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Overview

The relationship between obesity and cancer

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Abbreviations:
AMPK – 5'AMP-activated protein kinase;
BMI – body mass index;
COX – cyclooxygenase;
FDG – fluorodeoxyglucose;
IGF – insulin/insulin-like growth factor;
IPMK – inositol phosphate multikinase;
MCP – monocyte chemoattractant protein;
NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells;
PET/CT – Positron Emission Tomography / Computerized Tomography;
VEGF – vascular endothelial growth factor

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Abstract

Obesity is an urgent and growing global health problem. Among other co-morbidities, obesity is associated with a significantly increased risk of developing many cancers. The epidemiological evidence linking obesity and cancer has ignited multiple studies trying to understand how obesity contributes to cancer risk. Although mechanisms underlying the obesity-cancer link are becoming increasingly clearer, they are very complex and still under intense investigation. Strategies that prevent and/or reverse obesity may also be useful for reducing the progression of cancer. Recent interests are focused towards brown fat as a primary target to combat obesity. In this review, we integrate the classic understandings of the mechanistic role of obesity in cancer to the studies which suggest a beneficial role of brown fat to humans.

INTRODUCTION

Overweight and obesity are leading risks for global deaths *(1)*. The World Health Organization estimates that at least 2.8 million adults die each year as a result of being overweight or obese *(1)*. Although the increase in obesity over the last 35 years has been most dramatic in the US and western industrialized countries, similar trends have also been seen in urban areas of many developing countries. There are multiple common health consequences of an elevated body mass index (BMI), including risk for several metabolic disorders, some cancers *(1, 2)* and ultimately increased mortality *(3)*.

Cancer is the leading cause of death in developed countries and a second leading cause of death in developing countries *(4–6)*. About 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008 *(4)*. It is estimated that 1,660,290 men and women (854,790 men and 805,500 women) will be diagnosed with and 580,350 men and women will die of cancer of all sites in 2013 *(6)*. The number of cancer cases is expected to rise due to both world-wide population growth and an increasingly aged population.

The relationship between obesity and cancer was poorly understood until Eugenia Calle of the American Cancer Society (ACS), conducted a large prospective study examining the role of obesity or excess adiposity in increasing the risk of dying from most types of cancer, showing that increased body weight was associated with increased death rates for all cancers combined, and for cancers at multiple specific sites for both men and women *(7)*. Furthermore, she was trying to define why obesity was such an important determinant for cancer risk, and stimulated further research in this area *(8, 9)*. Obesity is also an important risk

factor for cancer survivors, complicating treatment and disease outcomes *(10–13)*. Taken together, given that obesity, diabetes and cancer rates have increased substantially, understanding the underlying mechanisms and interrelationships between these states is vital.

POTENTIAL MECHANISMS LINKING OBESITY AND CANCER

Chronic positive energy balance attributable to excessive energy intake and decreased energy expenditure produces obesity. Metabolic consequences are altered levels of adipokines, increased circulating levels and bioavailability of insulin and IGF-1, and chronic inflammation *(14, 15)*. Activation of downstream signal transduction pathways may increase cancer risk, development and progression. Understanding the link between overweight, obesity, and a wide variety of cancers, as well as the biological mechanisms involved, remains an evolving and currently very active area of research.

Although mechanisms underlying the obesity-cancer link are becoming increasingly clearer, they are very complex and still under intense investigation. They include modulation of energy balance and calorie restriction and inappropriate endocrine signaling (i.e. hormones, growth factors, multiple signaling pathways and inflammatory processes) *(14–27)*, all affecting cancer cell promotion and progression. Energy balance and caloric restriction and their impact on cancer have been studied very thoroughly over 30 years at cellular and whole body levels *(14–18)*. Although mostly what we know today comes from experiments with rodents, these studies have provided insights into the mechanistic links between obesity, energy balance and cancer, indicating new opportunities for cancer prevention *(14)*. Below, we briefly review the current understanding of metabolic alterations in white fat that increase levels of adipocyte-derived factors.

