

Body fatness as a cause of cancer: epidemiologic clues to biologic mechanisms

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Abstract

Carrying excess body fat is a leading cause of cancer. Epidemiologic evidence gives strong clues about the mechanisms that link excess adiposity to risk for several cancer sites. For postmenopausal breast cancer and endometrial cancer, the hyper-estrogenic state that is induced by excess body fatness is the likely cause. For esophageal cancer and gallbladder cancer, chronic local inflammation induced by acid reflux and gallstones is the likely cause, and for liver cancer, local inflammation induced by hepatic fatty infiltration is the likely cause. However, for several other cancers known to be associated with excess adiposity, including cancers of the colon, pancreas, ovary, kidney, and prostate, specific causes are not known. Possible candidates include elevated systemic or local tissue inflammation induced by adiposity and effects of the elevated levels of leptin, insulin, IGFs, and depressed immune function that are seen with excess adiposity. There is growing evidence that intentional weight loss not only reduces circulating levels of cancer-associated factors but that it also reduces cancer incidence and recurrence. Better research is needed to understand the mechanisms that link excess body fat to cancer risk as well as to understand the amount of weight loss needed for substantial cancer risk reduction. Finally, as we develop better understanding of the mediators of the effects of excess body fatness on cancer risk, we should identify pharmacologic interventions that target those mediators so that they can be used to complement weight loss in order to reduce cancer risk.

Key Words

- ▶ obesity
- ▶ neoplasia

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Introduction

In 2007, the World Cancer Research Fund (WCRF) conducted a thorough systematic review of the evidence that links various nutritional factors to cancer risk and concluded that carrying excess body fat is a cause of cancer at several sites (World Cancer Research Fund 2007). About 20% of these obesity-associated cancers in the United States can be attributed to excess adiposity *per se*. Although the proportion of cancers caused by excess adiposity is lower in many other countries

because of their lower levels of adiposity, the impact of obesity on cancer risk among those who are obese is similar around the world. The WCRF has estimated that excess body fatness causes about 17% of obesity-associated cancers in Great Britain, 13% in Brazil, and 11% in China (World Cancer Research Fund 2009). Arnold *et al.* (2015) recently estimated that 3.6% of all incident cancers in the world in 2013 were caused by obesity.

In the present review, we focus attention largely on evidence that ties excess adiposity to cancer risk in the United States, but as documented by the WCRF, obesity is a major risk factor for cancer everywhere (World Cancer Research Fund 2007). We consider the evidence for the cancer-causing effects of excess adiposity across a wide range of BMIs, including the categories known as 'overweight' (BMI levels 25–29 kg/m²) and 'obesity' (BMI levels 30 kg/m² and greater). In the present review, we use the terms 'excess adiposity' and 'excess body fatness' interchangeably to refer to the combined effects of overweight and obesity. We use as risk estimates those that are reasonably attributed to the independent effects of overweight and obesity, separated by multivariate adjustment where possible from other potential confounding factors, including socio-demographic factors and other nutritional factors, such as diet quality and physical activity. Physical activity is an especially important potential confounder of the association between cancer and excess adiposity, because it is strongly inversely correlated with adiposity and is itself an independent risk factor for several cancer sites.

Despite the importance of excess adiposity as a cause of cancer, our understanding of the mechanisms that link levels of body fatness to cancer occurrence is very incomplete (De Pergola & Silvestris 2013, Dobbins *et al.* 2013). For some cancer sites, such as the breast, endometrium, and esophagus, the epidemiologic evidence points to specific mechanisms, but for most other sites, the mechanisms are not known. In the present review, we describe the epidemiologic evidence that ties levels of body fatness to cancer at specific sites and discuss what we know and what we do not know based on epidemiologic clues that point to the mediating mechanisms that link excess adiposity to increased cancer risk.

