

Obesity and cancer: what's the interconnection?

Abstract

Obesity is one of the most prevalent nutritional diseases, associated with chronic morbidity and mortality. Persuasive evidence indicates a striking association between obesity and incidence of common neoplasms, such as those of the esophagus, endometrium, kidney and breast in post menopause women, prostate in men, in addition to colon, rectum and bladder. Such an association has been supported by clinical and laboratory experiments on humans and animals, respectively. The findings have revealed that obesity and increased body fatness, in general and visceral adiposity, in particular, increase the vulnerability to develop different cancers. Although the impact of obesity in cancer progression differs according to the type of cancer, all the obesity-related cancers are centered around body adiposity. This review highlights the different hormonal, biochemical and molecular changes that might be involved in obesity-related cancers. Increased serum insulin, insulin-like growth factor, steroids "sex hormones" and the disturbances in adiponectin and leptin hormones are included. Biochemical and metabolic changes that mediate obesity-related carcinogenesis involving elevated oxidative stress and inflammation levels in the body and the concomitant increment in circulatory proinflammatory cytokines are discussed.

Keywords: adipokines, cancer, inflammatory cytokines, insulin resistance, obesity

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Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; CRP, c-reactive protein; FASN, fatty acid synthase enzyme; IGF-1, insulin-like growth factor-1; WHR, waist hip ratio; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; VEGF, vascular endothelial growth factor; PAI, plasminogen inhibitor; PAF, platelet activating factor; SIP, sphingosine-1-phosphate; LPA, lysophosphatidic acid; PCB, polychlorinated biphenyls

Introduction

Obesity is one of the most deleterious diseases and amongst the most common etiological factors for chronic diseases and related deaths.¹ Obesity is defined as an excess accumulation of body fat and it is the amount of this excess fat that correlates with ill-health.² Increase in body mass over the acceptable limits compared to the height, expressed in terms of body mass index (BMI) is a popular measure of obesity. Accordingly, BMI (kg/m²) of 25.0-29.9 indicates overweight, 30.0-34.9 grade I obesity, 35.0-39.9 grade II and 40 or more grade III or morbid obesity, respectively.³ Cancer is simply "unregulated cell division". Such division is totally different from any other natural division in normal cells. Cancerous cell has its unique features that do not exist in any other body-growing cells such as wart.⁴

From the above definitions of obesity and cancer, one can speculate that there may be a connection between accumulation of body fat and the random, out-of-control cell division is explained through this review. During the last two decades, the number of studies related to obesity and cancer has escalated dramatically.⁵ The current mini-review will attempt to address the interconnection between obesity and cancer of those types that are mostly related to obesity. Also, it aims at explaining the hormonal, biochemical and cellular mechanisms that mediate carcinogenesis process in obese individuals.

Methods

This mini-review is based on plethora of sound scientific studies

generated from multiple search engines through electronic websites such as PubMed, Science Direct, Google Scholar, Wiley Online Library, Springer, EBSCO and many other scientific search engines during the period of January 2014 until May 2014. Relevant research articles as well as meta-analyses were searched using electronic databases. Searching terms used were "obesity, overweight and cancer" and "obesity, overweight and neoplasms" to identify research papers and review articles on relationship between obesity and cancer or different neoplasm's. The first step in screening for inclusion was based on the title, followed by the screening of the abstract and then the full text. The reference lists of short-listed articles were further screened for relevance and duplication was avoided.

