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Influence of excessive body weight on cancer development and prognosis

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Abstract

Introduction and purpose
According to the WHO, overweight and obesity are defined as excessive or abnormal accumulation of adipose tissue, leading to deterioration of health. Excessive body weight is a constantly growing public health problem that has reached the scale of a pandemic. Currently, there is ample evidence that excess body weight increases the risk of developing cancer and worsens the prognosis. The aim of this review is to analyze the impact of overweight and obesity on cancer development and prognosis, and to elucidate pathogenesis.

State of knowledge
Based on the current state of knowledge in epidemiology, it is estimated that approximately 20% of all malignancies are related to excessive body weight. So far, there is sufficient evidence to support an association between excess body fat and 13 out of 24 cancer sites: esophagus, gastric cardia, colon, liver, gallbladder, pancreas, postmenopausal breast, endometrium, ovary, kidney, meningioma, thyroid and multiple myeloma. Adipose tissue cells produce growth factors, hormones and cytokines that can interfere with the regulation of cell growth and survival. Excess adipose tissue leads to systemic chronic inflammation, oxidative stress, insulin resistance, hyperinsulinemia, increase in sex hormones, increase in leptin levels and a decrease in adiponectin levels. This leads to DNA defects, stimulation of angiogenesis, cell proliferation and inhibition of apoptosis, and thus promotes the development of cancer. In addition, studies have estimated that excess body weight is responsible for 14% of cancer deaths in men and 20% in women.

Conclusions
Due to the increasing problem of obesity and cancer worldwide and the proven causal relationship between these diseases, it is necessary to intensify nutrition education and promote a healthy lifestyle in order to minimize excessive body weight, and thus reduce the incidence of cancer.

Key words: cancer, malignancy; overweight; obesity; carcinogenesis

INTRODUCTION AND PURPOSE

According to the WHO, overweight and obesity are defined as excessive or abnormal accumulation of adipose tissue, leading to deterioration of health. Excessive body weight is a constantly growing public health problem that has reached the scale of a pandemic. As reported by World Health Organization (WHO), over 1.9 billion (39% of the population) adults were overweight in 2016, of which over 650 million (13%) were obese [1]. Risk of cancer is strictly tied to obesity. There is ample evidence that being overweight increases the risk of developing cancer and worsens the prognosis. Excessive body weight is considered the second major factor of getting sick with cancer, after smoking. According to The International Agency for Research on Cancer (IARC) data, high BMI can cause nearly half a million cases of cancer per year. Study conducted by IARC emphasizes that excessive body weight caused about 3.6% of all diagnosed cancer cases in 2012 [2]. The population attributable fraction of high body mass index (BMI) with respect to obesity-related cancers is 11.9% in men and 13.1% in women. [3] Obesity can interfere with the effective delivery of systemic cancer therapy compromising the efficacy and response to treatment. Excess body weight increases the risk of side effects and infections during treatment [4]. Moreover, studies have estimated that excess body weight is responsible for 14% of cancer deaths in men and 20% in women [5]. In 2016, the International Agency for Research on Cancer (IARC) found sufficient evidence to support the association between excess body fat and 13 out of 24 cancer sites: esophagus (adenocarcinoma), gastric cardia, colon, liver, gallbladder, pancreas, postmenopausal breast, endometrium, ovary, kidney, meningioma, thyroid and multiple myeloma [6]. Recent reports indicate an increase in the incidence of cancer related to overweight and obesity in people aged 20 to 49. Due to the significant increase in the incidence of obesity and overweight in young adults and children, there is a justified concern about the increase in the incidence of cancer in these age groups [7].

STATE OF KNOWLEDGE

Mechanisms linking increased body mass with the induction of neoplastic processes

Pathomechanisms responsible for the development of cancer in people with excessive body weight are very complex. Adipose tissue cells produce many growth factors, hormones and cytokines that can interfere with the regulation of cell growth and survival. Adipose tissue is an endocrine organ that produces and secretes both pro-

inflammatory substances (TNF-α, IL-6, visfatin, resistin, IGF, sex hormones) and anti-inflammatory substances (adiponectin, IL-1, IL-10). In physiological conditions, with a normal body weight, a balance is maintained between pro-inflammatory and anti-inflammatory factors, which determines the positive effect of substances secreted by adipose tissue on the functioning of the body and maintaining homeostasis. With excessive body weight, there is an advantage in the secretion of pro-inflammatory substances, which determines the formation of chronic inflammation and insulin resistance [8].

