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Obesity and Cancer Risk: Epidemiological Evidence, Dose–Response Relationship, and Causal Inference

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Abstract:

Obesity has become a global public health challenge with important implications for the occurrence and development of many cancers. Epidemiological studies have shown that body mass index (BMI), waist circumference, waist-to-hip ratio, and visceral fat measured by imaging are all closely associated with an increased risk of cancer, involving site-specific cancers such as colorectal, breast, endometrial, pancreatic, hepatocellular, renal, and esophageal adenocarcinoma. Prospective cohort studies and meta-analyses consistently confirmed a significant dose-response relationship, with an increase of approximately 18% in colorectal cancer, approximately 50% in endometrial cancer, and approximately 25% in kidney cancer for every 5 kg/m² increase in BMI. Mendelian randomized studies further support causal inference, and results from natural experiments and intervention studies such as bariatric surgery and long-term follow-up also show that obesity-related cancer risk is reversible to some extent. Despite the limitations of measurement error, reverse causality and detection bias, the triangulation of cohort, meta, MR and intervention effectively enhanced the robustness of the research conclusions. Overall, there is a clear, stable, and cross-methodologically consistent dose-response relationship between obesity and cancer risk, providing a scientific basis for cancer prevention and control.

Keywords: Obesity; Cancer risk; Dose–response relationship.

1. Introduction

Obesity has become more and more of a health concern to people, affecting millions of people worldwide. Obesity is defined as an excessive accumulation of body fat that poses a risk to people's health. This increases the risk to numerous chronic diseases, including diabetes, cardiovascular disease and even certain types of cancer. Research have started to uncover strong connections between obesity and

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cancer. Therefore, trying to understand this relationship between the two is essential for prevention, treatment and to improve overall public health. There has been links between obesity and certain type of cancers including breast, colorectal, esophageal, kidney, gallbladder, uterine, pancreatic and liver cancer. This is due to the increase in body fat that leads to higher levels of hormones like insulin and estrogen, which promotes cell division and growth, also triggering chronic inflammation and oxidative stress, damaging DNA and increasing mutation risk. The key biological mechanism on hormonal imbalance is that obesity is linked to insulin resistance, which results in the pancreas to produce more insulin. With high levels of insulin, it acts as a growth signal for cells, which allows cells to divide more often, increasing the chance of DNA errors and cancer. Fo the sex hormone, adipose (fat) tissue, it produces excess estrogen (particularly in postmenopausal women). High levels of estrogen can also stimulate cell division in tissues like the breast and uterus, which results in a raise of risk of cancer [1]. Obesity has become more and more of a health concern to people, affecting millions of people worldwide. Obesity is defined as an excessive accumulation of body fat that poses a risk to people's health. This increases the risk to numerous chronic diseases, including diabetes, cardiovascular disease and even certain types of cancer. Research have started to uncover strong connections between obesity and cancer. Therefore, trying to understand this relationship between the two is essential for prevention, treatment and to improve overall public health. There has been links between obesity and certain type of cancers including breast, colorectal, esophageal, kidney, gallbladder, uterine, pancreatic and liver cancer. This is due to the increase in body fat that leads to higher levels of hormones like insulin and estrogen, which promotes cell division and growth, also triggering chronic inflammation and oxidative stress, damaging DNA and increasing mutation risk. The key biological mechanism on hormonal imbalance is that obesity is linked to insulin resistance, which results in the pancreas to produce more insulin. With high levels of insulin, it acts as a growth signal for cells, which allows cells to divide more often, increasing the chance of DNA errors and cancer. For the sex hormone, adipose (fat) tissue, it produces excess estrogen (particularly in postmenopausal women). High levels of estrogen can also stimulate cell division in tissues like the breast and uterus, which results in a raise of risk of cancer. It is estimated that around approximately 4-8% of all cancers has been associated with obesity, with some individual type of cancer having up to a 32% association, it has come to people's attention the urgency of the need to address this issue. Although the relationship between obesity and cancer risk is complex, and has shown to vary amongst different patents, the association has been demonstrated to be more likely to happen in women than in men. In addition, it is also important to recognize that BMI may underestimate the fat mass of taller individuals, who typically would have a higher fat mass for the same BMI. This discrepancy will increase the risk of type 2 diabetes and may contribute to elevating the risk of cancer.