Results

Obesity-cancer connection

It has been noticed that there is a close link between the increase in obesity rates and development of different cancers in some European countries.⁶ This urged scientists to explore the underlying link and identify its mechanisms. Behaviour and lifestyle of obese patients were risk factors attributed to cancer incidence. Obese patients suffer from four dietary and lifestyle behavioural changes including increased dietary energy intake, increased intake of saturated fats, decreased intake of vegetables and fruits and reduced physical activity levels.⁷ Besides, four metabolic changes occur inside the body and contribute to the development of cancer: oxidative stress and the damage it causes to DNA; hormonal stress represented by an increase of anabolic hormones like insulin, steroid sex hormones and insulin-like growth factor-1 (IGF-I); increased level of inflammatory intermediate components; and increase in other biological factors linked to cancer such as C-Reactive protein (CRP).⁸

On the other hand, a decrease in total energy intake contributes to limiting cancer incidence as evinced in experimental animals.⁹ Further, human studies revealed that individuals who fast for specific periods and reduce energy intake have less chances of cancer incidence, less

likely to suffer from other chronic diseases and their life expectancy increases as compared to those who do not observe fast.¹⁰

According to the American Institute for Cancer Research (AICR), obesity increases the risk of developing the following types of cancer by 25-33%: colon, oesophagus, prostate, kidney, uterus lining and breasts after menopause.¹¹ Body size and shape are considered direct indicators of body fat content.¹² This is also linked to the extent and severity of cancer incidence.¹³ Researchers found a close link between body mass index (BMI) and increase in different cancer types; risk increases steadily with the increased index value. Among the earliest findings for the correlation between body fatness and cancer risk, Waist-hip ratio (WHR) was directly related to the risk for developing breast cancer and risk increased 6 times in females with WHR>0.80.¹⁴

Later, other studies confirmed similar findings and reinforced the relationship between the increased BMI and increased risk for developing of different types of cancer.^{15,16} Large prospective studies showed a significant association with obesity for several cancers and the International Agency for Research on Cancer has classified the evidence of a causal link as 'sufficient' for cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell) and esophagus (adenocarcinoma).¹⁷

The effect of obesity on cancer is associated with the increase in production of anabolic hormones in the body; such as insulin, growth hormone and sex hormones.¹⁸ These hormones are responsible for body cell growth and division; hence, contribute to the growth of cancer cells.¹⁹ Obese menopausal women have been found to have higher percentage of circulating oestrogen that is produced from adipose tissue. In turn, oestrogen stimulates the growth of body cells including cancer cells, making those women at higher risk for developing cancer.²⁰

Following section provides a brief description of the role of obesity in the development of common types of obesity-related cancers:

Colorectal cancer: Substantial evidence is established that the incidence of colon and rectum cancers in developed or industrial countries is almost ten times higher than reported in developing countries, which clearly indicates a close relation of ecological and nutritional factors with cancer occurrence.²¹ Nutritional behaviour reflects social and economic life directly, thereby making nutritional variations responsible for a considerable difference in the incidence rates between developing countries and industrially advanced countries.²² Recently, it has been established that obesity is a significant risk factor for developing colon and rectum cancers.^{23,24} In a comparative study on two groups of colon and rectum cancer patients, results revealed that BMI and blood glucose levels were higher in colon cancer patients as compared to control group.²⁵ Western diet is characterized by its high fat content; especially saturated fats, energy and red meat, while low content of vegetables and fruits, legumes rich in dietary fibre, folic acid and calcium.²⁶⁻²⁸

An experimental animal study confirmed the role of obesity causing high energy meals in colon cancer incidence and demonstrated that giving high fatty meals served in western restaurants to the experimental animals, led to a marked increase in cytokine level of TNF- α type in the colon of animals. This type of cytokine is linked with the increase of carcinogenesis in colon. Thus, this explains the high incidence of colon cancer in countries that are most affected with obesity.²⁹

Pancreas cancer: Pancreatic cancer is the ninth most common cause

of cancer with 277,000 new cases diagnosed in 2008 worldwide, accounting for about 2.2% of all cancer cases.³⁰ Epidemiological studies have suggested that overweight and obesity are associated with increased pancreatic cancer risk. The evidence that body fatness increases pancreatic cancer risk was considered conclusive in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report in 2007.³¹ However, more recent reviews of the evidence suggested an increased risk among women with higher BMI but not among men.³² In their systematic review on the relationship between body weight, waist circumference, BMI and abdominal fat with pancreas cancer incidence, Aune et al.,³³ showed a positive association between these anthropometric indexes (especially total body fat and abdominal fat) and pancreatic cancer, implying that obese and overweight individuals were more exposed to cancer incidence than those with normal weights.³³