Obesity is a state of chronic subclinical inflammation. Substances secreted by adipose tissue stimulate chemotaxis of immune cells, which then continue the cascade by producing cytokines and chemotactic factors that recruit and activate effector cells. In particular, factors such as platelet-derived growth factor, transforming growth factor β, monocyte chemotactic protein 1 (MCP-1), interleukin (IL) 1β, tumor necrosis factor α (TNF-α) attract mononuclear cells. Once established, these progenitor cells differentiate into mature macrophages, which take on a major role in the production of cytokines and growth factors. These macrophage products have profound effects on the local microenvironment, including the stimulation of angiogenesis [9]. Many pro-inflammatory cytokines increase tumor necrosis factor (TNFα) levels and IL-6, which are important cytokines in cancer development. Factor tumor necrosis by binding to the TNF receptor activates nuclear factor (NF-kB nuclear factor), blocking apoptosis and increasing proliferation of cancer cells. Interleukin 6 sends signals to the cell nucleus via a signal transformer signal transducer to transcription activator 3 (STAT3), an activated oncoprotein in many neoplastic tumors [10].

C-reactive protein is the main diagnostic marker of inflammation. Research has shown that an increase in circulating C-reactive protein (CRP) is associated with an increased risk of colorectal cancer, and in particular, genetic variation in the CRP gene has been shown to influence the risk of developing colorectal cancer [11]. High levels of CRP have also been shown to increase the risk of ovarian cancer in overweight women [12].

Oxidative stress and lipid dysregulation in obese individuals can result in elevated levels of reactive oxygen species (ROS), which can cause oxidative DNA damage. Reactive oxygen species contribute to inefficient DNA repair and genetic instability. Damage to the genetic material of cells plays a key role in the initiation and progression of cancer [13].

Obesity and excessive body fat leads to an increase in sex hormones. The stimulating effect of estrogens on carcinogenesis in breast, ovarian and endometrial cancer is well known. Aromatase activity is stimulated by pro-inflammatory factors derived from adipose tissue (IL-1β, IL-6, prostaglandin E2, and TNFα) and insulin growth factor-1 (IGF-1). In addition, excessive body weight decreases sex hormone binding globulin (SHGB), which causes an increase in biologically active hormones. Excess weight gain in men and postmenopausal women is thus associated with significant increases in adipose-derived aromatase activity, estrogen production, and systemic estrogen bioavailability, which may partly explain the increased risk of several gynecological cancers associated with obesity in postmenopausal women [14,15].

Excess body weight and chronic inflammation causes insulin resistance and hyperinsulinemia. Hyperinsulinemia stimulates the production of IGF-1 and reduces hepatic expression of IGF-binding proteins, which leads to an increase in the level and bioavailability of IGF-1. Both insulin and IGF-1 can stimulate in vitro tumor cell proliferation. Insulin activates ERK and PI3K signaling pathways to promote tumor growth, loss of epithelial integrity, and metastasis. IGFs promote tumor growth, migration, and invasion, and IGF-1 also stimulates HIF-1α, which corresponds with metastasis of some tumors [14]. Numerous epidemiological studies and in vivo studies have shown a significant impact of insulin resistance and hyperinsulinemia on the development of cancer [16]. Epidemiological studies indicate that elevated levels of insulin and IGF-1 contribute to the growth of colorectal, pancreatic, liver, postmenopausal breast and endometrial cancers [17]. It has been shown that up to 90% of breast cancer cells have increased expression of IGF and insulin, and the concentration of both substances is 10 times higher in breast cancer cells than in healthy ones breast cells [18].

Fat tissue leads to an increase in leptin levels and a decrease in adiponectin levels. The cause of adiponectin deficiency and leptin increase in obesity is the inhibition of its production by inflammatory cytokines, mainly IL-6 [19]. Adiponectin exhibits anticancer activity by inhibiting inflammation, proliferation, atherogenesis, angiogenesis, and insulin resistance. Adiponectin stimulates AMPK (AMP-activated protein kinase), which inhibits mTOR, and thus inhibits cell proliferation and tumor growth. AMPK has the ability to inhibit tumor growth by upregulating the p53 axis, reducing cyclin D1 levels, and inhibiting cyclin-dependent kinases, leading to G1 inhibition of the cell cycle. Adiponectin also stimulates the tumor suppressor LKB1, which contributes to the prevention of metastasis. Low levels of adiponectin are associated with an increased risk of many cancers [16,20]. Leptin is a peptide hormone secreted by adipose tissue, which in physiological conditions performs important functions in the body, such as appetite control and energy homeostasis. However, excess leptin promotes inflammation and activates several oncogenic pathways such as JAK/STAT, MAPK and PI3K/AKT. The leptin receptor belongs to the family of class 1 cytokine receptors and has been shown to play a key role in the pathogenesis of many types of malignancies. Leptin-leptin receptor signaling plays an important role in promoting several processes involved in cancer progression, including cell proliferation, metastasis, angiogenesis, and chemoresistance. Recent studies indicate that leptin receptors are abundant in many types of

cancer [21,22]. Systemic levels of leptin and adiponectin thus show a completely opposite effect on tumor development. A higher ratio of leptin to adiponectin is associated with a greater risk of cancer [23].

