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Interrelationship Between Obesity and Cancer (A Review)

Manmohan Singhal, V.R. Manchireddy Vishnu, S.V. Rama Raju and Yozana Upadhyay

School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India-302017

Abstract: Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight (pre-obese) if their BMI is between 25 and 30 kg/m^2 and obese when it is greater than 30 kg/m^2. Obesity increases the likelihood of various diseases; particularly heart disease, type 2 diabetes, obstructive sleep apnoea, osteoarthritis and certain types of cancer like colon, breast, endometrium, kidney and oesophagus are associated with obesity. Obesity and physical inactivity may account for 25 to 30 percent of several major cancers. The main mechanism involved in cancer cause is yet unknown but it may include alterations in sex hormones (e.g., estrogens, progesterone and androgens) and insulin and IGF-1 in obese people that may account for their increased risk for cancers. Sex-hormone binding globulin, the major carrier protein for certain sex hormones in the plasma, may also be involved in the altered risk for these cancers in obese people.

Key words: Cancer · Obesity · Body Mass Index · Insulin resistance · Leptin · Adepokines · Adiponectins

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. It is defined by BMI and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors. BMI is closely related to both percentage body fat and total body fat. In children, a healthy weight varies with age and sex. The WHO cut points for BMI and their corresponding interpretations are shown in Table 1. While the exact cut points are somewhat arbitrary, this BMI classification scheme was derived largely from observational and epidemiologic studies of BMI and disease outcomes and thus reflects the relationship of BMI to morbidity and mortality. 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 [1]. The international agency for research on cancer (IARC) report concluded that the avoidance of weight gain reduces the risk of developing cancers of the colon, breast (in postmenopausal women), endometrium, kidney (renal cell) and oesophagus (adenocarcinoma) [2].

Obesity-Related Cancers: Obesity has been consistently associated with higher risk of colorectal cancer in men (relative risks ~1.5–2.0) and women (relative risks ~1.2–1.5) in both case-control and cohort studies (Table 2) [2]. Similar relationships are seen for colon adenomas, with stronger associations between obesity and the incidence of larger colon adenomas [3]. A gender difference, in which obese men are more likely to develop colorectal cancer than obese women, has been observed consistently across studies and populations. The reasons for this gender difference are speculative. One hypothesis is that central adiposity, which occurs more frequently in men, is a stronger risk factor for colon cancer than peripheral adiposity or general overweight. Support for the role of central obesity in the development of colorectal cancer comes from studies reporting that waist circumference and the waist-to-hip ratio are strongly

Corresponding Author: Manmohan Singhal, Jaipur National University, Jaipur, Rajasthan, India, 302017.
Tel: +91-9829153193.

Table 1: Cutpoints of BMI for the classification of weight

BMI (kg/ m2)	WHO classification	Popular description
≤18.5	Underweight	Thin
18.5-24.9	Normal range	'Healthy', 'normal' or 'acceptable' weight
25.0-29.9	Grade 1 overweight	Overweight
30.0-39.9	Grade 2 overweight	Obesity
≥40.0	Grade 3 overweight	Morbid obesity

Table 2: Obesity Related Cancer

Type of cancer	Relative risk* with BMI 25-30 kg/m^2	Relative risk* with BMI of ≥ 30 kg/m^2	PAF (%) for US population‡	PAF (%) for EU Population
Colorectal (men)	1.5	2.0	35.4	27.5
Colorectal (women)	1.2	1.5	20.8	14.2
Female breast	1.3	1.5	22.6	16.7
Endometrial	2.0	3.5	56.8	45.2
Kidney (renal-cell)	1.5	2.5	42.5	31.1
Adenocarcinoma	2.0	3.0	52.4	42.7
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5-4.0	ND	ND
Gall bladder	1.5	2.0	35.5	27.1

