Obesity and Carcinogenesis

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Abstract.

Obesity is reaching epidemic levels worldwide, a troubling phenomenon that increases the risk of cardiovascular diseases and type 2 diabetes. Recently, it has been suggested that obesity has a pathological link with 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 are directly involved in carcinogenesis and cancer progression, such as insulin resistance, increased levels of leptin, plasminogen activator inhibitor-1, endogenous sex steroids, decreased levels of adiponectin, and chronic inflammation. Additionally, adipose tissue has also been hypothesized to act as a reservoir for lipophilic, liposoluble environmental carcinogens, so that chemical pollution may indirectly promote both overweight/obesity and cancer. Moreover, it has also been suggested that many carcinogens stored in the adipose tissue could be released in periodic doses in the circulatory system and therefore target peripheral tissues to induce carcinogenesis. Such carcinogens mainly include organochlorine pesticides and polychlorinated biphenyls (PCBs). Their association with an increased risk of cancer appears to have been demonstrated for breast and prostate carcinoma, as well as for lymphoma. In this study, we reviewed the relevant evidence focusing on adipose tissue dysfunction as a unifying causal factor for cancer, as well as the hypothesis of chemical pollutants and their link to obesity and carcinogenesis.

Keywords: obesity, dysfunctional adipose tissue, liposoluble environmental carcinogens, carcinogenesis
INTRODUCTION

The prevalence of overweight children and adolescents, and obesity in the adult population has increased over the last several decades, primarily in the wealthier industrialized countries. Similar trends towards obesity are mirrored in urban areas of many developing countries as well [1,2]. Environmental factors such as urbanization, an increased supply of calorie-dense, palatable foods, and decreased energy expenditure due to lack of physical activity can disrupt energy balance, and increase the prevalence of excess adipose tissue and obesity in the population. Moreover, obesity has long been recognized to be an important cause of type II diabetes mellitus, hypertension, and dyslipidemia [3]. The relationship between obesity and cancer has recently received much attention in the medical community. For instance, overweight women are known to have an increased risk of endometrial cancer and breast cancer post-menopause due to increased levels of circulating estrogen. There is also growing evidence that suggests increased adiposity may increase the incidence and/or mortality rates from a wide variety of cancers, including cancers of the colon and rectum, esophagus, kidney, pancreas, gallbladder, ovary, cervix, liver, prostate, and certain hematopoietic cancers.

In this review, obesity-associated changes in the physiological function of adipose tissue, which can lead to insulin resistance, chronic inflammation, and altered secretion of adipokines (indicated as direct pathogenic factors), are speculated to be involved in carcinogenesis and cancer progression as shown in Figure 1. On the other hand, adipose tissue also has been hypothesized to act as a reservoir for lipophilic, liposoluble environmental carcinogens indicated as indirect factors, such that chemical pollution may in fact facilitate the advancement of both overweight/obesity and cancer in adolescents and adults, as shown in Figure 2. Herein, the relevant evidence focusing on adipose tissue dysfunction as a unifying causal factor, as well as the hypothesis of chemical pollutants and the link between obesity and carcinogenesis will be reviewed.

OBESITY AND CANCER: PATHOLOGICAL MECHANISMS

Obesity-Associated Dysfunctional Adipose Tissue and Carcinogenesis

Adipokines

Adipose tissue dysfunction results in an increase in the synthesis and release of a variety of adipose tissue-derived hormones and cytokines known as adipokines, which in turn cause elevated plasma adipokine levels and may be directly involved in obesity-related carcinogenesis.

