Obesity as an Important Risk Factor for Certain Types of Cancer

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Abstract

Cancer could be described as the uncontrolled and unrestricted growth of malignant cells in any place of the body. It is a multifactorial disease which either heredity or environmental factors (such as nutrition, physical inactivity, alcohol, obesity, exposure to sun, environmental pollutants, infections) chip in incidence of cancer. In recent years, several researchers have focused on obesity as a potent cancer risk factor. Scientific evidences have suggested that obesity has associated with increased risk for a plenty of different types of cancer. The evidences are the most consistent for endometrial cancer, breast cancer between the postmenopausal women, and renal cell cancer. More contradictory results have reported about the colorectal, prostate, and pancreatic cancer. Although numerous studies have done according to the obesity and cancer relation or joint, but The molecular mechanisms in which obesity could increase the risks of cancer, have been poorly understood.

Keywords: Neoplasms; Obesity; Adipocyte; Adipokines; Adiponectin

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Introduction

Cancer is a dynamic and long-term process which could be considered as a group of diseases with at least this common characteristic: uncontrolled and invasive cell growth and proliferation [1]. Cancer has occurred when cell proliferation has been more than cell death, leading to an unrestricted division, then expanding of malignant cells in the body [2, 3].

Cancer is one of the most defined concerns of global health, as well as one of the most major cause of death, all over the world. It has accounted for more than 7 million deaths each year. Both genetic and environmental factors chip in the incidence and development of cancer. However genetic defects could approximately be responsible for 10% of the all cases of cancer, the environmental factors have comprised approximately 90%. The most important environmental risk factors of cancer, have included lifestyle associated factors (smoking, alcohol, nutrition and dietary habits, sedentary lifestyle, obesity, and excessive exposure to sunlight) as well as pollution, then viral and bacterial infection [4, 5].

Obesity is excess accumulation of adipose tissue in the body. It occurs when energy intake is more than energy expenditure within a long period of time. Obesity has regarded as a multifactorial disorder with a complex phenotype. Genetics and lifestyle-dependent factors (long-term excess energy intake more than body requirement and physical inactivity) could be the main obesity determinant . Of course the other causes of obesity social factors and metabolic and neuroendocrine alterations should be mentioned [6- 8]. The ability of storing calories in the form of adipose tissue was a crucial feature for human to survive during nutritional deprivation conditions [6]. But unfortunately today obesity has become epidemic in developed world [9] also in many developing countries [10].

Obesity correlates with the incidence of various chronic diseases especially some types of cancer

[11]. But this relation has appeared differently, because nowadays together with the rapid increase rate of children obesity prevalence, the risk of cancer incidence would be increased in their adulthood [12].

Recently, many investigators have been studying the impact of obesity on cancer. The findings of the research were inconsistent even among the patients whose suffering from the same cancer due to the cancer stage or cancer grade and diagnosis period of time [3]. This article has reviewed the effect of obesity on the risk of the cancer incidence and prevalence, then the probable mechanisms. The effects of obesity on cancer risks have described as below and in Figure.1.

Table 1 has indicated selective publications on the relations between the obesity with cancer.

