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Impact of the Obesity Epidemic on Cancer

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Abstract

There is growing appreciation that the current obesity epidemic is associated with increases in cancer incidence at a population level and may lead to poor cancer outcomes; concurrent decreases in cancer mortality at a population level may represent a paradox, i.e., they may also reflect improvements in the diagnosis and treatment of cancer that mask obesity effects. An association of obesity with cancer is biologically plausible because adipose tissue is biologically active, secreting estrogens, adipokines, and cytokines. In obesity, adipose tissue reprogramming may lead to insulin resistance, with or without diabetes, and it may contribute to cancer growth and progression locally or through systemic effects. Obesity-associated changes impact cancer in a complex fashion, potentially acting directly on cells through pathways, such as the phosphoinositide 3-kinase (PI3K) and Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathways, or indirectly via changes in the tumor microenvironment. Approaches to obesity management are discussed, and the potential for pharmacologic interventions that target the obesity–cancer link is addressed.

INTRODUCTION

Since the 1970s, much of the developed world has experienced an obesity epidemic; over two-thirds (68.8%) of the US population is currently classified as either overweight (33.1%) or obese (35.7%) (1). Increasing obesity rates have been reported in both adults and children, and in all ethnic and socioeconomic groups; somewhat higher rates have been reported in African Americans and Hispanics than in Caucasians. This obesity epidemic is extending to developing countries and is believed to reflect factors linked to food intake and physical activity at both individual and societal levels, including increased availability of low-cost calorie-dense food, increased portion sizes and caloric intakes, reduced physical activity programs in schools, the adoption of a more sedentary lifestyle, and increased screen time (i.e., watching television, using computers and mobile devices). There has been a recent debate (2) as to whether the rate of rise of obesity has begun to level off in the United States (the majority of the increases in prevalence occurred between 1980 and 2000). Any potential leveling off is occurring in the context of a very high rate of overweight/obesity.

Obesity has traditionally been viewed as a contributing factor for cardiovascular, kidney, and musculoskeletal diseases, and it has been associated with an increased risk of type 2 diabetes; worldwide, the association of obesity with diabetes has led to a parallel diabetes "epidemic" (3). Cancer has recently been added to the list of obesity-associated conditions; modest associations of diabetes with increased cancer risk (not reviewed in detail here) may reflect, in part, this parallel with the obesity epidemic. The increasing prevalence of obesity, coupled with a greater appreciation of an obesity–cancer link, has led to an explosion of research in this area. This interest has been accompanied by a greater appreciation of the potential contribution of patient/host factors to cancer risk and progression as well as enhanced understanding of the biology of obesity, the role of the tumor microenvironment in cancer progression, and the biology of carcinogenesis and tumor progression. What has emerged is a complex picture of a multifactorial association of obesity with cancer.

We review key aspects of the association of obesity with cancer incidence and mortality, explore the emerging understanding of key physiologic and endocrine aspects of obesity that are of greatest relevance to cancer, and outline potential mechanisms of obesity effects on tumor cells and tumor microenvironment.

WHAT IS OBESITY?

Obesity is a state of increased adiposity. The body mass index (BMI), calculated as weight (kilograms) over height (meters squared) (2), is widely used as a measure of obesity. The National Heart, Lung and Blood Institute (4) has categorized BMI into four categories: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (>30 kg/m^2). Obesity has been further subdivided into class I (BMI 30–34.9 kg/m^2), class II (BMI 35–39.9 kg/m^2), and class III (BMI >40 kg/m^2, also called morbid or extreme obesity). Different cut points are used for some ethnic groups; for example, Asians with a BMI >23 kg/m^2 are considered overweight and those with BMI >27.5 kg/m^2 obese (5). Despite its common use, BMI is an imperfect measure of adiposity; it may overestimate body fat in physically active individuals, and it may underestimate body fat in older individuals and those who have lost muscle mass. As an alternative, waist circumference [>88 cm ($\sim$34.6 inches) for women or >102 cm ($\sim$40.2 inches) for men] has been suggested as a measure of central or visceral obesity (most strongly associated with adverse health outcomes) (6).

Obesity leads to metabolic changes, including alterations in lipids (lower high-density-lipoprotein cholesterol, higher triglycerides, higher free fatty acids), glucose intolerance, and

insulin resistance/hyperinsulinemia with or without frank diabetes; it may also be associated with low-grade inflammation. Obesity is associated with hypertension, premature cardiovascular disease, nonalcoholic fatty liver disease, and sleep apnea. This clinical grouping has been called the metabolic (or insulin resistance) syndrome (7), and many of the metabolic changes associated with this syndrome have been implicated in cancer (see below). Although BMI correlates with this metabolic profile, some individuals with BMI >25 kg/m^2 have none of these changes (healthy obese), whereas others with BMI <25 kg/m^2 have many of these changes (normal-weight obesity).

