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Obesity and Cancer Risk: Recent Review and Evidence

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Abstract

The prevalence of overweight and obesity is increasing worldwide, and the evidence base for a link between obesity and cancer is growing. In the United States, approximately 85,000 new cancer cases per year are related to obesity. Recent research has found that as the body mass index increases by 5 kg/m², cancer mortality increases by 10%. Additionally, studies of patients who have had bariatric surgery for weight loss report reductions in cancer incidence and mortality, particularly for women. The goal of this review is to provide an update of recent research, with a focus on epidemiologic studies on the link between obesity and cancer. In addition, we will briefly review hypothesized mechanisms underlying the relationship between obesity and cancer. High priorities for future research involve additional work on the underlying mechanisms, and trials to examine the effect of lifestyle behavior change and weight loss interventions on cancer and intermediate biomarkers.

Keywords

Neoplasm; Obesity; Overweight; Cancer risk; Intervention; Review; Insulin; Insulin-like growth factors; Sex steroid hormones; Adipokines; Hypoxia; Oxidative stress

Introduction

Obesity continues to be one of the critical health issues worldwide. A 2005 pooled analysis indicated that approximately 937 million adults worldwide are overweight and 396 million are obese. Together approximately one third of the world population is considered to be overweight or obese, defined as a body mass index (BMI) ≥ 25 or <30 (overweight) or ≥ 30 . If the trend continues unabated, overweight and obesity worldwide is projected to reach approximately 58% [1]. Many health consequences may result, or are already apparent, from this increase in obesity. In the United States, quality-adjusted life years (QALY) lost due to obesity increased by 127% from 1993 to 2008, and are now slightly greater than the smoking-related loss in QALYs [2]. The link between obesity and cancer has been demonstrated in numerous cohort studies [3, 4]; this article will provide an update of recent

research, including updated meta-analyses of the link between obesity and cancer, weight loss interventions, and hypothesized mechanisms underlying the relationship.

Past Data on Obesity and Cancer Risk

In 2002, The International Agency for Research on Cancer (IARC) concluded that there is adequate evidence of an association between obesity and several cancers, including colon, postmenopausal breast, endometrial, kidney, and esophageal [4]. The percentages of cancer attributed to obesity were 11% for colon cancer, 9% for postmenopausal breast cancer, 39% for endometrial cancer, 25% for kidney cancer, and 37% for esophageal cancer [4]. Following the IARC report, a paramount work by Calle and colleagues [3] was published which examined a cohort of 900,000 adults in the United States between the years 1982 and 1998. Results from this prospective study indicated a link between obesity and additional cancers, such as liver, pancreatic, non-Hodgkin's lymphoma, and myeloma. Using BMI (kg/m^2) as the outcome, Calle and colleagues found a dose-response relationship with obesity for all cancer combined. For overweight and obese women, relative to those with a BMI <25, the risk of developing cancer was 8% higher for a BMI 25 to 29.9; 18% higher for a BMI 30 to 34.9; 32% higher for a BMI 35 to 39.9; and 62% higher for a BMI 40. For men, only BMI 30 was associated with increased risk; a BMI 30 to 34.9 elevated risk by 9%; 35 to 39.9 by 20%; and 40 by 52% [3].

These findings accelerated the research area of obesity and cancer. In 2005 and in 2007, the World Cancer Research Fund (WCRF) published comprehensive reviews of the international evidence that pointed to the relationship between food, nutrition, physical activity, and prevention of cancer [5]. Evidence summarized in the 2007 WCRF review confirmed previous findings and added additional cancers that are related to obesity. The WCRF concluded that there is convincing epidemiological and plausible mechanistic evidence for the link between excessive body fatness (BMI) and the following cancers: esophageal adenocarcinoma, pancreatic cancer, colorectal cancer, postmenopausal breast cancer, endometrial cancer, and kidney cancer. This report also presented data supporting excessive body fatness as a probable cause for gallbladder cancer. An inverse relationship was found between BMI and premenopausal breast cancer and lung cancer. However, mechanisms are unclear for these two cancer types [5]. Although some cancers are strongly associated with obesity or body fatness status and some are weakly associated [6], special attention is still needed because of the preventable nature of obesity.

