Review

Obesity and Cancer: The Role of Dysfunctional Adipose Tissue

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Abstract

Overweight and obesity are health problems of epidemic proportions, increasing the risk not only of cardiovascular disease and type 2 diabetes mellitus but also of various types of cancer. Obesity is strongly associated with changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation, and altered secretion of adipokines. Several of these factors, such as insulin resistance, increased levels of leptin, plasminogen activator inhibitor-1, and endogenous sex steroids, decreased levels of adiponectin, and chronic inflammation, are involved in carcinogenesis and cancer progression. This article reviews these mechanisms, focusing on adipose tissue dysfunction as a unifying causal factor. Although understanding of the link between obesity and cancer might provide therapeutic targets, preventing overweight and obesity still remains number one priority. (Cancer Epidemiol Biomarkers Prev 2009;18(10):2569–78)

Introduction

Excess body weight is a health problem of epidemic proportions that is not restricted to the developed countries (1-3), but affects people worldwide (3). Overweight and obesity increase the risk of cardiovascular disease and type 2 diabetes mellitus (4-6) and account for a substantial proportion of global morbidity and mortality (3, 4, 7). Moreover, overweight and obesity are now established risk factors for cancer and cancer-related mortality (8-11). It is thought that the metabolic changes associated with obesity, particularly abdominal obesity, and changes in adipocyte function underlie this increased risk. Knowledge of the pathophysiological mechanisms underlying the association between obesity and malignancy may be important for the development of preventive and therapeutic strategies for cancer.

The purpose of this overview is to evaluate the association between obesity and the occurrence of various cancers and to review the pathophysiological mechanisms involved. We propose that adipose tissue dysfunction has a prominent role in cancer pathogenesis and progression.

Obesity and Cancer Epidemiology

Overweight (defined as a body mass index [BMI] of 25 to 29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) are associated with an increased all-cause mortality (4, 7), and cancer accounts for a substantial proportion of obesity-related deaths (7, 10, 12). In 2003, it was estimated that overweight and obesity were responsible for 14% of all cancer deaths in men and 20% of those in women in the United States (12), which is consistent with the poorer outcome of cancer in overweight and obese subjects (10). Excess body weight is not only associated with cancer mortality but is also associated with an increased incidence of several types of cancer. Recent meta-analyses (10, 13, 14) have shown that an increased BMI is associated with an increased incidence of endometrial, colorectal, and postmenopausal breast cancer (Table 1). In addition, obesity has recently been shown to be associated with an increased risk of esophageal adenocarcinoma, thyroid cancer, renal cancer, multiple myeloma, gallbladder cancer in women, leukemia, pancreatic cancer, non-Hodgkin lymphoma, and ovarian cancer (10, 11, 15). However, data on the association between obesity and prostate cancer are ambiguous, with a high BMI being associated with a higher risk of high-grade prostate cancer but with a lower risk of low-grade prostate cancer (16).

The obesity epidemic is not limited to adults but affects children and adolescents. In 2003-2004, 17.1% of American children and adolescents aged 2 to 19 years were overweight or obese (1). A recent study has shown that excess body weight in adolescence carries an increased risk of colon cancer mortality in adulthood in men (relative risk [RR], 2.1; 95% confidence interval [CI], 1.1-4.1) and women (RR, 2.0; 95% CI, 1.2-3.5; ref. 17). These results underline the necessity of preventing childhood obesity.

Dysfunctional Adipose Tissue

In addition to its lipid-storing capacity, adipose tissue is a highly active endocrine and metabolic organ. Adipose tissue, which is made up of various cell types, such as adipocytes, pre-adipocytes, fibroblasts, macrophages, and blood vessels, produces numerous adipokines, such as leptin, adiponectin, plasminogen activator inhibitor
(PAI)-1, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and interleukin (IL) -6. As adipose tissue expands, adipocytes enlarge and the adipose tissue starts to produce chemotactic factors, such as monocyte chemoattractant protein (MCP) -1, that attract monocytes/macrophages into adipose tissue (18).

