**Body fatness associations with cancer: evidence from recent epidemiological studies and future directions**

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**A R T I C L E   I N F O**

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- Body mass index
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- Mendelian randomization
- Obesity

**ABSTRACT**

This narrative review highlights current evidence linking greater body fatness to risk of various cancers, with focus on evidence from recent large cohort studies and pooled analyses of cohort studies as well as Mendelian randomization studies (which utilized genetic variants associated with body mass index to de-brief the causal effect of higher body fatness on cancer risk). This review also provides insights into the biological mechanisms underpinning the associations. Data from both observational and Mendelian randomization studies support the associations of higher body mass index with increased risk of many cancers with the strongest evidence for digestive system cancers, including esophageal, stomach, colorectal, liver, gallbladder, and pancreatic cancer, as well as kidney, endometrial, and ovarian (weak association) cancer. Evidence from observational studies suggest that greater body fatness has contrasting effects on breast cancer risk depending on menopausal status and on prostate cancer risk depending on disease stage. Experimental and Mendelian randomization studies indicate that adiponectin, insulin, and sex hormone pathways play an important role in mediating the link between body fatness and cancer risk. The possible role of specific factors and pathways, such as other adipocytokines and hormones and the gut microbiome in mediating the associations between greater body fatness and cancer risk is yet uncertain and needs investigation in future studies. With rising prevalence of overweight and obesity worldwide, the proportion of cancer caused by excess body fatness is expected to increase. There is thus an urgent need to identify efficient ways at the individual and societal level to improve diet and physical activity patterns to reduce the burden of obesity and accompanying comorbidities, including cancer.

1. **Introduction**

Overweight and obesity are growing global health challenges. World Health Organization defines overweight and obesity as abnormal or excessive body fatness that may impair health [1]. Body mass index (BMI) is the most frequently applied population-level measure for overall body fatness. Among adults, overweight is defined as a BMI of 25 kg/m² or more, and obesity is defined as a BMI of 30 kg/m² or more. Globally in 2016, over 1.9 billion adults (39 %) were estimated to be overweight of which over 650 million adults (13 %; a tripling since 1975) were classified as obese [1]. Raised BMI is an important risk factor for many chronic diseases, particularly type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, and multiple malignancies [2-9]. It is however recognized that BMI has limitations as a marker of overall fat mass and it has been increasingly recognized that the fat accumulation outside the subcutaneous adipose tissue, namely intra-abdominal or inside the liver or muscles, is more closely associated with fat associated complications including cancer.

Cancer is another leading and rising health burden worldwide. Globally in 2019, there were an estimated 23.6 million new cancer cases (an increase of 26.3 % since 2010) and 10.0 million cancer deaths (an increase of 20.9 % since 2010) [10]. In addition, cancer deaths as a...
proportion of all deaths increased from 15.7% in 2010 to 17.7% in 2019 [10]. Cancer was second only to cardiovascular diseases for the number of deaths, years of life lost, and disability-adjusted life years globally in 2019 [10]. In addition to the aging population, the increase in cancer incidence is likely in part driven by the rising prevalence of overweight and obesity. An analysis of results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 revealed that among 82 environmental and occupational, behavioral, and metabolic risk factors, high BMI (>25 kg/m²) was the third leading risk factor for cancer death worldwide after smoking and alcohol use [11]. Furthermore, it was estimated that 4.6% of cancer deaths were attributable to high BMI in 2019, whereas 3.6% of new cancer cases were attributable to high BMI in 2012 [11].

The purpose of this narrative review is to highlight current evidence linking greater body fatness to risk of cancer at different anatomical sites and to provide insights into the biological mechanisms behind the associations. The research question was which cancer sites are likely causally linked to body fatness?

2. Methods

We collected information on observational evidence on the association between BMI and site-specific cancer risk from the most recent reports by the International Agency for Research on Cancer (IARC) Working Group [7] and World Cancer Research Fund International (WCRF) Continuous Update Project (CUP) Panel [4]. We also searched PubMed for large cohort studies and pooled analyses of cohort studies (comprising ≥100,000 participants) on BMI in relation to site-specific cancers in the general population and published since the IARC and WCRF reports. The search term used was “(body mass index OR BMI OR obesity) AND (cohort study OR prospective study OR pooled analysis) AND (cancer OR carcinoma)” and the time range was from 1 January 2018 to 15 September 2022. Estimates of the magnitude of the association between BMI and adiposity-associated cancers were obtained from the main dose-response meta-analyses performed by the WCRF CUP Panel [4] and a recent meta-analysis of MR studies [8]. In those meta-analyses, the overall risk estimates were obtained from random-effects and fixed-effects models, respectively, and heterogeneity among studies was assessed using the I² statistic [4,8]. We also report pertinent risk estimates from recent large cohort studies and pooled analyses. Where results from the same cohort were reported in more than one publication, only the most comprehensive study was included in this review. In the present review, statistical significance was defined as P < 0.05.

3. Body fatness-cancer associations

3.1. Previous evidence from observational studies (IARC and WCRF reports)

Greater body fatness has been associated with an increased risk of cancer at multiple anatomical sites [2–8]. Based on data from conventional observational studies (i.e., case-control and cohort studies), the IARC working group [7] and WCRF CUP Panel [4] concluded in 2016 and 2018, respectively, that there is probable or strong evidence that excess body fatness (overweight and obesity) increases the risk of cancers of the esophagus (adenocarcinoma), stomach (cardia), colon and rectum, liver, gallbladder, pancreas, kidney (renal cell), corpus uteri (endometrial cancer), ovaries, and breast (in postmenopausal women).

