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OBESITY AND LUNG CANCER (INVESTIGATING THE RELATIONSHIP)

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ABSTRACT

Obesity is a global issue, and it leads to various health comorbidities like cardiovascular disease, diabetes type II and certain cancers. The relationship between obesity and cancer, specifically the lung cancer has been studied by many researchers, and they have revealed a positive association of lung cancer with obese individuals, but the mechanism is still not completely understood. Higher BMI which usually falls between 25 to 34.9 kg/m2 is found to reduce the rate of mortality in lung cancer patients. It has been found that in obese individual the p53 tumor suppressor gene is highly upregulated which play a critical role in decreasing the risk of lung cancer. Different studies have suggested that lung cancer has different progression rates depending on smokers and nonsmokers, and the size of the waist including the waist circumference (WC), waist-to-hip ratio (WHR), and the measures of overall obesity in the body, is associated with increased in risk of lung cancer regardless of BMI. This review unveils the major relation between obesity with lung cancer.

INTRODUCTION

Numerous malignancies, including those of the breast (in post-menopausal women), endometrial, esophagus, gallbladder, kidney, colon, and pancreas, are associated with obesity. Obesity had long been known to have harmful consequences on health, and efforts to combat this global epidemic and lower the risk of many diseases have received considerable attention [1]. Lung cancer has a low survival rate despite the development in medical sciences such as surgery and other chemotherapeutical approaches [2]. Cancer is among the leading cause of mortalities across the globe. According to a survey conducted by WHO in 2012, men have a high prevalence of lung cancer as compared to women which is approximately 16.8% of overall cancer that occur across the world. In accordance with this data, breast cancer in women is secondly ranked which comprises a 12% prevalence rate and a major cause of mortality among women globally [3]. With the increasing ratio of obesity among individuals suffering from lung cancer, there are new challenges arising with time that is hard to tackle for healthcare practitioners. It has been observed that obese individuals having body mass index (BMI) ranging from 25 to 34.9 kg/m2 which is a large BMI are protecting the lung cancer and have reduced the rate of mortality in patients with lung cancer after surgery or chemotherapy[4]. From different epidemiological studies, it is evident that obesity is associated with low survival in various types of cancer. The development of cancer is different with varying obesity it has been noted that general obesity, and body fat distribution—particularly abdominal obesity plays a vital role in the prognosis of lung cancer. Cohort studies have revealed a positive link between obesity with the incidence of lung cancer in the population [5]. In fact, to date researchers have not fully understood the mechanism by which obesity influences cancer, and not enough evidence is present to show the specific association of obesity in the development of lung cancer [6]. However, this review focuses on the deep insight relationship between obesity which is a global health issue, and lung cancer.

THE PARADOXICAL BENEFIT OF OBESITY

Paradoxically, individuals with a high body mass index (BMI) are being found to be at low risk of developing lung cancer and significantly better outcomes for lung cancer patients. The "obesity paradox"—a benefit of obesity that has been repeatedly seen in numerous cohort studies—has no known cause [7]. Although they have been recognized as possible reasons, the hypotheses of a confounding influence from smoking or reverse causation due to cancer-associated weight loss have not been able to completely define the lung cancer obesity paradox [8].

ROLE OF DIHYDROPYRIMIDINASE LIKE 4 (DPYSL4) IN LUNG CANCER CELLS SUPPRESSION

DPYSL4 is a target of tumor repressor gene p53 which controls energy metabolism in the case of cancer cells and adipocytes. In

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lung cancer cells and preadipocytes, the researchers used RNA-seq and ChIP sequencing to find a group of p53-inducible genes that are associated with energy metabolism across both biological contexts [9]. The researchers demonstrated that DPYSL4 directly influences OXPHOS and ATP synthesis in mitochondria relying on the hypothesis that cancer cells are predominantly dependent on glycolysis to generate energy instead of oxidative phosphorylation (OXPHOS). The ability of lung cancer cells to invade Matrigel matrices in vitro was decreased when p53 or DPYSL4 was overexpressed in obese persons. DPYSL4 expression considerably slows down lung metastasis and tumor growth, according to in vivo studies employing mice xenograft and lung metastasis models. The mRNA levels of DPYSL4, CDKN1A, MCP1, and IFNg were also greater in the adipose tissues of obese individuals suffering from lung cancer compared to non-obese patients, and p53 was considerably up-regulated in the adipocytes of obese individuals [10, 11].