Because excess adiposity is such a major cancer risk factor, it is surprising that the discovery of this relationship seems to have been so recent. In the 1980s, Larry Garfinkel, a statistician working for the American Cancer Society (ACS), noticed that the actuarial evidence from life insurance companies that tied relative weight (weight as a function of height) to increased overall mortality could also be seen for cancer-specific mortality in a large cohort of Americans assembled by the ACS (Garfinkel 1985). He reported that relative weight was positively associated with cancer incidence for many different cancer sites. At that time, obesity was not widely accepted as a cancer risk factor, in part because of the nonspecificity of the obesity–cancer connection (which was observed for many different cancer sites) and also because of the possibility that obesity

might be only a marker of some aspects of the diet that were the more direct causes. When Calle *et al.* (2003) made similar observations about the cancer mortality connection to excess adiposity in a second ACS cohort 20 years later, the world took greater notice, in part because a year earlier the International Agency for Research on Cancer (IARC) had published a carcinogenesis handbook on obesity, which concluded that obesity was among the most important risk factors for cancer worldwide (International Agency for Research on Cancer 2002). Over the past 20 years, there has been a persistently accumulating body of evidence linking excess adiposity to cancer risk around the world.

We first examine the relationship between excess adiposity and circulating biomarkers of cancer risk; then we summarize the epidemiologic evidence, site by site, for the nine cancer sites for which the WCRF has concluded that evidence is convincing of a relationship between obesity and cancer risk (the breast in postmenopausal women, ovary, endometrium, colon, esophagus, gallbladder, pancreas, kidney, and prostate) and also for liver cancer, for which recent evidence strongly suggests a causal connection. The present summaries emphasize the specific aspects of epidemiologic evidence that are clues to the biological mechanisms that explain those relationships. We then close with comments about the priorities for both public health and research on questions regarding excess body fat and cancer.

Cancer-relevant biomarkers and obesity

Excess body fatness is associated with increased circulating concentrations of many types of compounds that are known to increase cancer risk via pathways that involve hormonal control, cellular proliferation, and immunity (Byers & Sedjo 2011, De Pergola & Silvestris 2013). After menopause, aromatase activity within adipose tissues constitutes the predominant source of endogenous estrogens. Among postmenopausal women, there is a clear positive association between BMI and circulating estrogens and also an inverse association between BMI and levels of sex hormone binding globulin (Hankinson *et al.* 1995). Intentional weight loss leads to substantial decreases in levels of circulating estrogens, with an ~3% decline in estrogen levels for every 1% of loss of body weight (Byers & Sedjo 2011). It is important to note, however, that those reductions in estrogens with weight loss have only been documented in the relative short term (6–12 months). The relationship between circulating estrogens and patterns of persistent weight

loss, weight regain, and weight cycling is unknown over the longer term.

Excess adiposity is a condition of hyper-inflammatory stress. This hyper-inflammatory state is thought to explain at least part of the association between excess adiposity and various other chronic conditions, including cardiovascular disease, diabetes, and arthritis, and it may also be relevant for cancer. There is a strong positive association between BMI and levels of cytokines in the circulation (Kitahara *et al.* 2014). Intentional weight loss leads to substantial decreases in levels of circulating cytokines, with an ~2% decline in circulating levels for every 1% of loss of body weight (Byers & Sedjo 2011). The immediate effects of acute weight loss following bariatric surgery on reducing levels of circulating cytokines are especially dramatic (Bueter *et al.* 2010). However, as with estrogens, the reductions in cytokine levels with weight loss have only been documented in the relative short term, but the longer-term relationships between circulating cytokines and weight patterns are still unknown.