Adiponectin

Adiponectin is exclusively derived from adipose tissue, and has significant anti-inflammatory and
Figure 1. Potential pathways directly linking obesity-associated dysfunctional adipose tissue 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-kB; 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; 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.

insulin-sensitizing effects [4,5]. An inverse relationship has been reported in clinical studies between serum levels of adiponectin and the risk of breast, endometrial, prostate, colorectal, and kidney cancer, but the pathological link between adiponectin and cancers remains ambiguous [6-10]. Adiponectin not only provides indirect protection against carcinogenesis, by affecting insulin sensitivity and inflammation, but also has direct anti-carcinogenic effects. Many of these effects are mediated through the AMP-activated protein kinase (AMPK) system via two receptors, AdipoR1 and R2, to phosphorylate the tumor suppressor,
tuberous sclerosis complex 2 [11], and then subsequently inhibit mammalian targeting of rapamycin to counteract carcinogenesis. Activated adiponectin could also regulate cell growth arrest and apoptosis by stimulating p53 and p21 [12]. On the other hand, adiponectin decreases the production of reactive oxygen species (ROS) [13] and thereby the inhibition of cell proliferation.

Leptin

Leptin is produced by adipocytes and circulates at levels proportional to the amount of body fat stored. Leptin has been considered to play an important role in regulating energy balance. Hyperleptinemia/leptin resistance are developed in the state of obesity [14]. Interestingly, there is an overexpression of the leptin receptor ObR in tumor cells of many colorectal, breast, and endometrial cancers [15,16]. In vitro experiments have demonstrated that leptin has a mitogenic effect in cancer cell lines, depending on the different type of cancer involved. For instance, leptin could stimulate the growth of breast, esophageal, and prostate cancers, but inhibit the growth of pancreatic cancer cells [17]. Mitogenic and anti-apoptotic effects of leptin have been described in both colon and prostate cancer cell lines via MAPK and PI3-K pathways [18,19]. However, the clinical significance of elevated levels of this pleiotropic hormone in relation to the link between obesity and cancer is still indeterminate, and requires further study.

Figure 2. Adipose tissue as a reservoir of carcinogens. Hypothetical mechanism according to which environmental low-dose xenochemicals can induce carcinogens
Plasminogen activator inhibitor (PAI)-1

PAI-1 is a serine protease inhibitor produced not only in adipocytes but also in endothelial cells, and adipose vascular stromal cells [20]. PAI-1 has been shown to significantly affect adipocyte differentiation and insulin signaling [21]. Overexpression of PAI-1 has been found in many obesity-related types of cancers and is associated with the progression of breast, endometrial, colorectal, thyroid, renal, and prostate cancers [22-26]. Elevated systemic levels of PAI-1 (e.g., produced by immune cells or adipocytes in obesity) appear to be essential for its tumor-promoting effects [27]. When Min mice were treated with a PAI-1 inhibitor, which have a defect in the adenomatous polyposis coli (Apc) gene, the treatment suppressed intestinal polyp formation [28]. It has been recently hypothesized that the up-regulation of PAI-1 expression predisposes breast cancer to more aggressive stages in tandem with metabolic syndrome [29] and supports the role of PAI-1 in promoting cell migration and tumor angiogenesis [30]. The results of clinical and experimental studies thus far make PAI-1 a plausible culprit associated with an increased risk of cancer mortality in obesity.

Hyperinsulinemia and Insulin Resistance

People who are obese generally have hyperinsulinemia and are insulin-resistant. The cause-effect relationship between insulin resistance and adipose tissue dysfunction is mutual and complicated. Clinical studies have shown that diabetes mellitus, a disease characterized by insulin resistance, is associated with an increased risk of breast, colorectal, pancreatic, and bladder cancer [31-34]. Hyperinsulinemia compensates for insulin resistance, and is also an independent risk factor for breast cancer in postmenopausal women [35] and increases the risk of colorectal and endometrial cancer; however, the above results are not consistent and remain ambiguous in other reports [36,37]. Patients with elevated levels of free insulin-like growth factor (IGF)-1 accompanied by hyperinsulinemia/insulin resistance have an increased risk of several types of cancer, including colorectal, prostate, and postmenopausal breast cancer [38]. In a state of insulin resistance, high plasma insulin up-regulates growth hormone (GH) receptors in the liver, which stimulates the hepatic production of IGF-1 [39]. In obese subjects, free IGF-1 levels do not respond to insulin administration and tend to be higher than in subjects who are not obese [40]. Both insulin and IGF-1 are believed to play a role in cancer development through the act of binding to the insulin receptor (IR) and IGF-1 receptor (IGF-1R). IGF-1 can inhibit apoptosis and stimulate cell proliferation through the phosphatidylinositol 3-kinase (PI3-K) -AKT system and the Ras/Raf/mitogen-activated-protein-kinase (MAPK) systems, respectively [38]. Interestingly, the expression of IGF-1 receptor is increased in some tumors, suggesting that these neoplasms may be stimulated by systemic levels of IGF-1 [41,42]. 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) [43]. However, serum IGF-1 levels would be expected to be correlated with body mass index (BMI), but levels of IGF-1 are normal or even low in some obese subjects [44]. This 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 [45,46]. On the other hand, insulin has mitogenic and anti-apoptotic properties mediated through pathways to some extent similar to those of IGF-1 [47,48]. 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 [38]. Insulin resistance is likely to play a prominent role in carcinogenesis, and it appears to be of one the major mechanisms involved in the obesity-cancer
Adipose Tissue Inflammation