The subsequent increased production of adipokines and inflammatory cytokines and the decreased production of adiponectin (19), in combination with the inability of adipose tissue to store the surplus free fatty acids (FFAs; ref. 20), can be considered to reflect adipose tissue dys-function (Fig. 1). These obesity-associated disturbances of adipose tissue function are believed to play a crucial role in the development of insulin resistance, type 2 diabetes, and obesity-related cardiovascular disease (21-24).

Despite being extensively studied, the pathogenesis of insulin resistance in obesity is still not completely understood. High levels of FFAs, as seen in obesity, reduce insulin-mediated glucose uptake by the GLUT4 transporter and inhibit the insulin receptor-mediated tyrosine phosphorylation of the insulin receptor substrate (IRS) -1 (25). TNF-α induces insulin resistance in a similar way. By stimulating the serine phosphorylation of IRS-1 and converting IRS-1 into an inhibitor of insulin receptor tyrosine kinase activity, TNF-α attenuates the insulin signaling cascade (26). In turn, the suppression of lipolysis by insulin is inhibited in insulin resistance, resulting in an increased release of FFAs, thereby setting up a vicious cycle of events (25, 26). Under normal conditions, adiponectin increases insulin sensitivity directly, by stimulating tyrosine phosphorylation of the insulin receptor. Adiponectin may also indirectly protect against the development of insulin resistance by activating 5′-AMP-activated protein kinase (AMPK), leading to increased fatty acid oxidation and decreased influx of FFAs into the liver, which contributes to reduced hepatic glucose production and VLDL synthesis (27). Conceivably, the paradoxical decrease in adiponectin levels in obesity (28) may play an important role in the development of insulin resistance.

Obesity is thought to induce a state of chronic low-grade inflammation (29, 30) and is associated with an increased number of macrophages in adipose tissue (31). The exact trigger for the chronic inflammatory response of adipose tissue is not known but may be hypoxia. It is proposed that as adipose tissue enlarges, individual cells are further from blood vessels and become poorly oxygenated (32). This state of relative hypoxia activates hypoxia-inducible factor (HIF) -1α, a key regulator of oxygen homeostasis. The subsequent increased expression of IL-6 and leptin (33), the decreased production of adiponectin (34), and the HIF-1α-mediated attraction of macrophages into adipose tissue (35) may initiate the inflammatory response in adipose tissue. Moreover, the increased production of TNF-α by adipocytes stimulates the production of MCP-1 by preadipocytes and endothelial cells (18), with the result that macrophages are attracted to adipose tissue. Additional chemotactic factors, including leptin (36), may also contribute to the accumulation of macrophages in dysfunctional adipose tissue. It has been shown that the number of macrophages in adipose tissue decreases significantly after obese individuals undergo bariatric surgery and that this decrease is associated with changes in the expression of genes of the stroma vascular fraction of adipose tissue, which are involved in macrophage attraction (35). Adipose tissue macrophages are largely responsible for TNF-α expression and, to a lesser degree, IL-6 expression in adipose tissue (31).

Distribution of adipose tissue is important in the metabolic complications of obesity. Abdominal adipose tissue, which is strategically located to the liver, is especially associated with an abnormal metabolic profile (37). Elevated macrophage infiltration in omental versus subcutaneous adipose tissue and increased concentrations of IL-6 in the portal circulation in obese subjects