Visceral adiposity is most strongly associated with the metabolic syndrome. Visceral adipose tissue is biologically active (8), secreting multiple factors, including adipokines (e.g., leptin, adiponectin) and other cytokines [e.g., tumor necrosis factor (TNF)-α, interleukin (IL)-6] that contribute to insulin resistance and attract inflammatory cells (including monocytes and macrophages), leading to a localized and systemic inflammatory state that has been implicated in cancer (9). Adipose tissue in the obese contains a higher proportion of preadipocytes compared to mature adipocytes than in non-obese, and it features increased numbers of monocytes and macrophages. These changes may contribute to cancer development locally (e.g., in fatty organs such as the breast). They may also promote tumor progression and invasion when present in a fat-containing tumor microenvironment, where they have been associated with enhanced mitogenesis, angiogenesis, epithelial-mesenchymal transition (EMT), and invasion. Moreover, adipose tissue reprograming and the associated systemic humoral effects can profoundly impact cancer development or progression throughout the body. In postmenopausal women, obesity is also associated with higher circulating estrogen levels, which is of greatest relevance to breast and endometrial cancers (see below).

THE OBESITY–CANCER LINK

During the past decade there has been an explosion of evidence linking obesity with increased cancer incidence and cancer mortality (see **Figure 1**) (10, 11). Obesity at cancer diagnosis may also be associated with a poor prognosis. Data from two large studies of the association of obesity with cancer incidence or mortality are summarized in **Figure 1**. Incidence and mortality of most cancers are elevated in obese versus non-obese individuals; lung cancer is a notable exception. Using data from the prospective American Cancer Society Prevention Study II involving more than 900,000 US adults, Calle et al. (11) estimated that 14% of all cancer deaths in men and 20% of all cancer deaths in women could be avoided if the current patterns of overweight and obesity in the United States could be reversed.

The relative risk (RR) estimates for incidence (left side of **Figure 1**) and mortality (right side of **Figure 1**) cannot be directly compared because they were based on different comparisons. Nonetheless, the generally higher RR for cancer mortality is consistent with a potential association of obesity not only with cancer incidence but also with cancer prognosis. This has been most clearly demonstrated for breast cancer. In a recent meta-analysis of 82 studies involving 213,075 breast cancer survivors (41,477 deaths, 23,182 from breast cancer) (12), for each 5 kg/m^2 increase in BMI, risk of breast cancer–specific mortality increased by 17% if BMI was measured prediagnosis, 18% if BMI was measured during the first year after diagnosis, and 29% if BMI was measured more than one year postdiagnosis. In other meta-analyses, BMI was associated with a higher risk of overall or breast cancer–specific mortality in pre- and postmenopausal breast cancer patients, in those with estrogen receptor-positive or -negative breast cancer, and in those diagnosed before and after 1995 (when more effective adjuvant systemic therapies were introduced) (13, 14). Evidence that obesity is associated with the outcome of other cancers is not as consistent; however, obese individuals with colorectal, endometrial, and other cancers may have worse outcomes (15–17).

	Cancer incidence (RR per 5kg/m² increase)		Cancer mortality (RR for high BMI [>30, 35 or 40 kg/m²] vs. normal BMI)	
	♀	♂	♀	♂
Thyroid	1.14	1.33	—	—
Lung	0.80	0.76	0.81	0.67
Breast:				
Pre	0.92	—	2.12	—
Post	1.12	—		
Esophagus:				
Adeno	1.51	1.52	2.64	1.94
Squamous	0.57	0.71		
Stomach	1.04	0.97	—	—
Liver	1.07	1.24	1.68	4.52
Gallbladder	1.59	1.09	2.13	1.76
Pancreas	1.12	—	2.76	2.61
Colon	1.09	1.24	1.46	1.84
Rectum	1.02	1.09		
Kidney	1.34	1.24	4.75	1.70
Endometrium	1.59	—	6.25	—
Ovary	1.03	—	1.51	—
Cervix	—	—	3.20	—
Prostate	—	1.03	—	1.34
Melanoma	0.96	1.17	—	—
Leukemia	1.17	1.08	—	—
Lymphoma	1.07	1.06	1.95	1.49
Multiple myeloma	1.11	1.11	1.44	1.71
All cancers			**1.88**	**1.52**

