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# Body fatness, related biomarkers and cancer risk: an epidemiological perspective

**Abstract:** Higher body fatness is not only associated with a higher risk of hypertension, type 2 diabetes, and coronary heart disease but also with certain types of cancer. The scope of this review is to summarize the epidemiological evidence for an association between body fatness and specific types of cancer and to outline the mediating role of obesity-related biomarkers in this context. Epidemiological studies have gathered convincing evidence that greater body fatness is associated with a higher risk of colorectal cancer, postmenopausal breast cancer, endometrial cancer, esophageal adenocarcinoma, renal cell carcinoma, and pancreatic cancer. Further, evidence for an association between higher body fatness and higher risk of ovarian cancer, advanced prostate cancer, and hepatocellular carcinoma is growing. Abdominal obesity is an independent risk factor for colorectal cancer beyond general obesity, whereas an independent role is less clear for other obesity-related cancer types. Epidemiological biomarker studies have shown that the positive association between body fatness and risk of cancer may be partly explained by hyperinsulinemia and altered concentrations in adipokines and sex-steroid hormones. In addition, obesity-associated low-grade inflammation plays a role in colorectal carcinogenesis. While epidemiology has contributed substantially to the understanding of the role of higher body fatness and related metabolic alterations in the development of cancer, further epidemiological biomarker studies are necessary to elucidate the complex interrelations between mediating pathways as well as to study novel pathways. Knowledge resulting from this research may help identify an obesity phenotype that is particularly strongly associated with cancer risk and thus pave the way for targeted prevention of cancer morbidity and mortality.

**Keywords:** abdominal obesity; adipokines; body fatness; cancer; insulin.

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## Introduction

The prevalence of overweight and obesity has increased dramatically in industrialized countries in the past few decades and keeps rising [1, 2]. As a consequence of economic development and growing wealth, body weight is on the rise also in certain low- and middle-income countries. Because body fatness (i.e., the amount of body fat) is associated with morbidity and mortality from a variety of chronic diseases, these trends indicate a major public health problem [3]. Higher body fatness is not only associated with a higher risk of hypertension, type 2 diabetes, and coronary heart disease but there is also convincing evidence for an association with certain types of cancer. In 2002, an expert review conducted by the International Agency for Research on Cancer (IARC) of the World Health Organization concluded that there is sufficient evidence that higher body fatness is associated with a higher risk of colorectal cancer, postmenopausal breast cancer, and cancers of the endometrium, kidney (renal cell), and esophageal adenocarcinoma [4]. These conclusions are largely consistent with the second expert report published by the World Cancer Research Fund (WCRF)/American Institute of Cancer Research (AICR) in 2007, although the report concluded by that time that there is also convincing evidence for pancreatic cancer [5]. Since the publication of that report, the evidence for food, nutrition, and physical activity has been updated regularly for breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, ovarian cancer, and prostate cancer within the Continuous Update Project (CUP) of the WCRF/AICR. So far, the list of cancers for which we have convincing evidence for a causal relationship due to body fatness did not change, although it was recently concluded that greater body fatness is probably also a risk factor for ovarian cancer [6] and advanced prostate cancer [7].

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to such an extent that health may be adversely affected” [1]. Both continuous BMI and overweight and obesity as defined by BMI cut-offs have been related to morbidity and mortality outcomes. However, BMI has several drawbacks, such as the inability to distinguish between lean and fat body mass [11]. In addition, BMI does not reflect body fat distribution, which determines the endocrine activity of adipose tissue [12]. Therefore, measures of body fat distribution, e.g., abdominal obesity defined by waist circumference or waist-to-hip ratio (WHR), are widely used to investigate the disease burden associated with higher body fatness [13, 14]. According to current guidelines, abdominal obesity is defined as a waist circumference of  $\geq 102$  cm or a WHR of  $\geq 0.95$  in men and as a waist circumference of  $\geq 88$  cm or a WHR of  $\geq 0.8$  in women [15–17]. Body fat distribution can also be determined by imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) scans, but these methods have not been used often in large-scale epidemiological studies.

In the following review on the epidemiological evidence for an association between body fatness and risk of cancer, general body fatness is defined based on BMI and abdominal fatness based on waist circumference or WHR.