In meta-analyses conducted by the WCRF CUP Panel, the relative risk per 5 kg/m² increase in BMI was 1.48 (95% confidence interval (CI) 1.35–1.62; I² = 37%; n = 9 studies) for esophageal adenocarcinoma 1.23 (95% CI 1.07–1.40; I² = 56%; n = 7 studies) for gastric cancer, 1.05 (95% CI 1.03–1.07; I² = 74%; n = 38 studies) for colorectal cancer, 1.30 (95% CI 1.16–1.46; I² = 78%; n = 12 studies) for liver cancer, 1.25 (95% CI 1.15–1.37; I² = 52%; n = 8 studies) for gallbladder cancer, 1.10 (95% CI 1.07–1.14; I² = 23%; n = 23 studies) for pancreatic cancer, 1.30 (95% CI 1.25–1.36; I² = 39%; n = 23 studies) for kidney cancer, 1.50 (95% CI 1.42–1.58; I² = 86%; n = 26 studies) for endometrial cancer, 1.06 (95% CI 1.00–1.12; I² = 55%; n = 25 studies) for ovarian cancer, and 1.12 (95% CI 1.09–1.15; I² = 74%; n = 56 studies) for postmenopausal breast cancer [4] (Fig. 1). The heterogeneity between studies was largely due to the magnitude of the positive associations.

The IARC Working Group further concluded that there was sufficient evidence that excess body fatness increases the risk of thyroid cancer and multiple myeloma as well as meningioma, and that there was limited evidence for associations between greater body fatness and increased risk of diffuse large B-cell lymphoma (the most common type of non-Hodgkin lymphoma), fatal prostate cancer, and male breast cancer [7]. The WCRF CUP Panel added fatal and advanced prostate cancer as well as mouth, pharynx, and larynx cancers to the list of cancers probably associated with greater body fatness [4]. In a meta-analysis conducted by the WCRF CUP Panel, the relative risk of fatal prostate cancer per 5 kg/m² increase in BMI was 1.08 (95% CI 1.04–1.12; I² = 19%; n = 23 studies) [4] (Fig. 1). In contrast to the positive association between BMI and breast cancer in postmenopausal women, a consistent inverse association was found between BMI and premenopausal breast cancer risk [4,7]. In a meta-analysis conducted by the WCRF CUP Panel, the relative risk of premenopausal breast cancer per 5 kg/m² increment in BMI was 0.93 (95% CI 0.90–0.97; I² = 55%; n = 37 studies) [4] (Fig. 1). Findings for body fatness in relation to cancer risk were generally consistent for BMI and waist circumference, for men and women, and across geographical regions [4,7]. The IARC Working Group concluded that the evidence for an association with greater body fatness was inadequate, owing to limited data, inconsistent findings, or no data indicating an association, for cancers of the brain or spinal cord (glioma), esophagus (squamous-cell carcinoma), gastric non-cardia, extrahepatic biliary tract, testis, bladder, lung, and skin (cutaneous melanoma) [7].

3.2. Recent evidence from large cohort studies and pooled analyses

A total of 10,606 articles were identified in the PubMed search. Details of relevant cohort studies and pooled analyses of cohort studies comprising >100,000 participants are provided below.

3.2.1. Studies of BMI and several cancers

Among cohort studies assessing the association between body fatness and cancer at several sites, a recent analysis of data from the European Prospective Investigation into Cancer and Nutrition study, including 185,361 participants, showed that each 5 kg/m² increase in adult BMI was associated with a statistically significant 13%, 11%, 28%, and 47% increased risk of colorectal, pancreatic, kidney, and endometrial cancer, respectively, and with a non-significant 6% increased risk of ovarian cancer [12]. In contrast, adult BMI was inversely associated with risk of lung cancer [12].

In a population-based cohort study based on UK primary care data from the Clinical Practice Research Datalink linked to national mortality registration data (n = 3,632,674 people), obesity (BMI ≥30 kg/m²) was associated with a statistically significant increased risk of most of the studied cancers compared with a normal BMI (18.5–25 kg/m²) [13]. The relative risk increase was 19% for esophageal cancer, 22% for stomach cancer, 24% for colorectal cancer, 85% for bladder cancer, 56% for prostate cancer, 67% for kidney cancer, 19% for bladder cancer, 172% for uterine cancer, 34% for ovarian cancer, 30% for breast cancer, and 13% for hematologic cancers [13].

In a cohort study including 437,393 participants of the UK Biobank, greater adiposity, irrespective of the adiposity marker (BMI, waist circumference, waist-to-hip ratio, and body fat percentage), was associated with a higher incidence of cancer of the stomach (cardia and non-cardia), colorectum, liver, gallbladder, pancreas, kidney, corpus uteri,
and breast (in postmenopausal women) [14]. Per one standard deviation increment in BMI, the relative risk increase was 35% for stomach cancer, 10% for colorectal cancer, 27% for liver cancer, 33% for gallbladder cancer, 12% for pancreatic cancer, 26% for kidney cancer, 73% for endometrial cancer, and 10% for postmenopausal breast cancer. At least one adiposity marker was also statistically significantly positively associated with incidence of bladder cancer and melanoma, and inversely associated with prostate cancer incidence [14]. There was no association between any adiposity marker and risk of brain, upper esophageal, oral, thyroid, ovarian, premenopausal breast, cervical, testicular, and lung cancer or multiple myeloma, non-Hodgkin lymphoma, and leukemia [14].

A cohort study of 3.5 million Spanish adults with 202,837 incident cancer cases diagnosed over 8.3 years of follow-up showed that higher BMI was associated with increased risk of nine cancers in the entire cohort (including colorectal, gallbladder, kidney, endometrial, and postmenopausal breast cancer as well as multiple myeloma, leukemia, and non-Hodgkin lymphoma) and with increased risk of three additional cancers among never smokers (brain and central nervous system cancer, head and neck cancer, and Hodgkin lymphoma) [15].