There are many other potential cancer-relevant compounds in the circulation that have been considered cancer biomarkers and that are also associated with excess adiposity, including insulin, insulin-like growth factor 1 (IGF1), IGF-binding protein 3 (IGFBP3), and leptin (Byers & Sedjo 2011). Although weight loss reduces insulin (Look AHEAD Research Group 2007), the effect of weight loss on circulating concentrations of IGF and IGFBPs is less clear (Byers & Sedjo 2011, Mason *et al.* 2013). Insulin as well as IGF and IGFBPs are growth factors that have mitogenic and anti-apoptotic properties (Louie *et al.* 2013). IGF and IGFBPs have been found to be associated with colorectal cancer and (less consistently) also with breast cancer (Endogenous Hormones and Breast Cancer Collaborative Group 2010, Rinaldi *et al.* 2010). Leptin is associated with a risk for cancer, but its independent effects are uncertain in part because it is so highly correlated with levels of adiposity. Also tied to the hyper-inflammatory state of obesity is a mild chronic suppression of immune function (Louie *et al.* 2013), so immune surveillance may be an important early event that contributes to the obesity–cancer connection.

Breast cancer

The WCRF has estimated that 17% of incident postmenopausal breast cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, 2010). The relationship between excess adiposity and breast cancer risk is quite different in

different age groups, however. Among premenopausal women, obesity is associated with a reduced risk for breast cancer, but among postmenopausal women, obesity is associated with an increased risk (Carmichael & Bates 2004). This difference by age is likely a result of the changes with age in the source of the hormonal drivers of cellular activity in the breast. In premenopause, when female hormones come from the ovaries, any factor that affects ovarian function will alter circulating hormone levels. Excess adiposity is one of those factors. Women with fewer menstrual cycles per year, longer cycles, and/or irregular cycles are at a lower risk of breast cancer, presumably because of some degree of ovarian insufficiency (Garland *et al.* 1998). Women who are obese tend to have irregular menses as well as reduced fertility; hence, ovarian dysfunction may explain the apparent ‘protective’ relationship between excess adiposity and breast cancer risk that has been observed among premenopausal women. Among premenopausal women, circulating estrogens are not consistently found to be associated with breast cancer, although a positive relationship has been observed with circulating testosterone (Kaaks *et al.* 2014a).

After menopause, when adipose tissue becomes the primary source of circulating estrogens, the association between excess adiposity and breast cancer risk becomes strongly positive, with progressively increasing risk with increasing BMI (Key *et al.* 2003, Ritte *et al.* 2012). Serum estrogen levels have been shown to be positively associated with breast cancer risk in prospective cohort studies, and postmenopausal hormone replacement therapy increases breast cancer risk, so estrogens and progestins clearly play roles in breast cancer etiology (Key *et al.* 2003, Anderson *et al.* 2004, Endogenous Hormones and Breast Cancer Collaborative Group 2011, 2013, Ritte *et al.* 2012). The observation that obesity does not appear to be a risk factor among women who are using hormone replacement therapy suggests that elevated estrogen levels, regardless of whether they come from endogenous or exogenous sources, increase breast cancer risk, and those effects are not additive. Because BMI is known to be positively associated with circulating estrogen levels, it is reasonable to conclude that the obesity–breast cancer association observed among postmenopausal women is mediated by estrogens. Further support of that hypothesis comes from comparing the BMI–breast cancer association among the two major subtypes of breast cancer – those that express estrogen receptors (ER-positive) and those that do not (ER-negative). Excess adiposity has been associated with increased breast cancer risk for ER-positive breast cancers but not for ER-negative breast cancers

in most studies, although in a large cohort, the risk for postmenopausal ER-negative breast cancer was also marginally increased by obesity among women who had never used hormone replacement therapy (Ritte *et al.* 2012). Overall, the epidemiologic evidence is compelling that among postmenopausal women, the BMI–breast cancer relationship is driven mostly by the production of endogenous estrogens by aromatase activity in adipose tissues.