related to risk of colorectal cancer and large adenomas in men [4]. Exogenous oestrogen (in the form of postmenopausal hormone therapy) reduces the risk o f colorectal cancer in women. However, this hypothesis is also quite speculative, as circulating levels of endogenous oestrogen are higher in obese men as well as obese women, compared with lean individuals [5] and oral intake of exogenous oestrogen could have different effects than endogenous oestrogen on the risk of colon cancer. Risk of breast cancer based on menopausal status- that heavier women were at increased risk of developing postmenopausal, but not premenopausal, breast cancer [2, 6]. In fact, among premenopausal women, there is consistent evidence of a modest reduction in risk among those with a high (≤ 28 kg/m2) BMI. This reduction in risk could be because of the increased tendency for young obese women to have anovulatory menstrual cycles and lower levels of circulating steroid hormones, notably of progesterone and oestradiol [7].

Obesity has been consistently shown to increase rates of breast cancer in postmenopausal women by 30–50% (Table 2). Some studies have found central adiposity to be an independent predictor of postmenopausal breast cancer risk. Both BMI and weight gain are more strongly related to risk of breast cancer among postmenopausal women who have never used hormone-replacement therapy, compared with women who have used hormones [8, 9]. Studies of mortality and survival among patients with breast cancer illustrate that adiposity is associated both with reduced likelihood of survival and increased likelihood of recurrence, regardless of menopausal status and after adjustment for stage and treatment [6, 10]. Very obese women (BMI ≤ 40.0 kg/m2) have breast cancer death rates that are three times higher than very lean (BMI < 20.5 kg/m2) women [11]. Endometrial cancer was the first cancer to be recognized as being related to obesity. There is convincing and consistent evidence from both case-control and cohort studies that overweight and obesity are associated strongly with endometrial cancer [2, 12]. The increase in risk generally ranges from 2–3.5 folds in overweight women (Table 2). Studies of populations worldwide have revealed that the risk of kidney cancer (specifically, renal-cell cancer) is 1.5–3 times higher in overweight and obese individuals [13]. In several studies, the increase in risk with increasing BMI was greater in women than in men [14], although at present this finding remains unexplained and was not confirmed in a review of published studies. Importantly, the obesity associated risk of renal-cell cancer seems to be independent of blood pressure, indicating that hypertension and obesity might influence renal-cell cancer through different mechanisms [13, 15]. 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 [16, 17].

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,

serum insulin levels increase to avert hyperglycaemia. Insulin up-regulates growth hormone (GH) receptors in the liver, which stimulates the hepatic production of IGF-1 [18]. 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. This fact might be explained by the inhibitory effect of high levels of insulin on the secretion of IGF binding protein (IGFBP)-1/2. 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 [19]. In obese subjects, free IGF-1 levels do not respond to insulin administration and tend to be higher than in lean subjects [20]. 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-1 can inhibit apoptosis and stimulate cell proliferation through several downstream signalling networks, including the phosphatidylinositol 3-kinase system and the Ras/Raf/ mitogen-activated-protein-kinase (MAPK) systems [21]. Interestingly, the expression of IGF-1 receptor is increased in some tumours, which suggests that these neoplasms may be stimulated by systemic levels of IGF-1. 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) [22]. Besides regulating glucose transport, insulin has mitogenic and anti-apoptotic properties mediated through pathways to some extent similar to those of IGF-1 [23]. This mitogenic, anti-apoptotic environment caused by increased serum levels of insulin and IGF-1 accelerates the stepwise accumulation of genetic mutations and thereby favours carcinogenesis. 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. Hyperinsulinaemia is also an independent risk factor for breast cancer in postmenopausal women and increases the risk of colorectal and endometrial cancer [24, 25]. In addition, diabetes mellitus, a disease characterized by insulin resistance, is associated with an increased risk of breast, colorectal, pancreatic and bladder cancer. 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 link.