In a cohort of 135,708 Norwegian women, BMI was strongly positively associated with risk of kidney and endometrial cancer, non-significantly or borderline positively associated with risk of colorectal, pancreatic, and breast (postmenopausal) cancer, but not associated with ovarian cancer [16]. A cohort study of 461,646 women (<49 years of age) registered in the Danish Medical Birth Registry found that the risk of premenopausal ovarian cancer increased by 23% per 5 kg/m² increase in BMI whereas the risk of premenopausal breast cancer decreased by 10% per 5 kg/m² increase in BMI [17].

3.2.2. Digestive system cancers

In a cohort study of 226,584 Australian adults, greater BMI was statistically significantly associated with an increased risk of colon cancer but not rectal cancer [18]. The HR of colon cancer for BMI $\geq 29.4$ kg/m² versus $<23.6$ kg/m² was 1.32 (95% CI 1.08–1.63) [18].

Small intestine cancer is a rare cancer with largely unknown etiology. In a recent pooled analysis including over 800,000 individuals from six European cohort studies, only 195 men and 144 women were diagnosed with small intestine cancer during a median follow-up of 16.9 years [19]. That study found evidence of a possible association between higher BMI and an increased risk of small intestine cancer in men but not in women [19]. Compared with lean men (mean BMI 21.8 kg/m²), the HRs were 1.53 (95% CI 1.02–2.29) for overweight and 1.31 (95% CI 0.86–2.00) for obese men [19]. An earlier analysis of data from a cohort study of 498,376 US men and women, including 147 and 90 small intestine cancer cases in men and women, respectively, showed that severe obesity (BMI $\geq 35$ kg/m²) was associated with an increased risk of small intestine cancer (HR 1.77; 95% CI 1.11–2.82) compared with a normal BMI ($<25$ kg/m²) [20].

The relation between BMI in late adolescence and risk of liver (hepatocellular) cancer was investigated in a cohort of 1,220,261 Swedish men, aged 17–19 years, who were followed for a mean period of 28.5 years [21]. There was a dose-dependent association between BMI in late adolescence and incident liver cancer, with a statistically significant 3.6-fold higher risk for men with BMI $\geq 30$ versus 18–22.5 kg/m² [21].

The associations of anthropometric factors with risk of biliary tract
cancers were examined in a pooled analysis of data from 27 cohort studies with over 2.7 million adults [22]. That analysis showed that for each 5 kg/m² increase in BMI, there were risk increases for cancers of the gallbladder (hazard ratio [HR] 1.27; 95% CI 1.19–1.36), intrahepatic bile ducts (HR 1.32; 95% CI 1.21–1.45), and extrahepatic bile ducts (HR 1.13; 95% CI 1.03–1.23) [22].

The association between BMI and pancreatic cancer mortality was examined in the Cancer Prevention Study II, including 8354 deaths from pancreatic cancer among 963,317 adults [23]. This cohort study found that BMI (per 5 kg/m² increase) before age 50 years was more strongly associated with risk of pancreatic cancer (HR 1.25; 95% CI 1.18–1.33) than BMI at older ages at enrollment (HR 1.13; 95% CI 1.02–1.26, in those aged 70–89 years) [23]. In contrast, in the US Women's Health Initiative cohort, which included 1045 pancreatic cancer cases among 156,218 women, BMI at age 50 years but not at ages 35 or 18 years was significantly positively associated with risk of pancreatic cancer [24].

3.2.3. Urinary tract cancers
A recent pooled analysis of three US cohort studies found that higher BMI was associated with a substantial increased risk of kidney (renal cell) cancer [25]. The overall HR was 2.16 (95% CI 1.77–2.63) for BMI ≥30 versus 18–25 kg/m² [25].

With respect to bladder cancer, a study based on three Swedish cohorts, including 4895 incident bladder cancer cases diagnosed among 338,910 men, BMI was positively associated with any non-muscle invasive bladder cancer (HR per 5 kg/m² increase 1.10; 95% CI 1.02–1.19), with a stronger association for grade 3 (corresponding HR 1.17; 95% CI 1.01–1.34) [26]. Another study including 811,633 participants from six European cohorts found that BMI was positively associated with risk of non-muscle invasive bladder cancer in men (HR per standard deviation increase 1.09; 95% CI 1.01–1.18) but inversely associated with risk of any bladder cancer in women (HR per standard deviation increase 0.90; 95% CI 0.82–0.99) [27]. No association between BMI and overall bladder cancer risk was observed in the Janus Cohort, comprising 292,851 Norwegian adults [28].

3.2.4. Sex hormone-related cancers
Among 108,136 postmenopausal women in the US Women's Health Initiative cohort, the risk of endometrial cancer increased with increasing BMI categories, with an over 3-fold higher risk for BMI ≥40 kg/m² versus BMI <25 kg/m² [29]. There was a corresponding non-significant 29% increased relative risk of ovarian cancer [29].

In a recent pooled analysis of 20 cohort studies, including 36,297 breast cancer cases among 1,061,915 women, BMI at cohort baseline was strongly inversely associated with risk of premenopausal breast cancer and strongly positively and nonlinearly associated with risk of postmenopausal breast cancer, particularly among women who had never used postmenopausal hormone therapy [30]. These associations were mainly observed for receptor-positive tumor subtypes. Early adult BMI (at 18–20 years) was inversely associated with both premenopausal and postmenopausal breast cancer risk (21% and 11% risk reduction, respectively, per 5 kg/m² increment of BMI) with stronger associations for receptor-negative tumor subtypes [30].

For prostate cancer mortality, a recent meta-analysis of 19 cohort studies found a combined HR of dying from prostate cancer (19,633 prostate cancer deaths) of 1.10 (95% CI 1.07–1.12) for each 5 kg/m² increase of BMI [31]. Weaker associations were found for other adiposity markers [31].