Recent Data on Obesity and Cancer Risk

A meta-analysis done by Renehan and colleagues [7••] reviewed updated prospective studies for 20 different cancer types including several newly published large cohort trials that were not included in the 2007 WCRF analysis. In addition, their meta-analysis included studies of less common cancers. Among men, results confirmed strong relationships between excess BMI (based on $5 \text{ kg}/\text{m}^2$ increase) and esophageal adenocarcinoma, thyroid cancer, kidney cancer, and colon cancer as found in the 2007 WCRF. Among women, results also confirmed strong relationships between endometrial cancer, gallbladder cancer, kidney cancer, and esophageal cancer, similar to the 2007 WCRF report. Weak associations among men were found for malignant melanoma, rectal cancer, leukemia, and non-Hodgkin's lymphoma; weak associations for women were leukemia, thyroid, postmenopausal breast cancer, pancreas, colon, and non-Hodgkin's lymphoma. Throughout different continents, the association between obesity and cancer was similar, except stronger associations for both premenopausal and postmenopausal breast cancer in the Asian-Pacific region [7••]. Overall, Renehan's study extended 2007 WCRF findings to less common cancer sites and found differences between genders regarding the magnitude of association between excess body

weight and risks of certain cancers. Table 1 is a summary of gender-specific cancer risks from the WCRF study and Renehan and colleagues' study.

In the United States, Polednak [8] abstracted the relative risks that compared obese (BMI ≥ 30) to normal weight (BMI < 25) individuals from cohort studies and/or meta-analyses. Using obesity prevalence data from the NHANES 2005–2006 database and number of new cancer cases in 2007 based on SEER registry data, Polednak calculated gender-specific attributable risk percentages (ARPs) for the United States [8]. The results indicated that in the United States in 2007 approximately 33,966 new cancers among males (4%) and 50,535 among females (7%) may have been related to obesity [8]. The percentages found from Polednak's study were higher than what was recently found among 30 European countries, which were 2.5% among men and 4.1% among women [9]. In the US study it was estimated that in 2007 approximately 16,000 cases of endometrial cancer and 13,000 of postmenopausal breast cancer could be obesity-attributed. Obesity accounts for over 9000 colorectal cancers among men, followed by kidney for both sexes, liver for men, esophageal adenocarcinoma and leukemia for men, and all other types by gender such as colorectal cancer among women, ovarian, thyroid for women, leukemia for both sexes, and non-Hodgkin's lymphoma for both sexes [8]. The authors concluded that without the increasing trend in obesity in the United States, incidence rates of endometrial and breast cancer might have declined rather than remaining stable as they did.

Obesity-related cancer mortality study is best exemplified by a recent analysis based on the 57 prospective studies from Europe and North America [10•]. In this study, 900,000 adults and approximately 6.5 million person-years of follow-up were included [10•]. Overall, the study confirmed that mortality was the lowest for those with BMI within the normal range (22.5–25 kg/m²) for both genders [10•]. With each increase of 5 kg/m², a 30% increase in all-cause mortality and a 10% increase in cancer mortality was found [10•].

Recent studies of cancer risk in individuals who have lost weight provide additional support for the link between obesity and cancer, and offer evidence that weight loss may be an effective cancer prevention strategy. Most of these studies compare obese individuals who have had bariatric surgery for weight loss to obese controls who have not. Bariatric surgery results in dramatic weight loss for most individuals, who see on average a loss of approximately 20% in the first 2 years [11]. Two studies have shown a relationship between bariatric surgery and reduced cancer risk. In a prospective observational study conducted in Sweden, Sjostrom and colleagues [12••] reported that compared to obese controls who received conventional weight loss treatment, obese individuals who had bariatric surgery had a reduced risk of developing cancer (HR=0.67; CI -0.53, -0.85). The effect was present primarily for women [12••]. A study by Adams and colleagues [13•] compared obese subjects who received bariatric surgery to obese controls recruited from the Utah driver's license or ID card database. In this study there was an overall risk reduction for all cancers (HR = 0.76, CI=0.65–0.89), women only (HR=0.73, CI=0.62–0.87), and obesity-related cancers (HR=0.62, CI=0.49–0.78). There was no relationship between bariatric surgery and cancer incidence for men. The only single cancer site for which there was a significant effect was uterine corpus/uterine NOS (HR=0.22, CI=0.13–0.40) [13•]. One possible explanation for the lack of effect in males is that the smaller sample size for males may have resulted in insufficient power to detect effects. Although both studies were large, fewer men than women were included because they are less likely to obtain bariatric surgery. In the Sjostrom study 29% were men, and in the Adams study men comprised 14% of the sample.