Breast cancer: Breast cancer is the second most prevalent female cancer in the world. It is caused by the interaction of genetic and environmental factors. Among the latter, diet has attracted considerable attention, as it is a modifiable risk factor and thus offers an opportunity to design preventive strategies.³⁴ A considerable variation was found in breast cancer incidence between developed and developing countries. Nutritional factors and lifestyle behaviour play a significant role in this variation.³⁵ It was found that the girl's age of puberty was connected to the nutritional status and nutrients level in her body because malnutrition in childhood and pre-puberty leads to delay in puberty for girls. On the other hand, over-nutrition and increase in dietary energy intake before puberty leads to early puberty and high chances of cancer incidence due to prolonged exposure periods to oestrogen hormone.³⁶

Other studies illustrated that obesity increases the possibility of the disease emergence in postmenopausal women to 50% as compared to the non-obese women, which may be due to the role of obesity in increasing the level of free estradiol in obese women.³⁷ Further, studies demonstrate that women who are overweight or obese at the time of breast cancer diagnosis are at increased risk of cancer recurrence and death as compared to leaner women; some evidence suggests that women who gain weight after breast cancer diagnosis may also be at increased risk of poor outcomes.³⁸

Endometrial cancer: Endometrial cancer is the most common gynecologic malignancy in the Western world and is strongly associated with obesity.³⁹ The incidence of endometrial cancer increases three times in obese women as compared to women with normal weight, attributed to the role of obesity in disturbing hormone regulation.⁴⁰ Evidence from case studies indicates that fruits and vegetables consumption can reduce the incidence of endometrial cancer in contrast to high fat foods, especially the saturated fat.⁴¹

Renal cancer: Epidemiological evidence indicates a positive association between obesity, expressed as BMI and risks of kidney disease outcomes. Wang et al.,⁴² estimated 24.2% and 33.9% of kidney disease cases among United States men and women, respectively and 13.8% in men and 24.9% in women in industrialized countries could be related to overweight and obesity.⁴² Further, it has been found that obesity increases the risk for renal diseases in the general population; association appears to be more significant in women than in men and that obesity adversely affects the progress of kidney diseases among patients with kidney-related diseases.⁴² Researchers have found that increased body weight is the most affective behavioral factor in renal cancer incidence that can be reduced through weight control and fat reduction.⁴³ Further, research findings in the United States indicated

that obesity and overweight are directly responsible for the death of one out of seven males and one out of five females who die because of renal cancer.¹⁶

Prostate cancer: Prostate cancer is the second most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality among men worldwide.⁴⁴ Obesity and prostate cancer affect substantial proportions of Western society. Epidemiologic and mechanistic findings represent a mounting evidence of an association between obesity and prostate cancer. Several studies showed a strong association between overweight or obesity in men and the increasing incidence of prostate cancer, metabolic imbalances after prostate surgery or radiotherapy, complications after hormone therapy and deaths in obese prostate cancer patients as compared to their normal weight counterparts.⁴⁵ Biochemical changes linked to the incidence of prostate cancer have been characterized by the increase in adipokines and represented in the high levels of vascular endothelial growth factor (VEGF), interleukin IL-6, tumor necrosis factor TNF- α and high blood levels of insulin and estrogen and low levels of adiponectin and androgen.⁴⁶

Ovarian cancer: Ovarian cancer remains the leading cause of death from gynecological malignancy.⁴⁷ Epidemiological studies have revealed a strong association between obesity and ovarian cancer and that the risk of developing ovarian cancer increases rapidly in the presence of obesity and overweight in women.⁴⁸ In an analytical scientific review, 24 out of 28 scientific studies confirmed a statistically significant positive relation between obesity and ovarian cancer.⁴⁹

