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From Fat to Tumor: Epidemiological Evidence, Biological Mechanisms, and Prevention Strategies

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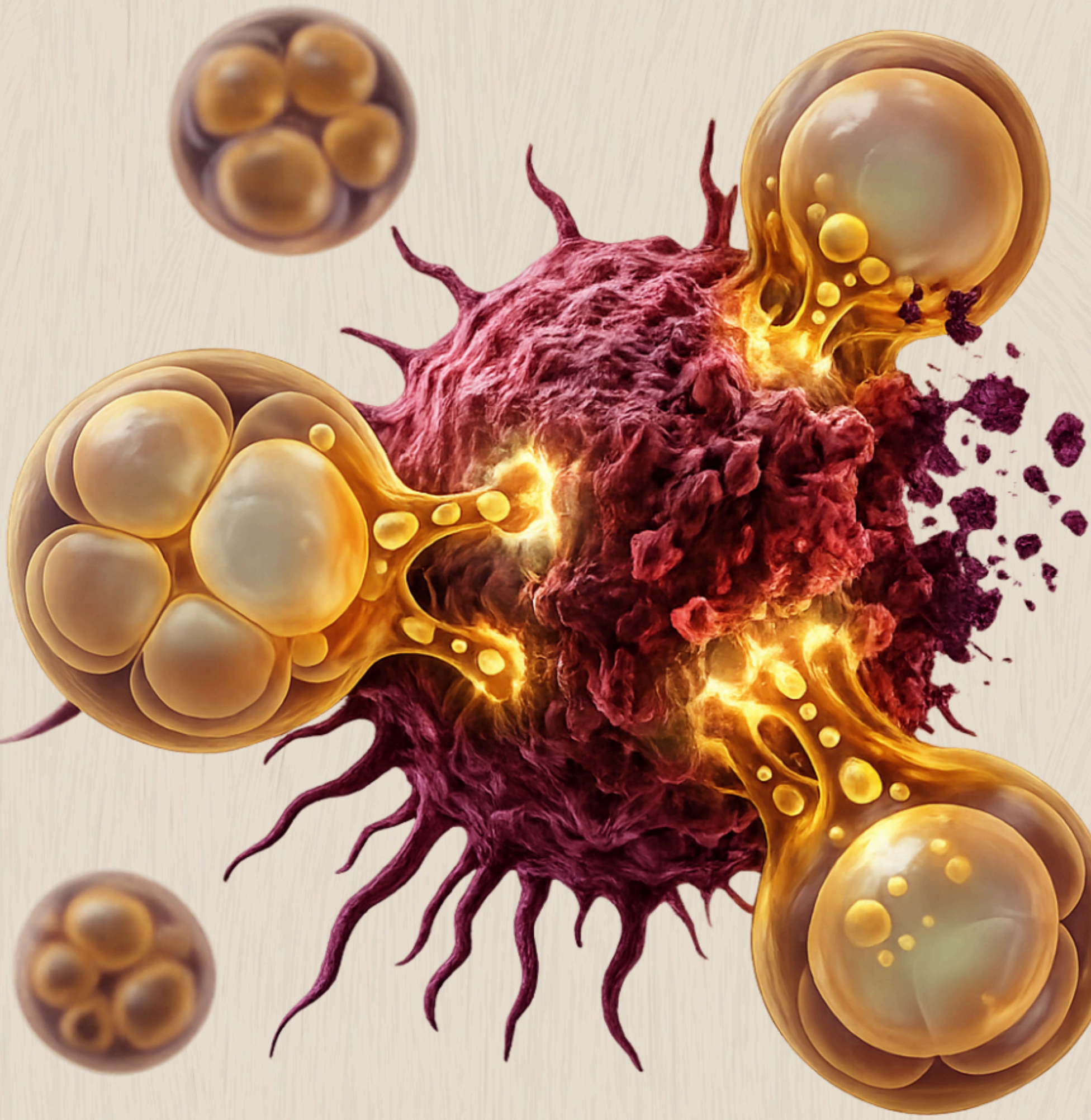