There have been various hypotheses that circulates this topic as why increased risk of cancer underlies with obesity. The first is the increases levels of testosterone and estrogen in patients with a raised BMI which may help to explain the connection between obesity and the elevated risk of cancer. Adipocytes (found in the aromatase enzyme) that are responsible for converting androgens into oestrone and oestradiol, and given the context of obesity, when body fat rises, levels of oestrogen will increase. The data suggests that highly active unbound forms of these hormones are linked to a higher risk of hormone-sensitive cancers, making it significant to the relationship between cancer and obesity. Epidemiological studies examining the relationship between androgen levels and tumorigenesis have yielded mixed results. ome research indicates that androgens may play a role in tumorigenesis and the regulation of cell growth in prostate cancer, whilst other studies suggest that the androgen-signalling pathway influences breast cancer carcinogenesis. However, evidence may still be quite conflicting and inconclusive. White adipose tissue (WAT), particularly when expanded in the context of obesity, functions as an active endocrine organ secreting a range of pro-inflammatory cytokines, chemokines, and adipokines speculated to contribute to elevated cancer risk in obesity.

Adipose tissues expand and exceeds its blood supply, it gives rise to hypoxic conditions, which induces adipocyte stress and cell death. This then results in an increased production of monocyte chemoattractant protein-1 (MCP-1). This stimulates the rise of macrophages which encircles the dying adipose cells they engulf, forming a histological arrangement, a crown-like structure (CLSs). These structures creates and inflammatory environment, enhancing the chance of tumorigenic processes, including increased cell proliferation and the resistance to apoptosis. Early studies have shown that the presence of CLS on tissue biopsy has been associated with the reduce of survival rates for both breast and tongue cancer sub-types.

2. Evidence Synthesis

Epidemiological studies on obesity and cancer have accumulated substantial evidence, and the diversification of exposure measurement methods has refined the conclusions. Body mass index (BMI) is the most used indicator

and is widely applied in large-scale prospective cohort studies. Both IARC and WCRF have confirmed consistent evidence linking elevated BMI with an increased risk of at least 13 cancer types [1]. Waist circumference and waist-to-hip ratio, as measures of central obesity, better reflect visceral fat accumulation. A follow-up of 5 million participants in the UK Biobank showed that an increase in waist circumference was still associated with higher risks of colorectal, pancreatic, and liver cancers, even after adjustment for BMI [2]. With the development of imaging techniques, visceral fat quantified by DXA and MRI has been shown to be significantly associated with the risk of pancreatic cancer and hepatocellular carcinoma [3].

Metabolic phenotype represents another important research direction. Individuals with elevated BMI but normal metabolic indicators are classified as metabolically healthy obese (MHO), whereas individuals with normal BMI but abnormal metabolic profiles are referred to as metabolically unhealthy normal weight (MUNW). Cohort studies in Korea and Europe found that the cancer risk in MHO populations was lower than in metabolically unhealthy obese individuals but remained higher than in metabolically healthy normal-weight individuals [4]. Life-course weight trajectory studies have also provided new evidence. Childhood overweight is associated with increased risks of breast and colorectal cancers in adulthood, and even when weight normalizes later in life, the risk remains elevated compared to those who were never obese, suggesting long-term effects of early exposure [5].

Regarding study design, prospective cohort studies remain the primary source of evidence, with large-scale cohorts such as the Nurses' Health Study and EPIC providing long-term follow-up data that reveal the associations between obesity and multiple cancers [6]. Systematic reviews and meta-analyses synthesize results from multiple cohorts to generate overall dose–response estimates. Mendelian randomization (MR), which uses genetic variants as instrumental variables, reduces confounding and reverse causality. MR studies in the UK Biobank and Finnish cohorts both support a causal link between elevated BMI and colorectal and endometrial cancers [7]. Natural experiments and intervention studies further provide "causal-like" evidence. The Swedish Obese Subjects Study, with more than 20 years of follow-up, demonstrated significant reductions in breast and endometrial cancer risks among women who underwent bariatric surgery [8]. Overall, exposure assessment has expanded from traditional BMI to multidimensional indicators, while study designs have evolved from observational approaches to causal inference and intervention-based validation, thereby establishing a relatively comprehensive evidence framework.

