

Investigating the relationship between obesity and cancer

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Abstract. Cancer has been a leading cause of death worldwide, and the role of obesity in cancer has become an alarming issue in recent years. Although the direct mechanism between obesity and cancer remains incompletely understood, the correlation between the carcinogenic disorders caused by obesity and the substantial number of obese patients shows the connection between the two. The chemicals produced from cells during inflammation, known as reactive oxygen species, can damage the DNA of normal cells, potentially causing cancer. Diseases associated with obesity such as Type II diabetes can also lead to inflammation from insulin resistance based on the presence of inflammation markers. This paper reviews connections between obesity and cancer by analyzing peer-reviewed literature over the past 20 years investigating with a focus on the mechanism of the carcinogenic disorders caused by obesity.

Keywords: Obesity, Cancer, Type II diabetes, Carcinogen.

1. Introduction

Obesity has been an emerging risk factor for various diseases, including diabetes, cardiovascular diseases, and cancer. Obesity has become prevalent reaching 41.9% in 2017 in the United States (US) alone [1]. According to World Health Organization (WHO), a body mass index (BMI) over 25 kg/m² is considered overweight, while BMI over 30 kg/m² is considered obese [2]. Obesity has turned into an epidemic with 4 million mortalities in 2017 from obesity-related disorders [2]. From 1975 - 2016, the prevalence of overweight or obese children from the age of 5-19 years increased from 4% to 18% [2]. According to the Centers for Disease Control and Prevention (CDC), 1 in 5 children in the US struggle with obesity [3]. The World Obesity Federation estimates that by 2020, around 770 million individuals will be affected by obesity, with numbers likely to reach one billion by 2023 [4]. Each year, obesity imposes a financial burden on society costing the US health system an estimated 173 billion dollars [3]. Obesity can lead to all causes of mortality, including type 2 diabetes, hypertension (high blood pressure), sleep apnea, breathing problems, coronary heart disease [5], and potential causes of cancer. Multiple factors, including easy access to high-calorie and low-nutrient food, a sedentary lifestyle, and an irregular sleep schedule have contributed to the higher prevalence of obesity worldwide [6]. Previously, obesity was considered a “rich people's disease” due to the excessive food available for people with higher income; however, as high-calorie products, such as fast foods and junk foods have become more widely available in recent years, obesity does not necessarily relate to social status; instead, it has become an epidemic proportion for all. Multiple factors, such as education and socioeconomic status can influence the prevalence of obesity as it has been shown individuals with college-level education

tend to have a lower prevalence of obesity than people without a college-level education [1]. This may be influenced by financial resources and time available to afford a healthier lifestyle.

Cancer is the second leading cause of death worldwide leading to roughly 10 million deaths yearly [7]. Obesity consists in about 4-8% of cancer patients, including breast, colorectal, esophageal, kidney, gallbladder, uterine, pancreatic, and liver cancer (Figure 1) [8].



Figure 1. Different types of cancer have a higher risk of occurring from obesity.

In a prospective study focusing on the 57,145 deaths caused by cancer among 900,000 adults in the US who were free of cancer in 1982, the death rates from all cancers combined were 52% higher for men and 62% higher for women in those with a BMI equal to or exceeding 40, compared to individuals of normal weight [9].

Cancer is a disease caused by uncontrolled and abnormal cell division. Cancer cells grow independently from the growing signal, ignore the stop signal, evade apoptosis, trigger angiogenesis, and undergo metastasis allowing them to move to other blood vessels causing damage to the whole body [10]. The newly formed cancer cells divide abnormally which means that they do not function as normal cells, and they compete with normal cells for nutrients. While the mechanism of obesity causing cancer has not yet been well understood, obesity increases mortality rates and influences treatment choices [10].

This paper explores the relationship between cancer and obesity, providing an overview of the characterization of cancer, and investigating the role of obesity as a risk factor for cancer, strategies to reduce the obesity burden, and its future impact on healthcare.

2. Methods

The research was conducted from scholarly sources including Google scholars, the National Center for Biotechnology Information (NCBI), the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the National Institutes of Health (NIH). The search was mostly limited to papers published in English over the past 20 years that were focused on the following keywords for research: "Obesity", "Cancer", "Diabetes", "Diet", "Nutrition", "Oncogene", "Growth factor", "Receptor protein", "Metabolism". Studies were included within the following criteria: (a) focused on the epidemiology of obesity and cancer, (b) were published in peer-reviewed journals or conference proceedings. Studies with a primary focus on specific populations (e.g., individuals with obesity and cancer) were also included if they provided relevant insights for the research topic. The figures were created using Biorender.

