

REVIEW ARTICLE

Cancer and Obesity: A Biological Perspective

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Abstract: The rising incidence and associated mortality of cancer on the worldwide scale has made cancer a global health problem. Although the cause of oncogenesis is multifactorial, certain well-established risk factors are known to play their part in cancer development. The risk for cancers can be reduced since these factors are manageable. For instance, tobacco and alcohol use can be avoided, and obesity can be controlled with the help of lifestyle modification. This review provides a brief insight into the postulated mechanisms on how obesity can lead to cancer initiation, progression, and even treatment resistance. Mediators and pathways with documented clinical evidence that connects obesity to cancer are also discussed. These mediators include various adipokines, free fatty acids, insulin and insulin-like growth factor-1, sex hormones, and products of chronic inflammation. The recent concept of obesity paradox has also been discussed. Exploring these biological mediators and pathways linking obesity to cancer will open new avenues for not only cancer treatment but also its prevention.

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1. Introduction

With an incidence of 18.1 million new cancer cases and 9.6 million deaths in 2018, cancer is a leading cause of death worldwide. These numbers are estimated to rise to 29.5 million new cases by 2040, unless drastic preventive measures are taken^[1]. Furthermore, for rapidly growing economies, the data suggest that there was a shift from poverty- or infection-related cancers to those associated with lifestyles such as obesity^[2,3]. In parallel with the rise in cancer, another pandemic that is gripping the world is that of obesity. The World Health Organization (WHO) indicated that the worldwide obesity rate has tripled since 1975, and globally, more than 1.9 billion adults were overweight and 650 million of these individuals were obese in 2016^[4]. The number of obese people in the world rose to approximately 2.1 billion in 2019, accounting for approximately 30% of the total population^[5]. It is estimated that 20% of new cancer cases and 17% of cancer-related deaths are causally linked to obesity^[6].

The worldwide rise of obesity and its established link to cardiometabolic diseases and cancer have impelled an intensified research for a better understanding of the underlying mechanism^[7]. It is now well known that fat or adipose tissue is not merely an energy storage site, but an active endocrine organ that could engender metabolic alterations^[8]. Based on extensive research, the International Agency for Research on Cancer has concluded that obesity is causally related to cancer at 13 anatomic sites which include that of breast (post-menopausal), colon and rectum, endometrium, esophagus (adenocarcinoma), gallbladder, gastric, kidney (renal cell carcinoma), liver, multiple myeloma, ovary, pancreas, and thyroid^[9]. In the advent of precision medicine, an understanding of pathways and determination of biomarkers linking obesity to cancer may improve the

clinical identification of obese individuals who are at risk of developing cancer, thereby leading to personalized prevention.

In addition to being a risk factor for cancer development, evidence suggests that obese individuals are at an increased risk of treatment failure, cancer recurrence, and death due to cancer^[10]. This review will focus briefly on those metabolic alterations seen in obesity which initiates and promotes the development of cancer.

2. Implications of obesity in cancers

Obesity is a state of excess adipose tissue mass which is practically equivalent to increased body weight. Although the exact definition of obesity is debatable, the WHO defines obesity as a body mass index (BMI) of $\geq 30 \text{ kg/m}^2$ ^[11]. Obesity leads to changes in adipose tissue distribution along with metabolic alterations producing various biological effects.

In the obese patients, adipose tissue contains an excessive amount of lipids that cause an increased plasma level of free fatty acids (FFAs). FFA may function as a substrate for oxidative process and release free radicals which act as oncogenic signals^[12]. FFA may also further act as an energy source for cancer cells, aiding their growth and thus cancer progression^[13].

Adipose tissues, especially the visceral fat cells, secrete a range of protein factors called the adipokines which are also responsible for the pathological consequences of obesity such as metabolic syndrome and cancer. Insulin and insulin-like growth factors (IGF), increased bioavailability of sex hormones, and a prolonged state of chronic low-grade inflammation have been postulated for linking obesity to cancer. Furthermore, these factors and biological events are interrelated in a complex manner with different pathways being implicated in different cancers^[14].