## Body fatness and risk of colorectal cancer

Worldwide, colorectal cancer is the third most common type of cancer in men and the second most common in women [18]. Highest incidence rates are observed in Australia, New Zealand, the United States as well as in countries in Western Europe. In contrast, incidence rates are very low in Africa and South Asia. Migration studies conducted in the 1970s have shown that incidence rates increased among migrants moving from countries with low incidence rates (such as Japan at that time) to countries with high incidence rates (such as the United States). These observations suggest that environmental factors associated with a Western lifestyle such as greater body fatness may play a role in colorectal cancer risk.

Numerous large-scale epidemiological studies have investigated whether greater body fatness is associated with a higher risk of colorectal cancer. A comprehensive meta-analysis from 2010 summarized the evidence from 56 observational studies, out of which 42 were prospective and 14 retrospective [19]. In the pooled analysis, each 5 kg/m<sup>2</sup> BMI increment was statistically significantly associated with an 18% higher risk of colorectal cancer (relative risk, RR, 1.18, 95% confidence interval, CI, 1.14, 1.21). This association was strongest in studies conducted in North

America (22 studies, RR per 5 kg/m<sup>2</sup>, 1.23, 95% CI 1.15, 1.28) and weaker, but statistically significant, in European studies (21 studies, RR per 5 kg/m<sup>2</sup>, 1.13, 95% CI 1.08, 1.19). In contrast, in studies from Asia, the association was not statistically significant (RR per 5 kg/m<sup>2</sup>, 1.18, 95% CI 0.83, 1.10), but the number of studies was substantially smaller (8 studies). When the overall pooled associations were investigated according to location of the cancer, a stronger association was observed for colon cancer (RR per 5 kg/m<sup>2</sup>, 1.21, 95% CI 1.17, 1.26) than for rectal cancer (RR per 5 kg/m<sup>2</sup>, 1.11, 95% CI 1.06, 1.16), but both associations reached statistical significance. Furthermore, the association with BMI was stronger in men (RR per 5 kg/m<sup>2</sup>, 1.25, 95% CI 1.20, 1.30) than in women (RR per 5 kg/m<sup>2</sup>, 1.12, 95% CI 1.06, 1.16), which could be related to sex-specific differences in body fat distribution. The association of higher body fatness and higher risk of colorectal cancer is likely mediated through a variety of hormones and cytokines secreted by the adipose tissue [20]. It has been shown that the endocrine activity varies depending on the location of adipose tissue. While subcutaneous fat exerts low endocrine activity, visceral adipose tissue is considered highly metabolically active [12]. Thus, it has been proposed that the weaker association between BMI and colorectal cancer risk observed in women can be explained by BMI not adequately reflecting the metabolic relevant visceral fat. Waist circumference correlates more strongly with visceral adipose tissue and has been shown to reflect the risk for metabolic diseases better than BMI [13, 14]. In the “European Prospective Investigation into Cancer and Nutrition” (EPIC), a multicenter cohort study with more than 500,000 study participants from ten European countries, this hypothesis was examined in detail for colorectal cancer [21]: a significant association between BMI and risk of colon cancer was observed in men, but not in women. In contrast, higher waist circumference was significantly associated with a higher risk of colon cancer in men as well as in women. This was confirmed by a meta-analysis from 2007, in which higher waist circumference was associated with a higher colon cancer risk in both men and women [22]. In the WCRF/AICR “Continuous Update Project”, the evidence for a positive association between greater body fatness and higher risk of colorectal cancer was judged “convincing” for both BMI and abdominal obesity [23].

While the bulk of epidemiological studies relating body fatness to risk of cancer focus on attained body fatness in adulthood, high body fatness is of substantial public health concern already in children and adolescents. Early body fatness is of particular importance because it is associated with a number of health impairments not only early on but also later in life. Greater body

fatness during childhood and adolescence is associated with a higher risk of various metabolic diseases including insulin resistance, type 2 diabetes, high blood pressure, and dyslipidemia [24]. Since early steps of carcinogenesis may occur early in life, even decades before the manifestation of cancer, it has been hypothesized that body fatness during childhood and adolescence may be relevant for later cancer risk [25]. However, very few epidemiological studies have been conducted to address this issue. This scarcity is largely due to the lack of information on body fatness during early life in the majority of large-scale cohort studies on cancer. However, in a US prospective cohort with female participants, the association between body fatness during childhood and adolescence and risk of colorectal adenomas, a precursor of colorectal cancer, was investigated [26]. Women participating in the study recalled their body fatness at ages 5, 10, and 20 years using a validated nine-level figure drawing [27, 28]. In that study, women who reported higher body fatness at age 5 years had a 44% higher risk of colorectal adenoma compared with women who were lean at that age. This observation was independent of adult BMI [26].