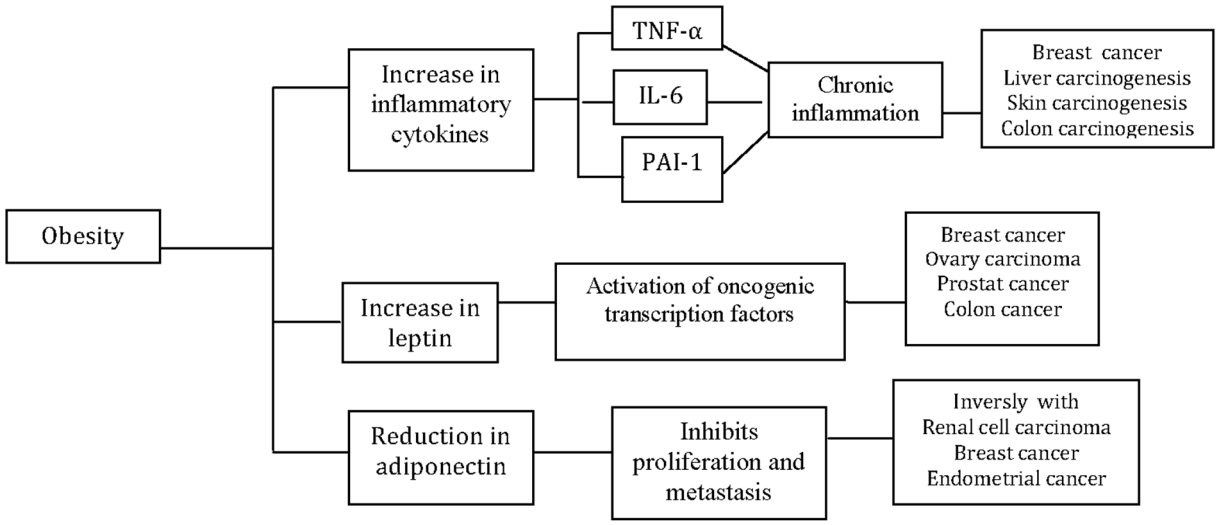

Figure 1. It shows the obesity and cancer relationship.

Table 1. Selected publications on obesity and cancers relationship

Type of caner	Mechanisms	eferences
Renal cell carcinoma	- Obesity cause to increased level of estrogen that effects on growth and proliferation of renal cells.	[71]
Colorectal cancer	- Steroid hormones - Chronic inflammation	[70, 65]
Breast cancer	- Decrease of sex hormone-binding globulin - Hormonal factors	[63, 64]
Pancreatic cancer	- Chronic inflammation - Hormonal factors	[70, 56]
Prostate cancer	- In obesity endogenous estrogen and progesterone increases and cause to inhibition of prostate cancer growth and metastasis.	[54, 55]
Endometrial cancer	- Decrease of sex hormone-binding globulin - Hormonal factors	[50, 51]

Properties of Adipose Tissue

Adipose tissue is a heterogeneous organ which consists of various types of cells. This tissue divided to White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT) , with different functions. WAT has located in subcutaneous layer, omentum and retroperitoneum. This adipose tissue mainly has considered as an energy reservoir which stores excess body energy in the form of *triglyceride* and increased during obesity. BAT has found in cervical and supra cervicular , and adipose of energy through thermogenesis. Both two types has divided to adipocytes and stromal-vascular section. Adipocyte has included of lipid-laden adipocyte and the stromal-vascular section including preadipocyte, endothelial cells and macrophage

and other immune cells. All types of cells in both sections could altered the metabolic hemostasis of the organ. So changes in the biology of adipocyte or non-adipocyte (in stromal-vascular section) could increased the risk of cancer in obesity [6, 13, 14].

Effects of Increased Adipose Tissue

Adipose tissues possess two main roles in the body [3]: storing excess calories as lipid [6], and having active role in endocrine signaling to other sites of the body [6, 13].

Previous studies have been shown that adipose tissues have secreted molecules signaling to the other metabolic organs and brain [15]. Probably some of these molecules have possessed a role in modulating the risk of cancer development (adipokines molecules such as leptin, adiponectin, proinflammatory molecules) [6].

Size and number of adipocyte cells have increased in obesity. These changes in adipose tissue have increased the leptin and inflammatory cytokine levels, and then have reduced the adiponectin secretion [6]. Below we have discussed some of the effects of adipokines and inflammatory cytokine on cancer:

Secreted Molecules From Adipose Tissue Inflammatory Cytokines

Inflammatory cytokines were the first polypeptides which have revealed from adipose tissue. They have exerted a systemic role in metabolic *hemostasis*. In vitro and in vivo research has shown the levels of the inflammatory cytokines such as Tumor Necrosis Factor-α (TNFα), Interleukin-6 (IL-6), and Plasminogen Activator Inhibitor-1 (PAI-1) raise obesity [16].