3. Association with Dose–Response

Epidemiological evidence consistently supports a positive dose–response relationship between obesity and multiple cancer risks. Meta-analyses have shown that for every 5 kg/m² increase in BMI, the risk of colorectal cancer increases by approximately 18%, endometrial cancer by 50%, and kidney cancer by 25% [1,6]. For breast cancer, risk differs by menopausal status, with premenopausal obesity showing weak or non-significant associations, while postmenopausal obesity is strongly linked to elevated risk [9]. Combined analyses also indicate that the risks of gallbladder cancer and esophageal adenocarcinoma increase by more than 50%, highlighting the strong association between central obesity and gastrointestinal cancers [10].

Waist circumference and waist-to-hip ratio exert independent effects on certain cancer types. Evidence from the UK Biobank suggests that colorectal cancer risk increases by 15% for every 10 cm increase in waist circumference at a given BMI [2]. Imaging-based assessments of visceral fat further demonstrate linear associations with pancreatic cancer risk [3]. Nonlinear patterns have also been observed, with some studies reporting steeper increases in colorectal and kidney cancer risks once BMI exceeds 27–28 kg/m² [7]. Causal inference approaches reinforce these findings. Observational studies are vulnerable to residual confounding and reverse causality, prompting the widespread use of Mendelian randomization (MR). Multiple two-sample MR studies have confirmed causal associations between elevated BMI and increased risks of colorectal and endometrial cancers [7]. Robustness has been improved through multi-instrument sensitivity analyses and pleiotropy testing. Intervention studies provide complementary causal evidence. The Swedish Obese Subjects Study demonstrated reduced incidence of breast and endometrial cancers among women who underwent bariatric surgery, with benefits persisting over 20 years of follow-up [8]. Randomized controlled trials of GLP-1 receptor agonists have reported weight loss accompanied by improvements in cancer-related biomarkers, suggesting potential clinical benefits [4].

Bias control remains critical for interpreting results. Reverse causality can attenuate associations, as early-stage cancers may induce weight loss. Measurement error is common in self-reported BMI or waist circumference. Selection and collider bias occur in both genetic and observational settings, requiring sensitivity analyses and triangulation. Detection bias is particularly problematic in breast and prostate cancer, as higher screening rates among obese individuals may inflate observed associations. To address these challenges, triangulation strat-

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egies—integrating evidence from prospective cohorts, meta-analyses, MR, and intervention studies—have been increasingly applied, strengthening causal inference across methodologies. Evidence of reversibility has also emerged. Long-term follow-up from the Swedish bariatric surgery cohort confirmed substantial reductions in breast and endometrial cancer risks among women who lost weight [8]. Latency analyses indicate that the carcinogenic effects of obesity can persist for decades; childhood obesity is associated with elevated colorectal cancer risk in adulthood, even after later weight normalization [5]. Confounding factors require careful consideration. Smoking is inversely associated with BMI yet increases lung cancer risk, potentially obscuring true associations [6]. Coexisting diabetes further amplifies oncogenic effects through hyperinsulinemia [4]. Collectively, obesity and cancer risk exhibit a consistent dose–response relationship across cancer types, with evidence supporting causality, reversibility, and long-term latency.

4. Conclusion

The results of the review showed a consistent positive association between obesity and the risk of multiple cancers, with a clear dose-response relationship. Central obesity and visceral fat accumulation are particularly prominent for digestive cancer risk. The evidence system has gradually expanded from traditional cohort studies to meta-analysis, genetic epidemiology and intervention research, forming a relatively complete causal chain. Despite challenges such as measurement errors, inverse causation, and detection bias, multi-source validation and sensitivity analysis enhance the robustness of the findings. The follow-up results of bariatric surgery and novel drug interventions suggest that the risk of obesity-related cancer is reversible to a certain extent. In the future, it is necessary to strengthen research on populations and different cancer types in low- and middle-income countries, and further integrate genetic, epidemiological and clinical evidence to improve the global evidence framework for obesity and cancer risk.

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