Correlation between excessive body weight and cancer incidence

In 2012, a population-based study was conducted to determine the global burden of cancer attributable to high body mass index. The study included cancers reported by the World Cancer Research Fund as having sufficient evidence to attribute a causal relationship with excessive BMI. These include kidney, pancreatic, gallbladder, endometrial, ovarian cancer, postmenopausal breast cancer, esophageal adenocarcinoma, and colorectal adenocarcinoma. In 2012, there were 481,000 new cases of malignant neoplasms attributable to excess body weight, which accounted for 3.6% of all malignant neoplasms. The incidence was higher in women (345,000) than in men (136,000) [24]. Obese women have a significantly increased risk of developing breast cancer. The recurrence rate of this cancer is also increasing in this group of women [12]. An estimated 18,639 cancers diagnosed in France in 2015 were linked with excessive body weight, which corresponds to 5.3% of all cancers diagnosed. This included 4,507 cases of postmenopausal breast cancer and 3,380 cases of colon cancer [25]. An increase in BMI of 5 kg/m2 contributes to a 7% increase in the incidence of NHL and an increase in NHL mortality by as much as 14% [26]. Based on a study conducted in Canada, it was estimated that in 2010, 9,645 cancer cases, which accounted for 5.7% of all registered cases in adults over 25 years of age, were associated with excessive body weight. The most diagnosed cases of cancer related to excessive body weight were colon, kidney and prostate cancer in men and cancer of the uterus, breast and colon in women [27]. A national survey of American adults found that the proportion of cancers attributable to excess body weight ranged from 3.9% to 6.0% among men and from 7.1% to 11.4% among women. It is estimated that approximately 37,670 cases of cancer in men (4.7% of all cases) and 74,690 cases of cancer in women (9.6%) aged 30 years or older in the United States each year were attributable to excess body weight between 2011-2015 [28]. A Canadian study found that men who gained ≥21 kg after the age of 20 were 60% more likely to develop colorectal cancer than men who gained only 1–5 kg. In addition, a study of Austrian adults showed a direct link between weight loss and a reduced risk of colon cancer in men [29].

The influence of excessive body weight on prognosis in malignant tumors

In the USA, a study was conducted to analyze the impact of excessive body weight on the risk of death due to cancer. Patients with the highest body mass index (BMI ≥40) had 52% higher rates of mortality from all cancers for men and 62% higher for women compared to women and men of normal weight. Death rates from cancers of the esophagus, colon, liver, gallbladder, pancreas, kidney, non-Hodgkin's lymphoma, and multiple myeloma were significantly higher in overweight patients In addition, higher BMI values were associated with a higher risk of death from gastric and prostate cancer in men and from breast, uterine, cervical and ovarian cancers in women. Studies have estimated that excess body weight is responsible for 14% of cancer deaths in men and 20% in women [30]. A retrospective cohort study conducted to examine the association between bariatric surgery and cancer-related mortality found that overall cancer mortality was reduced by 46% in gastric bypass patients compared to non-surgical controls, demonstrating perfectly the association of obesity with mortality in cancer [31]. Obese women are 2.5 times more likely to die from breast cancer than women with normal weight. According to research, an increase in body mass index by 5 kg/m2 increases the risk of death by 17% [12]. Obese men appear to be at greater risk of developing biologically aggressive prostate cancer, and are also more likely to have advanced disease when prostate cancer is diagnosed [4]. A recent study found that high childhood BMI was independently associated with increased overall cancer mortality in adulthood. Moreover, the association of BMI in childhood and subsequent cancer mortality persisted regardless of BMI in adulthood [32].

Conclusions

Overweight and obesity are well-known risk factors for cancer, and their incidence continues to increase worldwide. Due to the well-proven impact of obesity on the development of cancer, anti-cancer prophylaxis should be considered, consisting in preventing and combating obesity, especially that this problem is increasingly affecting young people. Continuation of the current patterns of weight gain in the population will lead to a further increase in the burden of cancer in all age groups in the future. Moreover, it is worth noting that excess body weight in patients with malignant tumors significantly worsens prognosis. It increases the malignancy of tumors, contributes to the formation of metastases, and worsens the response to anti-cancer treatment. Treatment of excessive body weight should be an integral part of anti-cancer treatment in order to

improve the prognosis in oncology patients. However, this should be done under professional supervision to avoid malnutrition, which can also worsen the prognosis**.**

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