Actually these cytokines have secreted by monocytes [17] and other immune cells. These immune cells have infiltrated adipose tissue in obesity [18]. The increased cytokines have caused chronic inflammation, which this inflammation has correlated with cancer incidence through various mechanisms [19].

TNF-α and Cancers

TNF-α is a cytokine that has been known as a modulator in endotoxin-induced tumor necrosis [20]. It has related to incidence and development of various cancers through activation of angiogenesis and metastasis [21, 22]. TNFα is necessary for azoxymethane-induced colon carcinogenesis also chemically induced skin and liver carcinogenesis [23-25]. The increased TNFα levels in obese rodent and humans have shown relation between obesity and tumor genesis [26, 27]. Removing TNFα signaling by deletion of its receptor gene has abrogated the ability of high-fat diet to promote liver carcinogenesis [28]. In contrast, removing this receptor in lean mice has not caused any effect on liver carcinogenesis [29]. This data has outstand the importance of relation between TNFα in obesity and cancers.

IL-6 and Cancer

One of the major pro-inflammatory molecules that has produced in adipose tissue is the cytokine IL-6 [30]. Circulating IL-6 levels has correlated with BMI [31], and adipose tissue has thought to account for up to 35% of circulating IL-6 in healthy subjects [32].

IL-6 has sent signals to nucleus through STAT3. IL-6 could bind to interleukin-6 (IL-6) receptor, and could activate JAK–signal Transducer and Activator of Transcription (STAT) signaling through STAT3 [6]. STAT3 was an oncoprotein which could be important in cancers risk [33]. The activation of STAT3 has increased in tumors that have grown in obese animals [28].

PAI-1 and Cancer

PAI1 is the primary inhibitor of the plasminogen activators urokinase and tissue plasminogen activator, and has been produced at high levels in adipose tissue. Plasminogen is the precursor of the extracellular protease plasmin, and is a key component for metastasis and angiogenesis [34, 35]. Activation of plasminogen might result to increased extracellular remodeling, which is a key process in cancer development [36, 37]. High levels of PAI-1 have correlated with poor outcome in breast cancer in human [38]. PAI-1 inhibitors could decrease risk of polyp formation in Adenomatous Polyposis Coli (APC) mice [39]. Increased expression of PAI1 in obesity might increase the vascularization and invasiveness of tumors, although this has not been formally demonstrated [6].

Leptin and Cancer

Leptin is an adipocyte-derived hormone that regulates appetite and energy homeostasis [40]. Several studies have shown Leptin Receptors (LEPR) expressed in several cancers like prostate, breast and colon [41-43]. Leptin levels have correlated with obesity in human [44]. Previous studies have demonstrated that this hormone has related to

increased incidence of cancer in obesity [6]. Many studies on leptin and cancer relation have shown different results. For example in an analysis of Greek men, after adjusting for *Body Mass Index* (BMI), leptin has not correlated with prostate cancer incident [45].

The results of a large scale study in Scandinavian men have shown relation between leptin levels and prostate cancer risk, although this was accurate for intermediate levels, but not at all for the higher levels [46].

Also the results of a regression analysis of women in Massachusetts, USA have shown that leptin has not associated with increased carcinoma in situ of the breast [47]. By contrast, the results of analysis of Japanese women with colorectal cancer have indicated that leptin has associated with increased risk, independently of BMI [48]. Leptin has caused stimulation growth of colonic epithelial cells, cancer cells in breast, prostate and ovary [49-52].

Adiponectin and Cancer

Adiponectin is another adipokine that might have a role in cancer. Adiponectin levels have reduced in obesity. Adiponectin acts on a number of tissues to regulate glucose and lipid metabolism [53]. Several studies have suggested that: adiponectin had antitumor effects [6].