### **Body fatness and risk of (postmenopausal) breast cancer**

Breast cancer is the most frequent type of cancer in women worldwide [18]. High incidence rates of breast cancer are observed in affluent societies, predominantly in industrialized countries. However, breast cancer incidence rates in Africa and large parts of Asia and South America are increasing, which is probably due to increased life expectancy, urbanization, and adoption of a Western lifestyle [29]. Because breast cancer in developing countries is often detected at a late stage, mortality rates are exceptionally high in these countries. Globally, 50% of all breast cancer diagnoses and 56% of all breast cancer deaths occur in developing countries [29]. Sex-steroid hormones, especially estrogens, play a role in breast cancer development. This is convincingly suggested by the observation that reproductive factors that are associated with prolonged exposure to endogenous estrogens, such as early menarche, late menopause, and late age at first birth, are associated with a higher risk of breast cancer. In breast cancer epidemiology, premenopausal and postmenopausal breast cancers are distinguished, because they may differ in etiology and pathophysiology.

The scientific evidence from epidemiological studies suggests that higher body fatness is associated with a moderately higher risk of postmenopausal breast cancer, while

no association is observed with premenopausal breast cancer. A meta-analysis from 2012 including 15 cohort studies and 35 case-control studies summarized the evidence for overweight and obesity defined by BMI cutoffs as risk factors for breast cancer [30]. Compared with normal-weight women (BMI 18.5–24.9 kg/m<sup>2</sup>), women who were overweight (BMI 25–29.9 kg/m<sup>2</sup>) had an 8% higher risk of postmenopausal breast cancer (RR 1.08, 95% CI 1.00, 1.17), while obese (BMI ≥30 kg/m<sup>2</sup>) women had a 21% higher risk (RR 1.21, 95% CI 1.08, 1.34). In the same meta-analysis, in contrast, being overweight or obese was not significantly associated with premenopausal breast cancer risk [30]. In an earlier meta-analysis from 2008 including 31 prospective studies, each 5 kg/m<sup>2</sup> increment in BMI was associated with a 12% higher risk of postmenopausal breast cancer (RR 1.12, 95% CI 1.08, 1.16) [31]. In the WCRF/AICR “Continuous Update Project” from 2010, the scientific evidence for a positive association between greater body fatness and higher postmenopausal breast cancer risk is considered “convincing”. The association between greater body fatness and higher risk of postmenopausal breast cancer has been shown to be modified by exogenous hormone use. In the EPIC study, higher BMI was associated with a higher risk of postmenopausal breast cancer in women not currently taking hormone replacement therapy (HRT), but not in HRT users [32]. These observations have been confirmed by the Multiethnic Cohort Study, where higher BMI was associated with a higher risk of postmenopausal breast cancer in women who never took HRT and former HRT users, but not in current users [33]. This finding was consistent across Caucasian, native Hawaiian, and Japanese women, while not clearly seen in African-American women. Abdominal obesity, which is a better indicator of the metabolically active visceral fat, has been associated with a higher risk of postmenopausal breast cancer [32]. However, evidence is less consistent, and in some studies the positive association was eliminated after adjustment for BMI [34], suggesting that the total amount of body fat may be more important than body fat distribution for postmenopausal breast cancer. Currently, abdominal fatness is considered a probable risk factor for postmenopausal breast cancer [35].

### **Body fatness and risk of endometrial cancer**

Endometrial cancer is the sixth most common type of cancer in women worldwide [18]. Highest incidence rates are observed in wealthy countries in North America and Europe, which raised the hypothesis that Western lifestyle and body fatness may play a role in the disease etiology

[18]. Incidence rates in developing countries are substantially lower, although increases are observed in parallel to economic development. The risk for endometrial cancer increases with age, and the majority of diagnoses occur after menopause.