Extracellular carriers could be another means by which p53-induced compounds with anticancer capabilities are transported from adipocytes to the target tissue (lung cancer cells) (EVs). Secreted EVs have the ability to transmit metabolic changes from distant receiving cells to adipocytes. As a novel type of adipokines, EVs can modify the molecular characteristics of recipient cells by acquiring new proteins (receptors, enzymes), or even genetic material (mRNAs, miRNAs regulating gene expression), from the adipocyte cells of origin. In fact, the greater quantity of exosomes released and the stronger effects of each individual exosome in obesity strengthen this horizontal transfer. It should be emphasized that past attempts to explain the positive correlations between BMI and EV have relied on both inflammation- and EV-related ideas [12].

POOLED ANALYSIS

Obesity is a significant causative factor for many types of commonly occurring cancers [13]. However, a high body mass index (BMI) has been identified as a lower risk factor for causing lung cancer, particularly among those individuals that are smokers [14]. The two primary reasons have been identified as smoking-related confounding and preclinical weight loss-related reverse causation. Some studies, however, detected similar inverse BMI-lung cancer connections among never smokers or after removing the first few years of follow-up, indicating that additional processes might be at play [5]. The majority of reported analyses, specifically those including individuals that never smokes, had somewhat small sample sizes. Large collaborative analyses incorporating several cohort studies are being required to be conducted in order to adequately identify the implications of confounding and reverse causation because lung cancer is less likely among people who have never smoked. Contrarily, measures of central obesity, such as waist circumference (WC) and waist-to-hip ratio (WHR), have been related to an elevated risk of lung cancer independent of BMI, however, the evidence is still less than that for overall obesity [15]. It has also been reported in many studies by different researchers that the relationship between obesity and lung cancer may vary depending on the tumor's histology and the patient's race or ethnicity, but most earlier studies lacked the necessary statistical power to investigate these connections, especially for the purpose of different histological specimens and among non-white individuals [16, 17]. In a large, pooled analysis performed by Vanderbilt et. al., 2018, it has been found that there is a general adverse relationship between BMI and positive associations of WC and WHR with lung cancer. The relationship between obesity and lung cancer may differ depending on race/ethnicity, tumor histology, or other factors. It may not entirely be caused by smoking or reverse causation. A "low BMI-high WC/WHR" phenotype may assist recognize high-risk groups that are linked to lung cancer along with considering the smoking history and other recognized risk factors. Our findings also point to the necessity of further investigation into the functions of body composition patterns, fat distribution, and metabolic problems associated with obesity in the emergence of lung cancer [18].

The research on obesity and cancer has made significant progress in the last ten years, and there is mounting proof that obesity has a negative impact on cancer risk. Additionally, there is growing knowledge of the biology underlying the linkage between obesity and cancer, as well as interest in taking action to break this relationship in order to reduce cancer risk and enhance cancer outcomes. According to current literature, the facts that currently link obesity to the development of lung cancer risk and its associated outcomes are still observational, and the small associations that are frequently observed may be due to bias and/or confounding; there is a lack of strong evidence that any detrimental effects of obesity on cancer can be avoided by a reduction in the weight of patients or by focusing on significantly potential biological or physiological mechanisms [19]. This is still unclear whether the reduction in weight or overweight individuals will be able to mitigate the potential impacts of obesity on the causative risk of lung cancer or other implications associated with lung cancer, even though avoiding overweight and obesity will ultimately eradicate obesity related cancer risk [20]. Weight reduction methods often result in minor weight loss (rather than attaining a normal weight), hence it is yet to be proven that weight loss can reduce risk and/or improve results since obesity may create non-curable cancer precursors or more aggressive, harder-to-treat malignancies [21].

CONCLUSION

This review focused on the evidence, that is related to obesity and lung cancer. The general body fat distribution and overall obesity play a significant role in lung cancer development. BMI is one of the key factors that cause several types of severe commodities. Different cohort studies conducted by researchers have revealed a positive relationship between obesity and lung cancer indicating that lung cancer decreases in obese individuals however the underlying mechanism is not known. DPYSL4 gene which is a tumor suppressor gene also plays a main role in

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suppressing the p53 gene and decreasing malignancies. It has also been noted that obesity is not the sole factor responsible for lung cancer, but it is also accompanied by other factors like smoking. Future research is required to reveal the facts that are involved in the mechanism by which obesity is linked with lung cancer.

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