Introduction

Obesity has rapidly become one of the greatest global health concerns of the 21st century. More than a billion people worldwide are currently living with obesity, a number that continues to climb each year (World Health Organization, 2024). While many are aware of its association with heart disease, type 2 diabetes, and metabolic disorders, fewer people recognize obesity as a major contributor to cancer development. Today, cancer stands among the leading causes of death globally, and growing evidence suggests that excess body fat plays a critical role in fueling the onset, progression, and recurrence of several malignancies, including breast, colorectal, liver, pancreatic, and endometrial cancers. Biological research has revealed a complex network of mechanisms that connect excess adipose tissue with tumor growth, ranging from chronic inflammation and hormonal disruptions to insulin resistance and altered cellular signaling pathways. These internal changes create an environment where cancer cells can thrive, invade, and metastasize more aggressively. As obesity rates continue to rise, especially among younger generations, understanding this connection is no longer optional; it is essential. If we aim to reduce the global cancer burden, prevention strategies must go beyond early detection and treatment. They must also address the lifestyle and environmental factors driving obesity in the first place. Only then will we be able to prevent thousands of cancer cases before they even begin.

Epidemiological Evidence

Over the past two decades, epidemiological studies have shown that individuals with obesity are more likely to develop cancer. Moreover, according to global health data, excess body fat is now considered a risk factor for at least 13 different cancer types, including post-menopausal breast cancer, colorectal, liver, kidney, pancreatic, esophageal, and endometrial cancers (Vucinek & Stains, 2012). Researchers estimate that obesity accounts for 4-8% of all cancer cases worldwide, with even higher proportions in high-income countries (Pati et al., 2023).

Research also shows that there is a link between the risk of cancer and body mass index (BMI). Among women, even modest excess body weight is linked with an elevated cancer risk: those who are overweight (BMI 25-29.9) have roughly an 8% higher chance of developing cancer compared to women with a BMI below 25. As BMI rises further into the obese range, cancer risk climbs steadily, with women having a BMI of 30-34.9 facing an 18% greater risk, those at 35-39.9 facing a 32% increase, and women with a BMI of 40 or higher facing more than a 60% elevated risk. In men, increased cancer risk becomes evident only once BMI reaches the obese range. Men with a BMI of 30-34.9 have a 9% higher risk than those under 25, and this risk increases to 20% at a BMI of 35-39.9 and over 50% at a BMI of 40 or above (Basen-Engquist & Chang, 2011). Thus, heavier body weight is associated with greater cancer risk in both sexes. Simply staying within a healthy weight range can make a major difference: people with a BMI

between 22.5 and 25 have the lowest chances of dying from cancer compared with those who are underweight or overweight.

In addition, recent research suggests that where fat is stored may be just as important as how much fat a person has. Visceral adipose tissue, the fat stored deep inside the abdomen around vital organs, has been linked with a higher risk of several cancers, independent of overall body mass index. A study using data from the UK Biobank investigated how the visceral adiposity index (VAI), which is a measure of the amount of visceral fat and related metabolic dysfunction, is associated with cancer risk. The research followed 385,477 adults over a median of more than eight years and found that individuals with higher VAI scores were at significantly greater risk of developing several types of cancer compared to those with lower scores. Specifically, people in the highest VAI group had more than double the risk of uterine cancer as well as increased risks of gallbladder, kidney, liver, colorectal, and breast cancers, and a modest elevation in overall cancer risk. Moreover, this suggests that not just overall body weight, but where fat is stored and how it affects metabolism, may influence the development of multiple cancers (Parra-Soto et al., 2024).

Moreover, younger populations are also becoming more vulnerable; adults under 50 are increasingly being diagnosed with cancers such as colorectal, endometrial, and kidney cancer, suggesting that the global rise in obesity is contributing to earlier cancer development and a growing future cancer burden (Terashima et al., 2025).

Given this evidence, the next step includes understanding how obesity drives cancer formation and progression at the cellular and molecular levels.

