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OBESITY AS A RISK FACTOR FOR CANCER

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ABSTRACT
Globally, obesity is a major health issue that is considered a risk factor for chronic metabolic syndrome and different types of cancers like breast, liver, colorectal, endometrial, and esophageal cancer. This article provides a review of the current literature on the association between obesity and cancer, exploring the underlying molecular pathways. This article also discusses the role of inflammatory cytokines, adipokines, and hyperinsulinemia in cancer development and survival. The review emphasizes the importance of reducing obesity in order to lower the risk of cancer and improve cancer outcomes, as well as the need for greater awareness of the relationship between obesity and cancer.

INTRODUCTION
Cancer is the second-most common cause of mortality, with an average of 14.1 million new cases and 8.2 million deaths per year (Ferlay et al., 2015). The prominent etiological factors for cancer development include genetic makeup, exposure to radiation, nicotine usage, bacterial and viral infections, alcoholism, inactive lifestyle, and other environmental factors. Besides all these etiological factors obesity is a proven risk factor for different types of malignancies (Dalamaga, Christodoulatos, & Mantzoros, 2018). The incidence of different types of cancer increases gradually due to the higher prevalence of risk factors like higher BMI and different metabolic syndromes (Arnold et al., 2016).

DEFINITION OF OBESITY AS A CHRONIC DISEASE
According to the world health organization (WHO), obesity or a higher BMI is abnormal fat deposition in different body parts considered a health risk. These conditions can lead to the development of chronic diseases such as type 2 diabetes and cardiovascular diseases. Furthermore, recent studies revealed that a higher BMI is a risk factor for the development of different types of diseases (Bandini, Gandaglia, & Briganti, 2017).

PREVALENCE OF OBESITY
Obesity or overweight is defined as a Body Mass Index (BMI) equal to or higher than thirty kilograms per meter square and is a public health threat, especially in Western countries. Its prevalence increases day by day leading to diverse and chronic health problems. Obesity affects 34.9% of adults over the age of 20 in the United States (N. Tzenios, M. Tazanios, & M. Chahine, 2022). Even though this ratio has been relatively consistent over the previous decade, there has been a considerable rise among women over the age of 65, from 31.5% in 2003-2004 to 38.1% in 2011-2012 (Ogden, Carroll, Kit, & Flegal, 2014; N. Tzenios, M. E. Tazanios, & M. Chahine, 2022). A study conducted in Spain reported that average people have a BMI in the overweight range which is 39.5% of the population in the country whereas 22.9% are considered obese (Gutiérrez- Fisac et al., 2012).

EPIDEMIOLOGICAL STUDIES OF OBESITY AND RISK FACTORS
According to the international agency for research on cancer (IRAC) reported higher BMI is a leading cause for the development of more than 13 different types of cancer including esophageal carcinoma, kidney, pancreatic epithelial carcinoma, liver, kidney, cerebral

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meningioma, plasma cell myeloma, bowel cancer, breast, ovarian, gallbladder carcinoma and thyroid cancer (Lauby-Secretan et al., 2016).

It is worth mentioning that a higher BMI during early life is not a prominent risk factor for the development of cancer. However, recent studies showed an association between a higher BMI in early life and a high risk of developing cancer in old age (Colditz & Peterson, 2018). High body adiposity index (BAI) during the early stages of life is linked with higher risks of pancreatic adenocarcinoma regardless of other metabolic syndrome and malignancies (Genkinger et al., 2015). When considering the higher incidence of obesity in the early stages of life, highlights the importance of preventing obesity in childhood and adolescence (Avgerinos, Spyrou, Mantzoros, & Dalamaga, 2019).

OBESITY AND CANCER: EXPLORING THE UNDERLYING MOLECULAR PATHWAYS

The underlying molecular pathways that link obesity with cancer are not fully understood. The effect of obesity on the normal cell to become cancerous is either due to the direct effect of adipose tissues, by the presence of inflammatory cytokines, and adipokines, or relate to the consequences of higher BMI such as metabolic syndromes (Khandekar, Cohen, & Spiegelman, 2011).

