation of endometrial tissue during the menstrual cycle (Barile et al., 1979; Klotz et al., 2002; Zhu & Pollard, 2007). In premenopausal endometrial tissue, the actions of estrogen are opposed by those of progesterone (Gao & Tseng, 1997). Consistent with these mechanistic data, use of unopposed estrogen postmenopausal hormone therapy is associated with a significantly higher risk of endometrial cancer, whereas use of the combined estrogen plus progestogen formulation appears to have a protective effect (Beral et al., 2005).

There are consistent epidemiological data linking higher circulating estrogen levels with increased risk of endometrial cancer. Five prospective investigations of estradiol concentrations and endometrial cancer have all reported relative risks between 2 and 4 for the comparison of high versus low estradiol levels in multivariate models that controlled for adiposity and other established endometrial cancer risk factors (Zeleniuch-Jacquotte et al., 2001; Lukanova et al., 2004a; Allen et al., 2008; Gunter et al., 2008a; Brinton et al., 2016). In addition, higher circulating levels of sex hormone-binding globulin (SHBG) were associated with significantly lower risk of endometrial cancer in three of these prospective studies (Zeleniuch-Jacquotte et al., 2001; Lukanova et al., 2004a; Allen et al., 2008).

(c) Cancer of the colorectum

See Table 4.4.

The role of sex hormones in CRC development is unclear and is likely to be complex. The Women's Health Initiative Clinical Trial reported a significant reduction in CRC incidence among women assigned to the combined estrogen plus progestogen intervention arm (Chlebowski et al., 2004); however, with additional follow-up of the trial participants, it was later suggested that this effect may be a consequence of diagnostic delay (Simon et al., 2012). Experimental data also suggest that estrogens may have protective effects on CRC development. ERβ has been demonstrated to play an important role in the anti-

proliferative effects of estrogens on colonic tissue (Hartman et al., 2009). Furthermore, expression of ERβ is low in human CRC cells (Waliszewski et al., 1997) and is inversely associated with the stage of colon cancer (Castiglione et al., 2008), suggesting a possible role in disease progression.

However, investigations of the relationship between endogenous circulating estrogens and CRC have produced inconsistent results. Of the five prospective studies published to date, all of which were mainly of postmenopausal women, three reported null associations between circulating estrogens and CRC risk (Clendenen et al., 2009; Lin et al., 2013; Falk et al., 2015) and a fourth reported a borderline significant positive association (Gunter et al., 2008b). More recently, in a case–control study nested within the non-intervention arms of the Women's Health Initiative Clinical Trial that included only postmenopausal women, higher endogenous levels of free estradiol were inversely associated with CRC risk (OR for highest vs lowest quartile, 0.43; 95% CI, 0.27–0.69) in a multivariate model that included established CRC risk factors as well as other obesity-related hormones such as insulin and IGF-1 (Murphy et al., 2015). Higher levels of SHBG were positively associated with CRC development (OR for highest vs lowest quartile, 2.30; 95% CI, 1.51–3.51), and this relationship strengthened after statistical adjustment for levels of circulating estradiol, estrone, insulin, IGF-1, and C-reactive protein (CRP) (OR for highest vs lowest quartile, 2.50; 95% CI, 1.59–3.92). Interestingly, the link between obesity and CRC is weaker in women than in men (see Section 2.2.1). Furthermore, in the study by Murphy et al. (2015) of postmenopausal women who were non-users of hormone replacement therapy (HRT), the inclusion of estradiol in the waist circumference–CRC model strengthened the risk estimate.

(d) Cancer of the prostate

See Table 4.5.

Sex steroids, and specifically androgens such as testosterone, play critical roles in the development and function of the prostate gland, and their involvement in prostate tumorigenesis has long been hypothesized (Hsing, 2001). However, testosterone levels tend to be lower in obese men than in men of normal weight.

Prospective studies that have investigated androgen levels and prostate cancer development have reported inconsistent findings. The Endogenous Hormones and Prostate Cancer Collaborative Group, which pooled data from 18 prospective studies evaluating individual data from 3886 incident prostate cancers and 6438 men without prostate cancer, reported null associations between testosterone, DHEA sulfate, androstenedione, or estradiol and incident prostate cancer (Roddam et al., 2008). It has been hypothesized that a hypoandrogenic environment promotes the development of higher-grade prostate tumours. At least two prospective studies have reported inverse relationships between serological testosterone levels and high-grade prostate cancer (Platz et al., 2005a; Severi et al., 2006a). Furthermore, in the Prostate Cancer Prevention Trial, finasteride, which lowers testosterone levels, reduced the risk of low-grade prostate cancer by 25% but led to a higher incidence of high-grade disease (Thompson et al., 2003). Interestingly, the association between obesity and prostate cancer is stronger for high-grade (fatal) tumours (see Section 2.2.14).

Collectively, these data point to a complex relationship between androgen levels and prostate cancer, with an indication of tumour subtype specificity, but offer limited insight into the mechanisms underlying the link between obesity and prostate cancer.

(e) Cancer at other sites

Sex hormones have been hypothesized to play a role in ovarian cancer development. Use of oral contraceptives confers a reduced risk of ovarian cancer, whereas use of postmenopausal HRT

is associated with increased risk (Beral et al., 2008, 2015). However, epidemiological studies that have investigated circulating estrogen and SHBG levels in relation to risk of ovarian cancer were generally null (Table 4.6; Helzlsouer et al., 1995; Lukanova et al., 2003a; Rinaldi et al., 2007; Trabert et al., 2016). [It is plausible that the associations may be specific to particular ovarian cancer subtypes, but to date individual studies have been of insufficient size to address this hypothesis with precision.]

For other cancer types, there are intriguing data that point to possible sex hormone-mediated mechanisms. In a case–control study, SHBG levels were strongly associated with risk of hepatocellular carcinoma (HCC) even after adjusting for all established risk factors (Lukanova et al., 2014; Table 4.7). Also, there are distinct sex differences in the incidence of cancers of the oesophagus, liver, pancreas, and kidney, all of which occur more frequently in men than in women (see Sections 2.2.2, 2.2.4, 2.2.7, and 2.2.16, respectively). However, to date there are no published data on the association of endogenous sex hormones with these cancers. Experimental data, mainly from studies of cell lines, indicate possible anti-proliferative and anti-tumorigenic effects of estrogen in renal cells (Yu et al., 2013).

(f) Impact of weight loss on sex hormones

Investigations of the effects of IWL on sex steroid levels are relatively consistent; however, these studies have largely been restricted to postmenopausal women. A comprehensive overview of the available literature until 2011 concluded that IWL reduces levels of sex steroid hormones in postmenopausal women and increases SHBG levels in premenopausal and postmenopausal women (Byers & Sedjo, 2011). In the Nutrition and Exercise for Women RCT, 439 overweight or obese postmenopausal women were randomized to one of four groups: control, dietary intervention only, exercise intervention only, or diet plus exercise (Foster-Schubert et al., 2012). Over a 12-month period, women in the diet group and the diet plus exercise group lost on average 8.5% and 10.8%, respectively, of their pre-intervention weight (Campbell et al., 2012). Compared with the control group, women in these two groups had statistically significant reductions in estrone and estradiol levels. SHBG levels increased significantly in the diet group and the diet plus exercise group, and decreased slightly in the control group and the exercise group.

Results from an analysis of overweight postmenopausal women enrolled in the Diabetes Prevention Program who underwent moderate weight loss did not reveal significant effects on estradiol or testosterone levels, although DHEA levels were reduced and there was a statistically significant increase in SHBG concentrations (Kim et al., 2012).

(g) Synthesis

Estrogen levels correlate with amount of body fat in postmenopausal women. Overall, data from observational and experimental studies support clear associations between higher levels of estrogens and increased risk of breast cancer and endometrial cancer. In addition, IWL affects sex steroid hormones and SHBG levels in postmenopausal women in a direction that would favour reducing their risk of breast cancer and endometrial cancer. For CRC, estradiol may be anti-tumorigenic and may in fact lessen the impact of adiposity on CRC development. For cancers of the prostate and ovary, the data are much less consistent and the associations are likely to be more complex. For other tumours, the role of sex hormones in their development is largely unknown.

4.3.2 Insulin resistance

Insulin resistance indicates the presence of an impaired physiological response to insulin, and is manifested by decreased insulin-stimulated

glucose transport. Hyperinsulinaemia, which is a consequence of insulin resistance, is more common in obese individuals than in those of normal weight, and metabolic indicators of hyperinsulinaemia, such as C-peptide levels, are positively associated with BMI and waist circumference (Bezemer et al., 2005).

Insulin, in addition to its metabolic effects, has mitogenic and anti-apoptotic activity and appears to play a significant role in normal organogenesis. Insulin has been shown to stimulate cell proliferation in normal tissues such as breast tissue and in human cancer cell lines (Ish-Shalom et al., 1997; Chappell et al., 2001), and administration of exogenous insulin promotes tumour growth in animal models (Heuson & Legros, 1972; Shafie & Grantham, 1981; Shafie & Hilf, 1981).

(a) Cancer of the breast

See Table 4.2.

A number of epidemiological studies have investigated the association of fasting insulin levels in women with higher BMI with incidence of breast cancer, with variable results. One study found a positive association between hyperinsulinaemia and postmenopausal breast cancer among women with BMI > 26 kg/m^2, but not among women with BMI ≤ 26 kg/m^2 (Muti et al., 2002). In an analysis conducted in the Women's Health Initiative Observational Study, fasting insulin levels were positively associated with postmenopausal breast cancer among women who were non-users of HRT, in a multivariate model that controlled for multiple breast cancer risk factors, including estradiol and BMI (hazard ratio for highest vs lowest quartile of insulin level [HR_{q4-q1}], 2.40; 95% CI, 1.30–4.41; $P_{trend} < 0.001$) (Gunter et al., 2009, 2015a). In a subsequent formal mediation analysis, it was demonstrated that insulin, rather than estradiol, explained the majority of the association between obesity and breast cancer risk in this population (Hvidtfeldt et al., 2012).

(b) Cancer of the endometrium

See Table 4.3.

Hyperinsulinaemia, whether assessed by fasting insulin levels or C-peptide levels, has been associated with increased incidence of endometrial cancer in several prospective investigations (Lukanova et al., 2004b; Cust et al., 2007a; Gunter et al., 2008a). In an analysis in the Women's Health Initiative cohort, baseline fasting insulin levels among women who were non-users of HRT were positively associated with risk of endometrioid adenocarcinoma after adjusting for estradiol levels and other factors (HR_{q4-q1}, 2.33; 95% CI, 1.13–4.82), and this association was stronger among women with BMI ≥ 25 kg/m^2 (HR_{q4-q1}, 4.30; 95% CI, 1.62–11.43) (Gunter et al., 2008a). Two additional studies that measured C-peptide concentrations also reported significant positive associations with endometrial cancer risk (Lukanova et al., 2004b; Cust et al., 2007a). An analysis from the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported an increased risk of endometrial cancer among women with high C-peptide levels compared with those with low levels; this association was independent of obesity, but the risk estimate was attenuated after adjustment for estradiol (Cust et al., 2007a). Recently, further support for a causal role of insulin in endometrial cancer development came from a Mendelian randomization analysis conducted in 1287 endometrial cancer cases and 8273 controls, which identified a robust positive association between genetically determined insulin levels and endometrial cancer (Nead et al., 2015).

(c) Cancer of the colorectum

See Table 4.4.

In laboratory models, high insulin levels have been shown to promote the development of

aberrant crypt foci in the colon (which are posited to be CRC precursors), as well as the growth of colon cancer cells (Koohestani et al., 1997; Tran et al., 2006). Furthermore, overexpression of the insulin receptor can induce cell transformation in vitro (Giorgino et al., 1991), and human colorectal adenocarcinomas have been shown to express the insulin receptor at high levels, indicating that these cells may be sensitive to the growth effects of insulin (Kiunga et al., 2004).

Epidemiological data on the association of hyperinsulinaemia with CRC are somewhat inconsistent. Of the five published studies to date that directly measured fasting insulin levels (Schoen et al., 1999; Palmqvist et al., 2003; Saydah et al., 2003; Limburg et al., 2006; Gunter et al., 2008b), three reported positive associations between hyperinsulinaemia and CRC (Schoen et al., 1999; Limburg et al., 2006; Gunter et al., 2008b), but the associations were attenuated after adjustment for other risk factors. In the largest of such studies, which was conducted in the Women's Health Initiative cohort, insulin levels were significantly associated with CRC ($HR_{q4–q1}$, 1.89; 95% CI, 1.33–2.69; P_{trend} = 0.0005); however, adjustment for waist circumference weakened the association ($HR_{q4–q1}$, 1.42; 95% CI, 0.91–2.23; P_{trend} = 0.11), just as adjustment for insulin also attenuated the relationship between obesity and CRC (Gunter et al., 2008b). The remaining two studies found no association between insulin and CRC [insulin was measured in non-fasting blood specimens, which complicates the interpretation] (Palmqvist et al., 2003; Saydah et al., 2003). Other prospective studies have assessed C-peptide concentrations in relation to CRC and have generally reported positive associations (Kaaks et al., 2000; Ma et al., 2004; Wei et al., 2005a; Jenab et al., 2007; Otani et al., 2007). Most recently, an analysis in the EPIC study demonstrated that individuals with a normal BMI but elevated C-peptide levels were at higher risk of CRC compared with those with a normal BMI and without elevated C-peptide levels, and were at equivalent risk of CRC as overweight and obese individuals with higher C-peptide levels. In contrast, overweight or obese participants without raised C-peptide levels were not at increased risk of CRC. These findings support an association of hyperinsulinaemia with CRC independent of obesity status (Murphy et al., 2016).

(d) Cancer at other sites

A number of prospective studies have investigated the association of insulin with prostate cancer development (Table 4.5), and the majority reported null associations (Stattin et al., 2000; Hubbard et al., 2004; Stocks et al., 2007; Parekh et al., 2013; Lai et al., 2014). A study nested within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study reported a 2-fold higher risk of prostate cancer when men in the highest quartile of insulin level were compared with those in the lowest quartile (Albanes et al., 2009).

A null association was also reported in the single study of ovarian cancer (Table 4.6; Lukanova et al., 2003b).

Hyperinsulinaemia has also been linked to development of liver cancer in a small number of prospective studies (Table 4.7). An investigation nested within the EPIC cohort demonstrated a more than 3-fold greater risk of HCC and an almost 10-fold greater risk of intrahepatic bile duct tumour among participants in the highest tertile of C-peptide level compared with the lowest tertile (Aleksandrova et al., 2014). Similarly, in a study of men chronically infected with hepatitis B virus, individuals with fasting insulin levels higher than 6.1 μU/mL were at more than 2-fold higher risk of HCC compared with those with insulin levels in the range 2.75–4.10 μU/mL (Chao et al., 2011).

For pancreatic cancer (Table 4.8), two studies that measured insulin levels in pre-diagnostic samples both reported statistically significant positive associations between insulin levels and risk of pancreatic cancer (Stolzenberg-Solomon

et al., 2005; Wolpin et al., 2013), whereas an investigation nested within the EPIC cohort reported no association between C-peptide levels and pancreatic cancer (Grote et al., 2011).

A single nested case–control study reported statistically significant associations between both insulin and C-peptide levels (highest vs lowest tertiles) and risk of stomach cancer (Table 4.9; Hidaka et al., 2015).

(e) Synthesis

Hyperinsulinaemia and insulin resistance are metabolic disturbances commonly observed in obesity. Insulin, in addition to indirectly raising free estrogen levels by suppression of SHBG expression, can directly activate cellular pathways that confer growth and survival advantages to the cell and therefore may promote cancer development. Experimental data in in vitro and animal models generally support a protumorigenic effect of insulin; studies in humans generally only support a positive association between hyperinsulinaemia and cancers of the endometrium and colorectum, whereas findings for breast cancer and prostate cancer are more heterogeneous. There are few data for cancer at other sites.

4.3.3 Insulin-like growth factors

The IGF system comprises two ligands, IGF-1 and IGF-2, as well as at least six binding proteins (IGFBPs) that sequester IGF-1 and IGF-2 and regulate their bioavailability and activity. IGF-1 and IGF-2 are growth factors that share significant structural similarities with insulin but have much stronger mitogenic and anti-apoptotic effects.