It is important to note that even though excess adiposity is positively associated with only postmenopausal breast cancer risk, it is positively associated with breast cancer recurrence and breast cancer-specific mortality among both premenopausal and postmenopausal women with breast cancer (Protani *et al.* 2010). Women who have excess adiposity at diagnosis, regardless of their age and regardless of their ER subtype, experience a higher risk of breast cancer recurrence and breast cancer-specific mortality than do women who do not carry excess body fat at the time of diagnosis. This adverse effect of adiposity on breast cancer prognosis is also seen among women who have been treated with anti-estrogens (Protani *et al.* 2010). These observations suggest different mechanisms for how excess body fat affects cancer incidence as compared to cancer recurrence. Hence, although estrogens are quite likely the mechanism through which the risk for postmenopausal breast cancer incidence is increased by excess adiposity, other factors, such as circulating or local tissue cytokines, IGF, and/or immune function, might be the mechanisms through which cancer recurrence risk is increased for women with excess adiposity at the time of diagnosis (Endogenous Hormones and Breast Cancer Collaborative Group 2010, Kaaks *et al.* 2014b).

Evidence suggests that a reduction of breast cancer risk is possible with weight loss. Because intentional weight loss in which lost weight is maintained over multiple years is relatively infrequent, only a few studies have evaluated this relationship. Prospective studies report a decrease in the incidence of postmenopausal breast cancer among women who lost weight and kept it off for several years (Parker & Folsom 2003, Harvie *et al.* 2005, Eliassen *et al.* 2006, Byers & Sedjo 2011). The Women's Intervention Nutrition Study was a randomized controlled trial of a low-fat dietary intervention among breast cancer survivors (Chlebowski *et al.* 2006). Although that trial was not specifically designed to evaluate weight loss changes, the caloric balance modifications associated with the low-fat dietary intervention led to a difference in body weight of about 6 lbs between the treatment groups after 5 years, which was accompanied by a 24% risk reduction of breast

cancer recurrence among women with ER-negative cancers. Studies that investigated patients who have undergone bariatric surgery have demonstrated a substantial reduction in cancer risk associated with the rapid and substantial weight loss following surgery (Christou *et al.* 2008, Sjöström *et al.* 2009, Tee *et al.* 2013). Interestingly, the effect of bariatric surgery on reducing cancer risk appears to occur primarily among women rather than men, which suggests that there may be a predominant early effect mediated by reductions in circulating sex steroid hormone levels.

Endometrial cancer

The WCRF has estimated that 50% of incident endometrial cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, 2013). The impact of excess body fat on endometrial cancer risk is much greater than it is on breast cancer, likely because circulating estrogens play a much larger role in endometrial cancer development. Postmenopausal estrogen hormonal replacement therapies are known to increase endometrial cancer risk (Allen *et al.* 2010), and levels of estrogens in the circulation are strongly associated with an increased risk for endometrial cancer (Allen *et al.* 2008). Bariatric surgery decreases the risk for endometrial cancer (Ward *et al.* 2014), and a pattern of weight cycling (repeated cycles of weight loss followed by regain) has been found to be associated with increased endometrial cancer risk (Stevens *et al.* 2012, Nagle *et al.* 2013). Endometrial cancers are commonly categorized into two types. Type 1 endometrial cancers, which comprise about 80% of all cases, are mostly endometrioid adenocarcinomas and tend to be hormone sensitive, whereas type 2 endometrial cancers, which represent about 20% of all cases, tend to be less hormone sensitive and to have poorer prognoses (Setiawan *et al.* 2013). Obesity is associated with both types of endometrial cancer, but the strength of the association is greater for type 1 (estrogen-driven) cancers (Setiawan *et al.* 2013). The positive association between BMI and circulating estrogens among postmenopausal women is likely the main mediator of the obesity–endometrial cancer relationship, although other factors, such as circulating or local tissue cytokines and insulin, may also play a role (Cust *et al.* 2007, Dossus *et al.* 2010).

Ovarian cancer

The WCRF has estimated that 5% of incident ovarian cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009,

2014a, Lahmann *et al.* 2010). BMI has been observed to be more strongly associated with less common (and less lethal) histologic subtypes of ovarian cancer (Olsen *et al.* 2013). Apart from the use of oral contraceptives to reduce risk, little is understood about the etiology of ovarian cancer. The mechanisms that link excess adiposity to ovarian cancer are only speculative, but they include systemic and local tissue inflammation. In a prospective analysis from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial cohort, substantial positive associations were observed between ovarian cancer risk and elevated concentrations of CRP, IL1 α , and TNF- α (Trabert *et al.* 2014). Supporting the hypothesis that the hyper-inflammatory state of obesity is an important mechanism for ovarian cancer is the observation from a recent meta-analysis of 14 case-control and seven cohort studies that ovarian cancer risk is reduced with frequent aspirin use (Baandrup *et al.* 2013).