Numerous epidemiological studies have investigated the association between body fatness and risk of endometrial cancer. In 2013, the WCRF/AICR concluded in the “Continuous Update Project” report that the evidence for greater body fatness as a causal risk factor for endometrial cancer is convincing [36]. In a dose-response meta-analysis of 26 prospective studies, it was estimated that a 5-unit increment in BMI is associated with a 50% higher risk of endometrial cancer (RR 1.50, 95% CI 1.42–1.59). In the EPIC study, 567 cases of endometrial cancer occurred during 6 years of follow-up. Compared with normal-weight women (BMI 18.5–24.9 kg/m<sup>2</sup>), a higher risk of endometrial cancer was observed in obese (BMI 30–40 kg/m<sup>2</sup> 1.78, 95% CI 1.41–2.26) and severely obese women (BMI ≥40 kg/m<sup>2</sup> 3.02, 95% CI 1.66–5.52), while in overweight women (BMI 25 to <30 kg/m<sup>2</sup>) the risk was not significantly increased (RR 1.11 95% CI 0.91–1.36) [37]. Whether abdominal obesity is a risk factor for endometrial cancer beyond general obesity is currently unclear. A positive association between waist circumference in relation to risk of endometrial cancer was observed in EPIC (≥88 cm versus <80 cm; RR 1.76, 95% CI 1.42, 2.19, p-trend <0.0001), although the association was partly attenuated after simultaneous adjustment for BMI (RR 1.50, 95% CI 1.10–2.04) [37].

### Body fatness and risk of esophageal adenocarcinoma

Worldwide, esophageal cancer is the eighth most common type of cancer [18]. The incidence of esophageal cancer is 2–3 times higher in men than in women. In contrast to many common types of cancer, esophageal cancer occurs most frequently in low-income countries in Africa, South and Central Asia, and South America. Histologically, two major types of esophageal cancer can be distinguished: squamous cell carcinoma, which is the more frequent type, and adenocarcinoma. During the last three decades, the incidence of esophageal adenocarcinoma has increased in Western Europe, North America, and Australia, making it the most rapidly growing cancer in the Western world. Although this rise may be partly explained by better diagnosis techniques [38], it has also been attributed to the parallel increase in the obesity prevalence. In contrast, incidence rates of squamous cell carcinomas of the esophagus have remained relatively stable over

time [39]. Smoking, alcohol consumption, and human papillomavirus infection are established risk factors for squamous cell carcinoma of the esophagus. Smoking and alcohol are also risk factors for adenocarcinomas of the esophagus, but associations are weaker. Gastro-esophageal reflux, which is more prevalent in obese than in non-obese people, is a strong risk factor for the disease [40].

An association between greater body fatness and higher risk of esophageal cancer is predominantly observed with adenocarcinomas [1]. In a meta-analysis from 2008, a 5 kg/m<sup>2</sup> increment in BMI was associated with a more than 50% higher risk of esophageal adenocarcinoma in men and women (RR in men 1.52, 95% CI 1.33–1.74; RR in women 1.51, 95% CI 1.31–1.74) [31]. All epidemiological studies included in a review from 2011 observed a positive association between obesity (BMI >30 kg/m<sup>2</sup> compared with BMI <25 kg/m<sup>2</sup>) and risk of esophageal adenocarcinoma [38], with relative risks between 2 and 11. In the large prospective NIH-AARP Diet and Health Study, abdominal obesity was positively associated with the risk of esophageal adenocarcinoma with a twofold higher risk when comparing the highest with the lowest quartile of waist circumference [41]. This association was attenuated but not eliminated by simultaneous adjustment for BMI. In the 2007 WCRF/AICR report, the evidence for greater body fatness and higher risk of esophageal adenocarcinoma was judged “convincing” [5].

### Body fatness and risk of renal cell carcinoma

Renal cell carcinoma is the most common form of kidney cancer (90% of all kidney cancer cases are renal cell carcinomas). The incidence rate of renal cell carcinoma is high in North America, Australia, and Europe, and substantially lower in India, Japan, Africa, and China [42]. Worldwide incidence rates were increasing by about 2% per year until the early 1990s. However, since the mid-1990s, a decrease in incidence rates has been observed in some European countries, such as Sweden, Poland, Finland, and the Netherlands [42]. Hypertension is a well-established risk factor for renal cell carcinoma [43].

Numerous epidemiological studies have observed that greater body fatness is associated with a higher risk of renal cell carcinoma. According to a meta-analysis of prospective studies from 2008, a 5 kg/m<sup>2</sup> increment in BMI was associated with a 24% higher risk in men (RR 1.24, 95% CI 1.15–1.34) and a 34% higher risk in women (RR 1.34, 95% CI 1.25–1.42) [31]. In the WCRF/AICR report from 2007, it was concluded that there is convincing evidence that higher body fatness increases the risk of renal cell carcinoma.