3. Results and discussion

Obesity has become one of the major epidemic issues in the world causing health challenges and leading to a higher chance of having diseases such as cancer. Adiposity, chronic low-grade inflammation, and hyperinsulinemia are essential factors of obesity that play a crucial role in tumor onset [11]. Even though

some levels of fat are required for normal body function, patients with obesity tend to have an abundance of visceral fat [12] and excessive fat can lead to serious health problems including long-lasting inflammation. Additionally, obesity can also lead to elevated levels of insulin, insulin-like growth factor, and sex hormones, which contribute to the development of cancer [13]. The risk of cancer increases with the more excess weight a person gains and the longer a person is overweight.

Obesity can be classified according to metabolic phenotypes into four phenotypes: Metabolically unhealthy non-obese (MUNO), Metabolically unhealthy obese (MUO), Metabolically healthy non-obese (MHNO), and Metabolically healthy obese (MHO) [14]. (Figure 2) Compared with individuals with MUO, patients with MHO are characterized by lower liver and visceral fat, but higher subcutaneous leg fat content, greater cardiorespiratory fitness and physical activity, insulin sensitivity, lower levels of inflammatory markers, and normal adipose tissue function [15].

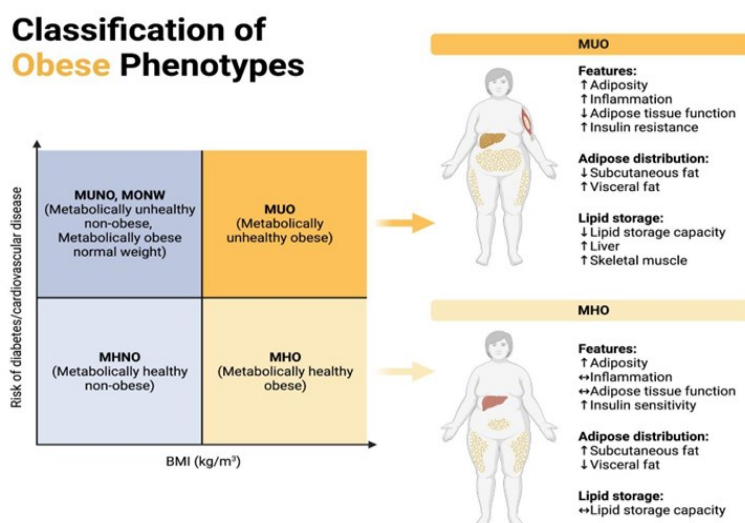


Figure 2. Classification of obese phenotypes with demonstrations of metabolically healthy and unhealthy obese.

Moreover, obesity can lead to difficulties in the treatment of cancer. For instance, obesity may hamper the treatment of endometrioid endometrial cancer (EEC) patients by external beam radiation therapy (EBRT) due to the difficulty in locating the tumors potentially causing the danger of under-dose to targets or over-dose to organs [16].

In obesity, the levels of various tumor suppressor proteins are decreased. TP53, a tumor suppressor protein, is inherently unstable within cells; however, its stability can be enhanced through phosphorylation by AMP-activated protein kinase (AMPK), an enzyme activated by adiponectin [17]. Consequently, a decline in adiponectin levels in obesity may lead to a reduction in TP53 concentration [17]. Contrary to previous findings that obesity could cause a decrease in TP53, there are also claims that in obesity, TP53 levels may increase, which can potentially worsen the release of inflammatory cytokines [17]. Nevertheless, the change of TP53 caused by obesity certainly relates to the formation of tumors.

3.1. Colorectal Cancer and Obesity

Colorectal cancer (CRC) is the third most common cancer in the US with an annual increase of 1% to 2% starting from the mid-1990s among individuals under the age of 50 [18]. There is a strong connection between obesity and CRC as excess body fat can increase the chance of an individual having cancer of the colon and rectum [19]. According to the American Cancer Society (ACS), the risk factors of colorectal cancer include being overweight or obese, having a bad diet, and lack of exercise [20]. Sex-specific MR analysis conducted by Bull, et al. [21] demonstrated that higher BMI (per 4.2 kg/m²) in men

was associated with 1.23 times higher CRC odds; and among women, higher BMI (per 5.2 kg/m²) was associated with 1.09 times higher CRC odds.