Adipokines. Adipose tissue is an endocrine organ, producing adipokines such as leptin and adiponectin, both of which are involved in cancer development *(28, 29)*. Leptin, which is secreted from white adipocytes, influences appetite and regulates energy expenditure. The physiologic role of leptin is to exert homeostatic control to maintain adipose tissue. However, in obesity circulating leptin becomes elevated in part due to increase in subcutaneous fat *(30)*. Signaling of leptin through its receptor activates numerous cascades, including the JAK-STAT, IRS-1/2, MAPK and Akt/PI3K, and decreases the activity of 5'AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis *(31, 32)*. Indeed, this profile of signal pathways suggests crosstalk with insulin/insulin-like growth factor (IGF)-1 signaling *(31)*. Importantly, signaling *via* the PI3K/Akt/mTOR pathway has become a focus of the obesity and cancer connection. This signaling network, which promotes cell proliferation and growth while inhibiting apoptosis, is among the most frequently mutated pathways in human cancers *(33–35)*. As a result of the regulation of these signaling pathways and their role in tumorigenesis, leptin has been viewed as a mediator of obesity related cancers *(20, 22, 24, 36, 37)*. Adiponectin is also secreted from adipose tissue, as well as from other tissues *(2)*. In contrast to leptin, adiponectin levels decrease with adiposity *(21, 22, 38, 39)*. In contrast to leptin, adiponectin has been associated with anticancer activity *(39)*, perhaps by modulating energy balance by decreasing insulin/IGF-1 and mTOR signaling *via* activation of AMPK and by exerting anti-inflammatory actions *via* the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) *(21)*. The associations between the adiponectin-to-leptin ratio with metabolic syndrome and some type of cancers have been suggested as an additional important parameter *(26, 40)*. The role of novel adipokines, such as omentin-1, visfatin and vaspin in obesity and cancer is under investigation. Omentin-1, a 34 kDa adipocytokine that is highly expressed in visceral adipose tissue, has been associated with metabolic syndrome and insulin insensitivity, but it is not clear if omentin-1 can affect cancer growth. It has been recently shown that omentin-1 has ability to promote apoptosis by p53 deacetylation *(41)*. Nicotinamide phosphoribosyl-transferase (Nampth or visfatin) found in visceral fat, with important role in the cellular energy metabolism, represents a novel pleiotropic adipokine, recognized for potential preventive and therapeutic properties *(42)*. Vaspin (visceral adipose tissue-derived serpin), a member of the family of serine protease inhibitors is additional novel adipocytokine with insulin-sensitizing effect. However, recently shown high circulating levels of omentin-1, visfatin, and vaspin in patients with colorectal cancer, indicate that their definite role in obesity and cancer connection has yet to be determined *(43)*.

Growth factors. Insulin and insulin-like growth factors (IGF) have been implicated in a wide range of cancers *(44)*. Obese patients with type 2 diabetes have increased cancer mortality, perhaps due to hyperinsulinemia, and/or elevated IGF-1, which could increase cancer cell growth, proliferation and survival. In contrast, patients with low circulating insulin and IGFs appear to be protected from cancer development *(23)*. Patients with type 2 diabetes who get insulin therapy or drugs to stimulate insulin secretion have a significant higher incidence of cancer than those who get metformin, the anti-diabetic drug that works to lower insulin levels *(45)*. Epidemiological studies have consistently associated metformin use with decreased cancer incidence and cancer-related mortality, and metformin is rapidly emerging as a potential anti-cancer agent *(45)*, underscoring the importance of insulin, IGF-1 and energy metabolism in cancer biology. Indeed, caloric restriction, which reduces circulating insulin and IGF-1, is a potent suppressor of the carcinogenesis *(17)*. In several preclinical models, the effect of caloric

restriction, which reduces PI3K/Akt/mTOR pathway activation *via* AMPK *(46, 47)*, on carcinogenesis can be abrogated by restoration of IGF-1 levels *(17, 40, 48, 49,)*, and tumors with mutations activating the PI3K/Akt/mTor signaling pathway are resistant to caloric restriction *(35)*. The PI3K/Akt/mTOR/AMPK axis is a common effector of insulin, IGF and leptin signaling, regulating tumor survival, growth and proliferation *(50)*. Accordingly, PI3K/Akt/mTOR inhibition has been an active strategy to reduce carcinogenesis and tumor incidence *(51–54)*.