A substantial body of epidemiological literature has now accumulated on the association of circulating IGF-1 levels with cancer development, and several meta-analyses and pooled studies have demonstrated robust associations of systemic IGF-1 concentrations with breast cancer (Table 4.2), CRC (Table 4.4), and prostate cancer (Table 4.5). However, the evidence that the IGF axis is dysregulated in obesity and is modified by IWL, although convincing in studies in animals, is less convincing in humans, at least in part due to current challenges in measuring bioavailable IGF-1 in human biospecimens. Although insulin levels generally rise with increasing BMI and waist circumference, most large, population-based studies have reported a non-linear relationship between measures of adiposity and IGF-1 levels. One study found the highest IGF-1 levels among those with a BMI in the range 26–27.9 kg/m^2 (Allen et al., 2003), and other studies suggest decreasing levels of IGF-1 as BMI rises above 25 kg/m^2 (Lukanova et al., 2004c). The non-linearity hypothesis relating circulating IGF-1 levels to adiposity is also supported by findings among women enrolled in the EPIC study, which reported a positive trend in IGF-1 levels as BMI and waist circumference increased, with levels peaking at a BMI of 24.6–26.6 kg/m^2, and then declining among participants with BMI > 26.6 kg/m^2 (Gram et al., 2006). In contrast, linear regression analysis of data from the United States National Health and Nutrition Examination Survey (NHANES) suggested an overall inverse relationship between circulating total IGF-1 levels and BMI (Faupel-Badger et al., 2009). This phenomenon may, in part, be explained by obesity-induced hyperinsulinaemia and growth hormone effects. Insulin inhibits the synthesis of IGFBP-1 and IGFBP-2, leading to an increase in unbound IGF-1 (Nam et al., 1997). Thus, as adiposity increases over time, IGF-1 levels rise, but with the development of obesity, elevated free IGF-1 levels exert a negative feedback effect on pituitary secretion of growth hormone, with subsequent attenuation of hepatic IGF-1 synthesis (Tannenbaum et al., 1983).

A comprehensive review of the literature on IGF-1 and IGFBPs presents an inconsistent portrait of how IWL affects IGF-1 and IGFBPs (Byers & Sedjo, 2011). In the Nutrition and

Exercise for Women RCT, published afterwards (Mason et al., 2013b), weight loss was positively associated with change in circulating IGF-1 and in the molar ratio of IGF-1 to IGFBP-3 in the diet group.

The IGF axis plays a major role in the regulation of cell growth and survival, and increased signalling through the IGF system can exert a pro-tumorigenic effect. Studies in humans support a role for systemic IGF-1 levels in determining risk of breast, prostate, and colorectal cancer, whereas for other malignancies the relationship is much less clear. However, the relationship between IGF-1/IGFBPs and obesity is uncertain and is still being investigated.

4.3.4 Chronic inflammation

Chronic inflammation, a key characteristic of carcinogenesis (Hanahan & Weinberg, 2000, 2011; Smith et al., 2016), has been associated with obesity in a large number of epidemiological and experimental studies. Obesity is considered a chronic pro-inflammatory state associated with progressive infiltration of adipose tissue by macrophages and other immune cells that secrete pro-inflammatory cytokines (including TNF-α, IL-1β, and IL-6) and other chemical mediators of a persistent, subacute (often referred to as smouldering) inflammatory response (Renehan et al., 2008). In addition, several clinical and experimental studies suggest that IWL – by behavioural interventions, bariatric surgery, or pharmacological approaches – can reverse some of the obesity-associated changes in certain inflammatory factors, particularly CRP. However, it is also clear from this literature that the underlying causes, cellular contributors, and molecular and metabolic factors involved in the obesity–inflammation–cancer triad are extremely complex.

The increase in white adipose tissue mass associated with obesity drives chronic inflammation through at least three established and interacting mechanisms, which are each discussed here: (i) altered production of inflammatory factors secreted from adipose and other tissues, (ii) increased adipose tissue inflammation (as measured by crown-like structures and other measures of infiltration by immune cells), and (iii) adipose tissue remodelling. In addition, several emerging contributors to the obesity-associated pro-inflammatory state, including the cyclooxygenase-2 (COX-2)/prostaglandin pathway, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, and inflammation-related molecules from the microbiome, are briefly discussed.

(a) Established markers and mechanisms

(i) Changes in inflammatory markers

Leptin, a peptide hormone produced by adipocytes (and thus referred to as an adipokine), is positively correlated with adipose storage and nutritional status, and functions as an energy sensor. Leptin interacts directly with peripheral tissues, interacts indirectly with hypothalamic pathways, and modulates immune function, cytokine production, angiogenesis, and many other biological processes (Münzberg & Morrison, 2015). At the high levels found with obesity, leptin also has pro-inflammatory activity and upregulates the secretion of TNF-α and IL-6 (Park & Ahima, 2015).

The leptin receptor is structurally and functionally similar to class I cytokine receptors and acts through the signal transducer and activator of transcription (STAT) family of transcription factors (Villanueva & Myers, 2008). STATs induce signalling pathways for several cellular processes, including cell growth, proliferation, survival, migration, and differentiation. The activity of STATs is commonly dysregulated in cancer (Yu et al., 2014).

Adiponectin is the most abundant hormone secreted from adipose tissue. In contrast with leptin, levels of adiponectin correlate negatively with adiposity. Adiponectin can reduce pro-

inflammatory cytokine expression and induce anti-inflammatory cytokine expression via inhibition of NF-κB (discussed below) (Fantuzzi, 2013; Park & Ahima, 2015).

CRP is a non-glycosylated circulating acute-phase reactant protein of the pentraxin family (Thiele et al., 2015). CRP has long been used as a marker of inflammation in studies in humans (see Section 4.3.4c), and data are accumulating that CRP (particularly the monomeric form that results from dissociation from the pentameric form on activated macrophages and platelets) may be a mediator of inflammation (Thiele et al., 2015).

In addition to adiponectin, leptin, and CRP, many other adipokines, cytokines, and acute-phase reactant proteins can be produced by adipocytes, by other cells in adipose tissue (e.g. macrophages, dendritic cells, fibroblasts, B and T lymphocytes), or by other tissues (e.g. stomach, skeletal muscle, liver) (Blüher & Mantzoros, 2015). With increased adiposity, the secretome (the conglomerate of secreted factors) can become dysregulated and have significant biological impacts on insulin sensitivity, inflammatory response, vascular endothelial function, estrogen metabolism, and cell proliferation.

At the intracellular level, inflammatory signals are transduced through multiple pathways to drive cellular responses. For example, NF-κB is a transcription factor activated in response to various stimuli, including cytokines and other inflammatory molecules, and is responsible for inducing gene expression associated with cell proliferation, apoptosis, angiogenesis, cytokine secretion, and other responses to inflammatory signals (Xia et al., 2014). Activation of NF-κB has been observed in many types of tumour cells (Karin, 2006). There is considerable cross-talk between growth factor signalling pathways and NF-κB signalling, and obesity and energy restriction modulate NF-κB activation, possibly through alterations in systemic cytokines, growth factors, and Akt signalling (Hursting et al., 2013). Activation of NF-κB by cytokines or Akt can lead to the translocation of the active NF-κB subunit, p65, from the cytoplasm to the nucleus (Adli & Baldwin, 2006), inducing multiple genes associated with inflammation and cancer, including IL-6, COX-2, and IL-1β (Karin, 2006).

(ii) Increased adipose tissue inflammation

A new role of adipose tissue inflammation in obesity and its connection to cancer has been proposed. Subclinical inflammation in visceral and subcutaneous white adipose tissue is characterized by rings of activated macrophages surrounding engorged or necrotic adipocytes and referred to as crown-like structures. Macrophages, T cells, and other immune cells infiltrate adipose tissue at the onset of weight gain. This adipocyte–macrophage interaction results in the production of a pro-inflammatory secretome from both cell types, which activates the cellular transcription factor NF-κB, increases levels of cytokines and other inflammatory factors, and triggers inflammation. Chronic inflammation eventually leads to systemic insulin resistance and altered levels of circulating adipokines, cytokines, and other factors that promote the development of obesity, and also plays a role in obesity-associated cancers (Wellen & Hotamisligil, 2003; Neels & Olefsky, 2006; Subbaramaiah et al., 2011).

(iii) Adipose tissue remodelling

Stored triacylglycerides undergo lipolysis within the cytoplasm of adipocytes and are released into the bloodstream as free fatty acids during times of low substrate availability or heightened energy requirements (Duncan et al., 2007). Once in the circulation, free fatty acids can be used to generate energy. In a state of obesity, white adipose tissue does not respond appropriately to changes in energy requirements, resulting in elevated production of adipokines and cytokines (Jung & Choi, 2014).

When lipid storage capacity in adipose tissue is exceeded, surplus lipids often accumulate

within muscle, liver, and pancreatic tissue, leading to impairment of lipid processing and clearance within these tissues (Henry et al., 2012; Suganami et al., 2012). As a result, lipid intermediates impair the function of cellular organelles and cause further release of cytokines, which foster inflammation as well as insulin resistance.

(b) Emerging markers and mechanisms

(i) COX-2, prostaglandins, and other lipid mediators

COX-2 can be highly induced in several tissue types as part of the inflammatory response; COX-2 levels are increased in many obesity-associated cancers, including breast, ovarian, and colorectal tumours, and are associated with a poor clinical outcome (Eberhart et al., 1994; Howe, 2007; Lee et al., 2013).

In addition, the increased lipolysis that occurs with obesity results in a higher concentration of circulating free fatty acids (Björntorp et al., 1969; Jensen et al., 1989; Nicklas et al., 1996), and saturated fatty acids can stimulate expression of COX-2 and secretion of prostaglandin E2 in cultured macrophages via activation of Toll-like receptor 4 and subsequent NF-κB signalling (Lee et al., 2001; Hellmann et al., 2013). This may be another contributor to obesity-associated adipose tissue inflammation. Also, serum concentrations of IL-6 and TNF-α are generally increased with obesity (Fain, 2006), and these cytokines have been shown to stimulate COX-2 expression and to promote production of prostaglandin E2 (Geng et al., 1995; Maihöfner et al., 2003).

(ii) Inflammatory contributions from the microbiome

An emerging field of research is the influence of the microbiome – the community of commensal, symbiotic, and pathogenic microorganisms that inhabit an individual – on obesity, inflammation, and related chronic diseases (discussed in Section 4.3.6a).

(c) Epidemiological evidence for the mediation of inflammatory factors between obesity and cancer

(i) Cancer of the breast

See Table 4.2.

Epidemiological studies on the association of adipokines and inflammatory factors with breast cancer have generally yielded inconsistent results. Adiponectin levels have been reported to be inversely associated with breast cancer incidence in several prospective investigations (Tworoger et al., 2007b; Gross et al., 2013) but not in others (Cust et al., 2009; Gaudet et al., 2013); three recent meta-analyses that included both prospective cohort and case–control studies reported an overall inverse relationship between adiponectin levels and breast cancer risk (Liu et al., 2013; Macis et al., 2014; Ye et al., 2014). Most recently, data from the Women's Health Initiative demonstrated an inverse association between adiponectin levels and postmenopausal breast cancer, but this relationship was attenuated after adjustment for insulin (Gunter et al., 2015b). Data on the association of other adipokines, such as leptin, plasminogen activator inhibitor 1 (PAI-1), and resistin, with breast cancer risk are also mixed (Gaudet et al., 2013; Gross et al., 2013; Gunter et al., 2015b).

CRP, a sensitive but nonspecific marker of the inflammatory response, has been investigated in relation to breast cancer risk in a large number of prospective studies. A recent meta-analysis that summarized data from 12 prospective studies concluded that moderately elevated CRP levels were associated with higher risk of breast cancer such that for every doubling in CRP concentration, the risk of breast cancer increased by 7% (Chan et al., 2015). An additional study not included in the meta-analysis also reported that higher circulating CRP levels were associated with increased incidence of breast cancer (Gunter et al., 2015b). Specifically, the breast cancer incidence in women in the upper two quartiles of

CRP levels was twice that of those in the lowest quartile of CRP levels among women who were non-users of HRT, even after controlling for estradiol, insulin, BMI, and established breast cancer risk factors. Furthermore, in that analysis CRP appeared to be a significant mediator of the relationship between BMI and breast cancer, along with insulin and estradiol.

(ii) Cancer of the endometrium

See Table 4.3.

A number of prospective studies have investigated the association of circulating inflammatory factors and adipokines with endometrial cancer. Within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, leptin levels were positively associated with endometrial cancer development (OR_{t3-t1}, 2.77; 95% CI, 1.60–4.79), whereas adiponectin levels were inversely related to risk (OR_{t3-t1}, 0.48; 95% CI, 0.29–0.80); both associations strengthened when analyses were restricted to women who were non-users of HRT (Luhn et al., 2013). Leptin levels were also positively associated with endometrial cancer risk in the B~FIT study, although this relationship was no longer significant after adjustment for BMI (Dallal et al., 2013). Within the EPIC study, adiponectin concentrations were significantly inversely associated with endometrial cancer risk, even after controlling for BMI (OR_{q4-q1}, 0.56; 95% CI. 0.36–0.86) (Cust et al., 2007a); however, other studies did not report significant inverse associations between adiponectin and endometrial cancer after adjustment for BMI (Soliman et al., 2011; Dallal et al., 2013).

Data from the Women's Health Initiative indicated a significant positive association between CRP levels and endometrial cancer; however, this relationship was attenuated and lost statistical significance after adjustment for insulin and estradiol levels (Wang et al., 2011). A case–control study nested within the EPIC cohort found levels of CRP and IL-6 to be positively associated with endometrial cancer, but the risk estimates were no longer significant after adjusting for BMI (Dossus et al., 2010). However, a subsequent study in the same population reported significant positive associations between circulating TNF-α levels and endometrial cancer, even after controlling for BMI and other endometrial cancer risk factors (Dossus et al., 2011), and a factor analysis of all metabolic and inflammatory markers revealed a distinct inflammatory pattern of markers that was predictive of endometrial cancer development (Dossus et al., 2013).

(iii) Cancer of the colorectum

See Table 4.4.

Several prospective studies have investigated the association of adipokines and inflammatory markers with CRC risk. In general, most studies have reported an inverse association between adiponectin levels and CRC (Wei et al., 2005b; Aleksandrova et al., 2012a; Song et al., 2013). In a nested case–control study of CRC in Norway, leptin levels were positively associated with colon cancer (OR_{q4-q1}, 2.72; 95% CI, 1.44–5.12) but not with rectal cancer (Stattin et al., 2004b). In the Women's Health Initiative Observational Study, a panel of pro-inflammatory adipokines, namely leptin, IL-6, and PAI-1, were associated with higher incidence of CRC, whereas adiponectin levels were inversely related to CRC risk (Ho et al., 2012). However, the associations were attenuated, and only leptin remained significant, after adjusting for insulin, suggesting that their effects on CRC risk may be attributed partly to insulin. A follow-up study conducted in the same population reported that higher levels of the soluble IL-1 receptor were associated with significantly lower risk of CRC, suggesting that regulators of cytokine signalling and availability may modify CRC development (Ho et al., 2014).

A substantial number of studies have investigated the link between circulating CRP levels and CRC, and the majority have reported positive associations. In a recent meta-analysis that

captured data from more than 4500 CRC cases, risk of CRC was increased by 12% for every unit change in the natural logarithm of CRP concentration (Zhou et al., 2014).

(iv) Cancer of the ovary

See Table 4.6.

A potential role for inflammation in ovarian cancer development was hypothesized several decades ago, but until recently, data from prospective cohort studies were sparse. In the EPIC cohort, CRP levels above 10 mg/L were indicative of higher risk of epithelial ovarian cancer compared with levels of 1 mg/L or below (OR, 1.67; 95% CI, 1.03–2.70), and this relationship was more pronounced among overweight and obese women (Ose et al., 2015). Similar findings were reported from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the Nurses' Health Study, and a combined analysis in the New York University Women's Health Study, the Northern Sweden Health and Disease Study, and ORDET Cohort, which all reported statistically significant positive associations between CRP levels and ovarian cancer risk when comparing levels above 10 mg/L with levels of 1 mg/L or below (Lundin et al., 2009; Poole et al., 2013; Trabert et al., 2014).

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial also identified significant associations between specific pro-inflammatory cytokines, namely TNF-α and IL-1α, and ovarian cancer risk (Trabert et al., 2014), and a case–control study nested within three prospective cohorts also found a significant link between specific cytokines related to a pro-inflammatory phenotype and ovarian cancer (Clendenen et al., 2011).

(v) Cancer at other sites

For cancer at other sites, studies of circulating inflammatory markers and adipokines are more sparse. Overall, there are inconsistent data for the association of leptin levels with prostate cancer risk (Table 4.5); one study reported a significant inverse relationship (Stocks et al., 2007), whereas other investigations generally reported null associations for both leptin and adiponectin (Hsing et al., 2001; Li et al., 2010; Lai et al., 2014).

Combined data from five cohorts in the USA yielded a significant inverse association between adiponectin levels and pancreatic cancer (OR_{q5-q1}, 0.63; 95% CI, 0.43–0.92) (Bao et al., 2013b). In the EPIC cohort, adiponectin was inversely related to pancreatic cancer risk, but only among never-smokers (Grote et al., 2012b).

Interestingly, data from a Japanese cohort and from the EPIC study reported a consistent positive association between circulating IL-6 levels and HCC development (Aleksandrova et al., 2014; Ohishi et al., 2014), with relative risks between 3 and 5. Levels of other cytokines and CRP were not associated with HCC in these studies.

(vi) Weight loss

Although the obesity–inflammation–cancer link is established for some cancers, namely CRC, the impact of IWL on inflammation and cancer risk has been much less studied. However, a consistent picture is emerging that IWL, particularly if more than 10%, can reverse some of the pro-inflammatory effects of obesity.