Role of adipose tissues in cancer development

Until recently, adipose tissue was considered as a metabolically inactive tissue. However, recent advances unraveled that adipose tissues are metabolically active and possess a list of physiological and biochemical functions. Visceral adipose tissue has been termed as an endocrine organ, in part, because it secretes adipocytokines and other vasoactive substances.⁵⁰ These adipokines mediate the inflammatory interactions and produce hormones that affect metabolism. For example, leptin hormone secreted from adipose tissue plays an important role in weight control and fat storage in the body.⁵¹ Experimental studies demonstrated association between leptin activity and colorectal cancer.⁵² Experimental studies on colon cancer cells *in vitro* have shown the ability of adding leptin in stimulating cell division and reproduction; thus increasing speed of carcinogenesis and accelerating growth of malignant tumor.⁵³

Recent evidence revealed that both fat content as well as fat distribution in the body affect the risk of developing cancer. As mentioned, visceral fat is more metabolically active than adipose tissue in other body parts and produces hormones and cytokines that mediate inflammation and carcinogenesis processes. It has been reported that increase in visceral adipose tissue above the normal level (represented by waist circumference >102cm in men and >98cm in women) is a risk factor in esophageal cancer and, to a lesser extent, colorectal cancer.⁵⁴ A strong association was reported between adipose tissue in the abdominal area (visceral fat) and increased levels of inflammatory markers leading to cancer initiation as a result of the imbalance in the counter-regulating hormones such as leptin and adiponectin.⁵⁵ Leptin and adiponectin were found to be inversely associated with body weight changes: those with higher body weights have higher levels of leptin, while those with lower body weight have higher adiponectin levels.⁵⁶

Further, researchers found that obesity causes an increase in the size and number of fat storing adipocytes, increase in the number of macrophages that mediate inflammatory process, as well as leptin and inflammatory cytokines such as TNF- α , IL-6 and plasminogen inhibitor PAI1, along with a decrease in adiponectin level. It is clear that increased inflammation, increased availability of lipids, insulin signaling and changes in adipokines may contribute to the conversion of epithelia to a malignant neoplasm and that the levels of cytokines such as TNF- α , IL-6 and plasminogen inhibitor (PAI), all mediate the inflammation and carcinogenesis processes.⁵⁵

Body fat induces not only cancer by virtue of its adipokines secretory function, but also causes metabolic changes that affect the level of fat in blood, which, in turn, help in cancer development.⁵⁷ It was found that cancer cells synthesize fat internally by increasing the production of fatty acid synthase enzyme (FASN), which is responsible for fat synthesis and storage in the cancer cell in anticipation of the likely coming division. The high level of FASN is an important indicator of the process of carcinogenesis, as observed in different types of cancer cells including that of breast, ovaries and prostate cancers and in primary cells of colon, stomach, esophagus and oral cavity cancers.⁵⁸

Due to a disorder in fat metabolism that occurs inside the cancerous cells, cytokine production is increased, representing an indication of carcinogenesis.⁵⁹ Further, production of leptin increases and adiponectin decreases from adipose tissue cells. The former disorder represents a risk because leptin is considered an anabolic hormone that increases the frequency of cell division and inflation, while the latter provides a sort of cell-division inhibition. Disturbance in these hormones leads to carcinogenesis and increases the frequency of tumor and incidence of cancer.⁶⁰ The more the fat forming activity in cancerous cells increases, the higher the level of free fatty acids; acting as a stimulator to a series of cellular interactions associated with the process of carcinogenesis through transition to fatty compounds at the molecular level such as platelet activating factor (PAF) and sphingosine-1-phosphate (S1P), lysophosphatidic acid (LPA), prostaglandins.⁵⁷