It is well recognized that inflammation is involved in the promotion and progression of cancer [49,50]. Obesity-induced inflammation, a key feature of adipose tissue dysfunction, is thought to be an important link between obesity and cancer. Several pro-inflammatory factors such as TNF-α and IL-6, which are released from obese adipose tissue, are believed to be involved in carcinogenesis [51].

TNF-α has been well-documented, playing a vital role in adaptive responses of the immune system and other organ systems [52]. TNF-α was considered to be a macrophage-derived factor, and also an anti-cancer agent that could induce necrosis in tumor cells [53]. However, in recent years, the role of TNF-α in malignancy is being reconsidered, and it is now proposed that TNF-α is involved in carcinogenesis and cancer progression [54-56]. Systemic TNF-α might also be involved in the early development of some tumors, as a recent study indicated elevated TNF-α levels to be associated with an increased risk of colorectal adenomas [57]. 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 [58]. This in turn leads to the up-regulation of several negative regulators of apoptosis, such as c-FLIP and cIAP1, which promote cell survival [59]. TNF-α has also been reported to be associated with tumor-promoting activity in various experimental cancers [60], and a variety of tumor cells produce TNF-α [50]. 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 [54]. However, the role of the increased systemic levels of TNF-α seen in obesity [51] in the promotion of tumor development and progression is not fully clear.

Adipose Sex Hormone

Peripheral conversion of androgenic precursors to estradiol by aromatase in adipose tissue is increased in obesity, leading to increased serum levels of estradiol [46,68]. 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) [46]. 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 [69].

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 [68,70-72]. The proliferative effect of estrogen on epithelial tissue of both the breast and endometrium is believed to be the underlying mechanism [71,73].

**Liposoluble Environmental Carcinogens**

In addition to the above hypothetical biological mechanisms, adipose tissue acts as a reservoir for liposoluble environmental carcinogens, so that chemical pollution may in fact promote both overweight/obesity and cancer. More precisely, it is also hypothesized that many carcinogens can be stored in the adipose tissue, be released at intermittent doses in the blood circulation and therefore target peripheral tissues to induce carcinogenesis as shown in Figure 2.

**Adipose Tissue as a Reservoir for Liposoluble Chemical Carcinogens**

Many environmental chemical carcinogens, referred as carcinogenic, mutagenic and/or reprotoxic (CMR) molecules are indeed lipophilic, so they can bioaccumulate in adipocytes. Adipocytes are capable of storing not only triglycerides, cholesterol and liposoluble vitamins, but also liposoluble chemical carcinogens, such as dioxins [74], organochlorines - organochlorinated pesticides [75], polychlorinated biphenyls (PCBs), dioxin-like polychlorinated dibenzo-pesticides (PCDD/PCDF) [76] and also some polybrominated flame retardants (BFRs) and other pollutants, such as phthalates esters [77,78]. Such a relationship between liposoluble xenocarcinogens and adipose tissue has been put forward experimentally in different animal models. For example, it has been shown that the level of the Lethal Dose 50 (LD50) for dioxins is inversely correlated with the body fat mass of animals [79], meaning that the acute toxicity of dioxins correlates positively with the total quantity of adipose tissue.