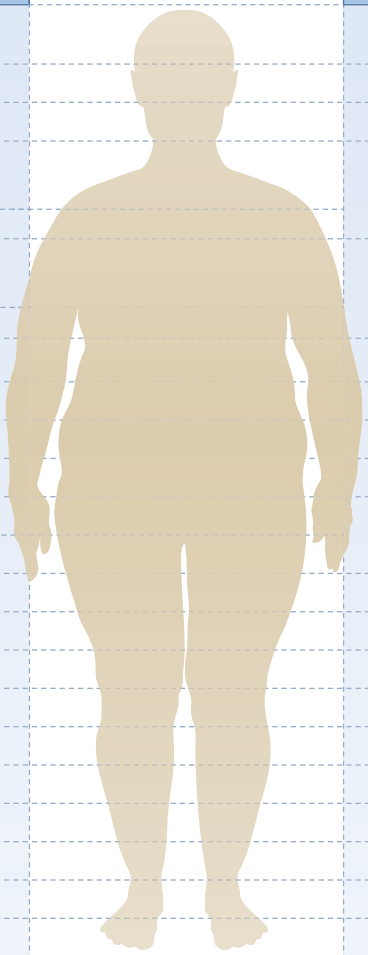

Figure 1

Associations of obesity with cancer incidence and mortality. The relative risks (RRs) of incidence of specific types of cancer in women and men per 5 kg/m^2 increase as reported by Renehan et al. (10) are shown on the left side of this figure. According to this report, the risks of many common cancers were increased, but the risks of tobacco-associated cancers (lung, esophageal, squamous) were decreased. The RRs of mortality from specific types of cancer and all cancers in healthy participants of the American Cancer Society Study II as reported by Calle et al. (11) are shown for men and women on the right side of this figure. Individuals with high body mass indexes (BMIs) (defined as >30, 35, or 40 kg/m^2, reflecting the highest category with reliable estimates) were compared to those with BMI 18.5–24.9 kg/m^2. For heavier individuals, the risk of mortality from many common cancers was higher, and the risk of lung cancer was lower.

The extent to which the obesity epidemic has already been reflected in population-based cancer incidence and mortality statistics is unclear. Age-adjusted US cancer statistics, as reported by the American Cancer Society (18), reveal a steady increase in cancer incidence in both men and women between 1975 and 2008. However, excluding lung cancer (which is not associated with obesity), cancer mortality rates have declined both overall and for most common cancer sites. Changes in incidence rates reflect not only true changes in incidence but also changes in screening/detection practices and in diagnostic criteria. Changes in mortality reflect these changes in incidence, stage at presentation, and treatment efficacy. When considering the contributions of obesity to cancer incidence, multiple factors, including lag time after obesity onset, severity of obesity, and the relative contribution of obesity versus other changing risk factors (such as declines in smoking, use of postmenopausal hormone replacement therapy), may be relevant. The absence of an increase in cancer mortality is a potential paradox. It is possible earlier diagnosis and improvements in treatment in recent years have overcome any adverse effects of obesity on cancer outcome; if this is the case, even greater reductions in cancer mortality may result if obesity rates could be lowered. It is also possible that obesity effects on cancer mortality have not yet been seen or that obesity is primarily associated with cancer incidence rather than cancer outcome. Given the potential for long lag times between exposure and diagnosis, and between diagnosis and death, the obesity epidemic may contribute to additional increases in cancer incidence and possibly mortality in upcoming decades.

THE RELATIONSHIP OF OBESITY WITH CANCER IS COMPLEX

The emerging understanding of the biologic nature of the association of obesity and cancer suggests a complex interplay of a range of factors at multiple levels: the whole patient, the adipose tissue, and the tumor cell and its fat-containing microenvironment (**Figure 2**). Obesity-associated metabolic and adipose tissue changes may contribute to cancer through direct effects on cancer precursors and cancer cells, or through indirect effects on adipose tissue in the tumor's microenvironment. The latter topic has been recently comprehensively reviewed by Gilbert & Slingerland in this journal (9). Here, we focus on the potential biologic basis for the obesity–cancer association, emphasizing the interface of physiologic and cellular/molecular influences.