Adipokines and Adiponectins: 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, an adipokine that is exclusively derived from adiposities, has significant anti-inflammatory and insulin-sensitizing effects [26]. Plasma concentrations of adiponectin are reduced in obesity 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. 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 [27]. Moreover, phosphorylation of the tumour suppressor, tuberous sclerosis complex (TSC) 2, by activated AMPK [28] and the subsequent inhibition of mammalian target of rapamycin may be an important downstream signalling pathway by which adiponectin counteracts carcinogenesis. Independent of AMPK activation, adiponectin decreases the production of reactive oxygen species (ROS), which may result in decreased activation of MAPK and thereby inhibition of cell proliferation [29, 30]. *In vitro*, adiponectin inhibits the growth of several breast cancer cell lines and induces apoptosis of myelomonocytic (leukemia) lineage cells. Adiponectin also has been shown to inhibit tumour angiogenesis *in vitro*. 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 [31]. 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 tumour formation and growth than are wild-type mice [32]. The accelerated tumour formation in mice without detectable adipokine levels suggests that adiponectin may protect against carcinogenesis. Thus, the decreased plasma levels of adiponectin in obesity 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 suggest that obesity is associated with leptin

resistance [33]. The findings of clinical studies of the relationship between systemic leptin levels and breast or prostate cancer are inconsistent, but an association has been reported for colorectal cancer and for endometrial cancer [34]. Interestingly, many colorectal, breast and endometrial cancers overexpress the leptin receptor ObR. Leptin has mitogenic effects in cancer cell lines, depending on the type of cancer: it stimulates the growth of breast, oesophagus and prostate cancer, but inhibits the growth of pancreatic cancer cells [35]. 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 [36].

PAI-1: PAI-1 is a serine protease inhibitor produced by adipocytes, endothelial cells and stromal cells in visceral adipose tissue [37]. PAI-1 is not only produced by adipose tissue, but also affects adipocyte differentiation and insulin signalling [38]. Moreover, PAI-1 inhibits uPA, which acts as an inducer of fibrinolysis and extracellular matrix degradation and is associated with tumour cell invasion and metastasis. Paradoxically, PAI-1 is involved in tumour growth, invasion, metastasis and angiogenesis by interacting with vitronectin, integrins and other components of the uPA system and by affecting the extracellular matrix [39]. Over-expression 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. In addition to autocrine production by tumour cells, systemic levels of PAI-1 appear to be essential for its tumour-promoting effects [40]. Treatment with PAI-1 inhibitor of Min mice, which have a defect in the adenomatous polyposis coli (Apc) gene, suppressed intestinal polyp formation. 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. This hypothesis supports the role of PAI-1 in promoting cell migration and tumour angiogenesis [41].

Inflammation: It is well recognized that inflammation is involved in the promotion and progression of cancer. For example, local chronic inflammation is seen in inflammatory bowel disease and Barrett's oesophagus, disorders that carry an increased risk of colorectal cancer and oesophageal adenocarcinoma, respectively. In fact, malignant lesions could be referred to as inflamed, because the tumour microenvironment contains a variety of leukocytes and inflammatory factors [42]. 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 and weight loss leads to a decrease in CRP concentration, whereas weight gain leads to an increase in CRP concentrations [43, 44]. Raised serum levels of CRP are correlated with an increased risk of cancer. 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. Several of the proinflammatory factors in obesity are believed to be involved in carcinogenesis (Fig. 1). TNF-α is involved in carcinogenesis and cancer progression. TNF-α binds to its primary receptor, TNF-R1, a downstream signalling cascade leads to activation of nuclear factor kappa B (NF-κB). This in turn leads to the up-regulation of several negative regulators of apoptosis, such as c-FLIP and cIAP1, which promote cell survival. TNF-α has been reported to have tumour-promoting activity in various experimental cancers and a variety of tumour cells produce TNF-α [45, 46]. 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 tumour progression. Whether increased systemic levels of TNF-α, as seen in obesity, act through the same signalling network to promote tumour 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 [45, 47]. Systemic TNF-α might also be involved in the early development of some tumours, as a recent study showed elevated TNF-α levels to be associated with an increased risk of colorectal adenomas [48].