Most of the studies in humans that addressed weight loss and inflammation assessed systemic markers of inflammation, including CRP (the most consistently changed inflammatory marker with weight loss), IL-6, and TNF-α. One review included about 30 observational cohort studies or RCTs that used various modes of weight loss, including surgical, dietary, physical activity, or pharmacological interventions, and encompassed a large range of weight-loss attainment (Byers & Sedjo, 2011). Consistent decreases in circulating levels of CRP, TNF-α, and IL-6 were observed in studies that reported weight loss of more than 10%; the findings are less clear with more moderate (and more achievable and sustainable)

levels of weight loss achieved through diet and/or exercise interventions.

In the Nutrition and Exercise for Women RCT, high-sensitivity CRP, serum amyloid A (another acute-phase reactant protein that can stimulate CRP), IL-6, and neutrophil counts decreased statistically significantly in both the diet group and the diet plus exercise group. The intervention reduced high-sensitivity CRP by 36% in the diet group and by 42% in the diet plus exercise group. Women who lost more body weight (> 5%) experienced the largest reductions (e.g. 50% and 49% for high-sensitivity CRP with diet and diet plus exercise, respectively) (Imayama et al., 2012). In another study (Fabian et al., 2013), obese women who lost more than 10% of their body weight had reductions of about 30–50% in the leptin-to-adiponectin ratio, IL-6, and CRP levels in their serum, whereas women who lost less than 10% of their body weight had little or no change in systemic biomarkers. [There appears to be a threshold below which inflammatory markers fail to respond to weight loss; this may be due partly to sensitivity in the analytical methods and partly to limitations of statistical power, as well as the heterogeneity in marker levels before weight loss is initiated.]

Few studies investigated weight loss and changes in tissue-specific biomarkers of inflammation. Campbell et al. (2013) reported that in overweight or obese postmenopausal women, weight loss through a 6-month dietary intervention, exercise, or the combination of the two resulted in significant changes in adipose tissue gene expression; in addition to significant reductions in leptin mRNA expression, steroid hormone metabolism, inflammatory genes, and IGF signalling also appeared to be altered. In overweight or obese postmenopausal women who underwent a weight-loss intervention (Fabian et al., 2013), the adiponectin-to-leptin ratio in fine-needle aspirate of breast tissue increased in response to weight loss.

(vii) Synthesis

Obesity is associated with a state of chronic, low-grade inflammation triggered by adipose tissue remodelling and reflected in several local and systemic changes in the levels of adipokines (e.g. increased leptin; decreased adiponectin released from hypertrophied adipocytes), cytokines (e.g. increased IL-6, TNF-α, secreted from adipocytes and macrophages), and acute-phase reactant proteins (e.g. CRP, secreted primarily from the liver). These secretome changes are accompanied by changes in tissue markers of inflammation (such as crown-like structures) and cancer-associated intracellular signals (such as activation of the NF-κB pathway).

Emerging contributors to the obesity–inflammation–cancer relationship include (i) the COX-2/prostaglandin pathway, which can be particularly activated in adipocytes and macrophages in response to an obesity-associated abundance of free fatty acids (catalysed to inflammatory prostaglandins and other lipid intermediates); (ii) the microbiome, particularly the community of organisms residing in the gut that can release short-chain fatty acids and other metabolites that have pro-inflammatory activity.

Data from epidemiological studies of inflammatory markers and cancer development have generally shown consistent positive associations between circulating levels of CRP, a highly sensitive but nonspecific marker of the inflammatory response, and cancers of the breast and colorectum, and suggestive positive associations for cancers of the ovary and endometrium. However, the specific inflammatory pathways that mediate this relationship, and the extent to which it might be specific to certain ovarian cancer subtypes, remain unknown. In weight-loss intervention trials, CRP concentrations were generally reduced in the individuals who lost more than 5–10% of their initial body weight. Data on the associations of specific circulating cytokines and adipokines with obesity-related

cancers are generally more limited, possibly because of technical challenges in measuring these proteins, which typically circulate at very low concentrations. A number of studies have investigated these markers in relation to endometrial cancer, with inconsistent results.

4.3.5 Vitamin D

(a) Vitamin D and cancer

Vitamin D can induce cell differentiation and apoptosis and can also inhibit proliferation, inflammation, and angiogenesis, as well as invasion and metastasis (Fleet et al., 2012; Feldman et al., 2014; Castronovo et al., 2015; Davis-Yadley & Malafa, 2015; Christakos et al., 2016; Meeker et al., 2016) and thus may have cancer-preventive effects. Despite these strong experimental data, the epidemiological data on Vitamin D levels and cancer risk have been limited and heterogeneous. Cohort studies that measure the biomarker 25-hydroxyvitamin D (25(OH)D) pre-diagnostically have shown a consistent reduction of CRC risk in the range of 30–40% among individuals with high versus low levels (Feldman et al., 2014). However, a large RCT of vitamin D supplementation showed no effects in preventing the recurrence of colorectal adenoma (Baron et al., 2015). Similarly, a meta-analysis of prospective studies of prostate cancer showed no inverse association (Gilbert et al., 2011), and one study even suggested an increased risk with higher vitamin D levels (Brändstedt et al., 2012). For breast cancer, only some studies observed inverse associations, and these were not linear and were limited to postmenopausal women (Chlebowski et al., 2008; Bauer et al., 2013). [This pattern of cancer risk – preventive for colon cancer and, to some extent, postmenopausal breast cancer – mimics the associations of physical activity with cancer risk (IARC, 2002), and 25(OH)D is strongly associated with physical activity. Therefore, a direct interrelation or residual confounding by physical activity (particularly levels of outdoor physical activity, which tend to be poorly measured) cannot be excluded.] Further background information about vitamin D and cancer can be found in the IARC Working Group Report on vitamin D and cancer (IARC, 2008).

(b) Vitamin D and obesity

Increasing BMI has been consistently associated with lower serum 25(OH)D concentrations and higher parathyroid hormone concentrations (Vanlint, 2013; Pereira-Santos et al., 2015). Moreover, body fat content is inversely associated with serum 25(OH)D concentrations, and this association may be stronger than that with BMI and body weight alone (Arunabh et al., 2003; Vanlint, 2013).

In a recent meta-analysis, the prevalence of vitamin D deficiency was 35% higher in obese individuals compared with a normal-weight group, and 24% higher compared with overweight individuals. There were no significant differences in this proportion between children and adults; however, there was a significant degree of heterogeneity between studies overall (Pereira-Santos et al., 2015). [A challenge of this meta-analysis was the change in the definitions of vitamin D deficiency over time, although the results appeared to be consistent independent of the cut-off points used.]

There are multiple potential reasons for the inverse associations between obesity and vitamin D (Soares et al., 2012; Pereira-Santos et al., 2015). One theory is that because of issues of low social acceptance, obese individuals reduce their exposure to sunlight, cover up their bodies more, and are less active outdoors. Nevertheless, in the Framingham Heart Study cohort, adjustment for outdoor physical activity did not entirely attenuate this association (Cheng et al., 2010).

It has also been proposed that vitamin D metabolites are retained by excess body fat, and that cholecalciferol that is synthesized in the skin or taken up through the diet is in part sequestered by the body fat before transport to the

liver for hydroxylation (Wortsman et al., 2000). Adipocytes of obese individuals show significant levels of 1-α-hydroxylase, which activates vitamin D; this could explain the greater local use of vitamin D. This hypothesis is consistent with the observation that after exposure to sunlight, obese individuals have shown a 53% lower increase in 25(OH)D compared with non-obese individuals, independent of the amount of the cutaneous precursor of vitamin D (Pereira-Santos et al., 2015).

Alternatively, some experimental data suggest that vitamin D deficiency may facilitate adiposity by causing higher parathyroid hormone levels and greater influx of calcium into adipocytes, thereby increasing lipogenesis (Pereira-Santos et al., 2015). There are several additional mechanisms, investigated mainly in experiments in animals, that link vitamin D, through vitamin D receptor-mediated activity, directly to energy regulation and effects in adipocytes (Martini & Wood, 2006).

Finally, there is increasing experimental evidence that vitamin D may also have anti-inflammatory properties, presumably via effects on the state of low-grade chronic inflammation in adipose tissues (Fleet et al., 2012; Song & Sergeev, 2012; Feldman et al., 2014). In an RCT of 218 postmenopausal women with BMI ≥ 25 kg/m^2 who underwent 12 months of weight-loss intervention plus either 2000 IU/day of oral vitamin D_3 or daily placebo, significantly decreased circulating levels of IL-6 were reported with vitamin D in an analysis stratified by weight loss ($P = 0.004$) (Duggan et al., 2015).

(c) Vitamin D and weight loss

Several studies have demonstrated effects of weight loss on improving vitamin D biomarker status in obese individuals.

Tzotzas et al. (2010) investigated changes of 25(OH)D at 4 weeks and 20 weeks after introduction of a weight-loss programme (low-calorie diet of ~1000 kcal/day) among 44 obese women. At baseline, 25(OH)D levels were lower in the obese women than in 25 normal-weight controls ($P < 0.001$). The 20-week low-calorie diet (26 completers) resulted in reductions of body weight and BMI by 10% and an increase in 25(OH)D (15.4 ± 6.0 ng/mL vs 18.3 ± 5.1 ng/mL, $P < 0.05$), compared with baseline. This increase was also associated with improvement in insulin resistance and the homeostasis model assessment index.

Rock et al. (2012) prospectively examined the effects of weight loss on serum 25(OH)D concentrations in 383 overweight or obese women who participated in a 2-year clinical trial of a weight-loss programme and recommendation to increase physical activity. More than half of the women lost at least 5% of baseline weight by 24 months, and serum 25(OH)D levels increased at the end of the intervention period, with a linear trend towards greater increases in women who lost more weight; 25(OH)D increased by 5.0 ng/mL for those who lost more than 10% of baseline weight ($P = 0.014$). [Although the programme included some increase in physical activity, this was not a major component of the intervention, and the resulting greater sun exposure during outdoor activity is unlikely to explain the observed effect.]

In 192 obese patients with knee osteoarthritis, Christensen et al. (2012) tested an 8-week formula weight-loss diet of 415–810 kcal/day, followed by 8 weeks on a hypo-energetic 1200 kcal/day diet combining normal food and formula products. They reported that this intensive programme increased bone mineral density and improved 25(OH)D concentrations. [It is not clear whether this increase in 25(OH)D was attributable to the effects of the calorie restriction or the supplementation with vitamin D as part of the formula.]

Several studies have also investigated the effects of bariatric surgery on vitamin D status, and suggest decreases in vitamin D status with surgery (Karefylakis et al., 2014; Costa et al., 2015; Luger et al., 2015). [This type of weight-loss

intervention can alter the resorption of dietary vitamin D, and therefore is not considered informative.]

(d) Synthesis

Vitamin D status can directly affect many cellular processes relevant to cancer prevention. Prospective studies of the blood biomarker 25(OH)D have found consistent inverse associations with CRC, and to a lesser extent with postmenopausal breast cancer. There is a clear inverse relationship between obesity and vitamin D status, but the causes for this association are not well defined and may range from societal factors and links via physical activity to physiological changes in the adipose tissue that result in a sequestering of vitamin D metabolites; weight loss appears to improve 25(OH)D status. The experimental data are limited and do not further inform the role of vitamin D as a mediator in the effect of obesity on cancer risk.

4.3.6 Other factors

This section summarizes factors that may play a role in mediating the obesity–cancer connection but for which there are limited data.

(a) The gut microbiome

Obesity is associated with an overall reduction in bacterial diversity in the gut microbiota (Turnbaugh et al., 2009) (see Section 1.3.8), and decreased bacterial richness has been linked to elevated systemic inflammation, measured by plasma CRP levels and white blood cell counts (Le Chatelier et al., 2013). Furthermore, weight loss does not significantly improve CRP levels in obese individuals with low microbiome richness (Cotillard et al., 2013), suggesting that resistance to the inflammation-reducing effects of weight loss may be mediated by differences in microbiome richness. Feeding mice a high-fat diet is accompanied by impairments in gut barrier function, including increased plasma levels of lipopolysaccharide, a component of the outer membrane of Gram-negative bacteria (Cani et al., 2008); lipopolysaccharide induces metabolic endotoxaemia, characterized by elevated infiltration of adipose tissue by macrophages and elevated expression of pro-inflammatory cytokines (Cani et al., 2007), thus inducing chronic systemic and adipose tissue inflammation. These effects were completely prevented by treatment with a broad-spectrum antibiotic (Cani et al., 2008). Given the known role that this type of inflammation plays in the progression of many cancer types (see Section 4.3.4), it is plausible that obesity-induced perturbations of the gut microbiota are a contributing factor in the obesity–cancer link.

(b) Gut hormones

The role of gut hormones and appetite regulatory factors in cancer development is an emerging area of research, and may be a mechanism linking obesity with cancer. Ghrelin, a hormone produced in the gastric fundic glands, is known to mediate appetite and fatty acid metabolism and to promote fat storage (Higgins et al., 2007). Ghrelin can also inhibit the expression and/or production of pro-inflammatory cytokines, and ghrelin treatment increases anti-inflammatory cytokines (Gonzalez-Rey et al., 2006; Baatar et al., 2011) (see Section 1.3.1).

In the three small prospective studies of the association of ghrelin with gastrointestinal cancer development, individuals in the lowest quartile of serum ghrelin at baseline, compared with those in the highest quartile, had an increased risk of oesophageal adenocarcinoma (31 cases; OR, 5.55; 95% CI, 1.28–25.0) (de Martel et al., 2007), oesophageal squamous cell carcinoma (82 cases; OR, 6.83; 95% CI, 1.46–31.84) (Murphy et al., 2012), gastric cardia cancer (98 cases; OR, 4.90; 95% CI, 2.11–11.35), and gastric non-cardia cancer (261 cases; OR, 5.63; 95% CI, 3.16–10.03) (Murphy et al., 2011). There is considerable cross-talk between ghrelin and other hormones

involved in energy metabolism, such as leptin, adiponectin, and insulin, and as more data become available on the association of ghrelin with cancer development, the gut hormones may emerge as an important pathway linking obesity with cancer development.

(c) *Non-alcoholic fatty liver and pancreatic diseases*

Obesity is the most common cause of non-alcoholic fatty liver disease (NAFLD), a spectrum of diseases including variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis (Papandreou & Andreou, 2015). Simple steatosis is benign, whereas NASH is characterized by hepatocyte injury, inflammation, and/or fibrosis, which can lead to cirrhosis, liver failure, and HCC (Hui et al., 2003). About 80% of cases of cryptogenic cirrhosis [end-stage liver disease of unknown etiology] present with NASH, and 0.5% of these cases will progress to HCC, a percentage that increases significantly with hepatitis C-associated cirrhosis (White et al., 2012). The prevalence of NAFLD has increased concomitantly with the increase in childhood obesity over the past 30 years (Berardis & Sokal, 2014).

Adipocyte infiltration and fat accumulation in the pancreas appear to be early events in obesity-associated pancreatic endocrine dysfunction, and can trigger pancreatic steatosis, non-alcoholic fatty pancreatic disease (NAFPD), and subclinical pancreatitis. In addition, "fatty pancreas" has been positively associated with visceral white adipose tissue mass and systemic insulin resistance (van Geenen et al., 2010; Smits & van Geenen, 2011). Together, pancreatic steatosis and NAFPD contribute to the already complex metabolic and inflammatory perturbations associated with obesity and metabolic syndrome.

(d) *Immune function*

The major mechanisms relating immunity to obesity focus on the inflammatory response that originates in the adipose tissue (see Section 4.3.4). For a description of the innate immune response to obesity, see Lumeng (2013).

Studies investigating immune competence in relation to calorie restriction or IWL are few. One cross-sectional study in 114 overweight or obese postmenopausal women reported that natural killer cell cytotoxicity (assessed by flow cytometry at four effector-to-target ratios) was inversely associated with increasing frequency of prior IWL (P_{trend} = 0.003) (Shade et al., 2004). Conversely, longer duration of recent weight stability was associated with significantly greater natural killer cell cytotoxicity (21.6% ± 11.9%, 24.4% ± 11.0%, and 31.9% ± 14.4% for ≤ 2, > 2 to ≤ 5, and > 5 years of weight stability, respectively; P_{trend} = 0.0002).

In one RCT, 91 obese women were randomized to control (n = 22), exercise (n = 21), diet (n = 26), or exercise plus diet (n = 22) groups. After 12 weeks of calorie restriction (1200–1300 kcal/day) with weight loss of about 9%, mitogen-stimulated lymphocyte proliferation was significantly reduced, whereas no changes were observed in natural killer cell cytotoxicity, monocyte and granulocyte phagocytosis and oxidative burst activity, or the number of days with upper respiratory tract infections (Nieman et al., 1998).