Obesity can potentially increase the chance of the occurrence of second cancer for cancer survivors. According to research conducted by Gibson et al. [22], which used Cox proportional hazards regression models to examine associations between baseline (prediagnostic) BMI and risk of second obesity-associated cancers (postmenopausal breast, kidney, pancreas, esophageal adenocarcinoma, endometrium) in CRC survivors, and compared the associations to those for first obesity-associated cancers in the full cohort, CRC survivors who were overweight or obese before their diagnosis faced a higher risk of developing second obesity-associated cancers compared to survivors with a normal weight, indicating that the elevated risk of second cancers in colorectal cancer survivors might be attributed to a higher prevalence of overweight or obesity rather than an increased vulnerability in this population when compared to the general public [22].

3.2. Breast cancer and obesity

Breast cancer affects over 250,000 women in the US each year [23]. The two most common kinds of breast cancer are invasive ductal carcinoma and invasive lobular carcinoma [24]. Breast cancer is common among women who are overweight or obese by having higher levels of insulin, which triggers rapid cell division and can cause cells to lose control of their DNA regulator genes [25]. Consequently, obese women face an elevated risk of developing breast cancer which can be influenced by having a greater amount of adipose tissue and attributed to higher estrogen levels [26] produced by the adipose tissue [27]. Estrogen can serve as a catalyst for the growth of cancer cells. Estrogen stimulates the division and proliferation of breast tissue, increasing the likelihood of mutations that can lead to the development of cancer [28]. However recent studies done by the Harvard University suggested that estrogen is a more central character in cancer genesis because it directly alters how cells repair their DNA [28].

3.3. Liver cancer and obesity

The liver is one of the most common sites for cancer metastasis which is responsible for almost 25% of all cases [29]. According to a study done by Larsson, et al., people who are overweight and obese have a nearly 2-fold increased risk of liver cancer compared with people of normal weight [30]. In fact, by 2035, it is estimated that 20% of liver cancer cases globally will be attributable to having a high body mass index [31]. Obesity is linked to a higher risk of nonalcoholic fatty liver disease (NAFLD) [32] which is characterized by steatosis when the liver's uptake and synthesis of fatty acids exceed their oxidation and export as triglycerides within VLDL [32]. Obesity-related NAFLD links to liver inflammation, leading to an increase in the production of different cytokines and adipokines, which have been implicated in hepatocarcinogenesis [33]. According to a mice study, extracellular vesicles (EVs), encouraged colorectal cancer to grow in the liver and prevented immune cells from attacking metastatic tumors in the liver by launching a cascade of actions through three microRNAs that helped the cells form and develop into tumors [34]. Compared to mice with livers that could make EVs, mice that are genetically engineered to lack the ability to make EVs in their livers have colorectal cancer cells forming far fewer metastatic liver tumors [34].

3.4. Diabetes and obesity

Obesity is often accompanied by hyperglycemia [35]. Inflammations occur during obesity by pro-inflammatory molecules such as TNF- α released by white adipose tissue (WAT) macrophages that directly disrupt insulin signaling and can also lead to the development of insulin resistance (IR) and ultimately type 2 diabetes (T2D) [36]. Hyperglycemia can provide cells with more energy for dividing and affects growth factor secretion [31]. T2D has been linked to an increase in cases of obesity-related cancers including colorectal, hepatic, pancreatic, breast, and endometrial [31]. People with diabetes have a greater risk of developing certain cancers, diabetic women have a 27% greater chance of developing cancer than healthy women, and diabetic men are 19% more likely to develop cancer than healthy men