2.1. Adipokines

Adipose tissue is comprised of mature adipocytes and other cells, including pre-adipocytes, fibroblasts, mast cells, endothelial cells, and immune cells, in the surrounding stroma. Normally, these cells secrete factors which regulate physiological functions such as appetite and metabolism of carbohydrates and lipids. However, there is an excessive fat accumulation associated with hypertrophy of adipocytes in obesity. These alterations to the adipocytes encapsulate dysregulated function of adipose tissue, which produce several hormones and signaling molecules called adipokines that elicit different biological effects on the body. These resultant biological effects facilitate processes such as the carcinogenesis, proliferation, and migration of cancer cells, as well as cancer progression^[15]. Over 20 different adipokines have been found to be released by the fat cells. Leptin, adiponectin, apelin, visfatin, resistin, chemerin, omentin, nesfatin, and vaspin are among the important adipokines that have an established role in

cancer promotion and progression^[10].

2.1.1. Leptin

The discovery of leptin, colloquially known as the hunger hormone, has been seminal in defining adipose tissue as an endocrine gland. In obese individuals, leptin induces Janus kinase 2 to phosphorylate various tyrosine kinases which further stimulate signal transducer and activator of transcription 3, mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K) pathways. These pathways stimulate cell cycle genes, resulting in cell proliferation and thus carcinogenesis^[16,17]. In addition, it also upregulates the expression of anti-apoptotic genes such as Bcl which causes prolonged cell survival^[18]. Leptin also induces vascular endothelial growth factor (VEGF) gene that stimulates angiogenesis to support the growth and metastasis of cancer cells^[19]. Overexpression of leptin in patients of breast, liver, gastroesophageal, and colorectal cancers has been reported^[20-23].

2.1.2. Adiponectin

Among the adipokines secreted by adipocytes, adiponectin is the only beneficial hormone. Adiponectin can enhance the activation of cell apoptosis and inhibit cell cycle. Besides, it also reduces the bioavailability of many growth factors, such as platelet-derived growth factor, fibroblast growth factor, and heparin-binding epidermal growth factor-like growth factor, which, in turn, attenuates cancer cell proliferation, invasion, and metastasis^[24]. However, the level of adiponectin decreases and the expression of the adiponectin receptors such as AdipoR1 and AdipoR2 becomes downregulated in obesity^[25]. Moreover, decreased adiponectin level has been found to be associated with a higher grade of endometrial cancer histologically and poor prognosis in breast and colorectal cancers^[26,27].

2.1.3. Apelin

Apelin is involved in epithelial proliferation and cytokine regulation. The receptors of apelin are present on the lymphatic endothelial cells which causes lymph node metastasis after activation^[28]. High level of apelin has been reported in endometrial cancer^[29].

2.1.4. Visfatin

Visfatin plays several biologically important roles and is also associated with carcinogenesis, cell survival, and migration. Visfatin can directly induce the production of cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) which promote carcinogenesis through Sirt6 pathway^[30]. In addition, this adipokine can also enhance cancer cell survival through chemokine receptors CXCR4 and CXCR7 which bind to stromal cell-derived factor-1 (SDF-1). SDF-1 induces activation of MAPK pathway such as ERK-1/2, PI3K, and protein kinase B which inhibits apoptosis and promotes cell proliferation, migration, and survival. SDF-1 also acts

synergistically with VEGF to accelerate tumor angiogenesis by recruiting endothelial precursor cells. Thus, SDF-1 promotes cancer cell survival through pro-proliferative and anti-apoptotic mechanisms and aids in metastases by promoting angiogenesis^[31]. Furthermore, SDF-1 increases the activities of antioxidative enzymes such as superoxide dismutase, catalase, and glutathione peroxidase which reduce reactive oxygen species (ROS), thereby protecting cancer cells from damage^[32]. Increased level of visfatin has been reported in colorectal and serous ovarian cancers^[31,33].