Table 1. Body mass index and risk of several cancer types

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Men (RR 95% CI)*</th>
<th>Women (RR 95% CI)*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial</td>
<td>2.89 (2.62-3.18)</td>
<td>1.59 (1.30-1.68)</td>
<td>Reeves (2007) (ref. 10)</td>
</tr>
<tr>
<td>Esophageal adenocarcinoma</td>
<td>1.52 (1.33-1.74)</td>
<td>1.51 (1.31-1.74)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Postmenopausal breast</td>
<td>1.40 (1.31-1.49)</td>
<td>1.12 (1.08-1.16)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Colon</td>
<td>1.13 (1.17-1.37)</td>
<td>1.02 (0.85-1.22)</td>
<td>Moghaddam (2007) (ref. 13)</td>
</tr>
<tr>
<td>Rectal</td>
<td>1.09 (1.06-1.12)</td>
<td>1.02 (1.00-1.05)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.14 (1.06-1.23)</td>
<td>1.12 (1.02-1.22)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Retal</td>
<td>1.34 (1.23-1.43)</td>
<td>1.10 (1.02-1.19)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.14 (1.03-1.27)</td>
<td>1.12 (1.02-1.22)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.03 (0.99-1.08)</td>
<td>1.02 (0.95-1.08)</td>
<td>Larsson (2007) (ref. 12)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.02 (1.00-1.05)</td>
<td>1.02 (1.00-1.05)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.17 (1.04-1.32)</td>
<td>1.12 (1.02-1.22)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.07 (1.00-1.14)</td>
<td>1.12 (1.02-1.22)</td>
<td>Renehan (2008) (ref. 11)</td>
</tr>
<tr>
<td>Prostate high-grade</td>
<td>0.85 (0.77-0.93)</td>
<td>0.85 (0.74-0.97)</td>
<td>Hsing (2007) (ref. 15)</td>
</tr>
</tbody>
</table>

*Relative risk (RR) and 95% confidence interval (CI).

†Estimated trends in the RR associated with every 10 kg/m2 increase in Body Mass Index (BMI).

‡RR associated with every 5 kg/m2 increase in BMI.

§RR with BMI ≥ 30 kg/m2 compared to BMI < 25 kg/m2.
contribute to systemic inflammation as seen in abdominal obesity (38, 39). Furthermore, serum levels of IL-6, associated with visceral adipose tissue, influence insulin levels (40).

**Obesity and Cancer: Pathophysiological Mechanisms**

Although BMI is an adequate indicator of overweight and obesity in clinical studies, it does not reflect the obesity-induced metabolic changes that may be involved in carcinogenesis. The presence of metabolic syndrome (defined as a cluster of abdominal obesity, hypertension, hypertriglyceridaemia, low HDL-cholesterol, and hyperglycemia ref. 41), might be a better qualitative indicator of the carcinogenic potential of obesity (42). Various pathophysiological mechanisms linking obesity to cancer have been postulated. We propose that dysfunctional adipose tissue is a unifying causal factor.

**Insulin Resistance**

The relationship between insulin resistance and adipose tissue dysfunction is complicated, as both can be caused by the other. Insulin resistance and the insulin-like growth factor (IGF) -1 system may explain in part the link between obesity and cancer. In a state of insulin resistance, which is frequently seen in obesity (43), serum insulin levels increase to avert hyperglycemia. Insulin up-regulates growth hormone (GH) receptors in the liver, which stimulates the hepatic production of IGF-1 (44). Thus, serum IGF-1 levels would be expected to be correlated with BMI, but levels of IGF-1 are normal or low in obese subjects (45). This fact might be explained by the inhibitory effect of high levels of insulin on the secretion of IGF-binding protein (IGFBP) -1 and 2. The subsequent increase in the levels of free IGF-1 leads to increased negative feedback on GH secretion, which ultimately leads to lower plasma levels of IGF-1 (46, 47). In obese subjects, free IGF-1 levels do not respond to insulin administration and tend to be higher than in lean subjects (48). Both insulin and IGF-1 are believed to play a role in cancer development through binding to the insulin receptor (IR) and IGF-1 receptor (IGF-IR). IGF-1 can inhibit apoptosis and stimulate cell proliferation through several downstream signaling networks, including the phosphatidylinositol 3-kinase (PI3-K) -AKT system and the Ras/Raf/mitogen-activated-protein-kinase (MAPK) systems, respectively (49). Interestingly, the expression of IGF-1 receptor is increased in some tumors, which suggests that these neoplasms may be stimulated by systemic levels of IGF-1 (50, 51). In addition, IGF-1 mediates cell migration and invasion in human pancreatic carcinoma cells, most likely by inducing the expression of urokinase-type plasminogen activator (uPA) and its receptor (uPAR) (ref. 52). Besides regulating glucose transport, insulin has mitogenic and anti-apoptotic properties mediated