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. Systemic levels of IL-6 are elevated in obesity and, akin to TNF-α, systemic levels of IL-6 are correlated with overall cancer death and increased risk of

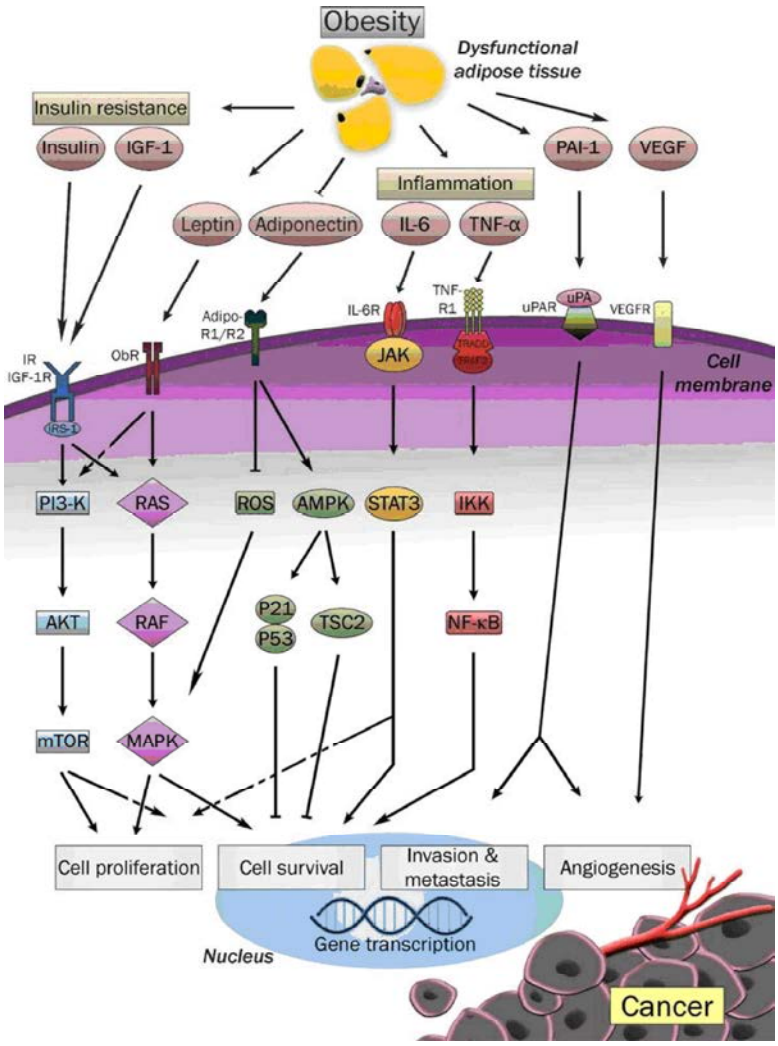

Fig. 1: Potential pathways directly linking obesity with cancer

cancer precursor lesions. In addition, levels of the IL-6 promoter genotype have been associated with several haematological cancers [48, 49]. 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 pathways [50]. Obesity-induced inflammation involves other inflammatory components that could contribute to the development of cancer. These components include matrix metallo-proteinases (MMPs), which are associated with cancer-cell invasion and metastasis [51]. 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 [52]. Oxidative stress, as part of chronic inflammation, may also create a microenvironment favourable to tumour development in obesity [53].

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. 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). 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 [54]. 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 [11, 55]. The proliferative effect of estrogen on epithelial tissue of both breast and endometrium is believed to be the underlying mechanism.

CONCLUSION

Even though Obesity is one of the factor in causing Cancer, but the exact mechanism is not clearly known, but is mainly due to adipose tissue dysfunction, alterations in sex hormones such as estrogens and androgens. Other mechanisms are related to insulin and related growth factors, adipokines, other metabolic and growth factors, inflammatory factors, altered immune response and oxidative stress, relative to all phases of cellular growth and cell death. Avoidance of weight gain reduces the risk of developing cancers of the colon, breast (in postmenopausal women), endometrium, kidney (renal cell), oesophagus (adenocarcinoma) and prostate cancer.

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