3.2.5. Hematologic cancers
A couple of recent pooled analyses of six US cohort studies have reported results on the association between body fatness and risk of multiple myeloma and non-Hodgkin's lymphoma [32,33]. In a pooled analysis with 2756 incident multiple myeloma cases diagnosed among 544,016 US adults, each 5 kg/m² increment in adult BMI was associated with a statistically significant 10% increased risk of multiple myeloma [32]. Another pooled analysis with 11,263 incident non-Hodgkin's lymphoma cases diagnosed among 568,717 US adults found no dose-response relationship between usual adult BMI and risk of non-Hodgkin's lymphoma (HR per 5 kg/m² increase in BMI 1.01; 95% CI 0.99–1.03) but found a statistically significant 20% increased risk in those with severe obesity (BMI ≥40 kg/m²) compared with normal-weight adults (BMI 18.5–22.9 kg/m²) [33]. Moreover, BMI in young adulthood was associated with a statistically significant 14% increased risk of non-Hodgkin's lymphoma per 5 kg/m² increment in BMI [33].

The association between BMI and leukemia risk was investigated in the Cancer Prevention Study II, which included 387 acute myeloid leukemias, 100 chronic myeloid leukemias, and 170 myelodysplastic syndromes diagnosed among 152,090 US adults over 21 years of follow-up [34]. No significant associations were observed [34].

A cohort study based on primary care data from the United Kingdom's Clinical Practice Research Datalink, including 5.8 million adults of whom 927 developed Hodgkin's lymphoma during 41.6 million years of follow-up, found that each 5 kg/m² increase in BMI was associated with a statistically significant 10% increase in Hodgkin's lymphoma risk [35]. The non-linear analysis suggested a J-shaped association, with risk increasing at BMI above 24.2 kg/m² [35].

3.2.6. Other cancers
A population-based cohort study consisting of 1.7 million American, Europeans, and Asians of which 23,732 were diagnosed with lung cancer, BMI was inversely associated with lung cancer risk after removing the first five years of follow-up [37]. The HRs per 5 kg/m² increment in BMI were 0.95 (95% CI 0.90–1.00) in former smokers, 0.92 (95% CI 0.89–0.95) in former smokers, and 0.89 (95% CI 0.86–0.91) in current smokers [37].

In a pooled analysis of cohort studies involving 1.6 million Americans, Europeans, and Asians of which 23,732 were diagnosed with lung cancer, BMI was inversely associated with lung cancer risk after removing the first five years of follow-up [37]. The HRs per 5 kg/m² increment in BMI were 0.95 (95% CI 0.90–1.00) in former smokers, 0.92 (95% CI 0.89–0.95) in former smokers, and 0.89 (95% CI 0.86–0.91) in current smokers [37].

3.2.7. BMI and cancer in Asian populations
Results from the Asia Cohort Consortium, including several cohort studies with over a half a million adults from southern and eastern Asia, showed U-shaped associations of BMI with esophageal cancer mortality [38] and stomach cancer incidence [39]. In the same consortium, a dose-dependent association between BMI and multiple myeloma mortality was observed; the HR for BMI ≥30 kg/m² versus 25–29.9 kg/m² was 1.61 (95% CI 0.99–2.64) [40]. Other studies based on the Asia Cohort Consortium showed a linear association between BMI and thyroid cancer incidence in men (HR per 5 kg/m² increase 1.25; 95% CI 1.10–1.55) but not in women (corresponding HR 1.07; 95% CI 0.97–1.18) [41], and no clear association between BMI and mortality from pancreatic [42] and prostate cancer [43].

The association between body fatness and risk of 15 major cancers were examined in the China Kadoorie Biobank study, which included half a million adults with a mean BMI of 23.7 kg/m² [44]. Each 5 kg/m² increase in BMI was associated with increased risk of colorectal (HR 1.17; 95% CI 1.10–1.25), endometrial (HR 2.01; 95% CI 1.72–2.35), postmenopausal breast (HR 1.29; 95% CI 1.18–1.40), and cervical (HR, 1.15; 95% CI, 1.03–1.29) cancer, whereas it was associated with a reduced risk of esophageal (HR 0.73; 95% CI 0.67–0.79), gastric (HR 0.88; 95% CI 0.82–0.94), liver (HR 0.85; 95% CI 0.79–0.92), and lung (HR 0.78; 95% CI 0.74–0.82) cancer [44]. In the same cohort, no association was observed between BMI and small intestine cancer (HR per standard deviation increase 1.06; 95% CI 0.89–1.25) [45].

The associations between BMI and risk of stomach, liver (hepato-cellular), pancreatic, and kidney cancer have been examined in studies based on the Korean National Health Insurance database, which included between 2.6 million [46] to 23.3 million adults [47].
studies found statistically significant associations; compared with normal-weight individuals, the risk of stomach cancer (n = 13,441 cases) was 20 % higher in those with BMI ≥ 25 kg/m², liver cancer (n = 47,308 cases) risk was over 2-fold higher in those with BMI ≥ 31 kg/m² [48], pancreatic cancer (n = 22,543 cases) risk was 16 % higher in those with BMI ≥ 28 kg/m² [49], and kidney cancer (n = 18,036 cases) risk was 77 % higher in those with BMI ≥ 30 kg/m² [47]. Another report based on this database showed an over 2-fold increased risk of kidney cancer in those with prolonged obesity [50]. Moreover, data from the same database that compared with BMI 18.5–23 kg/m², low BMI (<18.5 kg/m²), but not overweight or obesity, was associated with a statistically significant increased risk of head and neck cancers [51]. In another Korean cohort, including 255,051 adults, BMI ≥ 25 kg/m² versus BMI 18.5–22.9 kg/m² was associated with a statistically significant increased risk of thyroid cancer in both metabolic healthy and metabolic unhealthy men and with risk of thyroid cancer in metabolic unhealthy women [52].