[37]. Insulin sensitivity, influenced by body fat distribution, is associated with BMI regardless of weight gain, while lean individuals exhibit varying insulin sensitivity due to differences in fat distribution, with greater peripheral fat distribution associated with higher insulin sensitivity compared to central fat distribution in the abdomen and chest [38]. Obese individuals have elevated levels of several substances, such as non-esterified fatty acids, glycerol, hormones, cytokines, pro-inflammatory markers, and other factors that contribute to insulin resistance [38]. Insulin and C-peptide, which are crucial growth factors for colonic epithelial cells, are recognized as mitogens of tumor cells [39]. Hyperinsulinemia, a characteristic of metabolic diseases like type 2 diabetes, facilitates epithelial tumorigenesis by disrupting cell competition [40]. Through *Drosophila* genetic experiments conducted by Sabaki, et al., heterozygosity for the insulin receptor substrate chico enables oncogenic scribble (SCRIB – Scribble Planar Cell Polarity Protein) mutant cells to evade cell competition and progress into tumors [40]. Although the direct mechanism between insulin resistance and inflammation in the body remains unknown, in individuals with diabetes and insulin resistance, inflammation markers, such as tumor necrosis factor- α (TNF), interleukin-6 (IL-6), IL-8, and C-reactive protein (CRP) have been observed to be elevated, indicating the presence of inflammation [41] which can potentially cause cancer.

3.5. Obesity and inflammation

Inflammation is a complex defense mechanism employed by an organism to shield itself from harmful stimuli and initiate the recovery process. Normally, inflammation subsides promptly, but it can become chronic when the initial cause persists or remains unresolved. Individuals who are obese often experience a notable rise about two to three times in the levels of immune factors in their blood plasma, including TNF- α , Interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1, CRP, and various others than those found in non-obese individuals [35].

The adipose tissue can be divided into two major types: brown adipose tissue and WAT (white adipose tissue) with different distributions (Figure 3) [42]. The development of obesity depends not only on calorie intake but on the balance between adipose tissue distribution [43]. Brown adipose tissues help regulate the body temperature in colder conditions and help store energy and calories [44], and WAT is specialized for energy storage [43].

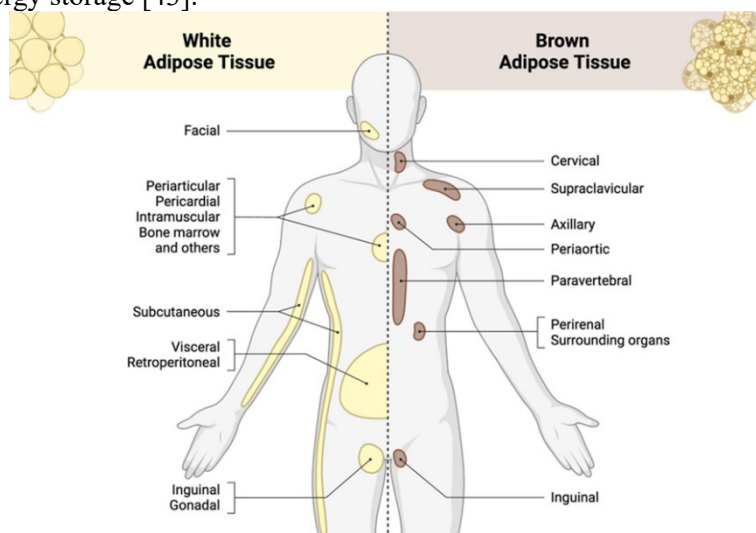


Figure 3. Distribution of white and brown adipose tissues in the human body.

The tumor microenvironment is adapted primarily by inflammatory cells, and this environment plays a crucial role in promoting the growth, survival, and motility of cancer cells. The primary source of obesity-related inflammation is WAT, which acts as an active endocrine organ by producing and releasing a variety of cytokines, hormones, and other substances called “adipokines” [36]. In the presence of metabolic stress, adipocytes produce inflammatory mediators and chemotactic molecules

such as monocyte chemoattractant protein (MCP)-1, which play a role in the recruitment and activation of immune cells particularly macrophages (M ϕ) and T lymphocytes that contribute to the persistence of inflammation within WAT [35]. Inflammation has been shown to promote mutagenesis, tissue damage, and ultimately carcinogenesis [45]. In addition, cancer cells exploit certain signaling molecules in the innate immune system, such as selectins, chemokines, and their receptors, to promote cancer invasion, migration, and spread to other parts of the body [46]. When inflammation occurs in the body, reactive oxygen and nitrogen species (RONS) are produced to battle pathogens and to vitalize tissue repair and regeneration; however, these chemicals can also damage DNA, which in turn can promote cancer through the mutations in the DNA sequences [45]. Additionally, RONS can interfere with the DNA repair mechanisms by reducing their efficacy [45]. Furthermore, damage signaling and cytotoxicity can promote inflammation, creating a loop of inflammation and cellular response to DNA damage to cause inflammation [47].