CANCER AND INCREASED PRODUCTION OF ADIPOKINES IN OBESITY

Different immune modulators like tumor necrosis factors (TNFα) conjugate with its receptors, TNF receptor. This conjugation generates a signal for the activation of nuclear factor-κB (NF-κB), which blocks apoptotic activity and stimulates mitogenic processes which lead to the development of different types of malignancies (Orosz et al., 1993). The interaction of the molecular component of cytokines with receptors motivates cyclin D1 and cyclin-dependent kinase 2 (CDK2). The inflammatory cytokine interleukin 6 (IL6) generates a signal for the nucleus by the interaction with the activator and transducer of transcription factor 3 (STAT3), an oncoprotein overexpressed in a diverse type of tumors (Bromberg et al., 1999).

Leptin is an adipokine secreted by adipose tissues which have a mitogenic effect on cells, activated by different signaling pathways. It can activate PI3K/Akt and MAPK pathways, involved in protein synthesis and phosphorylation respectively. Leptin also quickly and effectively activates the STAT3 pathway, and via vascular endothelial growth factor (VEGF) activation, it may encourage metastasis in breast cancer (Fusco et al., 2010)

Adiponectin prevents tumorigenesis by blocking the molecular signaling pathways required for the activation of mitogenesis. Additionally, it enhances ceramide's conversion to sphingosine-1-phosphate, which affects apoptotic activity by diverse pathways, presumably through MAPK. ‘Adipocyte progenitor cells’ may contribute to tumorigenesis through increased tumor angiogenesis or paracrine or endocrine signaling to malignant cells (Zhang, Bellows, & Kolonin, 2010).

The higher conversion of androgen to estrogen in breast tissue has been linked with a higher frequency of breast cancer. The increased concentration of pro-inflammatory cytokines in obese women is due to increase aromatase activity. It is due to the overexpression of cyclo-oxygenase 2 (COX-2) and prostaglandin E2 (PGE2) in breast tissue (Morris et al., 2011).

IMPACTS OF OBESITY ON CANCER DEVELOPMENT

Obesity can cause chronic inflammatory response in human body which interferes with physiological function of the body. It can also recruit tumor associated macrophages (TAMs), which is very essential in many malignancies. TAMs is well known to be involved in tissue incursion, angiogenic, and metastatic activity. The higher concentration of macrophage chemoattractant protein 1 (MCP1) protein extracts is the indication of breast cancer (Qian et al., 2011).

Binding of insulin and receptor also activates the PI3 pathway, resulting in phosphorylation of AKT and activation of mammalian target of rapamycin (mTOR) [24]. PI3K activation can also activate other mediators of transformation involved in cell division control, including phosphorylation of protein 42 (CDC42). Moreover, PI3K activation can activate protein kinase B (PKB), which inhibits negative regulators of the cell cycle such as p27 (also known as KIP1) and p21 (also known as CIP1). Activation of mTOR can promote protein synthesis and affect cell growth. AKT inhibits BCL2-antagonist of cell death (BAD), an anti-apoptotic protein, and activates cyclin D1. Phosphorylation of FOXO proteins, such as FOXO3A, by AKT results in nuclear exclusion of FOXO, which promotes survival and cell division. AKT also activates MDM2, which degrades p53, thus preventing control of cell cycle activation and apoptosis [15].

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The conjugation of insulin and receptor also triggers the PI3 signaling pathway, causing the activation of AKT by phosphorylation and mTOR. The activation of P13K can also induce other other mediators which are involved in the regulation of cell division like CDC42. Furthermore, PI3K can also triggers protein kinase b (PKB), which negatively regulate the cell division (Engelman, 2009).

SUMMARY

The article provides an overview of current studies on the association between obesity and cancer. Obesity, according to the research, is a substantial risk factor for a variety of malignancies, including colon, endometrial, kidney, and pancreatic cancer. Although the underlying processes through which obesity adds to cancer risk are unknown, evidence shows that hormone imbalances, inflammation, and dietary habits may all play a role. This article emphasizes the significance of more studies to better understand the association between obesity and cancer and to identify effective measures for lowering cancer risk in overweight or obese persons.

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