![Figure 1. Dysfunctional adipose tissue in obesity. FFA, free fatty acids; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor-α.](image-url)
through pathways to some extent similar to those of IGF-1 (53, 54). This mitogenic, anti-apoptotic environment caused by increased serum levels of insulin and IGF-1 accelerates the stepwise accumulation of genetic mutations and thereby favors carcinogenesis (49). Clinical studies have shown that patients with high levels of IGF-1 have an increased risk of several types of cancer, including colorectal, prostate, and postmenopausal breast cancer (49). Hyperinsulinemia is also an independent risk factor for breast cancer in postmenopausal women (55) and increases the risk of colorectal and endometrial cancer; however, these results are ambiguous (56, 57). In addition, diabetes mellitus, a disease characterized by insulin resistance, is associated with an increased risk of breast, colorectal, pancreatic, and bladder cancer (58-61). Insulin resistance is likely to play a prominent role in carcinogenesis, and it appears to be one of the major mechanisms involved in the obesity-cancer link.

**Adipokines**

Adipose tissue produces a variety of hormones and cytokines, known as adipokines. Adipose tissue dysfunction results in altered serum levels of adipokines, which may be directly involved in obesity-related carcinogenesis.

**Adiponectin.** Adiponectin, an adipokine that is exclusively derived from adipocytes, has significant anti-inflammatory and insulin-sensitizing effects (62, 63). Plasma concentrations of adiponectin are reduced in obesity (28), and clinical studies point toward there being an inverse relation between serum levels of adiponectin and the risk of breast, endometrial, prostate, colorectal, and kidney cancer (64-68). The role of adiponectin in cancer etiology is not yet fully understood. Although it is possible that adiponectin provides indirect protection against carcinogenesis, by affecting insulin sensitivity and the inflammatory state, it has direct anti-carcinogenic effects, many of which are mediated through the AMP-activated protein kinase (AMPK) system via two receptors, AdipoR1 and R2. Activated AMPK plays an important role in the regulation of growth arrest and apoptosis by stimulating p53 and p21 (69). Moreover, phosphorylation of the tumor suppressor, tuberous sclerosis complex (TSC) 2, by activated AMPK (70) and the subsequent inhibition of mammalian target of rapamycin may be an important downstream signaling pathway by which adiponectin counteracts carcinogenesis. Independent of AMPK activation, adiponectin decreases the production of reactive oxygen species (ROS; ref. 71), which may result in decreased activation of MAPK (72) and thereby inhibition of oxygen species (ROS; ref. 71), which may result in decreased activation of MAPK (72) and thereby inhibition of cell proliferation. In *vivo*, adiponectin inhibits the growth of several breast cancer cell lines (73) and induces apoptosis of myelomonocytic (leukemia) lineage cells (74). Adiponectin also has been shown to inhibit tumor angiogenesis in *in vitro* experiments (75). These effects appear to be partially mediated through the activation of a cascade of apoptosis executor proteins, caspase-8,-9, and -3, leading to apoptosis in vascular endothelial cells. A number of studies with fatless A-ZIP/F-1 transgenic mice have suggested that insulin resistance and inflammation have a greater role than adipokines (76). A-ZIP/F-1 mice, which are diabetic and display a state of inflammation but do not have detectable levels of adipokines, are more susceptible to carcinogen-induced tumor formation and growth than are wild-type mice (77). The accelerated tumor formation in mice without detectable adipokine levels suggests that adiponectin may protect against carcinogenesis. Thus, the decreased plasma levels of adiponectin in obesity (28) may be associated with the increased risk of cancer in obesity.