(e) *Cancer stem cells*

A link between obesity and cancer stem cells has been identified by Zheng et al. (2011), who showed that spontaneous tumours derived from mouse mammary tumour virus (MMTV)-Wnt-1 transgenic mice, when transplanted, were highly dependent on leptin for growth. Thus, when these tumours were transplanted into obese, leptin receptor-deficient ($Lepr^{db}/Lepr^{db}$) mice with high leptin concentrations, they grew to 8

times the volume of those tumours transplanted into wild-type mice, whereas in leptin-deficient (*Lep*^{ob}/*Lep*^{ob}) mice, tumour growth was impaired. The residual tumours in *Lep*^{ob}/*Lep*^{ob} mice were found to have fewer "cancer stem cells", and these cells were characterized by flow cytometry to express leptin receptor. When isolated by leptin receptor expression, these cells exhibited stem cell properties based on the ability to form tumourspheres in vitro, and their survival was regulated by leptin. Dunlap et al. (2012) used two types of cells – mesenchymal (M-Wnt) or epithelial (E-Wnt) – derived from spontaneous mammary tumours in MMTV-Wnt-1 mice, transplanted into ovariectomized C57BL/6 mice to emulate human claudin-low and basal-like breast tumours, respectively. They reported that M-Wnt, but not E-Wnt, mammary tumour cells were stably enriched in breast cancer cell markers, and exhibited stem cell properties. In addition, M-Wnt cells orthotopically injected into mice rapidly formed claudin-low tumours that were highly responsive to the tumour-enhancing effects of obesity, as well as the anti-cancer effects of DR.

(f) Synthesis

Emerging factors that are likely to contribute to the obesity–cancer link, but for which there is currently insufficient data, include the gut microbiome, gut hormones (such as ghrelin produced by the stomach), NAFLD (which drives secretion of CRP and other inflammation-related factors), the immune function, and cancer stem cells.

Table 4.1 Effect of obesity and weight reduction on selected serological factors involved in the carcinogenesis process

Serological factor	Obesity	Weight reduction
Sex hormones		
Estradiol	Increase	Decrease
Sex hormone-binding globulin	Decrease	Increase
Testosterone	Decrease (men) Increase (women)	Increase (men) Decrease (women)
Insulin and IGF-1		
Insulin	Increase	Decrease
IGF-1	Increase (overweight) Decrease (obese)	Decrease
IGFBP-1	Decrease	Increase
IGFBP-3	—	—
Inflammation		
Adiponectin	Decrease	Increase
Leptin	Increase	Decrease
C-reactive protein	Increase	Decrease

IGF-1, insulin-like growth factor 1; IGFBP, IGF binding protein.
Compiled by the Working Group.

Table 4.2 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the breast

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Hankinson et al. (1998b); USA; Nurses' Health Study	Nested case–control; 156, 312	Steroids: extraction, separation by column chromatography, radioimmunoassay Estrone sulfate: enzyme hydrolysis, organic extraction, separation by column chromatography, radioimmunoassay DHEAS: radioimmunoassay	Estradiol, quartiles RR = 1.91 (1.06–3.46), P_{trend} = 0.03 Estrone, quartiles RR = 1.96 (1.05–3.65), P_{trend} = 0.01 Estrone sulfate, quartiles RR = 2.25 (1.23–4.12), P_{trend} = 0.01 DHEAS, quartiles RR = 2.15 (1.11–4.17), P_{trend} = 0.01 Percentage free or percentage bioavailable estradiol, androstenedione, testosterone, DHEAS: NS
Key et al. (2002); USA, Japan, Italy; 9 prospective studies	Pooled analysis; 663, 1765; postmenopausal	NR	Estradiol, quintiles RR = 2.00 (1.47–2.71), P_{trend} < 0.001 Free estradiol, quintiles RR = 2.58 (1.76–3.78), P_{trend} < 0.001 Estrone, quintiles RR = 2.19 (1.48–3.22), P_{trend} < 0.001 Estrone sulfate RR = 2.00 (1.26–3.16), P_{trend} < 0.001 DHEA, quintiles RR = 2.04 (1.21–3.45), P_{trend} = 0.18 DHEAS, quintiles RR = 1.75 (1.26–2.43), P_{trend} = 0.002 Testosterone, quintiles RR = 2.22 (1.59–3.10), P_{trend} < 0.001 SHBG, quintiles RR = 0.66 (0.43–1.00), P_{trend} = 0.041
Kaaks et al. (2005); several European countries; EPIC	Nested case–control; 677, 1309; postmenopausal	DHEAS and testosterone: radioimmunoassay Androstenedione, estrone, estradiol, and SHBG: double-antibody radioimmunoassay	Estradiol, quintiles RR = 2.28 (1.61–3.23), P_{trend} < 0.0001 Free estradiol, quintiles RR = 2.13 (1.52–2.98), P_{trend} < 0.0001 Estrone, quintiles RR = 2.07 (1.42–3.02), P_{trend} = 0.0001 SHBG, quintiles RR = 0.61 (0.44–0.84), P_{trend} = 0.004 Testosterone, quintiles RR = 1.85 (1.33–2.57), P_{trend} < 0.0001 Free testosterone, quintiles RR = 2.50 (1.76–3.55), P_{trend} < 0.0001 Androstenedione, quintiles RR = 1.94 (1.40–2.69), P_{trend} < 0.0001 DHEAS, quintiles RR = 1.69 (1.23–2.33), P_{trend} = 0.0002
Gunter et al. (2009); USA; Women's Health Initiative Observational Study	Case–cohort; 835, 816	Vitros ECi immunodiagnostic assay	Estradiol, tertiles All, HR = 1.59 (1.00–2.55), P_{trend} = 0.04 Non-HRT users, HR = 1.59 (1.00–2.55), P_{trend} = 0.04 Further adjustments, HR = 1.87 (1.11–3.15), P_{trend} = 0.03

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Baglietto et al. (2010); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 197, 857; postmenopausal	Estradiol and testosterone: electrochemiluminescence immunoassay Estrone sulfate: radioimmunoassay DHEAS: competitive immunoassay Androstenedione: radioimmunoassay SHBG: immunometric assay	Total estradiol, quartiles HR = 1.44 (0.89–2.35), P_{trend} = 0.12 Free estradiol, quartiles HR = 1.75 (1.06–2.89), P_{trend} = 0.01 Estrone sulfate, quartiles HR = 2.05 (1.24–3.37), P_{trend} < 0.01 Testosterone, quartiles HR = 1.25 (0.78–2.01), P_{trend} = 0.37 DHEAS, quartiles HR = 1.41 (0.88–2.27), P_{trend} = 0.17 Androstenedione, quartiles HR = 1.49 (0.91–2.44), P_{trend} = 0.08 SHBG, quartiles HR = 0.33 (0.19–0.55), P_{trend} < 0.01
Farhat et al. (2011); USA; Women's Health Initiative Observational Study	Case–cohort; 317, 594; postmenopausal	Radioimmunoassay	Estradiol, quartiles ER+, HR = 1.86 (1.00–3.45), P_{trend} = 0.08 ER–, HR = 0.83 (0.43–1.61), P_{trend} = 0.60 Testosterone, quartiles ER+, HR = 1.55 (0.92–1.61), P_{trend} = 0.04 ER–, HR = 0.51 (0.28–0.94), P_{trend} = 0.03
James et al. (2011); several European countries; EPIC	Nested case–control; 554, 821; postmenopausal	Radioimmunoassay	Estradiol, ER+ Tertiles, OR = 2.58 (1.69–3.92), P_{trend} < 0.0001 Continuous, OR = 1.63 (1.29–2.107) Estradiol, ER+/PR+ Tertiles, OR = 2.91 (1.62–5.23), P_{trend} = 0.002 Continuous, OR = 1.58 (1.17–2.12) Free estradiol, ER+ Tertiles, OR = 2.05 (1.39–3.02), P_{trend} = 0.003 Continuous, OR = 1.63 (1.31–2.02) Free estradiol, ER+/PR+ Tertiles, OR = 2.09 (1.23–3.54), P_{trend} = 0.01 Continuous, OR = 1.61 (1.21–2.13) Testosterone, ER+ Tertiles, OR = 1.68 (1.16–2.44), P_{trend} = 0.006 Continuous, OR = 1.54 (1.27–1.87) Testosterone, ER+/PR+ Tertiles, OR = 2.27 (1.35–3.81), P_{trend} = 0.002 Continuous, OR = 1.79 (1.36–2.36)

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Tworoger et al. (2011); USA; Nurses' Health Study	Nested case–control; 265, 541; postmenopausal	Radioimmunoassay	Estrone, quintiles All, RR = 2.1 (1.3–3.4) ER+, RR = 2.8 (1.5–5.3) Estradiol, quintiles All, RR = 2.4 (1.4–4.1) ER+, RR = 2.9 (1.4–5.9) Estrone sulfate, quintiles All, RR = 2.4 (1.5–3.9) ER+, RR = 2.2 (1.2–4.0) Testosterone, quintiles All, RR = 1.8 (1.1–2.9) ER+, RR = 2.0 (1.0–3.7) Androstenedione, quintiles All, RR = 2.1 (1.3–3.6) ER+, RR = 2.6 (1.3–5.0) DHEA, quintiles All, RR = 1.5 (0.9–2.4) ER+, RR = 1.6 (0.9–2.9) DHEAS, quintiles All, RR = 2.5 (1.4–4.2) ER+, RR = 2.0 (1.0–3.8)
Fuhrman et al. (2012); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 227, 423; postmenopausal	LC-MS	Unconjugated estradiol, continuous HR = 2.07 (1.19–3.62), P_{trend} = 0.01 2-Hydroxylation pathway, continuous HR = 0.66 (0.51–0.87), P_{trend} = 0.003 2/16-Hydroxylation pathway, continuous HR = 0.62 (0.45–0.86), P_{trend} = 0.05
Sieri et al. (2012); Italy; ORDET Cohort	Nested case–control; 356; 1537	Chemiluminescence immunoassay	SHBG, quartiles, diagnosis > 55 yr RR = 0.60 (0.36–0.99), P_{trend} = 0.059
Würtz et al. (2012); Denmark; Diet, Cancer and Health Cohort	Nested case–control; 348, 348; postmenopausal	Radioimmunoassay	Non-HRT users Estradiol, tertiles RR = 1.56 (0.70–3.51), P_{trend} = 0.55 Estrone, tertiles RR = 2.02 (0.83–4.89), P_{trend} = 0.06 Estrone sulfate, tertiles RR = 4.21 (1.81–9.81), P_{trend} = 0.01

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Fortner et al. (2013); USA; Nurses' Health Study II	Nested case–control; 634, 1264 (514, 1030 with timed samples)	Estrogens and testosterone: organic extraction, celite chromatography, radioimmunoassay SHBG and progesterone: automated immunoassay or chemiluminescence immunometric assay	Follicular phase Estradiol, all Quintiles, OR = 1.0 (0.7–1.5), P_{trend} = 0.76 Doubling, OR = 0.6 (0.4–0.9), P_{trend} < 0.01 Estradiol, invasive Doubling, OR = 0.6 (0.4–0.9), P_{trend} < 0.01 Estradiol, ER+/PR+ Doubling, OR = 0.6 (0.4–0.9), P_{trend} = 0.01 Free estradiol, all Quintiles, OR = 0.8 (0.5–1.3), P_{trend} = 0.48 Doubling, OR = 0.5 (0.4–0.8), P_{trend} < 0.01 Free estradiol, invasive Doubling, OR = 0.5 (0.4–0.7), P_{trend} < 0.01 Free estradiol, ER+/PR+ Doubling, OR = 0.4 (0.4–0.7), P_{trend} < 0.01 Testosterone, all Quintiles, OR = 1.2 (0.9–1.7), P_{trend} = 0.32 SHBG, all Quintiles, OR = 1.2 (0.8–1.6), P_{trend} = 0.23
Key et al. (2013); USA, United Kingdom, several European countries; 7 prospective studies	Pooled analysis; 767, 1699	Radioimmunoassay, competitive immunoassay, LC-MS	Estradiol, quintiles OR = 1.41 (1.02–1.95), P_{trend} = 0.0042 Calculated free estradiol, quintiles OR = 1.19 (0.86–1.64), P_{trend} = 0.014 Estrone, quintiles OR = 1.50 (1.02–2.19), P_{trend} = 0.014 Androstenedione, quintiles OR = 1.68 (1.18–2.39), P_{trend} = 0.0026 DHEAS, quintiles OR = 1.45 (1.07–1.95), P_{trend} = 0.010 Testosterone, quintiles OR = 1.32 (0.98–1.76), P_{trend} = 0.018 Calculated free testosterone, quintiles OR = 1.25 (0.94–1.66), P_{trend} = 0.15
Schernhammer et al. (2013); Italy; ORDET Cohort	Nested case–control; 104, 225; premenopausal	Estradiol: radioimmunoassay Testosterone and free testosterone: radioimmunoassay SHBG: chemiluminescence immunometric assay	Free testosterone, tertiles OR = 2.43 (1.15–5.10), P_{trend} = 0.03 Total testosterone, tertiles OR = 1.27 (0.62–2.61), P_{trend} = 0.51 Progesterone, tertiles OR = 1.16 (0.60–2.27), P_{trend} = 0.75 Estradiol, tertiles OR = 0.69 (0.35–1.35), P_{trend} = 025 SHBG, tertiles OR = 0.93 (0.50–1.72), P_{trend} = 0.78

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Zhang et al. (2013); USA; Nurses' Health Study	Nested case–control; 707; 1414	Radioimmunoassay or LC-MS or solid-phase competitive chemiluminescence enzyme immunoassay	Estradiol, quartiles RR = 2.1 (1.6–2.7), P_{trend} < 0.001 Free estradiol, quartiles RR = 1.9 (1.4–2.4), P_{trend} < 0.001 Testosterone, quartiles RR = 1.5 (1.2–1.9), P_{trend} < 0.001 Free testosterone, quartiles RR = 1.9 (1.5–2.5), P_{trend} < 0.001 DHEAS, quartiles RR = 1.7 (1.3–2.3), P_{trend} = 0.001 SHBG, quartiles RR = 0.68 (0.52–0.88), P_{trend} = 0.004
Dallal et al. (2014); USA; Breast and Bone Follow-up to the Fracture Intervention Trial	Case–cohort; 407, 496; postmenopausal	LC-MS	Estradiol, quintiles HR = 1.86 (1.19–2.90), P_{trend} = 0.04 2-Hydroxylation pathway, quintiles HR = 0.69 (0.46–1.05), P_{trend} = 0.01 4-Hydroxylation pathway, quintiles HR = 0.61 (0.40–0.93), P_{trend} = 0.004 2/16-Hydroxylation pathway, quintiles HR = 0.60 (0.40–0.90), P_{trend} = 0.002
Kaaks et al. (2014b); several European countries; EPIC	Nested case–control; 801, 1132	Estradiol: immunoassay Progesterone and testosterone: radioimmunoassay SHBG: sandwich immunoradiometric assay	Estradiol, quartiles OR = 1.04 (0.93–1.15), P_{trend} = 0.52 Progesterone, quartiles OR = 1.00 (0.89–1.13), P_{trend} = 0.98 SHBG, quartiles OR = 0.98 (0.88–1.08), P_{trend} = 0.64 Testosterone, quartiles OR = 1.56 (1.15–2.13), P_{trend} = 0.02 Free testosterone, quartiles OR = 1.33 (0.99–1.79), P_{trend} = 0.04
Insulin			
Toniolo et al. (2000); USA; New York University Women's Health Study	Nested case–control; premenopausal: 172, 486; postmenopausal: 115, 220	Radioimmunoassay	C-peptide, quartiles Premenopausal, RR = 0.76 (0.44–1.31), P_{trend} = 0.90 Postmenopausal, RR = 1.24 (0.66–2.34), P_{trend} = 0.58
Kaaks et al. (2002); Sweden; Umeå Cohort	Nested case–control; 246, 454	Double-antibody immunoradiometric assay	Insulin, quartiles OR = 0.59 (0.30–1.18), P_{trend} = 0.88
Mink et al. (2002); USA; Atherosclerosis Risk in Communities Study Cohort	Cohort; 189, 7705	Radioimmunoassay	Insulin, quartiles RR = 1.01 (0.55–1.86), P_{trend} = 0.87
Muti et al. (2002); Italy; ORDET Cohort	Nested case–control; premenopausal: 69, 265; postmenopausal: 64, 238	Double-antibody radioimmunoassay	Insulin, quartiles Premenopausal, RR = 1.72 (0.71–4.15), P_{trend} = 0.14 Postmenopausal, RR = 0.85 (0.36–2.00), P_{trend} = 0.76