3.3. Evidence from Mendelian randomization studies

The associations of genetically predicted BMI, as a proxy for lifelong BMI, in relation to cancer risk have been investigated in several MR studies published during the last few years. In MR analysis, genetic variants that are reliably associated with the exposure (e.g., BMI) are used as instrumental variables to decipher whether the exposure has a causal relationship with the outcome (e.g., cancer) [53,54]. People who inherit genetic alleles that associate with higher BMI will on average have higher BMI than people who inherit alleles that associate with lower BMI. As genetic alleles are normally passed from parents to offspring independently of environmental factors and are largely unchanged by disease development (except for mutations in specific cancer genes), the MR design diminishes biases that are common in conventional observational studies, such as confounding and reverse causation bias [53,54].

MR studies of the association of genetically predicted BMI with site-specific cancers have confirmed the association between higher BMI and increased risk of cancer at several sites [8]. Specifically, a meta-analysis of MR studies showed that genetically predicted higher BMI was associated with an increased risk of digestive system cancers (including esophageal, stomach, colorectal, liver, gallbladder, and pancreatic cancers) as well as cancers of the kidney, corpus uteri, and ovaries [8] (Fig. 1). The odds ratio (OR) per one standard deviation increment in BMI (~5 kg/m²) was 1.75 (95 % CI 1.26–2.44; I² = 14 %; n = 3 studies) for esophageal cancer, 1.09 (95 % CI 1.04–1.15; I² = 83 %; n = 3 studies) for stomach cancer, 1.18 (95 % CI 1.05–1.32; I² = 0 %; n = 5 studies) for colorectal cancer, 1.62 (95 % CI 1.19–2.21; I² = 0 %; n = 3 studies) for liver cancer, 1.50 (95 % CI 1.06–2.13; I² = 4 %; n = 3 studies) for gallbladder cancer, 1.36 (95 % CI 1.20–1.55; I² = 0 %; n = 3 studies) for pancreatic cancer, 1.49 (95 % CI 1.38–1.60; I² = 64 %; n = 4 studies) for kidney cancer, 1.49 (95 % CI 1.38–1.61; I² = 90 %; n = 3 studies) for endometrial cancer, and 1.09 (95 % CI 1.00–1.18; I² = 32 %; n = 4 studies) for ovarian cancer (Fig. 1). The moderate to strong heterogeneity in the analyses of stomach, kidney, and endometrial cancer was caused by different magnitude of the positive association. The overall evidence from MR studies suggests possible associations between higher BMI and increased risk of multiple myeloma (OR 1.10; 95 % CI 0.99–1.21; n = 3 studies; heterogeneity: I² = 0 %), non-Hodgkin’s lymphoma (OR 1.15; 95 % CI 0.99–1.33; n = 2 studies; heterogeneity: I² = 0 %), and lung cancer (OR 1.09; 95 % CI 0.99–1.19; n = 4 studies; heterogeneity: I² = 90 %). There were also positive associations between genetically predicted BMI and risk of cervical (OR 1.13; 95 % CI 1.01–1.27; I² = 90 %; n = 3 studies) and urinary bladder cancer (OR 1.27; 95 % CI 1.03–1.50; I² = 78 %; n = 3 studies) but these associations were driven by a single study (the FinnGen Study) [8]. Genetically predicted higher BMI was associated with a decreased risk of total breast and prostate cancer, with ORs of 0.87 (95 % CI 0.82–0.92; I² = 57 %; n = 5 studies) and 0.90 (95 % CI 0.84–0.96; I² = 1 %; n = 4 studies), respectively [8] (Fig. 1). For breast cancer, genetically predicted higher BMI was associated with a reduced risk of both estrogen receptor positive and estrogen receptor negative tumors [55]. There was also an inverse association between genetically predicted BMI and non-melanoma skin cancer (OR 0.86 (95 % CI 0.77–0.95); I² = 0 %; n = 2 studies) [8].

Meta-analysis results of two MR studies, including a total of 586,353 UK and Finnish individuals, showed no association of genetically predicted BMI with risk of head and neck cancer (OR 0.96; 95 % CI 0.77–1.19; I² = 82 %), thyroid cancer (OR 0.96; 95 % CI 0.73–1.27; I² = 0 %), and leukemia (OR 1.14; 95 % CI 0.95–1.39; I² = 54 %), or with testicular cancer (OR 0.96; 95 % CI 0.68–1.34; I² = 0 %) among 263,949 UK and Finnish men [8]. A recent MR study found no association between BMI and glioma risk [56].

4. Biological mechanisms

Excess body fatness is associated with considerable metabolic and endocrine aberrations that can contribute to cancer development and progression. There are several connected pathways whereby excess body fatness may increase cancer risk. The most credible biological mechanisms are via alterations in circulating levels of adiponectin and other adipocytokines and chronic low-grade inflammation; elevated levels of insulin and insulin-like growth factor I (IGF-I); and increased levels and bioavailability of sex hormones. Other emerging yet unestablished biological mechanisms that might contribute to the obesity-cancer relations include alterations in the gut microbiome and gut hormones.

4.1. Adipocytokines and low-grade inflammation

Obesity and more specifically central obesity is related to chronic low-grade inflammation [57], which is an important hallmark of cancer development and progression [58,59]. Adipose tissue is an active endocrine organ that secretes many adipocytokines (also called adipokines), a collective term for hormones and cytokines that are mainly albeit not exclusively derived from the adipose tissue [57,60,61]. Adiponectin is the most abundant and most widely studied adipocytokine that along with other adipocytokines are thought to provide a key link between obesity, insulin resistance, and related inflammatory disorders [57,60,62]. Adiponectin, a 30kDa cytokine and member of the C1q/TNF superfamily, was first described by several groups in the mid-1990s [63]. It exerts a multitude of effects on numerous tissues, including the liver, kidney, pancreas, blood vessels, nervous system, bone and immune cells and is subsequently cleared by the liver [63]. Adiponectin effects are mediated by adiponectin receptor 1 and 2 (AdipoR1, AdipoR2) and T-cadherin [64,65]. Adiponectin receptors are ubiquitously expressed in healthy tissues as well as in malignant cells [66].