**Leptin.** The 16-kDa protein hormone leptin, which is secreted by adipocytes, plays a pivotal role in regulating the energy balance, by decreasing appetite and increasing metabolism. Levels of leptin are raised in obese subjects, which suggests that obesity is associated with leptin resistance (78). The findings of clinical studies of the relationship between systemic leptin levels and breast or prostate cancer are inconsistent (16, 79, 80), but an association has been reported for colorectal cancer (81-83) and for endometrial cancer (84, 85). Interestingly, many colorectal, breast, and endometrial cancers overexpress the leptin receptor ObR (86-88). Experimental studies have shown that leptin has mitogenic effects in cancer cell lines, depending on the type of cancer: it stimulates the growth of breast, esophagus, and prostate cancer, but inhibits the growth of pancreatic cancer cells (89). Mitogenic and anti-apoptotic effects of leptin have been described in both colon and prostate cancer cell lines. Inhibition of MAPK and PI3-K inhibited these effects, indicating that these pathways underlie the growth-promoting effect of leptin (90, 91). Although leptin appears to favor cancer cell growth locally, more studies are required to assess the clinical significance of elevated levels of this pleiotropic hormone in relation to the link between obesity and cancer.

**PAI-1.** PAI-1 is a serine protease inhibitor produced by adipocytes, endothelial cells, and stromal cells in visceral adipose tissue (92). PAI-1 is not only produced by adipose tissue, but also affects adipocyte differentiation and insulin signaling (93). Moreover, PAI-1 inhibits uPA, which acts as an inducer of fibrinolysis and extracellular matrix degradation, and is associated with tumor cell invasion and metastasis. Paradoxically, PAI-1 is involved in tumor growth, invasion, metastasis, and angiogenesis by interacting with vitronectin, integrins, and other components of the uPA system and by affecting the extracellular matrix (94-96).

Overexpression of PAI-1 has been found in many obesity-related types of cancer and is associated with the progression of breast, endometrial, colorectal, thyroid, renal, and prostate cancer (97-102). In addition to autocrine production by tumor cells, systemic levels of PAI-1 (e.g., produced by immune cells or adipocytes in obesity) appear to be essential for its tumor-promoting effects, though level dependent (103). Inhibition of PAI-1 might be a potential target in cancer therapy. Indeed, treatment with PAI-1 inhibitor of Min mice, which have a defect in the adenomatous polyposis coli (Apc) gene, suppressed intestinal polyp formation (104). It has been hypothesized recently that, as a consequence of metabolic syndrome, the up-regulation of PAI-1 expression predisposes breast cancer to more aggressive stages (105). This hypothesis supports the role of PAI-1 in promoting cell migration and tumor angiogenesis (106). Although the amount of studies of PAI-1 in obesity-induced carcinogenesis is modest, results so far make PAI-1 a plausible culprit for the increased risk of cancer mortality in obesity.
Inflammation

It is well recognized that inflammation is involved in the promotion and progression of cancer (107, 108). For example, local chronic inflammation is seen in inflammatory bowel disease and Barrett’s esophagus, disorders that carry an increased risk of colorectal cancer and esophageal adenocarcinoma, respectively (100-111). In fact, (pre-) malignant lesions could be referred to as inflamed, because the tumor microenvironment contains a variety of leukocytes and inflammatory factors (107). The precise role of these inflammatory components in carcinogenesis is not completely understood and therefore continues to be an appealing avenue of research.

Obesity-induced inflammation, a key feature of adipose tissue dysfunction, is thought to be an important link between obesity and cancer. Obesity reflects a state of low-grade systemic inflammation. Serum levels of CRP, an inflammatory marker, are increased in individuals with a higher BMI (112), and weight loss leads to a decrease in CRP concentration, whereas weight gain leads to an increase in CRP concentrations (113). Raised serum levels of CRP are correlated with an increased risk of cancer (114). Although the causes of inflammation in obesity are not fully understood, the consequences are more evident, with increased systemic levels of proinflammatory cytokines, such as TNF-α and IL-6, which are secreted in large quantities by dysfunctional adipose tissue (29). Several of the proinflammatory factors in obesity are believed to be involved in carcinogenesis (Fig. 2).