Colorectal cancer

The WCRF has estimated that 15% of incident colorectal cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, 2011). BMI is more consistently associated with colon cancer than it is with rectal cancer (Robsahm *et al.* 2013), and adult weight gain increases the risk of colon cancer but not rectal cancer among both men and women (Aleksandrova *et al.* 2013a). The mechanism that explains this association is not known, but sex differences in the relationship between excess adiposity and colon cancer suggest that mechanisms apart from hormonal ones are involved. The association between obesity and colon cancer risk is weaker among women than it is among men (Aleksandrova *et al.* 2013b), which may well be a result of the protective role that estrogens play for colon cancer in women (Rossouw *et al.* 2002). Even though the colon cancer association with excess adiposity is weaker among women than it is among men, it is important to note that there still remains an increased risk for colorectal cancer with excess adiposity among women. This suggests that a mechanism such as cytokines and/or IGF might mediate the link between excess adiposity and colon cancer risk in both sexes (Aleksandrova *et al.* 2010, Ho *et al.* 2012). Weight loss appears to produce a moderate reduction on colorectal cancer risk. A meta-analysis of four studies reported a 27% reduction in colorectal cancer risk among obese individuals who underwent bariatric surgery (Afshar *et al.* 2014).

Esophageal cancer

The WCRF has estimated that 35% of cases of incident adenocarcinoma of the esophagus in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009). There have been two opposite trends in esophageal cancer incidence in the United States over the past 20 years – a persistent decline in the risk of squamous cell cancer of the esophagus and a persistent increase in the risk of adenocarcinoma of the esophagus. Squamous cell carcinoma of the esophagus occurs mostly in the upper two-thirds of the esophagus, and it is increased by factors such as tobacco and alcohol. The declining use of tobacco in the United States is likely the main factor that has led to the declining incidence of squamous cell cancer of the upper esophagus. In contrast, esophageal adenocarcinoma occurs typically in the lower one-third of the esophagus, and it is clearly on the rise. Adenocarcinoma of the esophagus typically arises from a mucosa that has been chronically damaged, most commonly by the chronic reflux of acidic contents from the stomach into the lower esophagus. Obesity is the most important risk factor for acid reflux, which likely explains much of its relationship with adenocarcinoma of the esophagus (Singh *et al.* 2013). Although stomach cancer is not associated with obesity overall, cancers of the upper part of the stomach (gastric cardia) near the esophageal juncture are associated with excess adiposity (Chen *et al.* 2013).

Gallbladder cancer

The WCRF has estimated that 21% of incident gallbladder cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, Wang *et al.* 2012a). Gallstones are a major risk factor for gallbladder cancer, and obesity is a major risk factor for gallstones. Much of the association between excess body fatness and gallbladder cancer is likely explained by the precipitation of bile acids into stones in the gallbladder, which causes chronic local tissue inflammation.

Liver cancer

The WCRF has found conclusive evidence that links liver cancer to excess adiposity, and substantial evidence has been accumulated in recent years to support that conclusion (Wang *et al.* 2012b, Chen *et al.* 2012, Chen *et al.* 2013, Schlesinger *et al.* 2013, World Cancer Research Fund International 2015). Clearly, chronic viral infection in the liver is the leading cause of liver cancer, but any other factors that also cause hepatocellular injury

and hepatocellular proliferation, including alcohol use, chronic exposure to other chemicals, and excess adiposity, can increase risk. The mechanism that ties excess adiposity to liver cancer likely includes fatty infiltration and its accompanying chronic local inflammation (Aleksandrova *et al.* 2014). The high levels of circulating leptin associated with excess adiposity may also play a role (Polyzos *et al.* 2011). The continuing epidemic of chronic hepatitis C virus infection, combined with the obesity epidemic, have led to persistent increases in the incidence of hepatocellular cancer in the United States over the past 30 years. Although excess body fatness is associated with an increased risk for incident liver cancer, whether that excess risk might be reduced with weight loss is unknown.