Although adiponectin is primarily produced in adipose tissue, it stands out from the other adipocytokines as it circulates in very high levels in relation to other adipocytokines and is inversely correlated with fat mass, especially central obesity [67–69]. Normally, adiponectin is produced by the fat tissue and facilitates energy expenditure and tissue insulin sensitivity. In the setting of obesity, intrabdominal and ectopic fat distribution, tissue hypoxia induces a body wide chronic inflammatory state that perturbs the physiologic adipokine secretion leading to lower adiponectin levels [70]. Serum adiponectin levels are inversely associated with body fatness and are not affected by acute fasting [71]. Hypoadiponectinemia results in dysregulation of IGFs, chronic low-grade inflammation, sex hormone imbalance, and ultimately promotion of malignant transformation [66,72]. Evidence from observational studies links hypoadiponectinemia with increased risk of several obesity-related malignancies, including colorectal [73-75], stomach [76], liver [77], kidney [78–80], endometrial [81–83], ovarian [84], and breast cancer [85–87]. Adiponectin has been inversely associated with postmenopausal but not premenopausal breast cancer, independently of BMI or other known breast cancer risk factors [88].
Interestingly, AdipoR1 has been found to be higher expressed in breast tumor tissue than adjacent and control tissues [85]. Higher breast cancer risk has also been associated with genetic variants of the AdipoR1 that confer decreased adiponectin signaling [89]. Besides high risk for malignancy, low serum adiponectin has been linked to increased numbers and size of tumor foci in colorectal cancer [90], increased malignancy stage in stomach cancer [91], and more aggressive phenotype in breast cancer [66].

Adiponectin can influence cancer tissues through its receptors that have been shown to be widely in several cancers linked to obesity. Colorectal carcinoma cell lines display growth inhibition in the presence of adiponectin, and this effect is potentiated by glucagon deprivation [92,93]. Adiponectin has been shown to exert in vitro antitumor effects in esophageal [94–96], stomach [97], hepatocellular [98], endometrial [99,100], and prostate cancer [101]. Data have been inconsistent in breast cancer where the anticarcinogenic effect of adiponectin appears to be modified by estrogen receptor expression [102,103]. Besides suppression of tumorigenicity, adiponectin can reduce the metastatic potential of cancer cells, a phenomenon reported for hepatocellular [104] and breast [105] cancer cells.

The adipose tissue also secretes a number of other molecules, including certain cytokines, such as interleukin-6 (IL-6), IL-1 receptor antagonist, IL-18, tumor-necrosis factor α (TNF-α), pre-B cell colony-enhancing factor (also known as visfatin), and monocyte chemotactic protein-1 (also known as chemokine C-C motif ligand 2); fatty acid-binding protein-4; retinol binding protein 4; mediators of the clotting process, such as plasminogen-activator inhibitor-1; growth factors, such as vascular endothelial growth factor and angiopoietin-like protein-4; and some complement factors [57,60,61,69,106]. Circulating levels of several inflammatory biomarkers, such as C-reactive protein (an acute phase reactant) [69,107,108], IL-6 [107], IL-18 [57], and TNF-α [69], as well as plasminogen-activator inhibitor-1 [69] increase with increasing BMI and decline following weight loss [57,109]. MR studies have not supported a causal role of higher C-reactive protein or IL-6 levels in the development of colorectal, endometrial, ovarian, breast, and prostate cancer [110–115]. Genetically predicted circulating TNF-α levels have been reported to be significantly or suggestively inversely associated with risk of colorectal, endometrial, breast, and lung cancer [116].

Some adipocytokines modulate angiogenesis, which is essential in cancer development and progression. For example, adiponectin may inhibit angiogenesis, whereas leptin acts in synergy with vascular endothelial growth factor to promote angiogenesis [117].

4.2. Insulin and IGF-I

Circulating insulin and insulin like growth factor levels are frequently elevated in overweight and obese individuals as a consequence of reduced insulin sensitivity driven, at least partly, by alterations in adiponectin levels. MR studies have provided evidence of strong causal associations of greater BMI, waist-to-hip ratio, and fat mass with increased insulin resistance [118–121] and fasting insulin levels [107,118–120]. It has been estimated that each 1 kg/m² elevation in genetically predicted BMI increases fasting insulin levels by 8.5 % [107].

Observational and MR studies have demonstrated that elevated circulating levels of insulin or C-peptide (a marker of insulin secretion) are associated with several obesity-related cancers, including colorectal [122–124], stomach [125], liver [126,127], pancreatic [128–132], kidney [130,133], and endometrial cancer [111,122,130,134,135]. Moreover, insulin therapy among diabetes patients is associated with increased risk of colorectal [136,137], stomach [136], liver [136,138], pancreatic [136], and kidney cancer [136]. A recent MR study estimated that fasting insulin mediated 19 % of the relationship between genetically predicted BMI and endometrial cancer risk [111].

IGF-I is a peptide hormone that is primarily synthesized by the liver under the regulation of growth hormone (GH) but is also produced locally by most tissues where it functions in an autocrine or paracrine manner [139–141]. In addition to being a mediator of GH-stimulated somatic growth, IGF-I exerts GH-independent anabolic effects in many cells and tissues via activation of the IGF-1 receptor. The totality of evidence from observational and MR studies indicates that elevated circulating IGF-I levels modestly increase the risk of epithelial cancers including colorectal [142–144], prostate [142,143,145,146], and breast cancer [142,143,147]. In the bloodstream, over 99 % of IGF-1 is attached to one of six binding proteins (IGFBPs) that modulate IGF-1 activity [140]. The vast majority of serum IGF-I (75–85 %) is complexed with IGFBP-3 and a glycoprotein, while the remaining 20–25 % is complexed with one of the other IGFBPs [148]. Despite low GH secretion [149] and decreasing IGFBP-1 and IGFBP-2 levels with increasing adiposity and insulin levels [69,150–153], no consistent association has been observed between BMI and total or bioavailable IGF-I levels [149].