2.1.5. Resistin

Resistin plays a role in carcinogenesis by signaling through toll-like receptor 4 and induction of PI3K cascade which stimulate nuclear factor kappa-light-chain-enhancer of activated B cells^[34,35]. This hormone also promotes cell survival and metastasis by inactivating pro-apoptotic proteins and enhancing the expression of intracellular adhesion molecule and vascular cell adhesion molecule^[36]. The role of resistin has been investigated in a number of cancers including colorectal, breast, prostate, and liver cancers^[37-40].

Besides, other adipokines, such as chemerin, omentin, nesfatin, and vaspin, have also been studied and reported to be associated with carcinogenesis^[10].

2.2. Insulin and IGF-1

Obesity is notoriously associated with insulin resistance, which significantly reduces insulin-mediated uptake of blood glucose in skeletal muscle and liver, resulting in an elevated blood glucose level which is described as hyperglycemia. Persistent hyperglycemia promotes increased insulin production by pancreatic beta cells^[41]. Hyperinsulinemia increases the risk of developing cancer both directly and indirectly through the IGF-1 pathway^[42].

Chronic hyperinsulinemia increases the availability of bioactive IGF-1 by upregulating hepatic IGF-1 synthesis. Meanwhile, hyperinsulinemia also downregulates the hepatic production of IGF-binding proteins (IGFBP)-1 and IGFBP-2 which block the binding of IGFs to their receptors^[43]. Both insulin and IGF-1 promote cell proliferation and suppress apoptosis^[44]. These cell growth-promoting activities are mediated by specific receptors called insulin receptor and IGF-1 receptor that are expressed both on normal and cancer cells^[42]. This process of promoting uncontrolled cell proliferation leads to growth of cancer cells, which explains the incidence of higher cancer risk seen in type 2 diabetic patients as a result of obesity. Various studies have also shown the positive association of insulin and IGF-1 pathway with cancers, especially colorectal, breast, and prostate cancers^[45].

2.3. Sex hormones

Obesity is associated with the production of endogenous sex hormones, such as estrogen, progesterone, and

androgens^[46]. Besides, the state of hyperinsulinemia and presence of free IGF-1 decreases the hepatic secretion of sex hormone-binding globulin resulting in an increased bioavailability of sex hormones. These hormones contribute to a higher cell proliferation and decreased apoptosis, leading to an increased risk of cancer. This pathway has been well established; for instance, increased incidence of postmenopausal breast cancer has been noted in obese females^[47]. Adipose tissue is the main source of estrogen production in postmenopausal women. As the body weight increases, the amount of breast tissue present in breast will also increase. The dysregulated factors in adipose tissue of obese individuals induce high expression of aromatase in breast which catalyzes one of the final steps in the biosynthesis of estrogen^[48]. Estrogen further stimulates proliferation of breast epithelial cells and ductal morphogenesis^[49]. High rate of proliferation may cause accumulation of replication errors, leading to mutation and development of breast cancer^[50]. Proliferating cells that have higher energy demand are associated with increased mitochondrial activity which can lead to an elevation of ROS. ROS can form DNA adducts that culminate in DNA damage which is carcinogenic^[51]. The presence of high level of estrogen also increases breast cancer progression and metastasis, as well as endocrine resistance, leading to a poor prognosis^[52].

2.4. Products of chronic inflammation

In an obese individual, the adipocytes interact with the surrounding immune cells to create a state of chronic systemic low-grade inflammation in the body. Products of chronic inflammation, such as cytokines, chemokines, leucocytes, prostaglandins, cyclooxygenase, lipoxygenase, ROS, reactive nitrogen species, and various transcription and growth factors, have shown to impact all stages of carcinogenesis from initiation, promotion, to progression^[53]. It is also postulated that adipose tissue in obese individual is infiltrated by macrophages^[54]. These adipose tissue macrophages also secrete inflammatory mediators, such as TNF- α and ILs -12, -18, and -133^[55,56]. TNF- α and ILs enhance carcinogenesis by increasing cell proliferation and angiogenesis^[57,58].

3. Obesity paradox in cancers

Recently, a phenomenon known as the obesity paradox has been reported by several researchers. Obesity paradox refers to a contradiction where an excess of body fats or high BMI is associated with a better survival in certain cancer patients, as opposed to malevolent impact such as heightened mortality^[59]. This concept is highly controversial and more studies in reference to the timing and methods for measuring adiposity are warranted^[60].