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Keinan-Boker et al. (2003); The Netherlands; EPIC, PPHV	Nested case–control; EPIC: 71, 163; PPHV: 78, 170; postmenopausal	Competitive radioimmunoassay	C-peptide, quartiles OR = 1.3 (0.7–2.7)
Verheus et al. (2006); several European countries; EPIC	Nested case–control; 1141, 2204	Radioimmunoassay	C-peptide, quintiles Non-fasting ≤ 50 yr, OR = 0.74 (0.30–1.82), P_{trend} = 0.35 50–60 yr, OR = 1.08 (0.56–2.08), P_{trend} = 0.51 > 60 yr, OR = 1.69 (0.97–2.95), P_{trend} = 0.22 Fasting, all ORs: NS
Cust et al. (2009); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 561, 561	Radioimmunoassay	C-peptide, tertiles < 55 yr, OR = 0.75 (0.44–1.29), P_{trend} = 0.34 ≥ 55 yr, OR = 1.32 (0.84–2.05), P_{trend} = 0.20
Gunter et al. (2009); USA; Women's Health Initiative Observational Study	Case–cohort; 835, 816; postmenopausal	ELISA	Insulin, quartiles HR = 1.46 (1.00–2.13), P_{trend} = 0.2 Non-HRT users, HR = 2.48 (1.38–4.47), P_{trend} < 0.001 Adjusted also for estradiol, HR = 2.40 (1.30–4.41), P_{trend} < 0.001
Kabat et al. (2009); USA; Women's Health Initiative	Longitudinal study; 190, 5450; postmenopausal	ELISA	Insulin, tertiles HR = 2.22 (1.39–3.53), P_{trend} = 0.0008
Tworoger et al. (2011); USA; Nurses' Health Study	Nested case–control; 265, 541	ELISA	C-peptide, quintiles All, RR = 1.4 (0.8–2.4)
Sieri et al. (2012); Italy; ORDET Cohort	Nested case–control; 356, 1537	Chemiluminescence immunoassay	Insulin, quartiles Premenopausal, RR = 1.52 (0.92–2.51), P_{trend} = 0.08 Postmenopausal, RR = 1.31 (0.81–2.12), P_{trend} = 0.25
Parekh et al. (2013); USA; Framingham Heart Study-Offspring Cohort	Cohort; 217, 2152	NR	Insulin, tertiles HR = 1.41 (0.88–2.24), P_{trend} = 0.33
IGFs			
Hankinson et al. (1998b); USA; Nurses' Health Study	Nested case–control; 397, 620	ELISA	IGF-1 Premenopausal, tertiles RR = 2.33 (1.06–5.16), P_{trend} = 0.08 Adjusted for IGFBP-3, RR = 2.88 (1.21–6.85), P_{trend} = 0.02 Premenopausal, < 50 yr at blood collection, tertiles RR = 4.58 (1.75–12.0), P_{trend} = 0.02 Adjusted for IGFBP-3, RR = 7.28 (2.40–22.0), P_{trend} = 0.01 Postmenopausal, quintiles RR = 0.85 (0.53–1.39), P_{trend} = 0.63

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Toniolo et al. (2000); USA; New York University Women's Health Study	Nested case–control; premenopausal: 172, 486; postmenopausal: 115, 220	Radioimmunoassay	IGF-1 Premenopausal, quartiles OR = 1.60 (0.91–2.81), P_{trend} = 0.09 Adjusted for IGFBP-3, OR = 1.49 (0.80–2.79) Premenopausal, < 50 yr at blood collection, quartiles OR = 2.30 (1.07–4.94), P_{trend} = 0.03 Adjusted for IGFBP-3, OR = 1.90 (0.82–4.42) Postmenopausal, quintiles OR = 0.95 (0.49–1.86), P_{trend} = 0.87
Kaaks et al. (2002); Sweden; Umeå and Malmö Cohorts	Nested case–control; 513, 987	Double-antibody immunoradiometric assay	IGF-1, quartiles OR = 1.17 (0.84–1.63), P_{trend} = 0.55 < 50 yr at recruitment, OR = 0.63 (0.29–2.39) ≥ 50 yr at recruitment, OR = 1.29 (0.80–2.07)
Muti et al. (2002); Italy; ORDET Cohort	Nested case–control; premenopausal: 69, 265; postmenopausal: 64, 238	Double-antibody immunoradiometric assay	IGF-1, quartiles Premenopausal, RR = 3.12 (1.13–8.60), P_{trend} = 0.01 Postmenopausal, RR = 0.58 (0.24–1.36), P_{trend} = 0.25 All other analytes: NS
Keinan-Boker et al. (2003); The Netherlands; EPIC, PPHV	Nested case–control; 149, 333; postmenopausal	Immunoradiometric assay	IGF-1, quartiles OR = 1.1 (0.6–2.1)
Allen et al. (2005); United Kingdom; Guernsey Cohort	Nested case–control; premenopausal: 70, 209; postmenopausal: 47, 141	Double-antibody ELISA	IGF-1, tertiles Premenopausal, OR = 1.71 (0.74–3.95), P_{trend} = 0.21 Postmenopausal, OR = 0.73 (0.29–1.84), P_{trend} = 0.52
Rinaldi et al. (2005); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study Cohort, ORDET Cohort	Nested case–control; 220, 434; premenopausal	ELISA	IGF-1, quintiles OR = 1.41 (0.75–2.63), P_{trend} = 0.15
Lukanova et al. (2006); Sweden; Northern Sweden Maternity Cohort	Nested case–control; 212, 369	Immunoradiometric assay	IGF-1, tertiles OR = 1.7 (1.1–2.7), P_{trend} = 0.02

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Baglietto et al. (2007); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 423, 1901	ELISA	IGF-1, quartiles All, HR = 1.20 (0.87–1.65), P_{trend} = 0.38 Premenopausal, HR = 0.83 (0.49–1.38), P_{trend} = 0.29 Postmenopausal, HR = 1.59 (1.03–2.44), P_{trend} = 0.05 ≥ 60 yr at follow-up, HR = 1.61 (1.04–2.51), P_{trend} = 0.06
Vatten et al. (2008); Norway; Janus Biobank	Nested case–control; 325, 647	Double-antibody radioimmunoassay	IGF-1, quintiles, adjusted for IGFBP-3 OR = 1.46 (0.93–2.32), P_{trend} = 0.15 IGFBP-3, quintiles, adjusted for IGF-1 OR = 0.78 (0.49–1.23), P_{trend} = 0.12 T3 for IGF-1 and T1 for IGFBP-3 (tertiles) OR = 2.00 (1.01–3.96)
Gunter et al. (2009); USA; Women's Health Initiative Observational Study	Case–cohort; 835, 816; postmenopausal	ELISA	Total IGF-1, quartiles All, HR = 1.21 (0.85–1.72), P_{trend} = 0.92 Non-HRT users, HR = 0.99 (0.59–1.64), P_{trend} = 0.72
Sakauchi et al. (2009); Japan; Japan Collaborative Cohort Study	Nested case–control; 63, 187	Immunoradiometric assay	IGF-1, tertiles Premenopausal, OR = 1.2 (0.32–4.09), P_{trend} = 0.81 Postmenopausal, OR = 2.8 (0.73–10.6), P_{trend} = 0.17
Key et al. (2010); 12 countries; 17 prospective studies	Pooled analysis; 4790, 9428	NR	IGF-1, quintiles All, OR = 1.28 (1.14–1.44), P_{trend} < 0.0001 Premenopausal, OR = 1.21 (1.00–1.45), P_{trend} = 0.50 Postmenopausal, OR = 1.33 (1.14–1.55), P_{trend} = 0.0002 IGFBP-3, quintiles All, OR = 1.3 (0.99–1.28), P_{trend} < 0.062 IGFBP-3, quintiles Premenopausal, OR = 1.00 (0.82–1.22), P_{trend} = 0.921 Postmenopausal, OR = 1.23 (1.04–1.45), P_{trend} = 0.012
Tworoger et al. (2011); USA; Nurses' Health Study	Nested case–control; 265, 541; postmenopausal	ELISA	IGF-1, quintiles RR = 1.1 (0.6–2.0)

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Kaaks et al. (2014a); several European countries; EPIC	Nested case–control; 938, 1394	ELISA	IGF-1, all Quartiles, OR = 1.34 (1.0–1.78) IGF-1, ER+ Quartiles, OR = 1.41 (1.01–1.98) Continuous, OR = 1.17 (1.04–1.33), P_{trend} = 0.01 IGF-1, ER+, diagnosis ≥ 50 yr Tertiles, OR = 1.38 (1.01–1.89) Continuous, OR = 1.19 (1.04–1.36), P_{trend} = 0.01
Inflammatory factors			
Krajcik et al. (2003); USA; Kaiser Permanente Medical Care Program	Nested case–control; 81, 81; premenopausal	ELISA	TNF-α, quartiles OR = 0.60 (0.15–2.31), P_{trend} = 0.45 sTNFR1, quartiles OR = 0.67 (0.20–2.25), P_{trend} = 0.78 sTNFR2, quartiles OR = 0.46 (0.06–3.50), P_{trend} = 0.63
Stattin et al. (2004a); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 149, 258; postmenopausal	Double-antibody radioimmunoassay	Leptin, quartiles OR = 0.94 (0.53–1.67), P_{trend} = 0.54
Siemes et al. (2006); The Netherlands; Rotterdam Study	Cohort; 184, 3790	Particle immunoassay	CRP Tertiles, HR = 1.59 (1.05–2.41) > 3 vs < 1 mg/L, HR = 1.68 (1.14–2.47) Continuous, HR = 1.28 (1.07–1.54)
Tworoger et al. (2007a); USA; Nurses' Health Study and Nurses' Health Study II Cohorts	Nested case–control; 1477, 296	Radioimmunoassay	Adiponectin, quartiles RR = 0.89 (0.71–1.11), P_{trend} = 0.54 Postmenopausal, RR = 0.73 (0.55–0.98), P_{trend} = 0.08
Allin et al. (2009); Denmark; Copenhagen City Health Study	Cohort; 202, 1624	Turbidimetry/nephelometry	CRP Quintiles, OR = 0.9 (0.5–1.7) > 3 vs < 1 mg/L, HR = 0.7 (0.4–1.4)
Cust et al. (2009); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 561, 561	Double-antibody radioimmunoassay	Leptin, tertiles < 55 yr, OR = 0.80 (0.52–1.22), P_{trend} = 0.29 ≥ 55 yr, OR = 1.15 (0.76–1.74), P_{trend} = 0.53 Stage I, OR = 0.64 (0.41–1.00), P_{trend} = 0.06 Stage II–IV, OR = 1.37 (0.91–1.06), P_{trend} = 0.14 Adiponectin, tertiles < 55 yr, OR = 0.56 (0.28–1.11), P_{trend} = 0.08 ≥ 55 yr, OR = 0.96 (0.55–1.65), P_{trend} = 0.95 Stage I, OR = 0.74 (0.40–1.38), P_{trend} = 0.42 Stage II–IV, OR = 0.83 (0.46–1.51), P_{trend} = 0.53
Harris et al. (2011); USA; Nurses' Health Study II	Nested case–control; 330, 636; premenopausal	Enzyme immunoassay	Leptin, quartiles OR = 0.55 (0.31–0.99), P_{trend} = 0.04

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Gaudet et al. (2013); Cancer Prevention Study-II Nutrition Cohort	Nested case–control; 302, 302; postmenopausal	ELISA	Total adiponectin, tertiles OR = 0.84 (0.54–1.30), P_{trend} = 0.38 CRP, tertiles OR = 1.09 (0.70–1.70), P_{trend} = 0.16
Gross et al. (2013); USA; CLUE II Cohort	Nested case–control; 272, 272; postmenopausal	ELISA	Leptin, tertiles OR = 1.98 (1.20–3.29), P_{trend} = 0.05 Adiponectin, tertiles OR = 1.63 (1.02–2.60), P_{trend} = 0.08 sTNFR2, tertiles OR = 2.44 (1.30–4.58), P_{trend} = 0.008
Liu et al. (2013); 13 studies	Meta-analysis; 3578, 4363	NR	Adiponectin OR = 0.838 (0.744–0.943)
Prizment et al. (2013); USA; Atherosclerosis Risk in Communities Study Cohort	Cohort; 176, 7603	Immunoturbidimetric assay	CRP, continuous HR = 1.27 (1.07–1.51)
Touvier et al. (2013); France; Supplémentation en Vitamines et Minéraux Antioxydants Trial	Nested case–control; 218, 436	ELISA	hsCRP, quartiles OR = 1.25 (0.73–2.14), P_{trend} = 0.7 Leptin, quartiles OR = 0.64 (0.34–1.20), P_{trend} = 0.1 Adiponectin, quartiles OR = 1.13 (0.68–1.87), P_{trend} = 0.4
Dossus et al. (2014); France; Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale	Nested case–control; 549, 1040; postmenopausal	Particle-enhanced immunoturbidimetric assay	CRP, all < 1.5 vs 2.5–10 mg/L, OR = 1.24 (0.92–1.66) Continuous, OR = 1.13 (0.98–1.29), P_{trend} = 0.09 CRP, BMI ≥ 25 kg/m^2 < 1.5 vs 2.5–10 mg/L, OR = 1.92 (1.20–3.08) Continuous, OR = 1.52 (1.16–2.00), P_{trend} = 0.003
Macis et al. (2014); 15 studies	Meta-analysis; 4249	NR	Adiponectin SRR = 0.66 (0.50–87)
Chan et al. (2015); 12 studies	Meta-analysis; 3522, 69 610	NR	CRP, doubling concentration RR = 1.07 (10.2–1.12)

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Gunter et al. (2015b); USA; Women's Health Initiative	Case–cohort; 875, 839; postmenopausal	CRP: latex-enhanced immunonephelometry Leptin and TNF-α: Milliplex Human Adipokine Panel B Adiponectin, PAI-1, and resistin: Milliplex Human Adipokine Panel A IL-6: ELISA	CRP, quartiles All, HR = 1.24 (0.86–1.80), P_{trend} = 0.12 Non-HRT users, HR = 1.67 (1.04–2.68), P_{trend} = 0.029 Leptin, quartiles All, HR = 1.39 (0.93–2.09), P_{trend} = 0.279 Adiponectin, quartiles All, HR = 0.76 (0.55–1.06), P_{trend} = 0.78 Resistin, quartiles All, HR = 0.93 (0.68–1.27), P_{trend} = 0.664 PAI-1, quartiles All, HR = 1.33 (0.96–1.86), P_{trend} = 0.145 Non-HRT users, HR = 1.71 (1.02–2.89), P_{trend} = 0.077 IL-6, quartiles All, HR = 1.20 (0.85–1.69), P_{trend} = 0.528 TNF-α, quartiles All, HR = 0.82 (0.59–1.14), P_{trend} = 0.292
Wang et al. (2015); China; Kailuan Female Cohort	Cohort; 87, 19 437	Nephelometric assay	hsCRP, < 1 vs > 3 mg/L All, HR = 1.74 (1.01–2.97), P_{trend} = 0.047 Women < 50 yr, HR = 2.76 (1.18–6.48) Excluding CRP > 10 mg/L, HR = 1.89 (1.08–3.32), P_{trend} = 0.029

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; ER+, estrogen receptor-positive; HR, hazard ratio; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; LC-MS, liquid chromatography–mass spectrometry; NR, not reported; NS, no significant association; OR, odds ratio; PAI-1, plasminogen activator inhibitor 1; PPHV, Monitoring Project on Cardiovascular Disease Risk Factors; PR+, progesterone receptor-positive; RR, relative risk; SHBG, sex hormone-binding globulin; SRR, summary relative risk; sTNFR, soluble tumour necrosis factor receptor; TNF, tumour necrosis factor; yr, year or years.