Pancreatic cancer

The WCRF has estimated that 19% of incident pancreatic cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, 2012, Arslan *et al.* 2010, Genkinger *et al.* 2011). Apart from adiposity and the rare hereditary forms of pancreatic cancer, there are few known pancreatic cancer risk factors. The mechanism that ties excess adiposity to pancreatic cancer risk are unknown, but they may well be similar to those for the liver and may involve fatty infiltration of the pancreas with resulting local tissue inflammation, perhaps also including effects of circulating cytokines, IGF, and/or insulin.

Kidney cancer

The WCRF has estimated that 24% of incident kidney cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, Ljungberg *et al.* 2011). Apart from obesity, there are few known risk factors for kidney cancer (Wang & Xu 2014). Clearly, mechanical factors like those that may explain esophageal cancer risk, or fatty infiltrates, like those that may explain liver cancer risk, are not relevant for kidney cancers, where circulating factors that are tied to chronic inflammation, growth stimulating factors, and/or immune dysfunction are more likely.

Prostate cancer

The WCRF has estimated that 11% of incident advanced prostate cancer cases in the United States can be attributed to excess adiposity (World Cancer Research Fund 2009, 2014b, Golabek *et al.* 2014, Hu *et al.* 2014). There are few

known risk factors for prostate cancer. IGFs have been found to be modestly associated with prostate cancer risk (Price *et al.* 2012). One of the problems with prostate cancer epidemiology is that prostate cancer is a highly prevalent disease, so sorting out the prostate cancers that are more malignant from those that have more benign behavior is necessary in order to avoid dilution of the effects of any risk factor on this clinically important disease. Obesity is modestly associated with only the clinically aggressive forms of prostate cancer (Gleason scores of 7 or greater). One of the interesting complexities in prostate cancer epidemiology is the relationship between prostate cancer risk and the risk factors of excess adiposity and type 2 diabetes. Prostate cancer risk is lower among men with type 2 diabetes, despite the fact that obesity is a major driver for type 2 diabetes (Tsilidis *et al.* 2015). This may in part be a result of lower levels of androstenedione, total testosterone, and IGFBP3 among men with type 2 diabetes.

Discussion

Several common cancers are caused in part by carrying excess body fat. Because excess adiposity is such a common condition, there is a substantial preventable fraction (also known as the 'population attributable risk', or the proportion of all cases that could be prevented). The WCRF has estimated preventable fractions from obesity in the United States, as summarized in Table 1. Also in Table 1, we list what we believe are the strongest hypotheses for the mechanisms that tie obesity to cancer risk. The relationships between diet, physical activity, excess adiposity, and their pathways to cancer via mechanisms are summarized in Fig. 1. Although diet, physical activity, and excess adiposity are all inherently correlated, it is important to realize that the mechanistic pathways that connect them to cancer may not always be the same, and they may vary across different cancer sites.

Of course, there should be many question marks within both Table 1 and Fig. 1, because general explanations such as 'inflammation' are hardly specific enough to be regarded as true mechanistic explanations. The relationships between the levels of inflammatory cytokines in the circulation and the levels present locally in tissues are often weak, and local tissue inflammation may be more relevant for driving cellular proliferation than systemic inflammatory levels are. In addition, many factors that were thought to be capable of driving cancer cell growth, such as IGF, leptin, and insulin, have often not been observed to be any more strongly associated with

Table 1 Summary of the preventable fraction (population attributable risk) for selected cancers resulting from excess adiposity in the United States, as estimated by the World Cancer Research Foundation (World Cancer Research Fund 2009) and the possible mechanisms that link excess adiposity to cancer risk for selected cancers