Biological Mechanisms

Obesity increases cancer risk through several biological mechanisms that create a favorable environment for tumor development. The first mechanism includes sex hormones. In post-menopausal women, excess adipose tissue increases aromatase activity, converting androgen precursors into estrogen. As a result, elevated circulating estrogen levels stimulate cell proliferation, DNA stability, and genetic instability in breast and endometrial tissues (Renehan et al., 2015). Not only that, but in endometrial tissues, elevated estrogen levels stimulated the production of insulin-like growth factor 1 (IGF-1), thus resulting in cell growth and inhibiting apoptosis. Obesity also reduces sex hormone-binding globulin (SHBG) levels, which further increases the levels of biologically active estrogen in the body.

For men, the relationship between sex hormones, obesity, and cancer is less straightforward. Obesity is associated with low testosterone levels. However, studies have shown that men with obesity are more likely to develop a less differentiated and more aggressive cancer phenotype. But evidence remains limited. For example, medications that reduce dihydrotestosterone levels have been found to decrease early-stage prostate cancer but increase the risk of high-grade

tumors. So, while sex hormones help explain the relationship between obesity and cancer in women, there is limited evidence to understand that in men (Renehan et al., 2015).

Sex hormones have a huge role in helping us understand how obesity can result in cancer. However, this hypothesis has its limitations. First, it is challenging to measure a steady rate of risk as sex hormone levels fluctuate in premenopausal women. Second, research has mostly focused on circulating hormones in the bloodstream, but local signaling within fat tissue can also stimulate tumor development, especially in breast cancer. Finally, there are several potential sex hormones, and it is still unclear which of these are directly responsible for cancer (Renehan et al., 2015). Therefore, hormonal mechanisms are important. However, they only represent one part of a much more complex connection between obesity and cancer.

Another mechanism that links obesity to cancer is insulin resistance. As BMI increases, circulating insulin levels rise, and many obese individuals become insulin resistant. According to past research, hyperinsulinemia can contribute to cancer through two pathways: either directly by stimulating cell growth or indirectly through the insulin-IGF hypothesis. The latter states that when insulin levels remain high for long periods, the body reduces the production of proteins that bind and control IGF-1. This leads to higher levels of free IGF-1, which stimulates cell proliferation. Both insulin and IGF-1 activate intracellular signaling pathways that promote tumor growth, angiogenesis, and cancer cell survival. Through these mechanisms, metabolic changes driven by obesity can create conditions that stimulate cancer cells to develop and spread (Giovannucci, 1995). The insulin hypothesis also has its limitations. First, insulin levels are difficult to accurately measure because results may vary based on fasting time, lab methods, and genetic factors. Indirect markers of insulin secretion, such as HOMA-IR or insulin resistance, such as C-peptide, are often used. But these are poor indicators of individual insulin resistance (Xiang et al., 2014). Second, animal studies make most of the evidence linking levels of insulin to tumor formation, but these studies use insulin levels that are far greater than those found in humans (LeRoith et al., 2010). Finally, if insulin signaling drives cancer development, diabetic individuals who are treated with insulin should have a higher cancer risk. However, clinical trials still have not confirmed this association.

Moreover, polypeptide hormones derived from adipocytes, known as adipokines, show an important link between obesity and cancer. Among more than 50 known adipokines, leptin and adiponectin are the most studied types in the context of cancer risk. Leptin concentrations rise as body fat increases and promote inflammation, cell proliferation, angiogenesis, and reduced apoptosis. Leptin signals through receptors that activate cancer-related pathways such as PI3K, MAPK, and STAT, which enhance tumor cell survival and spread (Roberts et al., 2010). However, studies examining blood leptin levels and cancer risk have shown inconsistent findings. Thus, leptin alone may not fully explain the link between obesity and cancer.

In contrast, adiponectin levels, the most abundant adipokine, decrease as body weight increases. This hormone shows anti-cancer properties and has indirect and direct effects: it improves insulin sensitivity, reduces inflammation, and directly inhibits tumor cell growth