Another role for the adipose tissue in the long process of human carcinogenesis is through its role as a storage site for chemical toxins and carcinogenic chemical compounds.⁶¹ Adipose tissue is an optimum site for such toxins in the body, especially the fat soluble ones. High level of adipose tissue as in obese patients implies storing more of carcinogens, releasing them in large quantities to reach the damaged tissue and prolonging the process of carcinogenesis, thus leading to a malignant tumor.⁶² Toxins and chemical carcinogens are also spread in the atmosphere and surrounding humans such as chlorinated pesticides and polychlorinated biphenyls (PCB) used in generators and conductors of electric power. It has been found that most affected types of cancer are prostate cancer and cancers of the immune system (lymphoma). Obese and non-obese persons are affected by these chemical carcinogens due to the existence of the adipose tissue in both cases.⁶³

Role of insulin resistance in cancer

The link between insulin and obesity on one side and cancer on the other was highlighted in many epidemiological studies establishing a connection between the incidence of type II diabetes, obesity and cancer.⁶⁴ Hyperinsulinemia and insulin resistance represent the most prominent attributes in patients with type II diabetes. Further,

physicians of cancer patients with concurrent type II diabetes noted that these patients have a lower response to chemotherapy than non-diabetic cancer patients, their cancer complications were more advanced and they improved less after periods of cancer treatment than the non-diabetic cancer patients. Thus, concluding a direct connection between the incidence and development of cancer on one hand and high level of insulin hormone and insulin resistance on the other.⁶⁵

Epidemiological studies indicate that chronic high levels of insulin and insulin-like growth factor seen in obese people are connected to the high incidence of cancer, particularly colorectal cancer.⁶⁶ This connection has led to the assumption that one-third of cancer types that occur among men in modern human societies, especially Western ones, are attributed to dietary patterns and energy balance, which in turn affect the level of insulin in blood. The same applies to women, as one study concluded that weight loss of 20 pounds (40.4kg) or more in a group of post-menopausal women led to a reduced risk of breast cancer in them. This was attributed to the role of weight loss in reducing anabolic insulin hormone in blood.⁶⁵

To investigate the role of insulin as a cancer-inducing hormone, researchers tested the effect of insulin and sulfonylurea (compound that stimulates insulin production from beta-cells in the pancreas) and their role in cancer development in patients with type II diabetes in comparison with metformin (compound that inhibits hepatic glucose production). Results of cohort and retrospective studies showed that taking insulin and sulfonylurea were linked to cancer deaths among type II diabetics, unlike those who took metformin solely or in conjunction with the two above drugs.⁶⁷ Results on laboratory animal studies have shown that injecting animals with insulin increased the rate of cell division, thus increasing the chance for carcinogenesis.⁶⁸

Moreover, it has been found that obesity results in increasing the circulating concentrations of insulin and possibly IGF1 and IGF2. This increase in insulin and IGF1 leads to a cascade of signaling pathway reactions that end with increased cellular proliferation, increasing cell-division rate, survival of the cancer cell and disturbing apoptosis.⁶⁹

Discussion

Obesity has been recognized as a leading cause in the development of a list of major and highly prevalent cancers throughout the globe. Increased caloric intake above the body requirements and subsequent accumulation of extra calories in the adipose tissue represent the primary underlying factor in the obesity-driven cancers. Adipose tissue is being recognized as a source of adipokines that trigger the molecular signaling pathways ending into inducing carcinogenesis. The secretory role of adipose tissue, along with its ability to store chemical pollutant carcinogens, poses a major concern for the dietitians, oncologists and physicians in terms of body fat content and its distribution in the body. Obesity, a culprit in cancer initiation and development, emphasizes the importance of treating obesity as a front line strategy in the battle against cancer and necessitates fighting obesity as an early strategy in preventing cancer at initial stages.

Conclusion

Obesity is associated with increased risk of many types of cancers involving various mechanisms. A better understanding of mechanisms linking obesity to the cancer initiation, development and progression is important in order to develop strategies for prevention of obesity and cancer and to improve outcomes in obese cancer patients.

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Conflict of interest

The author declares no conflict of interest.

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