Insulin

The insulin/insulin-like growth factor (IGF) pathway has become a major focus of research into the obesity–cancer link. Insulin levels are higher in obesity, reflecting insulin resistance. In an early study, our group (19) reported a strong correlation of postoperative fasting insulin with BMI in a prospective study of 535 nondiabetic breast cancer patients (Spearman $r = 0.59$). Insulin was a stronger predictor of distant recurrence and death than BMI alone in these survivors; the hazard ratios, adjusted for tumor- and treatment-related factors for women with fasting insulin in the upper versus lower quartile, were 2.0 (95% CI 1.2–3.3) and 3.1 (95% CI 1.7–5.7), respectively. Higher insulin levels were associated with the presence of other components of the insulin resistance syndrome (20). Further analysis of the same data set (21), with longer follow-up, found that insulin was significantly associated with breast cancer outcome during the first five years postdiagnosis but not thereafter, whereas BMI was associated with outcome beyond ten years. Similar findings have been reported by other investigators (22, 23), who examined either fasting insulin or nonfasting C-peptide (cleaved from proinsulin when fasting insulin is released). Higher levels of insulin have also been associated with more advanced stages and/or poor outcomes in other obesity-associated cancers, including prostate and colorectal (24, 25).

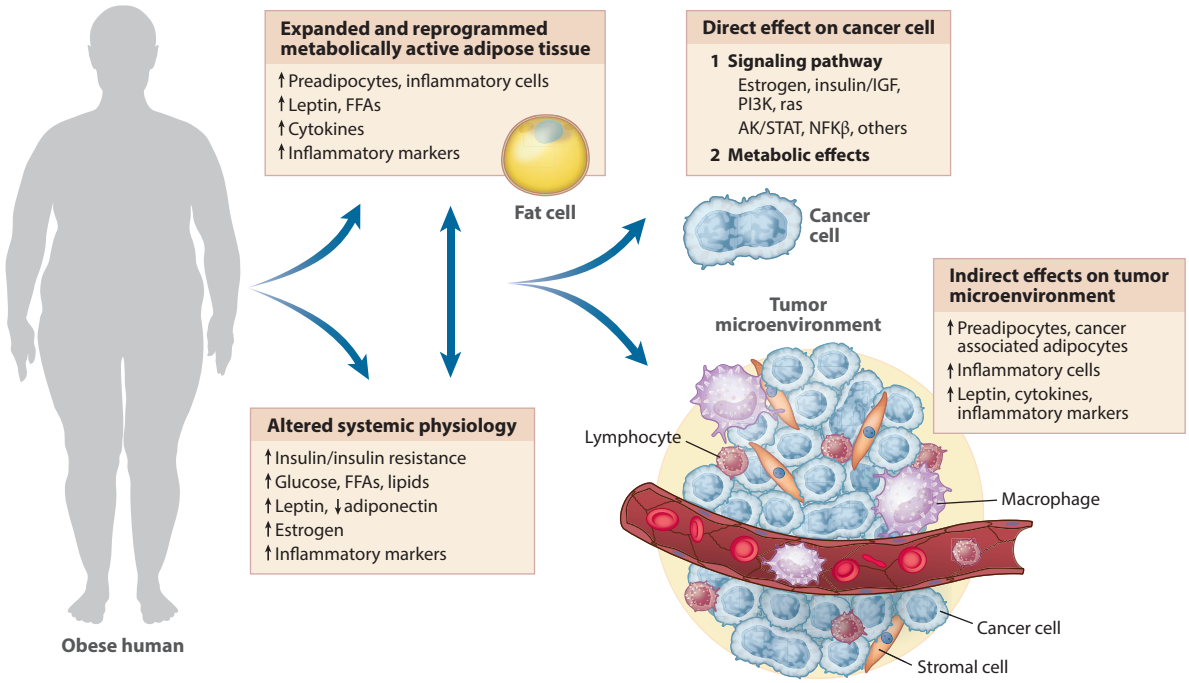

Figure 2

The complex association of obesity and cancer. Obesity is associated with expanded and reprogrammed adipose tissue that is metabolically active, leading to localized inflammation and altered cytokine/adipokine secretion; these local changes contribute to, and interact with, alterations in systemic physiology that reflect the insulin resistance/metabolic syndrome. Local adipose tissue and systemic obesity-associated alterations can impact cancer directly by (1) the activation of key signaling pathways or (2) an alteration in cellular metabolism, reflecting an abundance of glucose, free fatty acids (FFAs), and lipids. They may also act indirectly on the tumor microenvironment to promote proliferation, angiogenesis, invasion, and epithelial-mesenchymal transition.

Higher insulin levels in healthy individuals have also been associated with future cancer incidence and mortality (26) and, more specifically, with increased risk of colorectal and pancreatic cancer (27). A recent meta-analysis (28) of breast cancer failed to identify an association of insulin or C-peptide with breast cancer risk after adjustment for BMI; this may have represented overadjustment as BMI is associated with insulin levels.

