Obesity, inflammation, physical inactivity and risk for cancer.

Clévia Santos Passos[1]*, Rosemara Silva Ribeiro[2], Thiago Santos Rosa[3], Rodrigo Vanerson Passos Neves[3], Adalberto Alves Martins Neto[4]

[1]Heart Institute, InCor, FMUSP, Sao Paulo, Brazil
[2]Medicine, Division of Nephrology, Federal University of Sao Paulo, São Paulo, Brazil
[3]Graduate Program in Physical Education, Universidade Católica de Brasília, Taguatinga, DF, Brazil
[4]University of São Paulo (USP), School of Medicine and Cancer Institute of São Paulo (ICESP), Brazil

Abstract

Excess adipose tissue in the body is a prevalent public health problem in many parts of the world. Sedentary lifestyle and obesity are among the risk factors that isolated or associated with other risk behaviors, which increase chance of developing of cancer, type 2 diabetes and cardiovascular diseases and can reduce life expectancy. The purpose of this literature review was to analyze evidences for the effects of obesity, of physical activity and cancer. Were searched English-language Medline and PubMed publications about the involvement of the effects and mechanisms that obesity, comorbidities and sedentary lifestyle may contribute to the development and progression of cancer. Scientific evidence shows that exercise has beneficial effects on disease prevention and has also become an important adjuvant in health promotion. Therefore, imbalances of pro-inflammatory and anti-inflammatory molecules linked to adipose tissue are positively associated with risk of chronic diseases. Physical exercise used as a therapeutic approach is a strategy that will contribute to primary and secondary prevention of diseases, especially if combined with other therapies that control risk factors for the development of cardiovascular and oncological diseases in overweight or obese individuals.

Keywords: Obesity, Cancer, Physical inactivity, Exercise physical, Inflammation.

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Overweight and obesity are a major problem of public health worldwide, it is estimated that in 2013, more than 2.1 billion people were overweight [1]. Obesity can be defined as the excessive accumulation of body fat, which generally occurs when energy intake exceeds expenditure [2]. There are multiple factors that can trigger obesity, including genetic and environmental factors such as physical inactivity and high fat intake [3].

Overweight is considered significant risk factor for development of various complications such as insulin resistance, diabetes, dyslipidemia, fatty liver, hypertension, heart disease and cancer [4,5], these comorbidities often result in morbidity and mortality. Overweight is associated with an increased incidence of various cancers: esophagus, liver, endometrium, ovary, kidney, and pancreas, it is estimated that in 2012, over 8 million people died of cancer [5,6].

Adipose tissue is an endocrine organ and immunomodulator, which has the main function to store lipids [7,8]. The excess of visceral adipose tissue is associated with increased flux of free fatty acids, via the hepatic portal vein for liver tissue, determining factor for insulin resistance, defined by the reduced response to insulin by the tissues peripherals [3,9].

Insulin resistance and growth factor similar to insulin (IGF-1) may partly explain the relation between obesity and cancer. The interaction of insulin and IGF-1 with its receptor induces cell signaling mediated by the insulin receptor substrate (IRS), leading to activation of pathways (Ras/Raf/MAPK and PI3K/Akt/mTOR) that are cascades of signaling proteins in which effector kinases-such as Raf, MAPK, Akt, mTOR- are phosphorylated and activated to transduce signals from the extracellular milieu to the nucleus where specific genes are activated for cell growth, division and differentiation, and on the other hand to inhibit cell apoptosis [7,10]. The expression of IGF-1 receptor is unregulated in several types of cancer [10-12], demonstrating the participation of this mechanism in tumorigenesis.

Adipose tissue is a dynamic endocrine organ that secretes different proinflammatory cytokines and other factors that activate reactive oxygen and nitrogen species production (RONS) [13]. RONS causes damage in DNA, proteins and lipids, besides produces mutagenic metabolites. In addition, chronic increase of tumor necrosis factor α (TNF-α), interleukin-6 (IL-6) and Plasminogen Activator Inhibitor-1 (PAI-1) in obese individuals is associated with breast, liver, skin and colon cancer [13]. Obesity-induced hyperleptinemia activates oncogenic transcription factors that increase the chances of developing ovarian, prostate, colon and breast cancer and the reduction of adiponectin levels in obesity are inversely related to breast cancer, renal and endometrial carcinoma [14].

Furthermore, the vascular endothelial growth factor (VEGF) plays an important role in the genesis of cancer in obese individuals. The expansion of adipose tissue induces a number of changes, including

tissue hypoxia, which in turn leads to increased hypoxia-inducing factor (HIF-1α) [8]. The HIF-1α is an important factor in the development and growth of several cancers [7,15]. Furthermore, the increase of HIF-1α contributes to increased expression of VEGF [15,16]. It is known that VEGF plays an important role in tumorigenesis induced angiogenesis and metastasis [15,17].