4.3. Signaling pathways linking adiponectin, insulin, and cancer growth

Adiponectin exerts its tumor suppressing effects mainly through the interconnected SAMP-activated protein kinase (AMPK) and mammalian homologue of target of rapamycin (mTOR) intracellular signaling pathways [154,155]. Adiponectin activates AMPK, a key regulator of cellular energy. After adiponectin binds to AdipoR1/R2 the Ser/Thr liver kinase B1, it is transferred from the nucleus to the cytoplasm where it recruits the adaptor protein APPL1 and phosphorylates AMPK [156]. Under cellular stress, adiponectin activates AMPK and inhibits growth promoting and proliferative pathways, while upregulating catabolic pathways to increase energy production [157]. Moreover, AMPK interacts with a variety of signaling pathways to stimulate β-oxidation of free fatty acids, inhibits lipid biogenesis, effects that have been linked to tumor growth inhibition [158,159]. Activated AMPK also stimulates the expression of p21 and p53 and phosphorylates p53 to further suppress cancer cell proliferation and induce apoptosis [160].

Adiponectin can indirectly inhibit neoplastic activity by interfering with the insulin intracellular signaling [161]. Low adiponectin levels have been correlated with insulin resistance and elevated insulin levels [162]. Moreover, AdipoR2 mRNA expression in fatty tissue has been negatively associated with insulin resistance and several metabolic parameters independently of body fatness [163]. The insulin receptor protein kinase activates the mTOR pathway through phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) [164,165]. It is well established that alterations in PI3K/AKT/mTOR signaling underpin tumorigenesis [164]. Adiponectin inhibits the PI3K/AKT/mTOR axis hindering cancer cell growth imposed by insulin and other growth factors [166,167].

4.4. Sex hormones

In premenopausal women, estrogens are synthesized primarily in the ovaries, whereas in postmenopausal women and men, the primary site for estrogen synthesis is adipose tissue. Obesity and resulting hyperinsulinemia are related to decreased levels of sex hormone binding globulin (SHBG) [69,168], which binds estradiol and testosterone with high affinity. In peri- and postmenopausal women, high BMI associates with higher levels of bioavailable estradiol [168] and testosterone [168–170], whereas in men, high BMI associates with lower testosterone levels [170–172]. Obese men commonly present with hypogonadotrophic hypogonadism [172].

MR studies have provided evidence of causal relationships of higher circulating SHBG levels with decreased risk of endometrial cancer [111] and of high SHBG endogenous levels of total estradiol (proxied by a single genetic variant in the CYP19A gene, which encodes aromatase) with increased risk of cancers of the corpus uteri (particularly the endometroid subtype) [111,173] and breast (particularly estrogen receptor positive tumors) and possibly ovarian cancer of the endometrioid...
substance as well as stomach cancer in women [173]. Furthermore, MR studies have reported that genetically predicted higher endogenous levels of total and bioavailable testosterone are associated with increased risk of cancers of the corpus uteri [111,174] and breast (estrogen receptor positive tumors) [174], and that genetically predicted higher free and bioavailable testosterone endogenous levels are related to an increased risk of prostate cancer [174,175]. Thus, the observed positive associations between BMI and risk of cancers of the corpus uteri, breast (postmenopausal), ovaries (endometrioid subtype), and stomach may in part be mediated by higher sex hormone levels in women. A recent MR study estimated that bioavailable testosterone and SHBG mediated 15 % and 7 %, respectively, of the association between BMI and endometrial cancer risk [111]. The mediating effect of bioavailable estradiol could not be tested due to the lack of reliable genetic instruments [111].

In obese men, the low testosterone environment might contribute to an increased risk of advanced or fatal prostate cancer but possibly to lower risk of non-advanced prostate cancer [176]. The biological mechanism behind the association between obesity and decreased risk of breast cancer in premenopausal women is unclear, but oligo- and anovulation, which is more frequently observed in overweight and obese women than in normal weight women [172], and alterations in related hormones might be involved.

4.5. Emerging mechanisms

Evidence indicates that there is a mutual relationship between obesity and gut microbiota. In humans, obesity is associated with alterations in the gut microbiota composition as well as decreased bacterial diversity [177–179]. Low-calorie diets (fat- or carbohydrate-restricted) and weight loss has been revealed to change the relative abundance of major gut phyla (increased levels of Bacteroidetes and decreased levels of Firmicutes) in obese individuals [177]. Studies in mice have shown that obese-associated microbiome is associated with increased capacity to harvest energy from the diet [180] and weight gain [181]. Evidence from MR studies further indicates that certain gut microbiota taxa modify BMI and fat mass [182,183]. For example, a genetic variant in the LCT locus that predisposes individuals to lactose intolerance and is related to the abundances of Bifidobacterium is associated with adiposity-related phenotypes, such as BMI, waist circumference, and fat mass [183]. Nevertheless, little is known about the possible causal effect of gut microbiome on cancer risk, but a recent phenome-wide association MR study provided no evidence of any strong association between microbiome-related genetic variants and cancer outcomes [184].

There are several obesity-associated gut hormones (e.g., ghrelin, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, peptideYY, neurotensin, vasoactive intestinal peptide, and somatostatin) that have not yet been studied adequately but have been proposed to have either a protective role against cancer or increase cancer cell growth and proliferation [185]. Ghrelin is a peptide hormone produced primarily by the stomach and stimulates appetite and GH release and has diabetogenic and lipogenic effects [186]. Circulating ghrelin levels are decreased in obesity [186]. The ghrelin system is thought to be involved in the regulation of several important processes of digestive system cancer progression, although the exact roles of ghrelin in cancer are unestablished [187,188]. Observational studies have reported that low circulating ghrelin levels are associated with an increased risk of stomach cancer [189–191]. Moreover, low ghrelin levels were associated with a higher risk of esophageal squamous cell carcinoma in two observational studies [192,192], but with a lower risk of this cancer type in another study [180]. With regard to colorectal cancer, one study found that low ghrelin levels were strongly associated with an increased colorectal cancer risk in the years approaching diagnosis [193], but this association was not replicated in another study [194]. Studies of ghrelin in relation to other obesity-related cancers are scarce or lacking.