Given the overexpression of insulin receptors (IRs), which act as dimers, on many cancer cells, a direct biologic effect of insulin in breast cancer is plausible (29, 30). Adult insulin-responsive tissues express IR-β, the isoform lacking the 12 amino acids encoded by its exon 11, whereas fetal tissues express the promitogenic IR-α, a full-length protein, including the sequence encoded by the exon 11. Paradoxically, the fetal IR-α, which shares 80% homology with the IGF-I receptor, is the IR form found to be most frequently expressed in cancer tissue de novo. IR-α binds insulin, proinsulin, and IGF-II, and it can heterodimerize with the IGF-I or IGF-II receptors, gaining higher affinity for IGF-I. Both insulin and IGF-I have been implicated as mitogens and prosurvival factors and can contribute to processes such as EMT, which is associated with the invasive characteristics of many tumors.

Our group (31) has reported almost ubiquitous expression of IR in human breast cancers, which, importantly, did not correlate with circulating insulin levels. An independent study (32) reported IR expression in 59% of women with invasive breast cancer, whereas IGF-IR expression

was found in 37.5% of specimens. Although the expression of the IRs or the phosphorylation of the IR/IGF-IR heterodimers was associated with poor survival, such correlations were not found for the IGF-IR expression in breast cancer samples. Thus, it appears plausible that circulating insulin may directly impact breast cancer cells, activating pathways that promote cell proliferation, reduce apoptosis, and enhance protein synthesis (33).

The relative contributions of insulin and IGF-I (which shares 50% homology with insulin) to cancer risk and outcome have been areas of debate. Early reports suggested that IGF-I may also be involved in cancer risk and outcome (34). However, subsequent studies, including the ones that failed to establish anti-IGF-I agents as cancer therapeutics, significantly challenge previous views, and most recent research examines the joint effects of insulin and IGF-I on cancer (35, 36).

Glucose

In the 1950s, Otto Warburg proposed what is now called the Warburg effect (37), an enhanced utilization of glucose by rapidly proliferating tissues, including cancer cells, manifested as a shift of glucose metabolism from primarily oxidative phosphorylation to aerobic glycolysis. Although aerobic glycolysis produces less adenosine triphosphate (ATP) and therefore energy stores than oxidative phosphorylation (4 versus 36 molecules of ATP/glucose molecule), it generates carbons to meet the demands of rapid cell growth and proliferation (38).

Obesity is associated with dysglycemia and glucose intolerance—this can be manifested as frank hyperglycemia in individuals with type 2 diabetes. Higher levels of fasting glucose (even within the normal range) have been associated with increased overall cancer mortality in a combined analysis of 97 prospective studies, involving 820,900 healthy individuals and 123,205 deaths (39). Compared to those with fasting glucose <7 mmol/L, both those with an elevated fasting glucose (>7 mmol/L) and those with impaired fasting glucose (5.6 to <7 mmol/L) had an increased risk of cancer death (RR 1.39, 95% CI 1.22–1.59 for elevated glucose and RR 1.13, 95% CI 1.06–1.20 for impaired). Abnormal glucose tolerance or higher levels of fasting glucose have been associated with increased overall cancer risk (39, 40), as well as with higher breast and endometrial cancer risk (41–43). Higher levels of fasting glucose have also been associated with increased mortality in individuals diagnosed with breast and lung cancer (2, 21). In nondiabetic breast cancer patients, fasting glucose in the upper (mean 5.7 mmol/L) versus lower (mean 4.5 mmol/L) quartile was associated with a 1.9-fold and 1.8-fold increased risk of distant recurrence (adjusted $p = 0.034$) and death (adjusted $p = 0.014$), respectively (21).

Adipokines

Adipose tissue produces a number of biologically active agents, including leptin and adiponectin. In the obese, plasma levels of leptin are increased and adiponectin decreased. It is believed that this reprogramming reflects increased stimulation by insulin, estrogen, TNF-α, and other factors, as well as associated inflammation with an increased ratio of preadipocytes (which preferentially secrete leptin) to mature adipocytes (which secrete both leptin and adiponectin) in obese individuals. A feed-forward loop further propagates this, as leptin promotes an additional inflammatory response in adipose tissue (44). Elevated leptin has mitogenic, proangiogenic, and antiapoptotic effects (45). Leptin may also contribute to regulation of estrogen receptor signaling, as it participates in the control of aromatase and estrogen production by the adipose tissue. At a cellular level, leptin can activate its own receptor, OB. It may also impact phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), JUN N-terminal kinase (JNK), and signal transducer and activator of transcription (STAT) signaling pathways, which are mediators of cell survival,

proliferation, and differentiation (49). High leptin levels have been associated with increased risk of some cancers, including endometrium and breast (46–48), and with poor outcomes in early-stage breast cancer (1, 21, 45).