Whether abdominal obesity is a risk factor beyond general obesity for renal cell carcinoma is currently not clear [44, 45]. Obesity-associated hypertension has been suggested as mechanical explanation for the association between higher BMI and higher kidney cancer risk, although it has also been shown that BMI is associated with a risk of renal cell carcinoma independent of hypertension [46].

### Body fatness and risk of pancreatic cancer

In the WCRF/AICR expert report from 2007, the evidence for greater body fatness as a cause of pancreatic cancer is considered convincing [5]. Of the major types of cancer, pancreatic cancer has the lowest 5-year survival rate, which lies between 3% and 5% [47]. Furthermore, the severity of the disease, which is often accompanied by tumor cachexia, i.e., substantial weight loss that may occur even before diagnosis, makes it difficult to study this type of cancer in epidemiological studies, especially investigating higher body fatness as a potential risk factor. Nevertheless, a meta-analysis comprising 21 prospective studies estimated in 2007 that a 5 kg/m<sup>2</sup> increment in BMI is associated with a 16% higher risk of pancreatic cancer [48]. In the 2012 WCRF/AICR “Continuous Update Project” report on pancreatic cancer, the expert panel concluded that greater body fatness including abdominal fatness and adult weight gain is a convincing causal risk factor for pancreatic cancer [49].

### Body fatness and other types of cancer

In 2014, within the WCRF/AICR “Continuous Update Project”, the evidence for body fatness playing an etiologic role was considered for the first time “probable” for ovarian cancer [6] and prostate cancer [7]. In terms of ovarian cancer, the report based the conclusion on a meta-analysis of 34 prospective studies, which estimated that a 5-unit increment in BMI was associated with a 6% higher risk of ovarian cancer [6]. Regarding prostate cancer, body fatness seems to be only associated with a risk of advanced prostate cancer. In a dose-response meta-analysis, 24 studies on advanced prostate cancer were included, and per 5 kg/m<sup>2</sup> BMI increment an 8% higher risk of advanced prostate cancer was estimated [7]. In contrast, the current evidence does not suggest that body fatness is associated with a higher risk of total prostate cancer or non-advanced prostate cancer. In the 2007 WCRF/AICR second expert report, the evidence for body fatness playing a causal role in the development of liver cancer was considered limited [5].

However, more recent findings from the EPIC study showed that comparing obese men (BMI ≥ 30 kg/m<sup>2</sup>) with non-obese men (BMI < 30 kg/m<sup>2</sup>), a higher risk of hepatocellular carcinoma was observed in obese men (RR 3.66, 95% CI 1.46, 9.14) [50]. This observation was not found in women.

## Role of obesity-related biomarkers in the association between body fatness and cancer risk

The mechanisms underlying the observed association between greater body fatness and higher risk of cancer are not fully understood. However, several plausible mechanisms have been suggested. In particular, the association between higher body fatness and higher risk of cancer may be explained by hormonal pathways such as the insulin and insulin-like growth factor axis, adipokines, and sex-steroid hormones or chronic low-grade inflammation [9, 51]. It should be noted that these pathways are not exclusive, but rather interrelated with each other in a complex and not fully elucidated manner. For instance, high circulating insulin is associated with changes in sex-steroid and adipokine levels. Therefore, it is unlikely that one obesity-related pathway accounts alone for the association between higher body fatness and elevated cancer risk. Also, the importance of each of these pathways may differ by cancer site. Several epidemiological studies have investigated the association between obesity-related biomarkers and risk of specific types of cancer in order to find out if the hypothesized pathways play a role.

### Insulin and insulin-like growth factor pathway

Obesity and in particular abdominal obesity is associated with insulin resistance. Insulin resistance describes a state where the blood glucose lowering capacity of insulin is impaired [52]. As a means of compensation, more insulin is produced by the pancreatic beta cells, which results in chronically elevated insulin concentrations in the blood, also known as hyperinsulinemia. High circulating insulin concentrations have been hypothesized to promote tumor growth both directly and indirectly. Insulin itself has been shown to exert growth-promoting properties through suppression of apoptosis and promotion of cell proliferation [53, 54]. Furthermore, obesity-related hyperinsulinemia leads to higher bioactivity of insulin-like growth factor (IGF-1) through reduced hepatic secretion of two IGF

binding proteins, IGFBP-1 and IGFBP-2. IGF-1 is a potent mitogen with anti-apoptotic properties [55]. The tumor-promoting activities of both insulin and IGF-1 are mediated by specific receptors, i.e., the insulin receptor (IR) and IGF-1 receptor (IGF1R), which can be expressed on neoplastic cells [56].