Table 4.3 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the endometrium

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Zeleniuch-Jacquotte et al. (2001); USA; New York University Women's Health Study Cohort	Nested case–control; 57, 222; postmenopausal	Estradiol and estrone: organic extraction, celite chromatography, radioimmunoassay SHBG: chemiluminescence immunometric assay Free estradiol: ultrafiltration method Estradiol bound to SHBG: concanavalin A–agarose binding assay	Estradiol, tertiles OR = 1.8 (0.75–4.2), P_{trend} = 0.19 Free estradiol, tertiles OR = 2.8 (1.3–6.4), P_{trend} = 0.004 SHBG-bound estradiol, tertiles OR = 0.60 (0.26–1.4), P_{trend} = 0.22 Estrone, tertiles OR = 3.2 (1.3–7.8), P_{trend} = 0.008 SHBG, tertiles OR = 0.49 (0.22–1.1), P_{trend} = 0.08
Lukanova et al. (2004a); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 124, 236; postmenopausal, non-HRT users	Estrone: radioimmunoassay or double-antibody radioimmunoassay Estradiol: radioimmuno-assay or ultrasensitive double-antibody radio-immunoassay SHBG: immunometric chemiluminescence assay or immunoradiometric assay	Estrone, quartiles OR = 3.67 (1.71–7.88), P_{trend} = 0.0007 Estradiol, quartiles OR = 4.13 (1.76–9.72), P_{trend} = 0.0008 SHBG, quartiles OR = 0.46 (0.20–1.05), P_{trend} = 0.01
Allen et al. (2008); several European countries; EPIC	Nested case–control; 247, 481; premenopausal (55, 107) and postmenopausal (192, 374)	Estrone and estradiol: radioimmunoassay with double-antibody system SHBG: solid-phase sandwich immunoradiometric assay	Postmenopausal women: Estrone, tertiles OR = 2.66 (1.50–4.72), $P_{trend\ (continuous)}$ = 0.002 Estradiol, tertiles OR = 2.07 (1.20–3.60), $P_{trend\ (continuous)}$ = 0.001 Free estradiol, tertiles OR = 1.66 (0.98–2.82), $P_{trend\ (continuous)}$ = 0.001 SHBG, tertiles OR = 0.57 (0.34–0.95), $P_{trend\ (continuous)}$ = 0.004
Gunter et al. (2008a); USA; Women's Health Initiative	Case–cohort; 250, 465; postmenopausal	Vitros ECi immunodiagnostic assay	Estradiol, tertiles HR = 3.16 (1.71–5.81), P_{trend} < 0.001
Brinton et al. (2016); USA; Women's Health Initiative Observational Study	Nested case–control; 313 (271 type I, 42 type II), 354; postmenopausal	Stable-isotope dilution liquid chromatography-tandem mass spectrometry	Estrone, quintiles OR = 3.19 (1.69–6.04), P_{trend} = 0.0001 Estradiol, quintiles OR = 1.41 (0.75–2.67), P_{trend} = 0.4531 Unconjugated estradiol, quintiles OR = 6.19 (2.95–13.03), P_{trend} = 0.0001 Conjugated estradiol, quintiles 0.95 (0.51–1.77), P_{trend} = 0.6747

Table 4.3 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Insulin			
Lukanova et al. (2004b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 166, 315; premenopausal and postmenopausal	Radioimmunoassay	C-peptide, quintiles OR = 4.76 (1.91–11.8), P_{trend} = 0.0002 OR = 4.40 (1.65–11.7), P_{trend} = 0.003, adjusted for BMI, other confounders
Cust et al. (2007a); several European countries; EPIC	Nested case–control; 286, 555; premenopausal and postmenopausal	Immunoradiometric assay	C-peptide, quartiles All, RR = 2.13 (1.33–3.41), P_{trend} = 0.001 Postmenopausal, RR = 1.28 (0.67–2.45), P_{trend} = 0.42, adjusted for free estradiol
Gunter et al. (2008a); USA; Women's Health Initiative	Case–cohort; 250 (205 endometrioid adenocarcinoma), 465; postmenopausal	ELISA	Insulin, quartiles Endometrioid adenocarcinoma, non-HRT users, HR = 2.33 (1.13–4.82), P_{trend} = 0.02, adjusted for age, estradiol BMI ≥ 25 kg/m^2, HR = 4.30 (1.62–11.43), P_{trend} = 0.001
IGFs			
Lukanova et al. (2004b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 166, 315; premenopausal and postmenopausal	Immunoradiometric assay (IGF-1 after acid–ethanol precipitation of IGFBPs)	IGFBP-1, quintiles OR = 0.30 (0.15–0.62), P_{trend} = 0.002 OR = 0.49 (0.22–1.07), P_{trend} = 0.06, adjusted for BMI, other confounders IGF-1: NS
Cust et al. (2007a); several European countries; EPIC	Nested case–control; 286, 555; premenopausal and postmenopausal	IGFBP-1: immunoradiometric assay IGFBP-2: radioimmunoassay	IGFBP-1, quartiles RR = 0.76 (0.47–1.21), P_{trend} = 0.25 IGFBP-2, quartiles RR = 0.56 (0.35–0.90), P_{trend} = 0.03
Gunter et al. (2008a); USA; Women's Health Initiative	Case–cohort; 250 (205 endometrioid adenocarcinoma), 465; postmenopausal	ELISA	Free IGF, quartiles Endometrioid adenocarcinoma, HR = 0.53 (0.31–0.90), P_{trend} = 0.05, adjusted for age, HRT, estradiol Overweight or obese, HR = 0.43 (0.20–0.97), adjusted for age, HRT, estradiol Total IGF-1: NS
Inflammatory factors			
Cust et al. (2007b); several European countries; EPIC	Nested case–control; 284, 548	ELISA	Adiponectin, quartiles RR = 0.56 (0.36–0.86), P_{trend} = 0.006, adjusted for BMI
Dossus et al. (2010); several European countries; EPIC	Nested case–control; 305, 574	CRP and IL-6: ELISA IL-1Ra: bead-based immunoassay	CRP, quartiles OR = 1.58 (1.03–2.41), P_{trend} = 0.02 IL-6, quartiles OR = 1.66 (1.08–2.54), P_{trend} = 0.008 IL-1Ra, quartiles OR = 1.82 (1.22–2.73), P_{trend} = 0.004 All ORs adjusted for BMI: NS

Table 4.3 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Dossus et al. (2011); several European countries; EPIC	Nested case–control: 270, 518	ELISA	TNF-α, quartiles OR = 1.73 (1.09–2.73), P_{trend} = 0.01
Soliman et al. (2011); USA; Nurses' Health Study	Nested case–control; 146; 377	ELISA	Adiponectin, > 15 µg/mL RR = 0.86 (0.53–1.39), P_{trend} = 0.48, adjusted for BMI
Wang et al. (2011); USA; Women's Health Initiative	Case–cohort; 151, 301; postmenopausal, non-HRT users	CRP: high-sensitivity latex-enhanced immunonephelometry IL-6: ultrasensitive solid-phase ELISA TNF-α: Milliplex Human Adipokine Panel B	CRP, quartiles HR = 2.29 (1.13–4.65), P_{trend} = 0.012, adjusted for age, BMI HR = 1.70 (0.78–3.68), P_{trend} = 0.127, adjusted also for estradiol, insulin IL-6, TNF-α: NS
Dallal et al. (2013); USA; Breast and Bone Follow-up to the Fracture Intervention Trial	Nested case–control; 62, 124	ELISA	Leptin, tertiles OR = 2.96 (1.21–7.25), P_{trend} < 0.01, adjusted for estradiol, C-peptide OR = 2.11 (0.69–6.44), P_{trend} = 0.18, adjusted also for BMI Adiponectin: NS
Luhn et al. (2013); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 167, 327	Radioimmunoassay	Leptin, tertiles All, OR = 2.77 (1.60–4.79), P_{trend} < 0.01 Non-HRT users, OR = 4.72 (1.15–19.38), P_{trend} = 0.02 Adiponectin, tertiles All, OR = 0.48 (0.29–0.80), P_{trend} < 0.01 Non-HRT users, OR = 0.25 (0.08–0.75), P_{trend} = 0.01

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; NR, not reported; NS, no significant association; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; TNF-α, tumour necrosis factor alpha.

Table 4.4 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the colorectum

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Gunter et al. (2008b); USA; Women's Health Initiative	Case–cohort; 273, 442; F	Vitros ECi immunodiagnostic assay	Estradiol, tertiles HR = 1.43 (0.95–2.16), P_{trend} = 0.09
Clendenen et al. (2009); USA; New York University Women's Health Study	Nested case–control; 148, 293; F	Estrone and estradiol: radioimmunoassay SHBG: immunometric chemiluminescence assay	Estrone, quartiles OR = 1.6 (0.8–3.0), P_{trend} = 0.09 Estradiol, tertiles OR = 0.8 (0.4–1.7), P_{trend} = 0.43 SHBG, quartiles OR = 0.8 (0.4–1.4), P_{trend} = 0.48
Hyde et al. (2012); Australia; Health in Men Study	Cohort; 104, 3416; M	Chemiluminescence immunoassay	SHBG, 60 vs 40 nmol/L sub-HR = 0.98 (0.62–1.56), P_{trend} = 0.84
Lin et al. (2013); USA; Nurses' Health Study, Women's Health Study, Health Professionals Follow-up Study, Physicians' Health Study II	Nested case–control; M: 439, 719; F: 293, 437	Estrone and estradiol: liquid chromatography-tandem mass spectrometry SHBG: electrochemilumi-nescence immunoassay	Estradiol, quartiles M: RR = 1.15 (0.73–1.81), P_{trend} = 0.67 F: RR = 1.12 (0.62–2.03), P_{trend} = 0.93 Estrone, quartiles M: RR = 1.04 (0.68–1.62), P_{trend} = 0.96 F: RR = 1.30 (0.74–2.26), P_{trend} = 0.55 SHBG, quartiles M: RR = 0.65 (0.42–0.99), P_{trend} = 0.02 F: RR = 1.17 (0.63–2.20), P_{trend} = 0.68
Falk et al. (2015); USA; Breast and Bone Follow-up to the Fracture Intervention Trial	Case–cohort; 187, 501; F	NR	Estradiol, quartiles OR = 0.98 (0.58–1.64), P_{trend} = 1.00 Estrone, quartiles OR = 1.15 (0.69–1.93), P_{trend} = 0.54
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F	Estrone and estradiol: radioimmunoassay SHBG: immunometric chemiluminescence assay	Estradiol quartiles OR = 0.64 (0.43–0.97), P_{trend} = 0.12 Estrone, quartiles OR = 0.50 (0.33–0.75), P_{trend} = 0.002 SHBG, quartiles OR = 2.30 (1.51–3.51), P_{trend} < 0.0001
Insulin			
Schoen et al. (1999); USA; Cardiovascular Health Study	Cohort; 102, 5747; M&F	Solid-phase radioimmunoassay	Insulin, quartiles RR = 1.2 (0.7–2.1)
Kaaks et al. (2000); USA; New York University Women's Health Study	Nested case–control; 102, 200; F	Radioimmunoassay	C-peptide, quintiles OR = 2.92 (1.26–6.75), P_{trend} = 0.001
Palmqvist et al. (2003); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 168, 376; M&F	Double-antibody immunoradiometric assay	Insulin, quartiles OR = 1.22 (0.64–2.31), P_{trend} = 0.41
Saydah et al. (2003); USA; CLUE II Cohort	Nested case–control; colon: 132, rectum: 41, 346; M&F	Ultrasensitive ELISA	Insulin, quartiles OR = 0.78 (0.45–1.35), P_{trend} = 0.24
Ma et al. (2004); USA; Physicians' Health Study	Nested case–control; 176, 294; M	ELISA	C-peptide, quintiles RR = 2.7 (1.2–6.2), P_{trend} = 0.047

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Stattin et al. (2004b); Norway; Janus Biobank	Nested case–control; colon: 235, 235; rectum: 143, 143; M	Radioimmunoassay	C-peptide, quartiles Colon: OR = 1.82 (0.67–4.86), P_{trend} = 0.19 Rectum: OR = 0.44 (0.10–1.99), P_{trend} = 0.21
Wei et al. (2005a); USA; Nurses' Health Study	Nested case–control; 182, 350; F	ELISA	C-peptide, quartiles RR = 1.17 (0.63–2.20), P_{trend} = 0.94
Limburg et al. (2006); Finland; ATBC	Case–cohort; 134, 399; M	Two-site immunoenzymatic assay	Insulin, quartiles, age-adjusted HR = 1.84 (1.03–3.30), P_{trend} = 0.12 Insulin, quartiles, multivariate HR = 1.74 (0.74–4.07), P_{trend} = 0.40
Jenab et al. (2007); several European countries; EPIC	Nested case–control; 1078, 1078; M&F	Radioimmunoassay	C-peptide, quintiles OR = 1.37 (1.00–1.88), P_{trend} = 0.03
Otani et al. (2007); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; M: 196, 392, F: 179, 35	Radioimmunoassay	C-peptide, quartiles M: OR = 3.2 (1.4–7.6), P_{trend} = 0.0072 F: OR = 0.78 (0.38–1.6), P_{trend} = 0.49
Gunter et al. (2008b); USA; Women's Health Initiative	Case–cohort; 429, 800; F	ELISA	Insulin, quartiles HR = 1.89 (1.33–2.69), P_{trend} = 0.0005 Adjusted also for waist circumference, HR = 1.42 (0.91–2.23), P_{trend} = 0.11
Stocks et al. (2008); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 306, 595; M&F	Immunoradiometric assay	C-peptide, quartiles OR = 0.94 (0.62–1.41), P_{trend} = 0.82
Kabat et al. (2012); USA; Women's Health Initiative	Case–cohort; 80, 4669; F	ELISA	Insulin, ≥ 11.85 vs < 7.75 μU/mL HR = 1.11 (0.61–2.01), P_{trend} = 0.75
Ollberding et al. (2012); USA; Multiethnic Cohort Study	Nested case–control; 249, 1571; M&F	ELISA	Insulin, tertiles OR = 1.21 (0.84–1.75), P_{trend} = 0.29
Lin et al. (2013); USA; Nurses' Health Study, Women's Health Study, Health Professionals Follow-up Study, Physicians' Health Study II	Nested case–control; M: 439, 719; F: 293, 437	ELISA or electrochemiluminescence immunoassay	C-peptide, quartiles M: RR = 1.29 (0.80–2.08), P_{trend} = 0.27 F: RR = 1.73 (0.94–3.18), P_{trend} = 0.09
Parekh et al. (2013); USA; Framingham Heart Study-Offspring Cohort	Cohort; 71, 3433; M&F	NR	Insulin, ≥ 10.09 vs < 4.94 pmol/L HR = 2.10 (1.12–3.93), P = 0.0354
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F	ELISA	Insulin, quartiles OR = 0.76 (0.50–1.14), P_{trend} = 0.21
IGFs			
Ma et al. (1999); USA; Physicians' Health Study	Nested case–control; 193, 318; M	ELISA	IGF-1, quintiles RR = 1.36 (0.72–2.55), P_{trend} = 0.51 Adjusted for IGFBP-3, RR = 2.51 (1.15–5.46), P_{trend} = 0.02 IGFBP-3, quintiles RR = 0.47 (0.23–0.95), P_{trend} = 0.07
Giovannucci et al. (2000); USA; Nurses' Health Study Cohort	Nested case–control; 79, 158; F	ELISA	IGF-1, tertiles RR = 2.18 (0.94–5.08), P_{trend} = 0.10 IGFBP-3, tertiles RR = 0.28 (0.10–0.83), P_{trend} = 0.05

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Kaaks et al. (2000); USA; New York University Women's Health Study	Nested case–control; 102, 200; F	Double-antibody immunoradiometric assay	IGF-1, quintiles OR = 1.88 (0.72–4.91), P_{trend} = 0.25 IGFBP-3, quintiles OR = 2.46 (1.09–5.57), P_{trend} = 0.19
Probst-Hensch et al. (2001); China; Shanghai Cohort Study	Nested case–control; 135, 661; M	IGF-1: radioimmunoassay IGFBP-3: immunoradiometric assay	IGF-1, quintiles OR = 1.52 (0.82–2.85), P_{trend} = 0.34 IGFBP-3, quintiles OR = 1.72 (0.91–3.25), P_{trend} = 0.07
Palmqvist et al. (2002); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 168, 336; M&F	Double-antibody immunoradiometric assay	IGF-1, quartiles Colorectum: OR = 1.27 (0.65–2.47), P_{trend} = 0.51 Colon: OR = 2.66 (1.09–6.50), P_{trend} = 0.03 IGFBP-3, quartiles Colorectum: OR = 1.23 (0.68–2.22), P_{trend} = 0.24 Colon: OR = 1.93 (0.92–4.06), P_{trend} = 0.02
Nomura et al. (2003); USA; Honolulu Heart Program	Nested case–control; 282, 282; M	ELISA	IGF-1, quartiles OR = 1.5 (0.8–2.8), P_{trend} = 0.13 IGFBP-3, quartiles OR = 0.8 (0.4–1.6), P_{trend} = 0.45
Wei et al. (2005a); USA; Nurses' Health Study Cohort	Nested case–control; 137, 262; F	ELISA	IGF-1, quartiles, colon RR = 1.95 (0.97–3.91), P_{trend} = 0.09 IGFBP-3, quartiles, colon RR = 1.20 (0.62–2.30), P_{trend} = 0.62
Morris et al. (2006); United Kingdom; British United Provident Association Study	Nested case–control; 147, 440; M	ELISA	IGF-1, quartiles OR = 1.10 (0.56–2.18), P_{trend} = 0.65
Otani et al. (2007); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; M: 196, 392; F: 179, 358	Immunoradiometric assay	IGF-1, quartiles M: OR = 0.83 (0.40–1.7), P_{trend} = 0.91 F: OR = 0.83 (0.38–1.8), P_{trend} = 0.60 IGFBP-3, quartiles M: OR = 1.4 (0.65–2.8), P_{trend} = 0.60 F: OR = 1.1 (0.53–2.3), P_{trend} = 0.73
Gunter et al. (2008b); USA; Women's Health Initiative	Case–cohort; 438, 816; F	ELISA	Total IGF-1, quartiles HR = 1.04 (0.74–1.46), P_{trend} = 0.58 Free IGF-1, quartiles HR = 1.21 (0.86–1.72), P_{trend} = 0.16
Max et al. (2008); Finland; ATBC	Case–cohort; 134, 399; M	ELISA	IGF-1, quartiles RR = 0.92 (0.49–1.70), P_{trend} = 0.90 IGFBP-3, quartiles RR = 0.98 (0.51–1.88), P_{trend} = 0.85
Suzuki et al. (2009); Japan; Japan Collaborative Cohort Study	Nested case–control; 101, 302; M&F	Immunoradiometric assay	IGF-1, tertiles OR = 1.01 (0.49–2.10), P_{trend} = 0.35
Rinaldi et al. (2010); several European countries; EPIC	Nested case–control; 1121, 1121; M&F	ELISA	IGF-1, quintiles OR = 1.07 (0.81–1.40) IGFBP-3, quintiles OR = 1.17 (0.87–1.56)