Adiponectin, by contrast, increases fatty acid oxidation and insulin sensitivity while decreasing production of inflammatory cytokines. Adiponectin levels are inversely correlated with BMI and visceral adiposity (49). In certain cells, adiponectin may activate the adenosine monophosphate kinase (AMPK) pathway and inactivate the MAPK pathway, reducing proliferation as well as promoting apoptosis via a p53- and/or a B cell lymphoma 2 (Bcl-2)–mediated mechanism. The net effect is antiangiogenic and anti-inflammatory, with inhibition of cell migration (44, 50). Many cancer cells express adiponectin receptors that may mediate cellular effects. Higher levels of adiponectin have been associated with lower risk of breast (48, 51, 52), endometrial (47, 53, 54), colon cancer (55), as well as multiple myeloma (56). Higher adiponectin levels have also been associated with a better outcome in breast cancer (23) and with lower prostate cancer mortality (57).

Estrogen

Obesity is associated with increased total body aromatization, reflecting a greater volume of adipose tissue, leading to greater production of estrone and estradiol from androstenedione (58); lower levels of sex hormone–binding globulin in obesity may contribute to higher levels of bioavailable estrogen. Higher leptin levels and obesity-associated inflammation may also contribute to increased aromatase activity (59). Adipose tissue is the major source of estrogens in postmenopausal women in whom estradiol and estrone levels are significantly correlated with BMI ($r = 0.41$ and 0.38, respectively). Estradiol levels in women with BMI >30 kg/m^2 are almost double those seen in women with a BMI <27 kg/m^2. Estrone levels are about 50% higher in obese women compared to those that have a BMI <27 kg/m^2 (60). Higher circulating estrogen levels have been associated with increased breast cancer risk (61, 62) and with poorer survival (63).

Concerns have been raised that higher aromatase activity and higher estrogen levels in obese individuals may lead to reduced efficacy of aromatase inhibitors (AIs), a class of drugs that is used in breast cancer prevention and in both the adjuvant and metastatic treatment settings (64). There is conflicting evidence regarding the extent to which estrogen levels are suppressed by these agents in obese versus non-obese individuals (65, 66). Analyses of large randomized trials of AI versus tamoxifen adjuvant therapy suggest that there is no differential efficacy of letrozole across BMI categories (67); however, the relative efficacy of anastrozole may be lower in heavier women (68). Regardless, higher BMI was has been associated with increased risk of recurrence when either tamoxifen or AIs are administered (67, 68), suggesting that mediators other than estrogen, (e.g., insulin, adipokines, or inflammatory cytokines, discussed above) may be important in women receiving aromatase inhibitors, via direct effects or crosstalk with estrogen receptor signaling pathways (69).

A similar estrogen-mediated relationship appears to exist for endometrial cancer. Higher levels of estrogens in obese women may contribute to increased risk (70), although other mechanisms including adipose tissue reprogramming (discussed above) and hyperinsulinemia may also contribute (71).

Inflammation

Inflammation has been recognized as one of the hallmarks of cancer (72). In obese adipose tissue, increased free fatty acids and preadipocytes attract monocytes, which, in turn, are transformed into macrophages; together these cells secrete adipokines (notably leptin), inflammatory cytokines

[e.g., TNF-α, IL-6, IL-1β, transforming growth factor (TGF)–β] and other factors, including vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor (PAI) 1 (involved in angiogenesis and maintenance of the extracellular matrix) (9). Tumor-associated macrophages and cancer-associated adipocytes (reprogrammed adipocytes that secrete these factors) (73) in the tumor microenvironment may contribute to these effects. Enlargement of adipocytes in obesity can lead to hypoxia, cell death, and the formation of crown-like structures (dying adipocytes surrounded by inflammatory cells that secrete inflammatory cytokines) (74); the presence of these structures in the benign breast tissue of breast cancer patients has been associated with obesity (75). Inflammatory cytokines can activate nuclear factor kappa (NFK)–β, JAK-STAT, and other pathways, altering the expression of genes involved in proliferation, apoptosis, metastasis, and angiogenesis. These effects appear to occur in concert with the metabolic changes discussed above, for example, obesity-associated insulin resistance can contribute to a positive feedback loop with NFK-β activity (76). Taken together, these changes are procarcinogenic and proangiogenic, and they promote EMT, tissue invasion, and metastasis. They can occur in adipose tissue distant from a tumor, impacting cancer cells through systemic effects; they may also occur in the tumor microenvironment (9), providing a more direct impact on cancer growth, invasion, and metastasis.