through several pathways that inhibit DNA damage, cell proliferation, and angiogenesis. Epidemiological research shows that individuals with higher adiponectin levels have a lower risk of obesity-related cancers such as breast, endometrial, colorectal, pancreatic, and kidney cancers (Renehan et al., 2015). In addition, obesity results in chronic inflammation. As adipose tissue expands, inflammatory molecules like CRP, TNF-α, and IL-6 are released. An early epidemiological study showed an association of CRP levels with colorectal cancer (Erlinger et al., 2004), but subsequent analysis reported only modest correlations (Tsilidis et al., 2008). This sustained inflammatory environment can damage DNA and promote tumor initiation. Despite strong evidence, both hypotheses show some limitations. First, adiponectin has three major molecular forms, each with different roles. The ratio of high molecular weight to low molecular weight adiponectin is critical to insulin sensitivity and anti-cancer effects. In addition, both adiponectin receptors (ADIPOR1 and ADIPOR2) exist in tumor cells, but their functions are not well understood. Second, in experimental models, some mice lacked adipose tissue but still showed accelerated tumor development (Hursting et al., 2007). Finally, blood levels of leptin fluctuate based on the individual's health, medication, physical activity, and diet. This makes it difficult to determine their direct effect on cancer risk. Thus, even though both adipokines and inflammation are important to better understand the link between obesity and cancer, they do not fully explain the epidemiological patterns.

Together, these metabolic, hormonal, and inflammatory changes create a biological environment in which cancer cells can initiate, grow, and spread more easily throughout the body. As a result, obesity is not only correlated with cancer but also plays a role in the mechanisms underlying carcinogenesis.

Preventive and Therapeutic Interventions

For cancer survivors, weight management is critical as obesity increases the risk of cancer recurrence and leads to other chronic conditions such as diabetes and cardiovascular diseases. It is estimated that roughly one third of cancers in high-income countries are attributable to factors related to diet, nutrition, and physical activity (Wiseman, 2008). One of the most important factors is regular physical activity and consuming less salty foods, sugary drinks, alcohol, and energy-dense foods, in addition to consuming a healthy diet based on plants. For mothers, breastfeeding exclusively up to six months was recommended because lactation protects mothers against breast cancer and protects children from obesity (Vucinek & Stains, 2012). Moreover, evidence shows that a consistent calorie deficit results in weight loss regardless of the type of diet (Sacks et al., 2009). However, the nutritional quality of a diet still matters, as proven by the DIANA-5 intervention. Based on Mediterranean-style dietary principles, this intervention shows improvements in weight reduction and metabolic syndrome indicators in women with breast cancer (Bruno et al., 2021). When combined with diet, exercise reduces visceral fat, lowers blood pressure and lipid levels, and improves glycemic control

(Gaesser et al., 2011). Alongside physical activity and dietary modifications, behavioral therapy has been shown to help individuals maintain a healthy lifestyle. This type of therapy includes tracking calorie intake, physical activity, exercise planning, and setting achievable goals (Alamuddin et al., 2016). Therefore, diet, exercise, and achieving a healthy lifestyle are essential for minimizing cancer recurrence risk.

Clinical Implications

The growing body of evidence linking obesity to cancer development, progression, and recurrence shows an important need to integrate weight management strategies into routine clinical cancer care. Traditionally, oncology treatment has focused primarily on surgery, chemotherapy, and radiotherapy, with less attention given to metabolic health. As clinical evidence consistently shows that excess body weight can influence cancer prognosis, treatment response, and recurrence outcomes, major oncology organizations, including the American Society of Clinical Oncology, now recommend incorporating nutrition counseling, physical activity, and behavioral therapy into cancer treatment (Demark-Wahnefried et al., 2012; Ligbel et al., 2014). These approaches have been shown to improve physical function, reduce treatment side effects, and lower the risk of cancer recurrence, particularly among breast, colorectal, and endometrial cancer survivors. For cancer survivors in particular, lifestyle-based interventions offer a low-risk and cost-effective approach to mitigate long-term complications and improve survival outcomes.