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Ollberding et al. (2012); USA; Multiethnic Cohort Study	Nested case–control; IGF-1: 258, 1701; IGF-2: 255, 1571; M&F	ELISA	IGF-1, tertiles OR = 0.84 (0.60–1.17), P_{trend} = 0.30 IGFBP-3, tertiles OR = 0.63 (0.45–0.88), P_{trend} = 0.48
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F	ELISA	IGF-1, quartiles OR = 0.70 (0.48–1.03), P_{trend} = 0.15
Inflammatory factors			
Stattin et al. (2003); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 168, 327; M&F	Double-antibody immunoradiometric assay	Leptin, quartiles OR = 2.28 (1.09–4.76)
Stattin et al. (2004b); Norway; Janus Biobank	Nested case–control; colon: 235, 235; rectum: 143, 143; M	Radioimmunoassay	Leptin, quartiles Colon: OR = 2.72 (1.44–5.12), P_{trend} = 0.008 Rectum: OR = 0.91 (0.49–1.70), P_{trend} = 0.68
Tamakoshi et al. (2005); Japan; Japan Collaborative Cohort Study	Nested case–control; 58, 145; F	Immunometric sandwich enzyme immunoassay	Leptin, quintiles OR = 3.94 (1.04–14.9), P_{trend} = 0.02
Wei et al. (2005b); USA; Health Professionals Follow-up Study	Nested case–control; 179, 356; M	Radioimmunoassay	Adiponectin, quintiles RR = 0.42 (0.23–0.78), P_{trend} = 0.01
Stocks et al. (2008); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 306, 595; M&F	Leptin: radioimmunoassay Adiponectin: ELISA	Leptin, quartiles OR = 1.09 (0.74–1.61), P_{trend} = 0.29 Adiponectin, quartiles OR = 0.95 (0.63–1.44), P_{trend} = 0.61
Heikkilä et al. (2009); United Kingdom; British Women's Heart and Health Study, Caerphilly Cohort	Cohort; M: CRP: 41, 897; IL-6: 30, 845; F: 32, 3074	CRP: nephelometric assay IL-6: ELISA	CRP, continuous M: HR = 0.89 (0.66–1.22), P = 0.5 F: HR = 0.97 (0.70–1.34), P = 0.8 IL-6, continuous M: HR = 0.71 (0.41–1.23), P = 0.2 F: HR = 0.92 (0.53–1.60), P = 0.8
Chan et al. (2011); USA; Nurses' Health Study	Nested case–control; 280, 560; F	CRP: immunoturbidimetric assay IL-6 and sTNFR2: ELISA	CRP, quartiles RR = 0.65 (0.40–1.05), P_{trend} = 0.17 IL-6, quartiles RR = 1.18 (0.75–1.85), P_{trend} = 0.55 sTNFR2, quartiles RR = 1.67 (1.05–2.68), P_{trend} = 0.03
Aleksandrova et al. (2012a); several European countries; EPIC	Nested case–control; 1206, 1206; M&F	Multimeric ELISA	Adiponectin, quintiles OR = 0.71 (0.53–0.95), P_{trend} = 0.03
Aleksandrova et al. (2012b); several European countries; EPIC	Nested case–control; 1129, 1129; M&F	ELISA	Leptin, quintiles OR = 1.14 (0.81–1.61), P_{trend} = 0.85

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Ho et al. (2012); USA; Women's Health Initiative Observational Study	Nested case–cohort; 457, 841; F	Leptin, adiponectin, PAI-1, resistin, HGF, and TNF-α: multiplex assay IL-6: ultrasensitive solid-phase ELISA	Leptin, quartiles HR = 2.50 (1.70–3.67), $P_{trend} < 0.001$ Adiponectin, quartiles HR = 0.65 (0.45–0.94), $P_{trend} = 0.015$ PAI-1, quartiles HR = 1.87 (1.27–2.76), $P_{trend} = 0.006$ Resistin, quartiles HR = 1.16 (0.81–1.65), $P_{trend} = 0.329$ HGF, quartiles HR = 1.26 (0.87–1.82), $P_{trend} = 0.232$ TNF-α, quartiles HR = 0.97 (0.66–1.42), $P_{trend} = 0.969$ IL-6, quartiles HR = 1.41 (0.97–2.06), $P_{trend} = 0.043$ Adjusted for insulin, HR = 1.04 (0.68–1.58), $P_{trend} = 0.662$
Song et al. (2013); USA; Nurses' Health Study, Health Professionals Follow-up Study	Nested case–control; 616, 1205; M&F	ELISA	Adiponectin, quartiles M: RR = 0.55 (0.35–0.86), $P_{trend} = 0.02$ F: RR = 0.96 (0.67–1.39), $P_{trend} = 0.74$
Ho et al. (2014); USA; Women's Health Initiative Observational Study	Nested case–cohort; 433, 821; F	Milliplex Human Cytokine/ Chemokine Panel	sIL-6R, quartiles RR = 0.56 (0.38–0.83), $P_{trend} = 0.007$ sIL-1R2, quartiles RR = 0.44 (0.29–0.67); $P_{trend} < 0.001$ IL-1Ra, sgp130, sTNFR1, sTNFR2: NS
Zhou et al. (2014); CRP: 18 studies; IL-6: 6 studies	Meta-analysis; CRP: 4706 cases, IL-6: 1068 cases; M&F	NR	CRP, 1 unit change in natural logarithm RR = 1.12 (1.05–1.21) IL-6, 1 unit change in natural logarithm RR = 1.10 (0.88–1.36)
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F (postmenopausal)	Chemiluminescence immunometric assay	CRP, quartiles OR = 0.89 (0.60–1.34), $P_{trend} = 0.47$

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; HGF, hepatocyte growth factor; HR, hazard ratio; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; M, male; NR, not reported; NS, no significant association; OR, odds ratio; PAI-1, plasminogen activator inhibitor 1; RR, relative risk; SHBG, sex hormone-binding globulin; sTNFR, soluble tumour necrosis factor receptor; TNF-α, tumour necrosis factor alpha.

Table 4.5 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the prostate

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Gann et al. (1996); USA; Physicians' Health Study	Nested case–control; 222, 390	Testosterone, 3α-diolG, DHT, and estradiol: radioimmunoassay SHBG: radioimmunometric assay	Estradiol, quartiles OR = 0.56 (0.32–0.98), P_{trend} = 0.03 Testosterone, quartiles OR = 2.60 (1.34–5.02), P_{trend} = 0.004 DHT, quartiles OR = 0.71 (0.34–1.48), P_{trend} = 0.30 3α-diolG, quartiles OR = 1.60 (0.93–2.76), P_{trend} = 0.09 SHBG, quartiles OR = 0.46 (0.24–0.89), P_{trend} = 0.01
Platz et al. (2005b); USA; Health Professionals Follow-up Study	Nested case–control; 460, 460	Testosterone: chemiluminescence immunoassay SHBG: coated-tube non-competitive immunoradiometric assay	*Total prostate cancer* Testosterone, quartiles OR = 0.79 (0.48–1.31), P_{trend} = 0.79 SHBG, quartiles OR = 1.09 (0.66–1.82), P_{trend} = 0.97 *Gleason score ≥ 7 (n = 148)* Testosterone, quartiles OR = 0.26 (1.0–0.66), P_{trend} = 0.01 SHBG, quartiles OR = 2.72 (1.02–7.24), P_{trend} = 0.05
Severi et al. (2006a); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 524, 1859	Testosterone: electrochemi-luminescence immunoassay SHBG: immunometric assay DHEAS: competitive immunoassay Androstenedione: radioimmunoassay	*Aggressive prostate cancer* Total testosterone, doubling of concentration HR = 0.55 (0.32–0.95) Total testosterone, quartiles HR = 0.53 (0.28–1.03), P_{trend} = 0.03 SHBG, quartiles HR = 0.54 (0.28–1.04), P_{trend} = 0.1 DHEAS, quartiles HR = 0.38 (0.15–0.95), P_{trend} = 0.005 Androstenedione, quartiles HR = 0.46 (0.24–0.88), P_{trend} = 0.007
Wirén et al. (2007); Sweden; Västerbotten Intervention Project	Nested case–control; 392, 392	Testosterone: coated-tube radioimmunoassay SHBG: time-resolved immunofluorometric assay 3α-diolG: direct radioimmunoassay	Total testosterone, quartiles OR = 1.02 (0.62–1.68), P_{trend} = 0.83 Free testosterone, quartiles OR = 1.09 (0.67–1.78), P_{trend} = 0.92 SHBG, quartiles OR = 0.89 (0.55–1.46), P_{trend} = 0.56 3α-diolG, quartiles OR = 0.92 (0.60–1.41), P_{trend} = 1.00
Roddam et al. (2008); 18 prospective studies	Pooled analysis; 3886, 6438	NR	SHBG, quintiles RR = 0.86 (0.75–0.98), P_{trend} = 0.01 Testosterone, calculated free testosterone, DHT, DHEAS, androstenedione, androstanediol glucuronide, estradiol, calculated free estradiol: NS

Table 4.5 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Weiss et al. (2008); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 727, 889	Androstenedione and 3α-diolG: direct double-antibody radioimmunoassay Testosterone: direct radioimmunoassay SHBG: sandwich immunoradiometric assay	Androstenedione, quartiles OR = 0.96 (0.70–1.32), P_{trend} = 0.76 Testosterone, quartiles OR = 1.39 (0.92–2.08), P_{trend} = 0.22 Free testosterone, quartiles OR = 1.20 (0.87–1.65), P_{trend} = 0.36 SHBG, quartiles OR = 0.76 (0.52–1.10), P_{trend} = 0.22 3α-diolG, quartiles OR = 0.87 (0.60–1.18), P_{trend} = 0.31
Sawada et al. (2010); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; 201, 402	Testosterone: electrochemi-luminescence immunoassay SHBG: immunoradiometric assay	Total testosterone, quartiles OR = 0.71 (0.36–1.41), P_{trend} = 0.43 Free testosterone, quartiles OR = 0.70 (0.39–1.27), P_{trend} = 0.08 SHBG, quartiles OR = 1.38 (0.69–2.77), P_{trend} = 0.23
Hyde et al. (2012); Australia; Health in Men Study	Cohort; 297, 3338	Chemiluminescence immunoassay	Total testosterone, continuous HR = 1.10 (0.97–1.25), P = 0.140 Free testosterone, continuous HR = 1.13 (1.03–1.24), P = 0.013 SHBG, continuous HR = 0.97 (0.84–1.11), P = 0.615
Insulin			
Stattin et al. (2000); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 149, 298	Double-antibody radioimmunoassay	Insulin, quartiles OR = 0.98 (0.53–1.81), P_{trend} = 0.23
Hubbard et al. (2004); USA; Baltimore Longitudinal Study of Aging	Longitudinal study; 87, 823	Radioimmunoassay	Fasting insulin, quartiles RR = 0.72 (0.34–1.54), P_{trend} = 0.56 2-Hour insulin, quartiles RR = 0.64 (0.32–1.31), P_{trend} = 0.04
Stocks et al. (2007); Sweden; Västerbotten Intervention Project	Nested case–control; 392, 392	Immunoradiometric assay	C-peptide, continuous OR = 0.96 (0.79–1.16), P = 0.65
Albanes et al. (2009); Finland; ATBC	Case–cohort; 100, 400	Double-antibody immuno-chemiluminometric assay	Insulin, quartiles OR = 2.55 (1.18–5.51), P_{trend} = 0.2
Schenk et al. (2009); USA; Prostate Cancer Prevention Trial	Nested case–control; 698, 709	Multiplex sandwich ELISA	C-peptide, quartiles OR = 0.80 (0.59–1.08), P_{trend} = 0.31
Parekh et al. (2013); USA; Framingham Heart Study-Offspring Cohort	Cohort; 152, 1493	Radioimmunoassay	Insulin, tertiles HR = 1.21 (0.78–1.88), P_{trend} = 0.32
Lai et al. (2014); USA; Health Professionals Follow-up Study	Nested case–control; 1314, 1314	ELISA	C-peptide, continuous OR = 1.00 (0.93–1.08), P_{trend} = 0.99 C-peptide, quartiles OR = 1.05 (0.83–1.33)

Table 4.5 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
IGFs			
Chan et al. (1998); USA; Physicians' Health Study	Nested case–control; 152, 152	ELISA	IGF-1, quartiles RR = 2.41 (1.23–4.74), P_{trend} = 0.006
Stattin et al. (2000); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 149, 298	Double-antibody immunoradiometric assay	IGF-1, quartiles OR = 1.72 (0.93–3.19), P_{trend} = 0.006 < 59 yr, IGF-1, tertiles OR = 4.30 (1.19–15.50), P_{trend} = 0.01
Woodson et al. (2003); Finland; ATBC	Case–cohort; 100, 400	ELISA	IGF-1, quartiles OR = 1.00 (0.54–1.87), P_{trend} = 0.76
Stattin et al. (2004c); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 281, 560	Immunoradiometric assay	IGF-1, quartiles OR = 1.67 (1.02–2.71), P_{trend} = 0.05
Meyer et al. (2005); France; Supplémentation en Vitamines et Minéraux Antioxydants Trial	Nested case–control; 100, 400	Chemiluminescence immunoassay on an Immulite analyser	IGF-1, quartiles OR = 1.80 (0.76–4.27), P_{trend} = 0.13
Platz et al. (2005b); USA; Health Professionals Follow-up Study	Nested case–control; 462, 462	ELISA	IGF-1, quartiles OR = 1.37 (0.92–2.03), P_{trend} = 0.05
Severi et al. (2006b); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 524, 1826	ELISA	IGF-1, quartiles HR = 1.07 (0.79–1.46), P_{trend} = 0.5
Allen et al. (2007); several European countries; EPIC	Nested case–control; 630, 630	ELISA plus acid–ethanol precipitation	IGF-1, tertiles OR = 1.35 (0.99–1.82), P_{trend} = 0.08 Adjusted for IGFBP-3, OR = 1.39 (1.02–1.89), P_{trend} = 0.12
Weiss et al. (2007); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 727, 887	ELISA	IGF-1, quartiles OR = 1.14 (0.86–1.51), P_{trend} = 0.18
Mucci et al. (2010); USA; Physicians' Health Study	Nested case–control; 545, 545	ELISA	Free IGF-1, quartiles RR = 0.9 (0.6–1.3), P_{trend} = 0.78
Price et al. (2012); several European countries; EPIC	Nested case–control; 1542, 1542	DSL-10-5600 ACTIVE ELISA or IDS-iSYS immunoassay system	IGF-1, quartiles OR = 1.69 (1.35–2.13), P_{trend} = 0.0002 IGF-1, doubling OR = 1.38 (1.17–1.64), P_{trend} = 0.0002

Table 4.5 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Travis et al. (2016); 17 prospective and 2 cross-sectional studies	Pooled analysis; 10 554, 13 618	NR	*Prospective studies* IGF-1, quintiles OR = 1.29 (1.16–1.43), $P_{trend} < 0.001$ IGF-2, quintiles OR = 1.20 (1.00–1.43), $P_{trend} = 0.038$ IGFBP-1, quintiles OR = 0.81 (0.68–0.96), $P_{trend} = 0.053$ IGFBP-2, quintiles OR = 1.26 (1.03–1.54), $P_{trend} < 0.001$ IGFBP-3, quintiles OR = 1.25 (1.12–1.40), $P_{trend} < 0.001$
Inflammatory factors			
Stocks et al. (2007); Sweden; Västerbotten Intervention Project	Nested case–control; 392, 392	Double-antibody radioimmunoassay	Leptin, continuous OR = 0.93 (0.89–0.97), $P = 0.002$
Heikkilä et al. (2009); United Kingdom; Caerphilly Cohort	Cohort; CRP: 36, 897; IL-6: 40, 845	CRP: nephelometric assay IL-6: ELISA	CRP, continuous HR = 1.12 (0.81–1.56), $P = 0.5$ IL-6, continuous HR = 0.61 (0.40–0.96), $P = 0.031$
Schenk et al. (2009); USA; Prostate Cancer Prevention Trial	Nested case–control; 698, 709	Multiplex sandwich ELISA	Leptin, quartiles OR = 1.05 (0.73–1.50), $P_{trend} = 0.48$ Adiponectin, quartiles OR = 0.65 (0.47–0.87), $P_{trend} = 0.004$
Li et al. (2010); USA; Physicians' Health Study	Nested case–control; 654, 644	Competitive radioimmunoassay	Leptin, quartiles RR = 1.06 (0.65–1.72), $P_{trend} = 0.8$ Adiponectin, quartiles RR = 0.73 (0.46–1.14), $P_{trend} = 0.38$
Touvier et al. (2013); France; Supplémentation en Vitamines et Minéraux Antioxydants Trial	Nested case–control; 156, 312	ELISA	Leptin, quartiles OR = 0.69 (0.27–1.75), $P_{trend} = 0.9$ Adiponectin, quartiles OR = 1.34 (0.69–2.61), $P_{trend} = 0.3$ hsCRP, quartiles OR = 2.52 (1.18–5.39), $P_{trend} = 0.03$
Lai et al. (2014); USA; Health Professionals Follow-up Study	Nested case–control; 1314, 1314	ELISA	Leptin, continuous OR = 0.94 (0.86–1.02), $P_{trend} = 0.14$

3α-diolG, 5α-androstane-3α,17β-diol glucuronide; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; NR, not reported; NS, no significant association; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; yr, year or years.