Among weight loss interventions, bariatric surgery results in the most dramatic weight loss, and thus studies of these patients are the most likely to show reduced risk of cancer. However, several case-control or cohort studies have also shown associations between

weight loss and risk of endometrial cancer [14] and postmenopausal breast cancer [15, 16]. However, there are no randomized trials demonstrating that weight loss interventions result in reduced cancer risk. More research is needed on other weight loss methods and whether smaller weight losses than those typically achieved with bariatric surgery can have an impact on cancer risk. Research has shown that weight loss of 5% to 10% can have a beneficial effect on conditions such as diabetes and hypertension, and that such a weight loss can be achieved and maintained if some form of therapy is continued [17]. A range of strategies have been successful in helping people lose weight, including dietary approaches such as low calorie (ie, 600 cal/day deficit) with or without meal replacements or behavioral therapy [18]. Increasing physical activity in combination with dietary changes helps support long-term weight loss maintenance [19]. An evidence synthesis conducted by the AHRQ on the topic of obesity screening and treatment found that for obese individuals, intensive counseling and behavioral treatment reduces mean weight by approximately 3 to 5 kg after 1 year, while pharmacotherapy with sibutramine or orlistat produces similar losses [20]. Randomized trials and carefully constructed observational studies are needed to optimize effectiveness of nonsurgical weight loss interventions and determine if the smaller weight losses they produce can have an impact on cancer incidence or changes in biomarkers. However, identifying the appropriate biomarkers requires an adequate understanding of the mechanisms underlying relationships between obesity and cancer.

Mechanisms Underlying the Obesity–Cancer Link

In order to further determine the link between obesity and cancer risks, more studies are focusing on the mechanisms that link obesity and cancer. Due to the complexity of obesity and the many possible mechanisms, which may differ across cancer sites, numerous pathophysiological mechanisms have been hypothesized and tested [21•]. A comprehensive summary of all plausible obesity and cancer mechanisms is beyond the scope of this review but can be found in the recently published book edited by Berger [22••]. To highlight progress in this field, we will focus on recent publications of popular and emerging mechanisms linking obesity to carcinogenesis.

Currently, the biological mechanisms that have received the most study are insulin and insulin-like growth factors (IGFs), sex hormones, and adipokines. Calle and Kaaks [23] proposed that insulin and insulin-like growth factor 1 (IGF-1) are pathways that are linked to obesity and work to prohibit apoptosis and promote cell proliferation. Hyperinsulinemia triggers the insulin-IGF pathway, a complex pathway that includes insulin, IGF-1, and IGF-2 (three ligands), along with six receptors (insulin receptor, IR, IGF-1 receptor, IGF-2R, hybrid IGF-1R/IR, and hybrid IGF-1R/IR) and the seven IGF-binding proteins [24]. It is hypothesized that the increased level of insulin reduces the amount of IGF-BPs, which leads to an increase in the level of IGF-1 and a change in cell environment which promotes tumor growth [21•]. Growth hormone, which is regulated by insulin, stimulates production of IGF-1 and IGF-BP-3. The hypothesized pathways have been demonstrated within in vitro and in vivo (animal) studies [23]. In meta-analyses, an increased level of IGF-I has been associated with increased risk of pre and postmenopausal breast cancers and prostate cancer [25, 26]. Studies measuring IGF-BP-3, on the other hand, have had inconsistent results [21•]. A recent estimation of all-cancer mortality based on a group of 633 men ages 50 years and older indicated a significantly higher risk of cancer death associated with higher levels of IGF-I after adjusting for age, IGF-BP-1, adiposity, exercise, current smoking status, and previous cancer [27]. Gu and colleagues [28] found that variations in the circulating IGF-1 and IGF-BP-3 levels may be related to the variations in IGF1, SSTR5, IGF-BP3, and IGFALS genes.

Evidence is mounting regarding the possible effect of sex hormones and the link between obesity and cancer, specifically cancers considered to be hormone dependent such as endometrial, breast, uterine, ovarian, and prostate cancers [21•, 22••]. Sex steroid hormones are mainly produced by the adrenal glands, and endogenous hormones include estrogens (E1-estrone and E2-estradiol), androgens (testosterone, androstenedione, dihydrotestosterone, and dehydroepiandrosterone), and progestogens (such as progesterone) [22••]. Estrogen, for example, binds to the receptor (ER), activating the intracellular signaling pathways that will initiate tumor progression by stimulating the cell division. In addition, the excess aromatase from the adipose tissue can lead to even higher levels of estradiol that are not bound causing further DNA damage. Lastly, estrogens also interact with IGF, which promotes tumor growth through inhibition of apoptosis.

Adipokines, hormones produced from adipose tissue, also have been proposed as a possible link between obesity and cancer [29]. The most well-known adipokine is leptin; however, adiponectin, resistin, and visfatin have also been studied [21•]. Leptin hormone suppresses appetite indirectly through increased levels of α -melanocyte-stimulating hormone and binding of melanocortin receptors [22••]. Colon, prostate, and breast cancers have been associated with increased serum leptin levels [30]. However, the consistency of leptin's effect on tumorigenesis for various cancer types is still being investigated [22••]. Adiponectin has been found to be negatively associated with cancer risk among endometrial, breast, colon, and prostate cancers [22••, 31]. The effect of resistin and visfatin has not been well studied. Thus far, resistin only has been explored in small studies. Possible mechanisms for resistin may be related to inflammatory and angiogenic pathways [22••]. Visfatin is mainly being explored through in vitro studies and among patients with type II diabetes because it mimics insulin's effects. So far, the relationship between an increased level of visfatin and cancer has been observed only in colorectal cancer patients [22••].