Cancer site	Relative risk per five BMI units	Preventable fraction (%)	Most likely mechanisms
Breast (postmenopausal)	1.12	17	Endogenous circulating estrogens from adipose tissue
Endometrial	1.50	50	Endogenous circulating estrogens from adipose tissue
Ovary	1.06	5	Systemic or local tissue inflammation
Colorectal	1.10	16	Systemic inflammation and other circulating factors ^a
Esophageal	1.95 ^b	35	Acid reflux causing local inflammation
Gallbladder	1.23	21	Gallstones causing local inflammation
Pancreatic	1.10	19	Systemic inflammation and other circulating factors ^a
Kidney	1.31	24	Systemic inflammation and other circulating factors ^a
Prostate (advanced)	1.08	11	Systemic inflammation and other circulating factors ^a

^aFactors include leptin, IGFs, IGFBPs, and insulin.

^bMean of both sexes for high vs low categories of BMI (World Cancer Research Fund 2009).

cancer risk than BMI is *per se*. Hence, whether many of these factors that are correlated with adiposity are really primary factors or whether they are only bystanders to other factors that affect cancer risk is uncertain. There is particular uncertainty about the mechanisms that link excess adiposity to risk for cancers of the colon, prostate, pancreas, ovary, and kidney. In contrast, we see the evidence to be compelling for the mechanisms that explain most of the risk from excess adiposity for cancers of the endometrium, liver, gallbladder, esophagus, and the breast among postmenopausal women.

Clearly the best way to prevent the fraction of cancers that are attributable to excess adiposity is to prevent excessive weight gain throughout life. However, the more pressing question for the large proportion of adults who are already carrying excess body fat is whether anything can be done to reduce their excess cancer risk. The studies of the effects of bariatric surgery on cancer risk are very encouraging, in that there may be substantial cancer risk reductions after only a few years following intentional weight loss. Those findings are quite consistent with observational studies that indicate a lower cancer risk among people who have intentionally lost weight in adulthood (Byers & Sedjo 2011). Weight loss is known to reduce the levels of cancer-associated circulating factors, including estrogens, cytokines, insulin, and leptin. However, we know little about whether the short-term reductions in those factors with intentional weight loss that are well documented over months will be maintained with weight loss over years, because studies to date have followed subjects for only short periods of time. Longer-term follow-up studies are needed to assess the effects of

intentional weight loss over years on cancer-relevant biomarkers and hence on the apparent cancer risk reduction. In addition to using weight loss trials to study the effects of weight loss on biomarkers of cancer risk, we also need weight loss trials that are sufficiently powered to directly assess the effects on cancer risk and/or recurrence. Finally, recognizing that sufficient intentional weight loss may not be achievable by many, a better understanding of the mechanisms that link excess adiposity to cancer risk could lead to pharmacologic interventions to break those links.

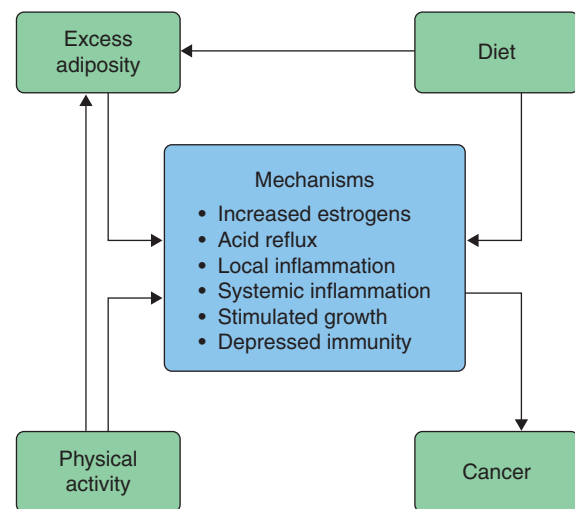


Figure 1

The inter-relationships between excess adiposity, diet, physical activity, mediating mechanisms, and cancer risk.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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