Likewise, the possible role of other gut hormones in cancer development in humans remains to be determined.

5. Discussion

A large body of evidence from both conventional observational studies and MR studies supports the association between greater body fatness and increased risk of a plurality of cancers, with the most consistent evidence for digestive system cancers, including esophageal, stomach, colorectal, liver, gallbladder, and pancreatic cancer, as well as kidney, endometrial and ovarian (weak association) cancer. Data from observational studies indicates that greater body fatness has contrasting effects on breast cancer risk depending on menopausal status (inverse association in premenopausal women and positive association in postmenopausal women) and on prostate cancer risk depending on disease stage (positive association for advanced prostate cancer only). In MR studies, genetically predicted higher BMI is associated with a reduced risk of overall breast cancer (possibly driven by the inverse association in premenopausal women) and overall prostate cancer. For cancers at other sites, including meningioma, head and neck, thyroid, small intestine, biliary tract, bladder, testicular, cervical, lung, skin, and hematologic cancers, the magnitude of the association with body fatness is weak or modest and data inconclusive.

With respect to biological mechanisms, data from experimental and MR studies indicate that adiponectin, insulin, and sex hormone pathways play an important role in mediating the association between excess body fatness and risk of cancer. The potential causal associations of the gut microbiome and gut hormones with cancer risk and their possible roles in mediating the adiposity-cancer associations warrant investigation in future studies.

BMI is the most used measure of body fatness in epidemiological studies but is not the best marker of fat mass, which is physiologically of higher relevance in cancer development. BMI is not designed to distinguish between adipose tissue and lean mass, which widely vary depending on gender, age, and ethnicity [195]. The associations of overall fat mass, visceral fat (also known as organ fat or intra-abdominal fat), and waist-to-hip ratio (as a measure of central obesity) with cancer risk have been reported in many studies. Data from two large US cohorts showed that BMI was merely as good predictor of colorectal cancer risk as predicted body fat percentage in a relatively healthy population [196]. In an MR study on different body composition measures (BMI, fat mass index [FMI], and fat-free mass index) in relation to 22 site-specific cancers, the magnitude of the associations with cancer risk was substantially stronger for FMI than for BMI per 1 kg/m² increase in the adiposity measure [55]. In that study, genetically predicted FMI was significantly positively associated with cancers of the liver (OR per 1 kg/m² increase in FMI 2.40; 95 % CI 1.02–5.65), pancreas (OR 1.68; 95 % CI 1.06–2.66), and lung (OR 1.57; 95 % CI 1.16–2.13) and inversely associated with melanoma (OR 0.68; 95 % CI 0.51–0.91) and prostate cancer (OR 0.77; 95 % CI 0.61–0.97) [55]. There were also strong albeit nonsignificant positive associations between FMI and cancers of the esophagus (OR 1.66; 95 % CI 0.97–2.83), biliary tract (OR 2.02; 95 % CI 0.94–4.30), and corpus uteri (OR 1.35; 95 % CI 0.92–1.98) [55]. The association of genetically predicted visceral adiposity with cancer at six sites, including colorectal, pancreatic, ovarian, lung, breast, and prostate cancer, was assessed in a recent MR study which found evidence of causal associations of greater visceral fat mass with risk of pancreatic, endometroid ovarian, and squamous-cell lung cancer but no strong association with colorectal, breast, and prostate cancer [197]. In other MR studies, genetically predicted BMI but not waist-to-hip ratio was significantly positively associated with risk of colorectal [198], pancreatic [199], endometrial [200], ovarian [198], and lung cancer [198]. Thus, overall and visceral fat mass, but not waist-to-hip ratio, appears to be a somewhat better predictor of cancer risk than BMI. This is potentially due to the fact that waist-to-hip ratio is also affected by subcutaneous adipose tissue and does not fully reflect visceral adiposity.
The most important preventive measures for obesity-associated cancers are based on weight loss interventions like bariatric surgery and medical nutrition. Bariatric surgery is a widely accepted option for long-term weight loss and reduction of comorbidities of morbidity obese patients [202]. Interestingly, bariatric surgery has been shown to decrease the risk for several obesity-associated cancers such as colorectal [203–205], liver [206], pancreatic [204,205], endometrial [204,205], ovary [208,209], and postmenopausal breast [204] cancer. Additionally, bariatric surgery can decrease cancer specific mortality by 40–50 % across the spectrum of malignancies a [207,210]. Recent evidence from secondary analyses of the randomized controlled Look AHEAD trial suggests that intensive lifestyle modifications aimed at weight loss can lead to reduction of obesity-related cancers in overweight or obese adult patients [211].

6. Conclusion

With rising prevalence of overweight and obesity globally, the proportion of cancer caused by excess body fatness is expected to increase. There is thus an urgent need to identify efficient ways at the individual and societal level to improve diet and physical activity patterns to reduce the burden of excess adiposity and accompanying diseases, including cancer. We believe that the role of modified peptide analogues of one or more than of these hormones in unimolecular forms or other formulations will play instrumental roles in limiting cancer prevalence and progression in the future via their major effects in decreasing body weight. This will be a major topic for future research efforts.

CRediT authorship contribution statement

SCL conducted the literature search, created the figures, and wrote the first draft of the paper. NS and GMS contributed to the drafting and revision of the paper.

Declaration of competing interest

The authors declare no competing interests.

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