Table 4.6 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the ovary

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Helzlsouer et al. (1995); USA; population-based serum bank	Nested case–control; 31, 62	Estrone and estradiol: solvent extraction, celite chromatography, radioimmunoassay Progesterone: radioimmunoassay	Estrone, estradiol, progesterone: NS
Lukanova et al. (2003a); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 258; postmenopausal women	Estrone: double-antibody radioimmunoassay SHBG: immunoradiometric assay	Estrone, quartiles OR = 1.15 (0.47–2.82), P_{trend} = 0.47 SHBG, quartiles OR = 1.66 (0.67–4.09), P_{trend} < 0.19
Rinaldi et al. (2007); several European countries; EPIC	Nested case–control; 192, 346	Sandwich immunoradiometric assay	SHBG, continuous $\log_2$ scale All cases: NS BMI < 26.8, OR = 0.31 (0.14–0.68) BMI ≥ 26.8, OR = 2.48 (1.31–4.71) $P_{heterogeneity}$ = 0.0001
Trabert et al. (2016); USA; Women's Health Initiative	Nested case–control; 169, 412	Stable-isotope dilution liquid chromatography-tandem mass spectrometry	Estrone, quintiles OR = 1.54 (0.82–2.90), P_{trend} = 0.05 2-Methoxyestrone metabolites, quintiles OR = 2.03 (1.06–3.88), P_{trend} = 0.02 4-Methoxyestrone metabolites, quintiles OR = 1.86 (0.98–3.56), P_{trend} = 0.01
Insulin			
Lukanova et al. (2003b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 263	Radioimmunoassay	C-peptide, quartiles OR = 0.89 (0.44–1.81), P_{trend} = 0.92
IGFs			
Lukanova et al. (2002); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 263	Peptides: double-antibody immunoradiometric assay IGF-1: acid–ethanol precipitation of IGFBPs	IGF-1, tertiles All cases: NS < 55 yr, OR = 4.97 (1.22–20.2) IGFBP-3, tertiles All cases: NS
Lukanova et al. (2003b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 263	IGFBP-1: immunoradiometric assay IGFBP-2: radioimmunoassay	IGFBP-1, quartiles OR = 0.79 (0.38–1.62) IGFBP-2, quartiles OR = 0.87 (0.45–1.68)

Table 4.6 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Peeters et al. (2007); several European countries; EPIC	Nested case–control; 214, 388	Peptides: ELISA IGF-1: acid–ethanol precipitation of IGFBPs	IGF-1, tertiles All, OR = 1.1 (0.7–1.7), P_{trend} = 0.94 Diagnosis ≤ 55 yr, OR = 2.4 (0.9–6.4), P_{trend} = 0.08 Diagnosis > 55 yr, OR = 0.9 (0.5–1.6), P_{trend} = 0.74 IGFBP-3, tertiles All, OR = 1.1 (0.7–1.8), P_{trend} = 0.65 Diagnosis ≤ 55 yr, OR = 2.1 (0.8–5.4), P_{trend} = 0.12 Diagnosis > 55 yr, OR = 1.0 (0.6–1.7), P_{trend} = 0.91
Tworoger et al. (2007b); USA; Nurses' Health Study, Nurses' Health Study II, Women's Health Study	Nested case–control; 222, 599	ELISA after acid extraction	IGF-1, quartiles RR = 0.56 (0.32–0.97), P_{trend} = 0.14 IGFBP-2, IGFBP-3, IGF-1 ratio to IGFBPs: NS
Inflammatory factors			
Lundin et al. (2009); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 237, 427	High-sensitivity immunoturbidimetric assay	CRP, > 10 vs ≤ 1 mg/L All, OR = 4.4 (1.8–10.9) Diagnosis > 2 yr after blood donation, OR = 3.0 (1.2–8.0) Diagnosis > 5 yr after blood donation, OR = 3.6 (1.0–13.2)
Clendenen et al. (2011); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 230, 432	Luminex xMAP technology	IL-2, quartiles OR = 1.57 (0.98–2.52), P_{trend} = 0.07 IL-4, quartiles OR = 1.50 (0.95–2.38), P_{trend} = 0.06 IL-6, quartiles OR = 1.63 (1.03–2.58), P_{trend} = 0.03 IL-12p40, quartiles OR = 1.60 (1.02–2.51), P_{trend} = 0.06 IL-13, quartiles OR = 1.42 (0.90–2.26), P_{trend} = 0.11
Poole et al. (2013); USA; Nurses' Health Study, Nurses' Health Study II, Women's Health Study	Nested case–control; Nurses' Health Studies: 217, 434; Women's Health Study: 159, NR	CRP: validated immunoturbidimetric method IL-6: quantitative sandwich enzyme immunoassay TNF-α-R2: ELISA	CRP Quartiles, RR = 0.53 (1.05–2.23), P_{trend} = 0.01 > 10 vs ≤ 1 mg/L, RR = 2.16 (1.23–3.78) IL-6, TNF-α-R2, Nurses' Health Studies: NS

Table 4.6 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Trabert et al. (2014); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 149, 149	Luminex bead-based assay	CRP, tertiles OR = 2.04 (1.06–3.93), P_{trend} = 0.03 IL-1α, detectable vs undetectable OR = 2.23 (1.14–4.34) TNF-α, tertiles OR = 2.21 (1.06–4.63), P_{trend} = 0.04 IL-8, tertiles OR = 1.86 (0.96–3.61), P_{trend} = 0.05 *Serous ovarian cancer* (n = 83) CRP, tertiles OR = 3.96 (1.14–11.14), P_{trend} = 0.008 IL-8, tertiles OR = 3.05 (1.09–8.51), P_{trend} = 0.03
Ose et al. (2015); several European countries; EPIC	Nested case–control; 754, 1497	CRP: high-sensitivity immunoassay IL-6: high-sensitivity quantitative sandwich enzyme immunoassay	CRP All cases: NS > 10 vs ≤ 1 mg/L, OR = 1.67 (1.03–2.70) IL-6 All cases: NS Waist circumference ≤ 80 cm, OR_{log2} = 0.97 (0.81–1.16) Waist circumference 80–88 cm, OR_{log2} = 0.85 (0.66–1.11) Waist circumference > 88 cm, OR_{log2} = 1.78 (1.28–2.48) $P_{heterogeneity}$ ≤ 0.01

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; NR, not reported; NS, no significant association; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; TNF-α, tumour necrosis factor alpha; TNF-α-R, tumour necrosis factor alpha receptor; yr, year or years.

Table 4.7 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the liver (including the biliary tract)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Lukanova et al. (2014); several European countries; EPIC	Nested case–control; 125, 247; M&F	Radioimmunoassay	SHBG, tertiles HCC: OR = 6.64 (2.58–17.1), P_{trend} < 0.001
Insulin			
Chao et al. (2011); Taiwan, China; Hepatitis B virus-positive Cohort	Case–cohort; 124, 1084; M	Radioimmunoassay	Insulin, > 6.10 vs 2.75–4.10 µU/mL HCC: HR = 2.36 (1.43–3.90), P_{trend} = 0.014
Aleksandrova et al. (2014); several European countries; EPIC	Nested case–control; HCC: 125, 250; IBDC: 34, 68; GBTC: 137, 274; M&F	Immulite 2000	C-peptide, tertiles HCC: RR = 3.13 (1.20–8.12), P_{trend} = 0.009 IBDC: RR = 9.89 (1.21–80.45), P_{trend} = 0.03 GBTC: RR = 0.77 (0.39–1.52), P_{trend} = 0.58
IGFs			
Mazziotti et al. (2002); Italy; Hepatitis C virus-related cirrhosis Cohort	Cohort; 20, 84; M&F	Immunoradiometric assay	IGF-1 HCC: significantly lower levels, P < 0.001
Lukanova et al. (2014); several European countries; EPIC	Nested case–control; 125, 247; M&F	ELISA	IGF-1, tertiles HCC: OR = 0.21 (0.09–0.50), P_{trend} < 0.001
Inflammatory factors			
Aleksandrova et al. (2014); several European countries; EPIC	Nested case–control; HCC: 125, 250; IBDC: 34, 68; GBTC: 137, 274; M&F	CRP: Turbidimetric Modular system Leptin and adiponectin: ELISA IL-6: ECLIA Modular system	CRP, tertiles HCC: RR = 1.41 (0.67–2.96), P_{trend} = 0.05 IBDC: RR = 3.92 (0.78–19.68), P_{trend} = 0.05 GBTC: RR = 2.26 (1.26–4.07), P_{trend} = 0.009 Leptin, tertiles HCC: RR = 1.18 (0.43–3.26), P_{trend} = 0.94 IBDC: RR = 3.73 (0.36–38.47), P_{trend} = 0.14 GBTC: RR = 0.52 (0.24–1.13), P_{trend} = 0.05 Adiponectin, tertiles HCC: RR = 1.50 (0.69–3.28), P_{trend} = 0.29 IBDC: RR = 0.42 (0.11–1.29), P_{trend} = 0.23 GBTC: RR = 1.82 (0.93–3.53), P_{trend} = 0.04 IL-6, tertiles HCC: RR = 3.85 (1.31–11.38), P_{trend} = 0.004 IBDC: RR = 1.87 (0.43–8.12), P_{trend} = 0.22 GBTC: RR = 1.19 (0.54–2.62), P_{trend} = 0.68
Ohishi et al. (2014); Japan; Adult Health Study Cohort	Nested case–control; 188, 605; M&F	CRP: autoanalyser and high-sensitivity assay kit IL-6: multiplex bead array assay	CRP, tertiles HCC: RR = 1.94 (0.72–5.51) IL-6, tertiles HCC: RR = 5.12 (1.54–20.1)

CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; GBTC, gall bladder and biliary tract cancers outside of the liver; HCC, hepatocellular carcinoma; HR, hazard ratio; IBDC, intrahepatic bile duct cancer; IGF, insulin growth factor; IL, interleukin; M, male; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin.

Table 4.8 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the pancreas

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Insulin			
Stolzenberg-Solomon et al. (2005); Finland; ATBC	Case–cohort; 169, 400; M	2-site immunoenzymatic assay	Insulin, quartiles HR = 2.01 (1.03–3.93), P_{trend} = 0.03
Grote et al. (2011); several European countries; EPIC	Nested case–control; 466, 466; M&F	Double-antibody radioimmunoassay	C-peptide, quartiles OR = 1.15 (0.70–1.91), P_{trend} = 0.886
Wolpin et al. (2013); USA; 5 prospective studies	Nested case–control; 449, 982; M&F	NR	Insulin, quintiles OR = 1.57 (1.08–2.30), P_{trend} = 0.002 Proinsulin, quintiles OR = 2.22 (1.50–3.29), P_{trend} < 0.001
IGFs			
Stolzenberg-Solomon et al. (2004); Finland; ATBC	Case–cohort; 93, 400; M	ELISA	IGF-1, tertiles OR = 0.67 (0.37–1.21), P_{trend} = 0.17
Wolpin et al. (2007); USA; 4 prospective studies	Nested case–control; 212, 635; M&F	ELISA	IGF-1, quartiles OR = 0.94 (0.60–1.48), P_{trend} = 0.97 IGF-2, quartiles OR = 0.96 (0.61–1.52), P_{trend} = 0.93
Douglas et al. (2010); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 187, 374; M&F	ELISA	IGF-1, quartiles OR = 1.58 (0.91–2.76), P_{trend} = 0.25 IGF-2, quartiles OR = 0.86 (0.49–1.50), P_{trend} = 0.31
Rohrmann et al. (2012); several European countries; EPIC	Nested case–control; 422, 422; M&F	ELISA	IGF-1, quartiles OR = 1.21 (0.75–1.93), P_{trend} = 0.30
Inflammatory factors			
Stolzenberg-Solomon et al. (2008); Finland; ATBC	Case–cohort; 311, 510; M	ELISA	Adiponectin, quintiles OR = 0.65 (0.39–1.07), P_{trend} = 0.04
Grote et al. (2012a); several European countries; EPIC	Nested case–control; 455, 455; M&F	CRP: multiplex immunoassay IL-6: ELISA	CRP, quartiles OR = 1.02 (0.66–1.57), P_{trend} = 0.6 IL-6, quartiles OR = 1.01 (0.64–1.61), P_{trend} = 0.7
Grote et al. (2012b); several European countries; EPIC	Nested case–control; 452, 452; M&F	Multiplex immunoassay	Adiponectin, quartiles OR = 1.10 (0.69–1.75), P_{trend} = 0.71
Bao et al. (2013a); USA; 5 prospective studies	Nested case–control; 470, 1094; M&F	NR	CRP, quintiles OR = 1.10 (0.74–1.63), P_{trend} = 0.81 IL-6, quintiles OR = 1.19 (0.81–1.76), P_{trend} = 0.08
Bao et al. (2013b); USA; 5 prospective studies	Nested case–control; 468, 1080; M&F	ELISA	Adiponectin, quintiles OR = 0.63 (0.43–0.92), P_{trend} = 0.01
Stolzenberg-Solomon et al. (2015); USA, Finland; 3 prospective studies	Nested case–control; 731, 909; M&F	ELISA	Leptin, quintiles OR = 1.13 (0.75–1.71), P_{trend} = 0.38

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; HR, hazard ratio; IGF, insulin growth factor; IL, interleukin; M, male; NR, not reported; OR, odds ratio; RR, relative risk.

Table 4.9 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the stomach

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Insulin			
Hidaka et al. (2015); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; 77, 477; M&F	Human Endocrine Milliplex kit	Insulin, tertiles OR = 1.91 (1.15–3.18), P_{trend} = 0.01 C-peptide, tertiles OR = 1.31 (0.82–2.11), P_{trend} = 0.26
IGFs			
Yatsuya et al. (2005); Japan; Japan Collaborative Cohort Study	Nested case–control; 210, 410; M&F	Immunoradiometric assay	IGF-1, mean cases/controls ± SD M: 127 ± 52 vs 131 ± 54 ng/mL, P = 0.70 F: 121 ± 53 vs 117 ± 53 ng/mL, P = 0.41 IGF-2, mean cases/controls ± SD M: 548 ± 127.4 vs 571 ± 139.2 ng/mL, P = 0.13 F: 618 ± 122 vs 607 ± 118 ng/mL, P = 0.40
Inflammatory factors			
Wong et al. (2011); China; Shanghai Women's Health Study	Nested case–control; 141, 282; F	LINCOplex kit	IL-6, > 4.06 vs < 1.76 pg/mL OR = 1.73 (1.00–3.00), P_{trend} = 0.04 TNF-α, > 7.17 vs < 4.86 pg/mL OR = 0.74 (0.42–1.30), P_{trend} = 0.27
Epplein et al. (2013); China; Shanghai Men's Health Study	Nested case–control; 180, 358; M	Milliplex MAP high-sensitivity Human Cytokine Magnetic Bead Panel assay kit	IL-8, quartiles OR = 2.30 (1.26–4.19), P_{trend} = 0.008 TNF-α, quartiles OR = 1.37 (0.77–2.44), P_{trend} = 0.22

CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; F, female; IGF, insulin growth factor; IL, interleukin; M, male; OR, odds ratio; RR, relative risk; SD. standard deviation; TNF-α, tumour necrosis factor alpha.

Table 4.10 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the kidney

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
IGFs			
Major et al. (2010); Finland; ATBC	Nested case–control; 100, 400; M	ELISA	IGF-1, quartiles OR = 0.40 (0.18–0.90), P_{trend} = 0.03
Inflammatory factors			
Liao et al. (2013); Finland; ATBC	Nested case–control; 273, 273; M	ELISA	Leptin, continuous OR = 0.93 (0.84–1.03) Adiponectin, continuous OR = 0.87 (0.78–0.97) Resistin, continuous OR = 1.04 (0.94–1.16)

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; IGF, insulin growth factor; M, male; OR, odds ratio; RR, relative risk.

Table 4.11 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the oesophagus

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Inflammatory factors			
Hardikar et al. (2014); USA; Seattle Barrett's Esophagus Study	Case–cohort; CRP: 43, 386; IL-6: 45, 394; M&F	CRP: immunonephelometric assay IL-6: ELISA	CRP, quartiles HR = 1.55 (0.56–4.24), P_{trend} = 0.04 IL-6, quartiles HR = 1.17 (0.42–3.26), P_{trend} = 0.87
Keeley et al. (2014); Islamic Republic of Iran; Golestan Cohort Study	Nested case–control; 36, 81; M&F	Luminex xMAP multiplex assay	Interferon-γ, quartiles OR = 5 (1.87–13.36) TNF-α, quartiles OR = 8.2 (2.66–25.31)

CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; F, female; HR, hazard ratio; IL, interleukin; M, male; OR, odds ratio; RR, relative risk; TNF-α, tumour necrosis factor alpha.

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