As a member of the TNF superfamily, TNF-α plays a vital role in adaptive responses of the immune system and other organ systems (115). When TNF was identified as a macrophage-derived factor that could induce necrosis in tumor cells (116), hopes were raised that the cytokine would be a powerful anticancer agent. However, in recent years, the role of TNF-α in malignancy is being reconsidered, and it is now suggested that TNF-α is involved in carcinogenesis and cancer progression (117-119). These contradictory effects of TNF-α can partly be explained by its role in the regulation of apoptosis. When TNF-α binds to its primary receptor, TNF-R1, a downstream signaling cascade leads to activation of nuclear factor (NF)-κB (120). This in turn leads to the up-regulation of several negative regulators of apoptosis, such as c-FLIP and cIAP1, which promote cell survival (121). TNF-α has been reported to have tumor-promoting activity in various experimental cancers (122), and a variety of tumor cells produce TNF-α (108). TNF-α produced by ovarian cancer cells was recently found to stimulate a constitutive network of factors, including VEGF and chemokines CXCR4 and CXCL12, that promote tumor progression (117). Whether increased systemic levels of TNF-α, as seen in obesity (29), act through the same signaling network to promote tumor development and progression is not fully clear; however, increased TNF-α serum levels are correlated with an increased risk of cancer-related death and, to a lesser degree, with overall cancer events (123). Systemic TNF-α might also be involved in the early development of some tumors, as a recent study showed elevated TNF-α levels to be associated with an increased risk of colorectal adenomas (124).

Under physiological conditions, IL-6 has an essential role in the acute inflammatory response and affects the maturation of B cells. Recent findings, however, suggest that this essential cytokine is associated with several disease processes, including chronic inflammatory diseases and cancer (125). Systemic levels of IL-6 are elevated in obesity (29) and, akin to TNF-α, systemic levels of IL-6 are correlated with overall cancer death and increased risk of cancer precursor lesions (123, 124). In addition, levels of the IL-6 promoter genotype have been associated with several hematological cancers (126). Effects of IL-6 on cell proliferation and cell survival are likely to be mediated through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)3 pathway (127).

Obesity-induced inflammation involves other inflammatory components that could contribute to the development of cancer. These components include matrix metalloproteinases (MMPs), which are associated with cancer-cell invasion and metastasis (128). Strongly induced mRNA levels of several MMPs in obesity, as well as their role in adipocyte differentiation, might represent a potential molecular link between obesity and cancer (129, 130). Oxidative stress, as part of chronic inflammation, may also create a microenvironment favorable to tumor development in obesity (131).

Sex Steroids

The impact of adiposity on the synthesis and bioavailability of endogenous sex steroids is of substantial importance in understanding the increased risk of postmenopausal breast and endometrial cancer in obese women. Peripheral conversion of androgenic precursors to estradiol by aromatase in adipose tissue is increased in obesity, leading to increased serum levels of estradiol, which, in turn, are insufficiently counterbalanced by levels of progesterone (47, 132). Furthermore, increased serum levels of insulin, as a result of adipose tissue dysfunction, can result in both increased ovarian androgen synthesis and reduced hepatic synthesis of sex-hormone-binding globulin (SHBG) (ref. 47). Recent findings of increased plasma concentrations of bioavailable estradiol and testosterone and decreased plasma concentration of SHBG in obese postmenopausal women are compatible with these mechanisms (132).

The role of endogenous sex steroids in the development and progression of breast and endometrial cancer is well established. Prospective studies show that levels of endogenous sex steroids are strongly associated with postmenopausal breast and endometrial cancer risk (133-136). The proliferative effect of estrogen on epithelial tissue of both breast and endometrium is believed to be the underlying mechanism (134, 137).