Lipophilic and liposolubility properties of carcinogens make them likely to persist in the adipose tissue until they could be released from adipocytes directly during lipolysis [74], and/or indirectly, presumably through apoptosis, after reaching a toxic levels in adipocytes.

Synthetic chemicals must be fundamentally distinguished from natural plant products, because in contrast to natural molecules, most synthetic compounds are capable of accumulating in the organism. This implies that the enzymes required for effective detoxification and excretion of non-natural molecules are absent or deficient.

As shown in Figure 2, following environmental exposure to low-dose chemical pollutants over the course of many years, accumulation of carcinogens in the adipose tissue might in fact correspond to greater exposure, similar to what is observed in hot-spot polluted areas. Accordingly, many exogenous chemical carcinogens are persistent organic pollutants, accumulating in fat and can be released in the organism at doses which do not correspond to those observed in the environment. Therefore, during prolonged environmental exposure, cancer may be induced by repetitive lower doses than would be typically expected [80,81]. Furthermore, it has been shown that mixtures of pollutants may have synergistic effects and that some types of “cocktail effects” occur in adipose tissue and therefore may contribute to carcinogenesis [82] and/or cancer cell proliferation [76].

Some evidence allows us to consider that adipose tissue itself can contribute to carcinogenesis in subjects with normal or even decreased total fat body mass, i.e. with normal or lower BMI, as is the case in patients with pancreatic cancer, lymphoma or even breast cancer. In addition, it has been shown that locally, there are some close relationships between glandular cells and adipocytes in target organs such as the breast, colon–rectum or pancreas. This suggests that in these organs, the local release of carcinogens from the adipocytes might directly contribute to carcinogenesis.
Moreover, body weight loss increases serum concentrations of toxic pollutants in obese individuals [78,83,84], so acute weight loss can exacerbate toxicity and thus may contribute to carcinogenesis in people subject to toxic contamination [83,84]. It has been observed in animal models that fasting can also contribute to the release of xenobiotics from adipose tissue through lipolysis. For instance, \(\beta\)-Hexachlorocyclohexane (\(\beta\)-HCH) - a pesticide with weak estrogenic activity, whose release during fasting has been shown to occur in quantities sufficient to stimulate estrogen target tissues and the promotion of estrogen-responsive tumors [81].

Finally, environmental lipophilic pollutants can enter the organism via food, water and air, accumulate and concentrate in the adipose tissue, be permanently released in the blood circulation and exhibit their effect in peripheral tissues at convenient doses according to their potential toxicity. This concept applies to many liposoluble and fat-stable molecules, such as organochlorines. Accordingly, it is speculated that diets rich in animal fat might be a risk factor for cancer, although this hypothesis has not been validated [85].

**Recent Supportive Evidence from Cancer Studies**

**Breast cancer**

Because half of breast cancer risk cannot be attributed to established risk factors [86,87], there is a growing interest to consider that environmental factors may play a role in this tumor [88]. Exposure to estrogen throughout a woman's life is a risk factor for the development of breast cancer. Organochlorine compounds such as organochlorinated pesticides and polychlorinated biphenyls (PCBs) are persistent lipophilic xenochemicals identified as endocrine disruptors, mainly with estrogenic effects. In several studies, the presence of CMR organochlorine pesticides [89] appeared to be positively correlated with this type of cancer, although there has been some negative studies [90].

On the other hand, a pathologic link between breast cancer risk and the organochlorine insecticides dieldrin and heptachlor epoxide (HE) belonging to the cyclodiene family – has been established in a studies dosing these pesticides in adipose tissue [91]. HCB, especially \(\beta\)-HCH as well as PCBs have been also found to be associated with an increased risk of breast cancer when dosing these xenochemicals in adipose tissue, especially the PCB congeners 105, 118, 170, 180 and so on [92-94], meaning that PCBs, due to their CMR properties, are potential causal agents of breast carcinoma. Organochlorine residues in adipose tissue adjacent to breast carcinoma can also generate an estrogenic microenvironment that may influence the biological behavior of breast carcinoma locally in postmenopausal women. In this study, the most frequently detected compounds were p,p'-DDE, hexachlorobenzene (HCB) and \(\beta\)-HCH [95]. Such an estrogenic microenvironment may explain why detection of high concentrations of PCBs in tumoral and peritumoral adipose tissue is associated significantly with a poor prognosis [96,97].