An important etiologic role of the insulin/IGF-1 pathway has been implicated for colorectal cancer. It has also been suggested that this pathway may explain the positive association between greater body fatness and other types of cancer, such as pancreatic cancer, renal cell carcinoma, and esophageal adenocarcinoma, but evidence is less clear.

Plausible evidence for obesity-related hyperinsulinemia playing a role in the etiology of colorectal cancer comes from the epidemiologic observation that type 2 diabetes, a condition that is characterized by insulin resistance and hyperinsulinemia, is associated with a higher risk of colon cancer [57]. Numerous prospective studies have investigated the association between pre-diagnostic blood concentrations of insulin or C-peptide, which is an indicator of insulin secretion with a longer half-life than insulin itself, and risk of colorectal cancer [58–60]. In the EPIC study, high concentrations of C-peptide in serum were associated with a higher risk of colorectal cancer, and the association was slightly attenuated after adjustment for BMI [61]. The findings in EPIC are in line with a meta-analysis from 2008 in which positive associations between markers of hyperinsulinemia, including circulating levels of insulin and C-peptide, and risk of colorectal cancer were observed [62]. The EPIC study is so far the largest study that has investigated the association between pre-diagnostic IGF-1 concentrations and risk of colorectal cancer [63], but no significant association was observed. However, a meta-analysis of 11 prospective studies including EPIC concluded that higher circulating IGF-1 was associated with a moderately higher risk of colorectal cancer (RR per 1 standard deviation higher IGF-1 1.07, 95% CI 1.01, 1.14) [63]. Taken together, these findings support the hypothesis that part of the observed positive association between body fatness and risk of colorectal cancer may be explained by the insulin/IGF-1 pathway.

It has been hypothesized that the observed positive association between body fatness and renal cell cancer as well as esophageal adenocarcinoma may be mediated by the insulin/IGF-1 pathway, but to date studies specifically investigating this hypothesis are scarce. The risk of pancreatic cancer is increased in people with long-standing type 2 diabetes, suggesting that insulin and IGF-1 play a role in the etiology of this cancer [64]. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, pre-diagnostic

insulin concentrations were associated with a higher risk of pancreatic cancer [65].

## Adipokines

Biomedical research of the last two decades has gathered evidence that adipose tissue is an active endocrine organ that secretes a number of adipocyte-derived hormones, i.e., adipokines, some of which have been implicated in the pathogenesis of obesity-related cancers. In particular, adiponectin and leptin have been suggested as adipokines that may play an etiologic role in certain types of cancer.

### Leptin

Leptin, which is primarily expressed in adipose tissue [66], acts in the hypothalamus as a long-term regulator of food intake and energy balance [67]. It has also been shown in experimental studies that leptin exerts carcinogenic activities such as promoting cell proliferation and migration, reducing apoptosis, and inducing tumor angiogenesis [68]. Plasma leptin concentrations reflect adipose tissue mass and are increased in obese individuals [69]. In epidemiological studies, circulating leptin has been associated with several obesity-associated cancers, including colorectal cancer, breast cancer, endometrial cancer, and pancreatic cancer [68].

A positive association between leptin concentrations and risk of colon cancer was observed in two Scandinavian studies [70, 71], but associations were only seen in men and not in women. However, positive associations between leptin and risk of colorectal cancer in women were observed in the Japan Collaborative Cohort Study [72] and in the Women's Health Initiative cohort of postmenopausal women [73]. In the EPIC study, pre-diagnostic leptin concentrations were not associated with a risk of colorectal cancer. However, soluble leptin receptor (sOB-R), which determines the bioactivity of leptin, was strongly inversely associated with a risk of colorectal cancer [74].

### Adiponectin

Adiponectin is an adipose tissue-derived hormone which plays a role in the regulation of energy homeostasis. In contrast to most adipokines, adiponectin concentrations are lower in obese individuals than in normal-weight individuals [75]. Adiponectin has been suggested to play a role in reducing carcinogenesis, through direct

mechanisms such as inducing apoptosis and inhibiting cancer cell growth [76]. Studies relating prediagnostic adiponectin concentrations to obesity-related cancer types are scarce. To date, a few studies have related adiponectin to colorectal cancer risk, while studies for other obesity-related types of cancer remain to be conducted. In the large prospective Health Professionals follow-up study, high plasma adiponectin levels were associated with a lower risk of colorectal cancer [77]. In the EPIC study, total adiponectin and non-HMW (high molecular weight) adiponectin, which has a stronger anti-inflammatory potential than HMW adiponectin, were associated with a lower risk of colorectal cancer [78]. In contrast, HMW adiponectin was not significantly associated with a risk of colorectal cancer. Counter-intuitively, however, high total and non-HMW adiponectin levels were associated with a *higher* risk of hepatocellular carcinoma in the EPIC study [79]. More research is needed to clarify the role of adiponectin in health and disease.