Secreted hormones. Another interesting connection between obesity and cancer in the pathologic impact of sex hormones, including estrogen, progesterone, androgens and adrenal *(55, 56)*. For example, adipose tissue can produce estrogens *via* aromatase-catalyzed conversion of gonadal and adrenal androgens to estrogen in men and postmenopausal women *(56)*. Estrogen and estrogen receptor-α have been implicated in the pathogenesis of several cancers by inducing cell proliferation, vascular endothelial growth factor (VEGF) expression and angiogenesis, and inhibiting apoptosis, and targeting estrogen as a preventive intervention has been pointed out by clinical data *(12)*. Selectively reducing aromatase expression and excessive estrogen production has been suggested to reduce the obesity and cancer *(57)*, and a treatment with exemestane, an aromatase inhibitor, has shown a decrease in relative risk of invasive breast cancer by 65% *(14, 58)*.

Inflammatory cytokines. Another possible link between obesity and cancer is inflammation *(59)*. Growing evidence supports that chronic inflammation is part of the cancer etiology, playing important role in each step of carcinogenesis *(26, 60, 61)*. Body adiposity is associated with higher levels of proinflammatory cytokines, including prostaglandin E2, TNFα, IL-6, IL-8, IL-10, monocyte chemoattractant protein (MCP)-1. Activation of NF-κB complex is a possible mechanism through which inflammation stimulate cancer development *(14, 25, 26, 62-64)*. Another important cancer-related inflammatory mediator is cyclooxygenase (COX)-2, an enzyme that catalyzes the synthesis of prostaglandin E_2, a potent inflammatory lipid metabolite. COX-2 is upregulated in many tumors and is related to poor prognosis *(65)*. The presence of inflammatory mediators and certain immune cells in the tumor environment is known to accelerate disease progression *(14, 26)*. The contribution of two pathologists to the association of inflammation and microenvironment to the tumor development deserves merit. In 1863, Rudolf Wirchow hypothesized a link between microinflammation and subsequent cancer development *(66)*, and in 1889, Stephen Paget proposed his famous "seed-and-soil" hypothesis, the concept that the microenvironment of developing tumor is a crucial regulator of carcinogenesis *(67)*. While inflammation stimulates the development of cancer, components of the tumor microenvironment, such as tumor cells, stromal cells in surrounding tissue and infiltrated inflammatory and immune cells generate an intratumoral proinflammatory state *(68)*. Obesity can mediate tumor microenvironment, because many obesity-associated endocrine, metabolic and inflammatory mediators might play a role in carcinogenesis *(69)*.

PREVENTION OF OBESITY AND CANCER

Based on known mechanistic pathways and scientific evidence, guidelines and recommendations for prevention of cancer and obesity have been developed for public health goals and individuals by the American Institute for Cancer Research / World Cancer Research Fund (AICR/WCRF). These guidelines and recommendations are designed to be integrated and to contribute to healthy dietary patterns and healthy ways of life *(70, 71)*. Strategies, either diet, lifestyle, or pharmacological, that disrupt the obesity-cancer axis may be useful for reducing the rise of cancer or its progression.

In our strategy for obesity prevention, some phytochemicals, such as resveratrol, curcumin and quercetin have been shown to be potent in breaking the obesity-cancer link *(72)*. However, more agents that can effectively target the molecular mediators of the effects of obesity on cancer progression are needed. Inositol phosphates, also naturally appearing compounds and widely distributed in animal and plant tissues, may represent an important, but still understudied signaling pathway that could affect the cancer-obesity connection. Inositol phosphates act as second messengers in cells. Inositol 1,4,5 triphosphate, or $InsP_3$, which signals the release of calcium from intracellular stores, is the mostly widely studied. However, additional inositol polyphosphates exist and have biologic functions inside of cells. For example, inositol phosphate multikinase (IPMK), which generates $InsP_4$ and $InsP_5$ and has PI3K activity, and IP6K1, which makes InsP7, regulate the PI3K/Akt pathway and affect growth and metabolism, including obesity and insulin homeostasis *(73, 74)*. $InsP_7$ acts as an inhibitor of the Akt and mTOR signaling downstream of insulin *(75)* and is involved in the release of insulin from the pancreatic beta cells *(76, 77)*. Another kinase responsible for the production of IP_7, IP6K2 has been implicated in tumor biology *(78, 79)*. IP6K2 is a regulator of apoptosis affecting signaling through Akt and p53 *(80-82)*. Deletion of IP6K2 predisposes to certain carcinomas *(83)* and sensitizes tumors to chemotherapeutic treatments *(84, 85)*. Also, the anticancer activity of extracellular $InsP_6$ has been shown in different experimental models *(86, 87)*. Perhaps $InsP_7$ could uncouple obesity and cancer by modulating the activity of the PI3K/Akt/mTOR cascade. Future studies are needed to determine if inositol phosphate producing enzymes and/or their signaling mediators can be modulated to affect the coupling of obesity and tumorigenesis.