The Future

Despite growing evidence linking diet, physical activity, and body composition to cancer risk, many of the underlying biological mechanisms remain poorly understood. Future research should prioritize clarifying how lifestyle factors influence cancer development at the molecular level. Advances in “omics” technologies, like genomics, transcriptomics, proteomics, and metabolomics, offer promising opportunities to understand how diet and physical activity interact with biological pathways involved in carcinogenesis. These approaches that are supported by improved bioinformatics tools may significantly enhance our ability to assess individual and population-level cancer risk. Another rapidly emerging area of interest is the role of the gut microbiome in cancer development. Evidence suggests that diet and physical activity can alter the microbiome in ways that may influence inflammation, metabolism, and tumor growth. This represents a promising direction for future research. In addition, there is a growing need for more well-designed human studies that use relevant biomarkers to directly assess biological responses to diet and physical activity. Emerging technologies such as liquid biopsies, which analyze circulating tumor DNA (ctDNA) in blood, offer a noninvasive approach for early

cancer detection and real-time monitoring of tumor dynamics and may play an important role in future prevention and risk stratification strategies (Wan et al., 2017).

Nutritional epidemiology will also depend on more accurate and objective tools to measure dietary intake, physical activity, and energy balance. Future cohort studies should aim for more precise assessments of body composition to distinguish between fat mass and muscle mass rather than relying solely on BMI. Research should also focus on defining dose and response relationships as the effects of diet and physical activity on cancer risk are unlikely to be linear.

Finally, future studies must consider cancer as a heterogeneous disease. Classifying cancers solely by tissue of origin is insufficient; incorporating molecular and genetic subtypes, such as hormone receptor status or genomic profiles, will improve our understanding of how lifestyle factors influence specific cancer types. Host genetic variability also plays a major role in how individuals metabolize nutrients and respond to dietary exposures, yet this complexity is rarely integrated into epidemiological research (Clinton et al., 2020). Furthermore, incorporating genetic and epigenetic data into future studies will be essential for advancing personalized cancer prevention strategies. Large-scale genomic initiatives such as The Cancer Genome Atlas (TCGA) have transformed cancer research by enabling molecular classification of tumors beyond tissue of origin. By integrating genomic, transcriptomic, and epigenetic data, TCGA has provided critical insights into cancer heterogeneity and established a foundation for precision prevention and treatment strategies (Hutter & Zenklusen, 2018).

Public Health and Policy Implications

Individual action alone is not sufficient. Comprehensive dietary guidelines emphasize not only individual behavior change but also supportive food and activity environments to reduce obesity and its downstream health consequences, including cancer (McGuire, 2015). Many people face difficult barriers, including limited access to health education, a lack of skills to implement behavioral change, and social and economic constraints that make healthy choices difficult to sustain. In addition to that, historical public health successes such as tobacco control, occupational safety, and infectious disease prevention prove that meaningful population-level health improvements require coordinated societal efforts. For these reasons, governments and public institutions should improve their role in supporting healthy dietary patterns and physical activity. This could be done through policy, regulation, and infrastructure. Investment in such public health strategies not only improves population health but also leads to substantial long-term reductions in healthcare costs. Global organizations, including the United Nations and the World Health Organization, should further support these efforts by promoting international cooperation to ensure sustainable food systems that protect both human health and the environment. Furthermore, the World Cancer Research Fund International/American Institute for Cancer Research provided a public policy report for cancer prevention policy, which emphasized three core domains: health-enhancing environments,

systems change, and behavior change communication (Marmot et al., 2007). Effective public health change can occur through multiple ways, coordinated efforts by governments, healthcare and professional organizations, the private sector, and civil society. These stakeholders influence health behaviors across many settings, such as schools, workplaces, healthcare systems, communities, digital platforms, and family environments (WCRF/AICR, 2018). While all sectors share responsibility for promoting public health, cancer prevention requires strong leadership and commitment at the government level. However, these efforts are often challenged by opposition from segments of the food industry and conflicting interests within trade and agricultural policies (Clinton et al., 2020). To address these challenges, strong advocacy is needed to prevent financial interests from discouraging public health policy. Without decisive government leadership and accountability, efforts to reduce obesity and its cancer burden are unlikely to succeed at the population level.

Conclusion

Obesity is a major risk factor for cancer. It induces tumor development, progression, and recurrence through metabolic, hormonal, and inflammatory mechanisms. Addressing this link requires more than individual lifestyle change. It demands weight management in clinical care, continued investment in mechanistic research, and strong public health policies that support healthy environments. Without coordinated action across clinical, scientific, and policy domains, the rising burden of obesity related cancers is unlikely to be reversed.

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