Recently, Roberts and colleagues [21•] provided a new perspective on the biological mechanisms by which obesity may influence cancer by highlighting obesity-related hypoxia, shared genetic susceptibility, migrating adipose stromal cells, and other biological candidates (obesity-related inflammation, oxidative stress, and nuclear factor- κ B system). They point to the relationship between adipose tissue hypoxia (ATH) and the development of insulin resistance that leads to reduction of adiponectin and increased leptin gene expressions. The in vivo study showed there may be lower oxygen levels in obese mice than lean mice. The in vitro studies found that melanoma grew more readily in a hypoxic microenvironment. With the improvement in technology and accelerated pace in genome-wide association studies, obesity genetics and its relationship with cancer genes are widely studied within breast and colorectal cancers. When the obesity gene map is superimposed with cancer gene maps there seem to be connections with chromosomes 11p and 16q for breast cancer and 18q for colorectal cancer [21•].

Migrating adipose stromal cells have been hypothesized as a mechanism because of their potential neovasculature development which helps supply nutrients and oxygen to tumor cells [21•]. A recent in vivo study found that an increase in white adipose tissue leads to an increase in the recruitment of adipose stromal cells and adipose endothelial cells for tumor cells, which in turn promotes tumor growth [32].

Substantial evidence has been shown between obesity, chronic inflammation, and insulin resistance. Based on previous research on obesity-related inflammation and insulin resistance, researchers have hypothesized and extrapolated the relationship to include tumorigenesis. However, there is no strong evidence. A prospective study showed an association between increase in C-reactive protein and development of colorectal cancer, but results were not confirmed with another cohort study [33, 34]. The nuclear factor- κ B

(NF-kappaB) system, which promotes inflammation through increased cytokine production, has been shown to be related to tumorigenesis of colitis-related cancer in an *in vivo* study [35], but this has not been seen in prospective studies in humans [21•]. There has been a recent surge of interest regarding the hypothesized relationship between obesity, oxidative stress, and cancer development [21•]. Oxidative stress is related to an imbalance between the amount of free radicals or reactive oxygen species and the elimination process [36]. Gago-Dominguez and colleagues suggest that obesity may decrease the antioxidant activity and induce oxidative stress [21•, 37]. In addition, *in vivo* studies indicated that the UV-induced oxidative stress may activate the NF-kappaB pathways, which promotes tumor growth [21•]. Even though advances in the molecular studies are continuing, more studies are needed to elucidate the underlying biological mechanisms linking obesity and cancer.

Conclusions

The rising obesity rates in the United States and worldwide are worrisome given the links between obesity and cancer. Numerous cohort studies, summarized in systematic reviews, have shown a link between obesity and cancer incidence overall and for selected cancer sites (eg, endometrial, postmenopausal breast, colon, and esophageal adenocarcinoma). Data showing reduced cancer incidence and mortality among individuals who lose weight and maintain the loss strengthen confidence in the obesity–cancer link, and also provide a note of hope that weight loss in obese individuals may help them prevent cancer. Research on the biological mechanisms underlying the obesity–cancer link is still in early stages, but may lead to a better understanding of the process of carcinogenesis in obesity-related cancers as well as potential treatments and preventive agents.

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Table 1

Cancers related to excess body weight by gender and strength of evidence

	Male	Female
Strong/convincing evidence of increased cancer risk related to excess body weight	<ul style="list-style-type: none"> • Colorectal cancer • Esophageal adenocarcinoma • Kidney cancer • Pancreatic cancer • Thyroid cancer 	<ul style="list-style-type: none"> • Colorectal cancer^a • Endometrial cancer • Esophageal adenocarcinoma • Gallbladder cancer • Kidney cancer • Pancreatic cancer^a • Postmenopausal breast cancer^{ab}
Weaker/probable evidence of increased cancer risk related to excess body weight	<ul style="list-style-type: none"> • Leukemia • Malignant melanoma • Multiple myeloma • Non-Hodgkin's lymphoma • Rectal cancer 	<ul style="list-style-type: none"> • Leukemia • Thyroid cancer • Premenopausal breast cancer (Asia-Pacific population group only)^{ab} • Non-Hodgkin's lymphoma

^aFindings from the study by Renehan et al. showed smaller magnitude of association between cancer risk and body mass index compared to the 2007 WCRF report [5, 7••]

^bHighest risk among women within the Asia-Pacific region [7••]