New emerging areas of research in obesity and cancer that might provide additional insights and strategies for prevention and treatment of both obesity and cancer, are epigenetics and gut microbiota. Many obesity-responsive genes involved in cancer development and progression are under epigenetic control, including DNA methylation, histone modification and microRNA. One of the most utilized approaches to the epigenetic alterations in cancer is dietary intervention, controlling also the quantities of consumed calories *(88)*. The influence of gut microbiome on obesity-cancer connection is another novel emerging area of investigation *(89, 90)*. Modulation of gut microbiota can control inflammation and insulin resistance and affect both obesity and cancer risk and progression *(91, 92)*.

ANOTHER TYPE OF FAT

Historically, adipose tissue has been subdivided into white and brown fat. In contrast to white fat, composed of cells with a single (unilocular) large lipid droplet as storage for energy, brown fat is composed of cells with numerous (multilocular) small lipid droplets with capillaries that weave through individual brown adipocytes to facilitate the burning of lipids for heat production, a process known as "non-shivering thermogenesis" *(93, 94)*. This thermogenic process in brown fat is mediated by the unique mitochondrial uncoupling protein 1 (UCP1) which uncouples oxidative phosphorylation and renders the inner membrane of the mitochondria "leaky" to promote the dissipation of cellular biochemical energy as heat, particularly in young animals *(93, 94)*. Until recently, it had been assumed that brown fat was either nonexistent or nonfunctional in adult humans. This was based on the general notion that brown fat is gradually lost postnatally when its specific role in non-shivering thermogenesis was normally concluded *(93, 94)*. However in 2009, several research groups independently confirmed the existence of brown fat in adults through the use of ^{18}F-fluorodeoxyglucose (FDG)-Positron Emission Tomography/Computerized Tomography (PET/CT) imaging in the classic areas of the upper neck and chest regions *(95–100)*. A "browning" phenomenon, the process by which brown (UCP1-expressing, multilocular) adipocytes appear at anatomical sites of classical white fat, has also been described *(101)*. This process occurs after a thermogenic stimulus, such as prolonged cold exposure *(102)*, but also can be mimicked by chronic treatment with β_3-adrenergic receptor activators *(103)*. To eliminate confusion, researchers typically use the terms "beige" and "brite" (from "brown in white") to designate brown adipocytes that appear in white fat after permanent thermogenic induction, whereas those present in the standard brown fat depots are often called "constitutive", "classical" or "developmentally programmed" brown adipocytes *(101)*.

Notably, the amount of brown fat is inversely correlated with obesity and body mass index (BMI). Most recent studies have shown that brown fat may be potential player in human energy balance and obesity *(104)*. Experimental brown fat transplantation studies have demonstrated improvements in obesity-associated disorders, including improved glucose tolerance and insulin sensitivity mainly by influencing hepatic and cardiac function *(105, 106)*. It has been proposed that these effects are due to the release of endocrine factors by brown fat, such as insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6) or fibroblast growth factor-21 (FGF-21) *(107)*. These and other findings have led to the current thinking that maintenance of brown fat activity throughout life may protect against obesity and diabetes. This has led to an explosion of research that seeks to pharmacologically stimulate brown adipose tissue and induce "browning" in order to burn off excess calories and combat human obesity *(108-110)*.

Interestingly, an emphasis has been made on the association of specific brown fat features and the so-called white fat browning with the functions of normal and mutated tumor suppressor genes, such as *PTEN* and *BRCA1* *(111–113)*. More research is needed to clarify the potential of brown fat and to better understand its role in obesity and cancer.

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