3.6. Obesity and Cancer Metastasis

Obesity can influence cancer metastasis. Metastasis attributes to over 90% of cancer mortality [48]. The process of cancer metastasis begins with the development of a tumor, which then progresses through stages of localized invasion, intravasation, and extravasation. Eventually, this culminates in the formation of micrometastasis and the subsequent development of macrometastasis. Cases of prostate, pancreatic, breast cancer, and esophageal adenocarcinoma, are similar, as these cancers are situated close to adipose tissue depots [49]. The adjacent adipose tissue creates an optimal microenvironment that fosters tumor growth, progression, and metastasis where adipocytes secrete adipokines, fatty acids, and other soluble factors that support tumor cells, while immune cells infiltrate the tumor region [49]. Obese adipose tissue exhibits numerous characteristics that closely resemble the tumor microenvironment that supports cancer metastasis [49] (Figure 4).

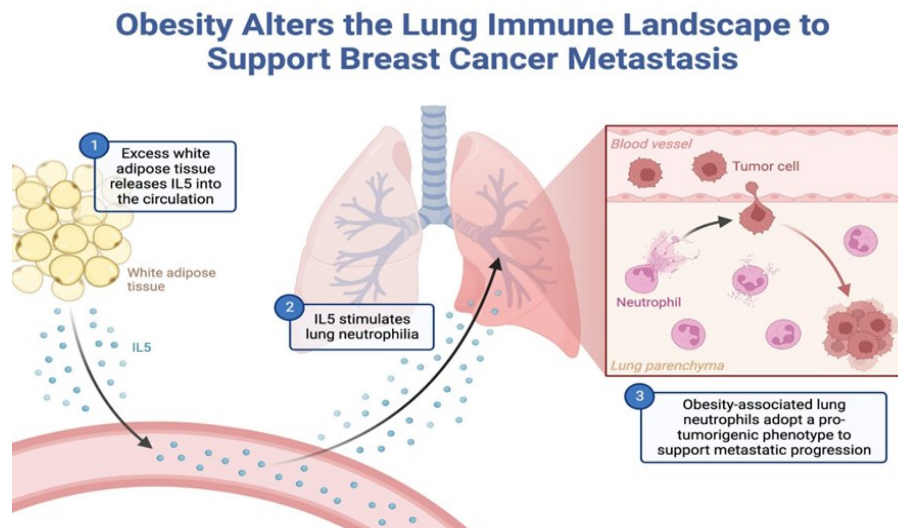


Figure 4. Schematic representation of the proposed mechanism associated with obesity-associated lung neutrophilia. IL5 derived from adipose tissue signals to IL5 α cells, causing their expansion and upregulation of Csf2. This creates an environment supporting neutrophilia in the circulation and the lungs. Lung neutrophils then adopt pro-tumorigenic transcriptional signatures and ultimately facilitate metastatic progression.

3.7. Resolutions for Obesity

There are possible solutions to resolve the obesity crisis. WHO recommends nations collaborate to establish an improved food environment that ensures universal access to and affordability of nutritious meals by regulating the promotion of high-fat, high-sugar, and high-salt food and beverages to children,

implementing taxes on sugary drinks, enhancing the availability of affordable and healthy food options, and allocating areas for secure walking, cycling, and recreational activities. At the same time, schools should assist families in teaching children healthy behaviors right from the start [50]. Epidemiological studies have shown that the quantity and quality of food pregnant females consume during pregnancy affects birthweight and, in turn, the likelihood of individuals born for small or large gestational ages being obese as adults [51]. Therefore, providing nutritious food to pregnant women can help to reduce obesity. The proper method of decreasing the obesity issue is understanding the potential consequences of an unhealthy diet and knowledge about how to live a healthier one.

4. Conclusion

Obesity has become one of the major epidemics worldwide in the past few decades, leading to diseases and costing a considerable burden on the global medical system while being entirely preventable. There are strong correlations between obesity and various types of cancers or carcinogenic conditions such as inflammation, type II diabetes, or NAFLD. Obesity has become an issue only in recent years; therefore, the current healthcare system still needs further data to adjust to obese individuals in cancer treatment and detection.

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