Adiponectin secreted from adipocytes has bound to its own receptors (ADIPOR1 and ADIPOR2), and inhibits proliferation and metastasis. Adiponectin has increased the conversion of ceramide to sphingosine-1-phosphate, which had a variety of effects on apoptosis and insulin resistance, possibly via AMP-Activated Kinase (AMPK) [6]. Prospective analyses have shown adiponectin levels have inversely associated with breast cancer risk in postmenopausal women [54]; endometrial and renal cell carcinoma [55].

However in later prospective study, adiponectin levels were not predictive for the endometrial cancer risk [56]. The results of study have shown that using a case-control design, a Single Nucleotide Polymorphism (SNP) in the 5′ region of adiponectin has been found in association with colorectal cancer risk [57].

Relation Between Obesity and Cancers

Endometrial Cancer

The relation between obesity and endometrial cancer was obvious in both case-control and follow-up studies particularly in postmenopausal women [58,59]. For example, a case-control study about the prevalence of obesity on women affected with this malignant tumor in Mexico City has shown this relation [60, 61]. The results have demonstrated that obesity has occurred in 77 % (Odds Ratio [OR] 8.1, 95% Confidence Interval [CI] 2.46-26.6); diabetes mellitus in 41 % (OR:4.3, CI:1.31-14.7); and systemic arterial hypertension in 41% (OR: 2.3, CI: 0.78-7.1). So, they have concluded that obesity was the most frequent risk factor for these women with endometrial cancer [61].

These relations have based on hormones. Endometrial epithelial cells has stimulated by high levels of estrogen. This stimulation has not suppressed by progesterone and so, it has caused to cancer [62].

Obese women had more levels of estrogen and estradiol in their serum [63]. This was because of aromatization of androstenedione in the adipose tissue. Also, obese women had lower levels of sex hormone-binding globulin so estrogen levels increase [64].

Prostate Cancer

According to previous studies, there is a positive but weak association between obesity and prostate cancer. For example, the results of meta analyses have demonstrated the relation between BMI and weight and moderately increased risk of advanced disease but there was low association with risk of localized disease. Although this results has seen about weight just among cohort studies [65].

In addition, Swedish workers studies have shown the positive association between BMI and weight and risk of prostate cancer [66]. In a prospective study, in Japanese-American men have shown positive relation between prostate cancer and muscle area, not fat area [67].

In obesity, endogenous estrogen and progesterone have increased, then caused to inhibition of prostate cancer growth and metastasis. So, obese men with prostate cancer had better prognosis than those with normal weight [68].

Pancreatic Cancer

There is a positive relation between obesity and pancreatic cancer. For example, the meta analysis of 21 prospective studies have reported a relative risk of pancreatic cancer per 5-unit increased in BMI of 1.16 in men and 1.10 in women [69]. In a case-control study, there were positive correlation between overweight (BMI: 25-29.9) and obese

individuals (BMI>30) and risk of pancreatic cancer [70]. Also, the results of several studies have shown the relation between obesity and pancreatic cancer [71, 72].

Obesity is one of the few modifiable risk factors that has associated with increased risk of pancreatic cancer, which has related to increased risk of diabetes, a condition which has been associated with pancreatic cancer development. The recent data has shown that nearly 70% of United States adults are overweight or obese, a clarification of the complex association between obesity and pancreatic cancer might disclose targets for prevention and intervention to decrease incidence and improve prognosis of this highly fatal disease [71].

In one population-based case-control study in Urban Shanghai, 908 patients with pancreatic cancer and 1067 normal controls, aged 35-79 years, have recruited. The results have demonstrated that energy density has positively associated with pancreatic cancer risk (OR: 1.16 per unit increase; 95% CI: 1.07, 1.27; $P < 0.001$). In this case-control study, dietary energy density has positively associated with risk of pancreatic cancer [72].