Another relevant factor is the inflammation. It´s known that the obesity provides a state of low-grade chronic inflammation. A recent study has demonstrated that obesity induces an inflammatory microenvironment in bone marrow that primes mesenchymal stem cells (MSCs) to adipogenesis [18]. Furthermore, obese adipose tissue is characterized by T-helper 1 (Th1)-type immune environment based on its cell surface markers and cytokine profile secretion heavily reliant on interferon-gamma (IFN-γ), in which classically activated macrophages (M1 macrophage phenotype polarized in the presence of IFN-γ or lipopolysaccharide and which promote the generation of a Th1-type immune response via the secretion of proinflammatory cytokines), Th1 polarized cells ($CD4^+$ T lymphocytes that can mediate a cellular immune response through the secretion of IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-beta) along with the other immune cells and activated adipocytes support the metabolic changes associated with obesity [19].

Accumulation of CD8+ T cell in obese adipose tissue initiate and propagate inflammatory cascades, including the recruitment of monocytes and macrophages and their subsequent differentiation, migration and activation in this tissue [20]. It has been established through of gene expression analysis a correlation of body mass with the expression of multiple genes characteristic of macrophages, suggesting that the macrophages content of adipose tissue is positively correlated with adiposity [21].

Interestingly, mechanisms by which macrophages are enriched in adipose tissue during weight gain are being unraveled. For example, studies investigating cell-to-cell adhesion contacts, the secretion of soluble factors and microvesicles have demonstrated as adipocytes can regulate the accumulation and phenotypic switch of macrophages during the pathogenesis of obesity. Adipocyte-derived microvesicles can modulate macrophage polarization toward a pro-inflammatory M1-like state [22]. Cell-to-cell contact between preadipocytes and macrophages partially induces the phenotype conversion from preadipocyte into typical macrophages, as noted by the acquisition of high phagocytic activity as well as expression of macrophage-specific antigens in those cells [23].

As a result of this local inflammation in adipose tissue, circulating levels of inflammatory cytokines are altered. In fact, it has been shown that elevated expression of pro-inflammatory markers such as, C-reative protein (CRP), TNF-α, IL-6 and leptin contributes to the progression of obesity and other chronic metabolic conditions [24-26].

A better understanding of the molecular mechanisms of disease pathogenesis will be important to conduct more effective therapeutic approaches. Currently, few studies have examined the impact of anti-inflammatory nutrients on obesity-associated metabolic-inflammation [27]. In addition, physical activity programs for obesity treatment are able to reduce body fat mass, waist circumference, visceral adipose tissue, serum levels of inflammation and oxidative stress markers, improve insulin resistance and hepatic inflammatory condition [28].

Interestingly, a combined aerobic and resistance physical activities program was able to reduce fatigue and improve quality of life in cancer survivor [29] and to reduces blood pressure and the measurement of the waist circumference [30]. Although some studies that exist are inconclusive and controversial results, untreated hypertension has been linked to the increases the risk of developing of certain cancers, including prostate [31] and renal [32]. Recent meta-analysis reported that in women in post-menopausal stage, high blood pressure is associated with increased risk of breast cancer [33].

However, uncontrolled high blood pressure appears risk to increase to cancer when is associated with higher body mass index (BMI), but controlling hypertension may lower the risk of kidney cancer [34]. Recent evidence indicates that the long-term, renal dysfunction, angiogenic and growth factors appear to increases the risk of developing renal cell carcinoma [32,35].

Aerobic training can reduce resting blood pressure levels, and improve insulin sensitivity, body composition, with a reduction of visceral adipose tissue and systemic inflammation during treatment of cancer [36]. Furthermore, exercise reduces the adverse effect of the antitumor treatment to modulate the behavior of macrophages and monocytes [37].

Sedentary lifestyle is among the risk factors that isolated or associated with other risk behaviors, have a high risk of developing chronic diseases and reduced life expectancy [38]. Exercise has been shown to be an effective adjuvant strategy in the treatment of cancer patients. During cancer therapy, exercise has played an important role related to side effects of medications for the treatment of cancer, improved fatigue, physical performance, associated with musculoskeletal conditions and cardiovascular [36].

The exercise used as therapeutic approach is a strategy that will contribute to the primary prevention of diseases and health promotion [38]. Scientific evidence report that regular exercise increase life expectancy with improvement of components of health related fitness and reduce the risk factors caused by disease [38,39]. Thus, is important encourage regular exercise practice at all stages of life, as well as new researches should always advance understanding of the beneficial mechanisms of exercise in health and disease.

In summary, dysfunctional adipose tissue in obesity increases proinflammatory mediators and chronic inflammatory states are associated with thus cancer. So, the prevalence of sedentary, obesity and associated comorbidities, in the world population is worrisome. Further research should focus particularly on the intervene in primary care, because it is a multifactorial and complex disease, it needs to be managed by a multiprofessional team that can to prevent the increase of cases of obesity or reduce this epidemic that poses health risks in population, including cancer control. There is evidence that regular physical exercise contributes to the combat against obesity, sedentary lifestyle and chronic diseases.

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***Correspondence to:**

Clévia Santos Passos
Instituto do Coração HC/FMUSP
Av. Dr. Enéas de Carvalho Aguiar
Bairro Cerqueira Cesar
São Paulo
Brasil
Tel: +55-11995570466
E-mail: cleviasp@gmail.com