Localized inflammation has been associated with some types of cancer (e.g., inflammatory bowel disease is associated with an increased risk of colorectal cancer) (77, 78). The association of generalized inflammation with cancer has been less well documented. For example, highly sensitive C-reactive protein (hsCRP) (a systemic marker of low-grade, chronic inflammation) has been associated with poor prognosis in some cancer settings; however, it is not clear whether this reflects a causal association or a response to disseminated cancer.

Numerous recent reviews (e.g., 9, 76, 79) have explored the role of inflammation in mediating the obesity–cancer link; as a result, this area is not discussed in greater detail here. These reviews highlight the complexity of the obesity–cancer association, exploring the interplay of inflammation, adipokines, and cytokines, as well as the role of insulin resistance and sex hormones in mediating this association.

Summary of Mediators and Mechanisms

The association of obesity with cancer is biologically plausible, but the mechanisms are complex, involving multiple interrelated processes that operate at the level of the whole patient (e.g., insulin resistance), in the cancer cell (e.g., the Warburg effect), and in the tumor microenvironment (e.g., inflammation) (**Figure 2**). Although much research has focused on specific aspects of the obesity–cancer link, it is unlikely that a single process is primarily responsible. Future research should investigate obesity-associated processes at multiple levels and include an examination of a broad range of biologic factors to avoid erroneous conclusions regarding causality in relation to single factors. This will help ensure that interventions developed to counter obesity effects are not too narrowly focused to have a clinically relevant impact on cancer.

POTENTIAL INTERVENTIONS

The most direct approach to reversing the effect of the obesity epidemic on cancer would be to promote weight loss in overweight and obese individuals and to prevent weight gain in normal-weight individuals. Interventions can be targeted at the individual or societal level, but these goals are difficult to achieve and even more difficult to sustain.

Weight loss at the level of the individual involves a reduction in caloric intake and increases in physical activity; the latter augments the caloric deficit associated with reduced intake and is

particularly important in the maintenance of weight loss (80). Using modern lifestyle approaches, which incorporate behavioral components and frequent contact to enhance compliance and motivation, an average weight loss of 7–10% at 6–12 months is feasible (81). This proportionate weight loss is seen across the range of BMI (82). Partial regain of weight has been reported in virtually all studies. More frequent contact and ongoing support enhance both initial weight loss and maintenance (6). More modest weight loss, approximately 5%, has been reported with a lifestyle intervention delivered in the primary care setting (83) or through the use of computer-based interventions (84). Commonly held beliefs about weight loss (e.g., the optimal speed of weight loss, the importance of breakfast, the effects of weight cycling) have recently been called into question and a focus on evidence-based weight-loss facts (e.g., use of meal replacements or medications to promote weight loss, contributions of physical activity) emphasized (85).

Although a 7–10% weight loss may not lead to a normal BMI, there is evidence that it results in important changes in insulin, glucose, and other potential mediators of the obesity–cancer link. Mason et al. (86), using an intervention based on diet or on diet and physical activity that led to a weight loss approximating 10%, reported a 22% reduction in fasting insulin, a 2.5% reduction in fasting glucose, and an approximately 25% improvement in insulin resistance [reflected by the homeostasis model assessment (HOMA)]. These changes are clinically meaningful and could potentially alter the obesity–cancer link.

In the obese and morbidly obese, bariatric surgery can produce durable weight loss of 20% or more (87). Bariatric surgery is associated with almost immediate improvements in insulin and glucose, prior to important weight loss. Sustained physiologic changes reflect sustained weight loss after all types of bariatric surgery (88). In observational studies, bariatric surgery has been associated with up to 50% reduced risk of future cancer in women but not men (89). A recent meta-analysis concluded that cancer incidence was lower after bariatric surgery with no heterogeneity by gender (90). These data come from nonrandomized studies, and patient selection could have led to a healthier population undergoing bariatric surgery. In a small randomized trial of bariatric surgery involving 150 obese diabetic patients, with three years of follow-up, two cases of cancer occurred in each of the three study arms (no surgery, gastric bypass, sleeve gastrectomy) (87). These results are difficult to interpret given the small sample size and short follow-up. The major and consistent reductions in cancer incidence in women seen in observational studies of bariatric surgery are intriguing, and further investigation is warranted.