## Sex-steroid hormones

Higher body fatness is associated with higher formation and bioavailability of endogenous sex-steroid hormones such as estrogens, progesterone, and androgens [9]. In men and postmenopausal women, BMI is directly associated with circulating estrogens including estrone and estradiol [80]. Furthermore, it has been shown that obesity-associated hyperinsulinemia and the related high bioactivity of IGF-1 reduce the hepatic secretion of sex-hormone-binding-globulin (SHBG), which results in higher bioavailability of estradiol. Epidemiological studies suggest that obesity-induced alterations in sex-steroid hormones may largely explain the observed positive associations between body fatness and risk of postmenopausal breast cancer as well as endometrial cancer. There is evidence from experimental studies showing that sex-steroid hormones, in particular estrogen and progesterone, increase cell proliferation, and reduce apoptosis in breast cells and endometrial cells [9].

Within EPIC, one of the most comprehensive analyses of the association between pre-diagnostic blood concentrations of various sex-steroid hormones and risk of breast cancer in postmenopausal women was conducted [81]. In this study, an approximately twofold higher risk of postmenopausal breast cancer was observed in women who had high blood concentrations of total and bioavailable androgens and estrogens. Furthermore, high SHBG concentrations, which relate to lower bioavailability of estrogen, were associated with a lower risk of postmenopausal breast

cancer. Free testosterone, estrone, and estradiol correlated significantly with both BMI and waist circumference in EPIC. The association between higher BMI and higher risk of postmenopausal breast cancer was attenuated substantially after adjustment for total or free estrogens, while adjustment for serum androgens did not change risk estimates. This finding suggests that a substantial proportion of the association between obesity and risk of postmenopausal breast cancer can be explained by the obesity-related increase in endogenous estrogen concentrations. The observations in EPIC are in line with a pooled analysis of nine earlier prospective studies [82].

With respect to endometrial cancer, higher risks associated with endogenous hormones have been observed in both case-control and prospective studies [83]. In a case-control study nested within three prospective cohort studies, one in the United States and two from Europe (Sweden and Italy), a strong direct association of circulating estrogens and androgens and an inverse association of SHBG levels with endometrial cancer risk were observed in postmenopausal women [84]. Adjustment for BMI reduced the strength of the associations of endogenous with endometrial cancer risk, suggesting that obesity-associated alterations in hormone levels may partly explain the strong positive association between body fatness and risk of endometrial cancer.

## Chronic low-grade inflammation

Besides being associated with alterations in the insulin/IGF-1 axis, adipokines, and sex-steroid hormones, obesity is also considered a state of chronic low-grade inflammation. The production of pro-inflammatory cytokines (e.g., tumor necrosis factor- $\alpha$ , interleukin-6) is triggered by adipose tissue and stimulates the hepatic secretion of acute phase proteins, such as C-reactive protein (CRP) [51]. Thus, greater body fatness is associated with low-grade inflammation both locally, i.e., in adipose tissue, and systemically (reflected by elevated plasma concentrations of inflammatory markers) [85]. Higher circulating inflammatory cytokines have been observed when comparing obese with non-obese individuals [86, 87]. Furthermore, it has been shown that diet-induced weight loss reduced inflammation not only systemically, but also in tissues such as the colorectal mucosa [88]. There is convincing evidence that inflammatory processes fostering cell proliferation, cell survival, and migration play an important role in carcinogenesis, particularly in the development of colorectal cancer [89]. Thus, inflammatory processes may account, at least in part, for the association between greater body fatness and

higher colorectal cancer risk. In line with this hypothesis, the inflammatory marker CRP was positively associated with a risk of colon cancer in the EPIC study, and the association was attenuated after adjustment for BMI and waist circumference [90]. Interestingly, in a Mendelian randomization analysis within the EPIC study, it was shown that genetically elevated CRP levels were associated with a risk of colorectal cancer, which is in line with the hypothesis that CRP may have a causal effect [91]. The inflammatory markers interleukin-6 and CRP were also associated with hepatocellular carcinoma in the EPIC study [79].