The timing for BMI measurement varies in different studies. Notably, three time points, i.e., before diagnosis, at the time of diagnosis, and after diagnosis, were widely

referenced. Many patients experience weight loss because of cancer-targeted therapies or cachexia as a result of cancer progression^[61]. These patients were associated with a lower BMI and poor survival as compared to their counterparts in good condition who are also in the similar stage of cancer. Hence, the timing for measuring adiposity is important as paradoxical findings could result if different time points are used. Meyerhardt *et al.* reported that weight loss after diagnosis that resulted in low BMI was associated with a worse cancer-specific mortality after evaluating the association between weight change and survival in 2781 patients with colorectal cancer^[62]. On the other hand, weight gain after diagnosis resulting in high BMI showed no significant effect on survival. The probable reason for this finding could be the decrease in muscle mass attributed to weight loss which may promote insulin resistance, resulting in a state of low-grade systemic inflammation and cancer progression^[62,63].

Using BMI to measure adiposity in most trials and clinical studies represents an important indication of obesity paradox that is worth mentioning. BMI that measures only the total body weight relative to height has an inherent limitation to discriminate between fat and lean body mass, which represents the mass of all organs, including muscles and bone, with the exception of fats. Therefore, an individual with a high fat-free mass (FFM) relative to height might have a high BMI, but the individual cannot be essentially categorized as obese^[64]. A meta-analysis of 31,968 individuals showed that in the identification of obese individuals, the use of BMI was coupled with good specificity but a poor sensitivity of only around 50%, suggesting that many individuals who were labeled as obese might not necessarily have excess adiposity^[65].

Adipokines and other factors released by adipose tissues could form the biological basis of obesity-related carcinogenesis and cancer progression. Accordingly, any persons with a high BMI due to high lean body mass will not be exposed to carcinogenic growth factors because the dysregulated adipocytes in excessive adiposity that secretes these factors are almost absent. Therefore, these individuals will not be at an increased risk of having cancer or dying from it. Furthermore, patients having a low BMI because of loss of FFM as seen in those with a sedentary lifestyle and cancer cachexia have been found to have worse clinical outcome and increased treatment toxicity. As compared to a sedentary lifestyle, high physical activity has a beneficial effects on health, including improvement of hyperinsulinemia and decreased production of inflammatory adipocytokines^[66].

Many elderly individuals with normal or even low BMI are subject to the underestimation of body fat, particularly those with pot belly, low muscle mass, and osteoporotic bones. On the contrary, merely based on the measurement results of high BMI, lean persons such as the athletes can be the victims of an overestimation of body fat because of high muscle mass. Thus, different methods,

such as (i) anthropometric parameters (e.g., abdominal circumference and skinfold thickness), (ii) dual-energy X-ray absorptiometry which measures total body fat mass, FFM, and bone mineral density, (iii) bioelectrical impedance analysis which estimates the total body water through the resistance of the body to a small alternating current, (iv) computed tomography scan, (v) magnetic resonance imaging, and (vi) densitometry, are required to measure both body fat and lean mass instead of using BMI alone to analyze the observed phenomenon of obesity paradox^[67-69].

Hence, understanding body composition such as adipose tissue and muscle as well as the limitation of BMI in obesity identification is instrumental in interpreting the reported phenomenon of obesity paradox in cancer since other than metabolism, fat and lean tissues also play their roles in carcinogenesis.

Conclusion

Metabolic alterations, biological factors released from dysregulated adipocytes, and surrounding stromal cells in obesity can initiate and promote the process of carcinogenesis. Large, clearly defined, prospective studies are required to investigate and delineate the underlying pathways, and unravel the role of the products of obesity, such as adipokines, sex hormones, IGF-1, and products of chronic inflammation, in cancer initiation and progression. These pathways and products of obesity could be the potential targets for preventing cancer development and improving clinical outcomes of obese cancer patients.

Conflicts of interest

The author declares no conflicts of interest.

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