Other Proposed Mechanisms

Several other obesity-associated risk factors could also contribute to the increased risk of some specific cancers. Gastric acid reflux is more common among obese subjects (138). Since gastric acid reflux is a known risk factor for the development of esophageal adenocarcinoma, it is tempting to speculate that this is a mechanism contributing to the higher risk of this cancer in obesity. Interestingly, obesity is a risk factor for esophageal adenocarcinoma independently of acid reflux, which suggests that other factors associated with obesity are involved as well (139).
HIF-1α is considered an important factor in the development, growth, and metastasis of a large variety of cancer types (140-142). Of interest, recent studies show that HIF-1α is involved in the mechanisms underlying the overexpression of leptin in colorectal and breast tumors (86, 143). Hyperinsulinemia might induce HIF-1α-mediated overexpression of leptin in breast cancer cells and so contribute to disease progression (143, 144).

**Figure 2.** Potential pathways directly linking obesity with cancer. AdipoR1/R2, adiponectin receptor 1/2; AMPK, 5′-AMP-activated protein kinase; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; IKK, IκB kinase; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; IR, insulin receptor; IRS-1, insulin receptor substrate-1; JAK, Janus kinase; MAPK, mitogen-activated-protein-kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; ObR, leptin receptor; PAI-1, plasminogen activator inhibitor-1; PI3-K, phosphatidylinositol 3-kinase; ROS, Reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; TNF-R1, tumor necrosis factor-receptor 1; TRADD, TNFRSF1A-associated via death domain; TRAF2, TNF receptor-associated factor 2; TSC2, tuberous sclerosis complex 2; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Furthermore, hypoxia in adipocytes increases the expression of MMFs and VEGF, suggesting that hypoxia in adipose tissue might be a modulator of the angiogenic process (145). These findings are consistent with clinical data that VEGF levels increase with increasing BMI (146). Because VEGF plays an important role in tumor angiogenesis (147), increased levels of this key endothelial mitogen may contribute to the poorer outcome of cancer in obese subjects.

Research interest is focusing on PPAR-γ, a ligand-inducible transcription factor, and its role in diabetes mellitus, arteriosclerosis, and cancer. PPAR-γ, which is mainly expressed in adipose tissue, is an important regulator of adipocyte differentiation and function, as well as cell proliferation and survival (148, 149). Down-regulation of PPAR-γ by TNF-α in obesity is believed to contribute to the dysfunction of adipose tissue (150). Because activation of PPAR-γ is associated with antitumor effects (151, 152), further attention should be paid to the role of PPAR-γ in carcinogenesis and the link between cancer and obesity, especially because it could become a therapeutic target.

Many tumors have increased levels of obesity-related factors, both adipokines and inflammatory components, in their microenvironment, and in some cases it is these tumors that are more aggressive (87, 94, 108, 117). Thus, the role of local obesity-related factors should be better determined in comparison to systemic levels. These local factors could be crucial in carcinogenesis and the role of peritumoral adipose tissue herein is yet to be established.

Although the above-mentioned and several other potential pathophysiological mechanisms have been proposed, their significance in the obesity-cancer link needs further exploration. It is possible that in obese individuals these mechanisms act synergistically to promote a multifactorial tumor-promoting environment. The significance of these mechanisms probably differs by tumor type, and so research should focus on the role of obesity in one particular cancer type at a time.

Concluding Remarks

Adipose tissue dysfunction, as a consequence of obesity, is likely to play a role in carcinogenesis, by affecting insulin resistance and the production of several adipokines and inflammatory cytokines. Though the precise mechanisms may differ between different types of cancer, it is plausible that these mechanisms synergistically contribute to the increased cancer risk. While understanding the link between obesity and cancer might provide therapeutic targets, lifestyle improvement remains the most important component in preventing obesity-related morbidity and mortality. This needs to be addressed in intervention studies.

Search Strategy and Selection Criteria

We searched for papers in PubMed and the Cochrane database, using search terms including “obesity,” “overweight,” “cancer,” “adipose tissue dysfunction,” “insulin resistance,” and “inflammation.” Bibliographies of included papers were scanned for other relevant papers. References were selected on the basis of relevance, importance, and novelty. Papers published in peer-reviewed journals as well as papers published in the past 3 years were preferentially treated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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