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Obesity and Cancer

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Globally, the prevalence of obesity has almost tripled since 1975, according to the World Health Organization (WHO). It affects adults and children and not only those living in high-income countries; the rates of obesity have increased dramatically in middle- and low-income countries. In children and adolescents, obesity increased from 0.7% to 5.6% in boys, and from 0.9 to 7.8% in girls worldwide between 1975 and 2016 [1]. Obesity is a risk factor for a number of health conditions, including cardiovascular diseases, diabetes, fatty liver disease, as well as a number of cancers. In 2016, the International Agency for Research on Cancer (IARC) identified 13 cancer sites that were associated with increased body mass index (BMI): esophagus (adenocarcinoma); gastric cardia; colon and rectum; liver; gallbladder; pancreas; breast (postmenopausal); corpus uteri; ovary; kidney (renal cell); meningioma; thyroid, and multiple myeloma [2]. In 2012, it was estimated that 3.9% of new cancers worldwide were attributable to overweight and obesity, and it has long been known that obesity is associated with cancer mortality [3].

The articles in this Special Issue, examine in detail the association between obesity and these obesity-associated cancers from multidisciplinary perspectives, by evaluating epidemiology, molecular mechanisms, and the interactions between these elements. Additionally, they explore the potential benefits of weight loss strategies on obesity-associated cancer.

A number of important epidemiology questions are addressed herein, including whether genetic risk of obesity is associated with cancer risk, whether obesity in early life contributes to cancer risk, or whether weight gain in particular phases of life increases the risk. Over recent years, Mendelian Randomization has been used as a method to study whether an exposure such as obesity has a causal effect on a disease, such as cancer. Although the method dates back to the 1980's, the recent availability of large genomic databases has allowed it to be applied more broadly. The method has advantages over observational studies of obesity and cancer, as it is less susceptible to confounding, and is not biased by reverse causality, as genes are not modified by the development of cancer [4].

Another critical question addressed in this Special Issue is how obesity may contribute to racial disparities in breast cancer outcomes. In the US, the five-year survival for female breast cancer is almost 10% lower in Black women compared with White women [5]. To a large extent, disparities in socio-economic status, access to medical care, the quality of medical care, and other co-morbidities contribute to the differences in cancer outcomes.

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However, in women with breast cancer even when treatments are the same, disparities in outcomes exist. As the disparities in breast cancer survival are incompletely understood, it is hypothesized that obesity, which is more common in Black women than White women in the US, may contribute to differences in survival [6].

There are a number of mechanisms through which obesity can contribute to cancer growth and progression. Obesity is associated with systemic hyperinsulinemia, and differences in circulating insulin-like growth factors, adipokines, cytokines, hormone bioavailability, and changes in the microbiome, all of which have been proposed to contribute to cancer. The increase in adipose tissue in the tumor microenvironment is a source of lipids which can be used by tumors for metabolism, and as structural and signaling molecules. Tumor-associated adipose tissue is also a local source of adipokines and cytokines. Obesity also leads to changes in the extracellular matrix, adipose stromal cells, and immune cells creating a cancer-permissive microenvironment. Relatively less is known about bone marrow adipose tissue than other adipose tissue depots. Bone marrow adipose tissue potentially contributes to hematological cancers, and bone metastasis from other sites, and is an emerging area of research.

Despite the strong associations between obesity and cancer, and the evolving understanding of the mechanisms involved, whether weight loss can reduce the risk, and the best strategies to implement sustained weight loss are not fully understood. Various lifestyle interventions which include behavioral, exercise and dietary components with in-person or remote strategies have previously shown some benefit in reducing cancer risk, although a major challenge is achieving meaningful weight loss using these methods outside of clinical trials. Specific dietary interventions, such as caloric restriction, intermittent fasting, short term fasting, fasting mimicking diets, and ketogenic diets are being widely examined for their effects on cancer. Short term pre-clinical and clinical studies show some of these strategies are potentially beneficial, may affect circadian rhythm genes and the immune system; however, the long term sustainability and benefits of such interventions in cancer remains to be determined. While circadian disruption in shift workers increases the risk of obesity, there are controversies regarding the impact of circadian rhythm on cancer metastases. A recent study surprisingly reported that breast cancer metastases occur more commonly during the sleep cycle [7]. Therefore, much remains to be learned about how circadian rhythm dysregulation and re-synchronization may impact obesity-associated cancers.

Pharmacological interventions to promote weight loss are also a topic of interest. To date most the most widely studied treatment is metformin, although it has modest effects on weight reduction. In May 2022, the results of the MA.32 study, a large prospective clinical trial was published. The trial examined the effect of metformin vs placebo on breast cancer outcomes. Despite a wealth of pre-clinical and observational studies suggesting benefits of metformin in cancer, the study was largely negative [8]. Newer more effective weight loss therapies such as glucagon-like peptide 1 (GLP-1) receptor agonists and combined glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists have now been approved for the management of obesity and diabetes. However, individuals with a history of cancer are typically excluded from clinical trials with these novel weight loss medications; therefore it will take some time to discover whether these therapies reduce cancer risk and

mortality [9]. It is notable that a weight loss medication (locaserin) was withdrawn from the US market in 2020 due to increased cancer risk, highlighting the need to carefully evaluate weight loss medications and their effects on cancer.

Bariatric surgery achieves significant and long term weight loss and appears to be effective in reducing the risks of certain cancers. In the recently published SPLENDID (Surgical Procedures and Long-term Effectiveness in Neoplastic Disease Incidence and Death) cohort study, greater weight loss from bariatric surgery reduced obesity-associated cancer incidence in a dose-dependent manner [10]. However, from a global perspective access to bariatric surgery is limited to a small fraction of the population; therefore, may not be a feasible strategy to greatly reduce obesity-associated cancers worldwide.

Overall, this Special Issue provides novel insights into the obesity and cancer link from epidemiology, translational and clinical perspectives, and highlights some of the knowledge gaps and challenges in developing methods to mitigate obesity-driven cancer. Given the escalation in adult and childhood obesity worldwide, it is essential to address this major public health issue.

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