**Prostate cancer**

Results from several large studies focusing on an associative link between obesity and prostate cancer are not consistent [98]. Several lines of evidence have shown that contamination by CMR molecules, including Biphenol A, organochlorine pesticides and PCBs may be associated with prostate cancer and that in utero fetal exposure to low dose xenoestrogens or antiandrogens in the presence of androgens may be the first step leading to prostate cancer later in life [99,100].

On the other hand, a large prospective cohort study in the United States investigated the use of agricultural pesticides in 55,332 male pesticide applicators with no prior history of prostate cancer. This study concluded that the use of chlorinated pesticides among applicators over 50 years of age and methyl
bromide use are significantly associated with prostate cancer risk [101]. In addition, a case–control study in Italy concerning farmers exposed to organochlorine pesticides and difacol [102] has demonstrated that the high levels of adipose tissue concentrations of PCB 153, β-HCB, transchlordane and chlordane type M6 are associated with an increased risk of prostate cancer [103]. These observations suggest that prostate cancer genesis and progression may be related to some organochlorines including pesticides, and PCB accumulated in adipose tissue and overweight/obesity is a less well established risk factor.

Lymphoma

The association between lymphoma and overweight/obesity has not yet been proven. However, several cohort and case–control studies have reported that PCB contamination is associated with an increased risk of non-Hodgkin lymphoma (NHL) [104]. In a nested, case–control study dosing organochlorine pesticides in adipose tissue, high levels of p,p′-DDE, oxychlordane, β-HCB as well as dieldrin and heptachlor epoxide have been found to be associated with an increased risk of NHL [105].

These data therefore further point to a growing body of evidence of an association between exposure to PCBs and/or organochlorine pesticides in adipose tissue and the risk of NHL, although the underlying mechanisms of these associations still need to be further investigated.

**Environmental Carcinogens as a Cause of Overweight/Obesity and Associated Dysfunctional Adipose Tissue**

In addition to overnutrition and physical inactivity, xenocochemicals including carcinogens have been speculated to be one of the important environmental risk factors contributing to the growing incidence of overweight/obesity. It is suggested that synthetic chemicals may induce obesity by changing hormone levels or altering gene expression in adults [80]. Fetal exposure to exogenous endocrine disruptors has been proved not only to promote cancer [85], but also to cause obesity [106,107].

The concept about carcinogen-induced overweight/obesity has been strengthened by the fact that repetitive administration of low doses of benzo[a]pyrene, a well-known environmental carcinogen, can induce overweight/obesity in mice [80]. Tributylin, an endocrine disruptor which has been shown to be carcinogenic, can also increase the adipose mass [108]. In addition, benzo[a]pyrene intercalates into the lipid bilayer of the cell membrane, hence inactivates β-adrenergic receptors and consequently inhibits adrenalin-induced lipolysis [80]. Therefore, since overweight/obesity has been found to be associated with several types of cancers, these observations suggest that environmental carcinogens may play an unexpected role in cancer genesis, not only directly by inducing cancers, but also indirectly by inducing overweight and/or obesity associated dysfunctional adipose tissue [80,106-110].

**CONCLUSIONS**

Taken together with these observations, obesity clearly is a risk factor contributing to the genesis and development of certain types of cancer, not only through biological mechanisms, but also, and probably predominantly, through the multiple environmental carcinogens that are stored in the adipose tissue. Such carcinogens mainly include organochlorine pesticides and PCBs. Their association with an increased risk of cancer seems demonstrated not only for cancer-associated overweight/obesity, such as breast cancers, but also for cancers for which the association with overweight/obesity has not been proven, such as prostate cancer, and even for cancer not associated with overweight/obesity, such as lymphoma. Ultimately, this means that the role of adipose tissue as a reservoir of carcinogens should be of concern not only to obese patients, but also to those patients within normal weight parameters, even including lean pa-
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