Breast Cancer

Several studies have shown that obesity increases risk of breast cancer especially in postmenopausal women [73]. For example, the results of a study in women from 7 different countries have shown risk of breast cancer increased with body mass, in low and moderate-risk countries, among premenopausal women, but in postmenopausal women the risk increased in all groups [74]. Probably breast cancer has affected by distribution of body fat. When central adiposity increases, the risk of breast cancer has increased in postmenopausal women particularly when there is a family history of breast cancer [75].

Also, breast cancer patients had more visceral fat compare to subcutaneous fat than control groups [76]. In several studies it has approved that increasing of body mass correlated with poorer survival [77].

Breast cancer has strongly affected by hormonal factors. Diversities in metabolism of steroid hormone cause to different effects on obesity and breast cancer in pre- and postmenopausal women [75]. Before menopause, ovaries are the main source of production of estrogen and after menopause secretion of estrogen has reduced. Instead of that, estrogen has produced in adipose tissue (because of aromatization of androstenedione). This happening is important in obese people. Other factors like decrease of sex hormone-binding globulin enhance risk of breast cancer [78].

Breast cancer would be initiated from epithelial tissue in mammary. Because this tissue is near to adipose tissue of mammary gland, which influence each other [79].

Colorectal Cancer

Many studies have shown changes in regulation of energy hemostasis has related to colorectal carcinoma. There is positive relation between increase in body size and colorectal cancer [80]. Colon and rectum cancer have considered together as a colorectal cancer, but rectum and colon were different in some properties [81]. So they should be studied separately.

The results of study have shown an increase of 25% in body weight has associated with rectum cancer in men and women but correlated with colon cancer just in men [82]. Although BMI has correlated with risk of colonic adenomas positively in both men and women, but it has not related to rectal adenomas in women. Also waist circumference and waist-to-hip ratio have related to colon adenomas in men [83]. In addition, another study has shown an increase in the risk of colon cancer in person who had unfavorable energy balance, physically inactive, more energy intakes, and large BMI [84].

In general, men have greater risk for colorectal cancer in comparison to women, because men have possessed greater tendency to store fat in abdomen than women [85].

Renal Cell Carcinoma

Various studies have indicated that renal cell carcinoma has associated with obesity [86- 88]. According to epidemiological studies, obesity is an effective risk factor of renal cell cancer [86].

The results of cohort study which have analyzed 592 men and 263 women with renal cell cancer, during a median follow-up of 10 years, have shown high levels of BMI among men and women have associated with increased risk of renal cell cancer [87].

A case-control study and a multicenter study have shown body weight strongly affected on renal cancer particularly in women in comparison to men. This strong relation among women has resulted from increased level of estrogen which affect growth and proliferation of renal cells by

receptors of renal cells or through paracrine growth factors [89].

Conclusion

The increasing prevalence of obesity in many parts of the world has emphasized the importance of learning more about the relationship between obesity and cancer and the mechanisms involved in their interaction which have reviewed in this article.

In conclusion, obesity has associated with increased risk for different types of cancer. The evidence has been most consistent for endometrial cancer, breast cancer in postmenopausal women, and renal cell cancer. More variable results have reported for colorectal, prostate and pancreatic cancer.

Possible mechanisms which have affected in association of obesity and risk of cancers include alteration in hormonal patterns such as sex hormones and distribution of fat in body. The evidence have suggested that combination of factors which have secreted by the adipocyte, such as increasing leptin, decreasing adiponectin and increasing inflammatory cytokine secretion resulted in the increasing incidence of cancers.

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Conflict of Interest

The authors have no conflict of interest in this article.

Authors' Contribution

This article has written in collaboration between all authors. Dr Sayed Hossain Davoodi and Saeideh Esmaeili have designed and revised the study. Talieh Malek-Shahabi has contributed to the literature review and writing-up process. Dr Ali Malekshahi-Moghadam and Roghieh Shahbazi have helped in writing and overall correction of the manuscript. All authors have read and approved it finally.

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