## Other proposed mechanisms

Other biological mechanisms linking greater body fatness to elevated cancer risk have been proposed. For instance, obesity-related hypoxia, i.e., low oxygen levels in adipose tissue, has been suggested to contribute to carcinogenesis through induction of insulin resistance, as well as modulation of gene expression resulting in decreased adiponectin and increased leptin secretion [51]. It has also been proposed that the nuclear factor  $\kappa$ B (NF- $\kappa$ B) signaling pathway plays a mediating role in obesity-related cancer risk [92]. In addition, oxidative stress, which is enhanced in obese individuals, may play a role in cancer development, in particular in the development of renal cell carcinoma [93]. These potential mechanisms linking obesity with carcinogenesis warrant further study. Due to the potentially complex interrelations between biological pathways explaining the association between greater body fatness and higher cancer risk, it is also important that future prospective studies investigate the mediating pathways such as insulin/IGF-1 axis, adipokines, and sex-steroid hormones jointly.

## Expert opinion

To date epidemiological studies have gathered convincing evidence that body fatness is associated with a higher risk of six types of cancer, namely colorectal cancer, postmenopausal breast cancer, endometrial cancer, esophageal adenocarcinoma, renal cell carcinoma, and pancreatic cancer. There is also growing evidence for body fatness playing a role in the development of ovarian cancer and advanced prostate cancer. Among the obesity-related types of cancer, general body fatness represented by BMI appears to be most strongly associated with a risk of endometrial cancer in women. However, most studies have investigated only one type of cancer, making comparisons

in the strength of association difficult. Abdominal obesity contributes to the development of colorectal cancer as an independent risk factor beyond general obesity. However, positive associations between abdominal obesity and risk of other obesity-related cancer sites, such as postmenopausal breast cancer, endometrial cancer, esophageal adenocarcinoma, and renal cell carcinoma, were largely attenuated after accounting for general obesity. Taken together, the current epidemiological evidence suggests that large numbers of obesity-related cancers could be prevented by reducing the prevalence of overweight and obesity. Thus, individual as well as community-level intervention strategies aiming at reducing body fatness may contribute to a lower cancer burden.

## Outlook

The biological mechanisms linking body fatness to carcinogenesis are insufficiently understood. Several obesity-related biomarkers, such as insulin, IGF-1, adiponectin, leptin, and sex-steroid hormones, likely at least partly explain the association between higher body fatness and elevated risk of certain types of cancer. However, further prospective studies are necessary to elucidate the complex interrelations between mediating pathways as well as to study novel pathways. As such, large-scale prospective cohort studies investigating a large spectrum of biomarkers simultaneously are warranted. High throughput technologies such as metabolomics will help identify novel pathways. Furthermore, for many obesity-related cancer sites, it is currently unclear whether abdominal obesity is an independent risk factor beyond general obesity. Whether more sophisticated technical solutions to quantify body fat distribution, such as bioelectrical impedance analysis or imaging techniques, will add to the current knowledge remains to be investigated in future large-scale prospective studies. To date, there is also insufficient knowledge in terms of how body fatness during early life influences later cancer risk, and this should be addressed appropriately in long-term prospective studies monitoring body fatness from early on. Thus, while the past decade of epidemiological research has contributed substantially to the understanding of the role of body fatness, related metabolic alterations, and development of cancer, further research is needed. Knowledge resulting from this research may be used to identify an obesity phenotype that is particularly strongly associated with cancer risk and thus pave the way for targeted prevention of cancer morbidity and mortality.

## Highlights

- High body fatness is an important risk factor for colorectal cancer, postmenopausal breast cancer, endometrial cancer, esophageal adenocarcinoma, renal cell carcinoma, and pancreatic cancer. High body fatness may also play an important role in the development of ovarian cancer and advanced prostate cancer.
- Abdominal obesity contributes to the development of colorectal cancer as an independent risk factor beyond general obesity. Whether abdominal obesity is an independent risk factor for other types of obesity-related cancer is currently unclear.
- The role of body fatness in early life in relation to later risk of cancer warrants further investigation.
- The positive association between body fatness and risk of cancer may be explained by hyperinsulinemia and altered concentrations in adipokines and sex-steroid hormones. The positive association between body fatness and colorectal cancer may be partly explained by obesity-induced chronic low-grade inflammation.
- The interrelations of the mechanistic pathways potentially linking obesity and risk of cancer should be specifically addressed in future biomarker studies.

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