The feasibility of weight loss in cancer patients, notably those with breast cancer, has been demonstrated in small studies that have used in-person (individual or group) or remote (telephone- or mail-based) interventions (91). Weight loss is modest (typically less than 5%), and information on long-term maintenance is lacking. Several groups, including our own, have conducted vanguard studies involving hundreds of patients demonstrating the feasibility of these approaches in a broad range of breast cancer patients (92, 93). Randomized trials of a lifestyle approach to weight loss (94) or a Mediterranean diet combined with physical activity (95) in the adjuvant breast cancer setting are ongoing in Europe; they will provide information on the effects of these lifestyle-based interventions on breast cancer outcomes. There is concern that sample size of these studies may be inadequate to detect the clinically important benefits of weight loss. Adequately powered trials of effective weight-loss interventions in cancer patients are urgently needed. These should initially focus on cancers, such as breast, where obesity has been significantly associated with poor outcome.

Given the magnitude of the obesity epidemic in North American society, the delivery of individual interventions to all individuals at risk for, or with, obesity is costly and unlikely to be feasible. The importance of changes at a community and societal levels was highlighted in a recent Institute of Medicine report (96). A full discussion of these changes is beyond the scope of this review; however, changes in societal norms regarding portion size, caloric intake, acceptability of

calorie-dense nutrient-poor foods, and the advertising of such foods to children and adolescents, will likely be beneficial. It is anticipated that promotion of greater physical activity at a population level, coupled with modification of the built environment to facilitate more activity, enhancement of safety to allow greater outdoor activity, reduction in screen time, and introduction of more extensive physical activity programs for children, will also be beneficial. The potential contributions of economic policies and incentives (including taxation) are gaining increasing attention (97). As with individual interventions, these population-based approaches will be challenging, but they may have a greater effect on the association of obesity with cancer risk than individual interventions.

Pharmacologic interventions may also prove to be useful in targeting the obesity–cancer link. These interventions may include Food and Drug Administration–approved weight-loss drugs (orlistat, locaserin, phentermine-topiramate, and naltrexone-bupropion) (98). These drugs lead to modest weight loss (3% locaserin, 7% phentermine-topiramate, and 4% naltrexone-bupropion, all versus placebo); they are associated with side effects that may not be acceptable to patients.

In individuals with cancer, pharmacologic interventions that target the obesity-associated physiology and/or signaling pathways discussed above may be beneficial. One such agent, currently under investigation, is metformin, a biguanide commonly used in the treatment of type 2 diabetes. In nondiabetic cancer patients, it lowers insulin levels (by up to 20%), reduces glucose levels, and improves insulin sensitivity (as reflected by HOMA); it also lowers leptin and reduces systemic inflammation (reflected by hsCRP). Additionally, it may exert direct anticancer effects, in part mediated by an inhibition of complex-I of the respiratory chain in the mitochondrion (99). As such, it is a dirty agent that modifies a broad range of obesity-associated parameters, with the potential for additional obesity-independent effects. Metformin is being evaluated in over 90 clinical cancer trials registered at the National Institutes of Health (**http://nih.gov/**), involving breast, prostate, endometrium, colorectal, pancreatic, and other cancers. Metformin has been shown to reduce aberrant crypt foci in the rectal epithelium in patients with colorectal polyps, suggesting potential benefits in colorectal cancer prevention (100). Its effects on polyp formation are currently being evaluated in a small randomized trial involving familial adenomatous polyposis patients. It is also being evaluated in a small number of other trials that may inform prevention efforts. None of these trials has cancer incidence as an endpoint; however, three trials in breast cancer are examining the effects of metformin on breast density, metabolism, and protein phosphorylation. Other trials, including one in Li–Fraumeni patients, are evaluating the effects of metformin on blood biomarkers. Our group has completed accrual to a phase III randomized trial of metformin in the adjuvant breast cancer setting; results of the effect of metformin on invasive cancer-free survival are anticipated in two to three years (101).

Importantly, other anticancer agents under development, including numerous classes of PI3K inhibitors, have a profound impact on overall body metabolism and body weight. Further evaluation of such agents, as well as anti-inflammatory drugs as disruptors of the obesity–cancer connection, may lead to their incorporation in treatment regimens of obese cancer patients.

CONCLUSIONS

The obesity epidemic has been associated with increases in non-tobacco-related cancer incidence and mortality. It has not been associated with increased cancer mortality at a population level (possibly reflecting earlier diagnosis and/or improved treatment); however, it has been associated with poor outcomes in many common cancers, including breast, colorectal, pancreas, and endometrium. There is a strong biologic rationale for the association of obesity with cancer. Emerging evidence suggests a complex interplay of physiologic factors and local adipose tissue changes that, together, may impact cancer directly or through changes in the tumor microenvironment.

The evaluation of the potential for pharmacologic agents, including metformin, and lifestyle and societal interventions that will minimize obesity in our population are urgently needed.

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