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Obesity as a Risk Factor for Various Cancers: A Systematic Review

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ABSTRACT

Obesity is often assessed through body mass index (BMI), which is a ratio of body weight to height, as defined by the World Health Organization (WHO). Several studies have shown a clear association between obesity and an increased risk of several cancers, including esophageal adenocarcinoma, breast cancer in postmenopausal women, pancreatic cancer, colorectal cancer, endometrial cancer, kidney cancer, and liver cancer. This review aims to synthesize the available evidence on obesity as a risk factor for different types of cancer. The articles in this review were selected using the PubMed database and EBSCO information services, focusing on the articles that were most relevant to the topic. Articles unrelated to the subject were excluded. The data were extracted following a specific protocol. Obesity is a key risk factor for the development and progression of various types of cancer, especially gastrointestinal cancers such as colorectal, gastric, and liver cancer. This association is attributed to various pathophysiological mechanisms, including impaired immune function in obese individuals. However, in some cases, the evidence linking obesity to cancer risk is not conclusive, and factors such as gender may influence how obesity acts as a risk factor for cancer.

Keywords: Malignancy, Obesity, Overweight, Cancer

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Introduction

Obesity occurs when the energy intake from food exceeds the energy expended through physical activity and metabolic processes, leading to abnormal fat accumulation. The World Health Organization defines obesity based on body mass index (BMI), which is calculated by dividing a person's weight by the square of their height. In clinical settings, overweight is categorized as a BMI between 25 and 29.9 kg/m², while a BMI of 30 kg/m² or higher signifies obesity. The WHO's 2016 report found that 13% of the global population was obese and 39% of adults were overweight. As overweight and obesity are established risk factors for metabolic and cardiovascular diseases, their growing prevalence poses significant challenges for health systems. Moreover, obesity, particularly visceral fat, is increasingly recognized for its influence on cancer development by affecting tumor cell proliferation, spread, and treatment response, which connects obesity to cancer risk, prognosis, and mortality [1-5].

Primary liver cancer is one of the most common forms of cancer, responsible for about 9% of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC), the most frequent type of liver cancer, accounts for 80-90%

of primary liver malignancies. Some studies, including one by Chen *et al*. found no direct link between obesity and HCC, but other research supports obesity as a risk factor for liver cancer [6-11].

Research has consistently shown that obesity elevates the risk of numerous cancers, including esophageal adenocarcinoma, pancreatic, colorectal, postmenopausal breast, endometrial, kidney, and liver cancers, as highlighted by the World Cancer Research Fund (WCRF). Tahergorabi *et al*. found that individuals with high blood glucose levels had 3.35 times the risk of gastrointestinal cancers compared to those with normal glucose levels, while the risk was 2.37 times higher in individuals with low HDL cholesterol and 10.4 times higher in overweight individuals—factors commonly associated with metabolic syndrome [12, 13].

Obesity's link to cancer is driven by several biological mechanisms, such as dysregulation of the insulin-like growth factor (IGF)-I system, chronic low-grade inflammation, altered sex hormone metabolism, oxidative stress, changes in the gut microbiome, and disturbed adipokine signaling. The imbalance created when calorie intake exceeds expenditure leads to obesity and associated metabolic changes, including elevated insulin levels and altered bioavailability of steroids and IGF-I, all of which contribute to cancer risk. Obesity also increases interleukin-6 (IL-6) levels, prompting the liver to produce C-reactive protein, further promoting carcinogenic processes. These mechanisms play both general and tumor-specific roles in cancer progression [14].

While specific foods such as allium vegetables, broccoli, and micronutrients like selenium, vitamin D, and carotenoids have been studied for their anti-cancer properties, evidence suggests that overall dietary patterns are more beneficial than focusing on individual nutrients. The Mediterranean diet, which emphasizes plant-based foods, limited meat and dairy, and moderate alcohol intake (mostly in the form of wine), has shown notable health benefits compared to other dietary patterns. More than just a dietary plan, the Mediterranean lifestyle is a comprehensive approach to healthy living [1].

This review aims to synthesize the existing evidence on obesity as a risk factor for various types of cancer.

Materials and Methods

Study design

To establish a comprehensive empirical research framework building on previous knowledge, a systematic evaluation of the current evidence on obesity as a risk factor for different types of cancer was utilized as a reliable method to locate and compile peer-reviewed studies in this field. This review focused on synthesizing qualitative data to draw clear, relevant, and meaningful conclusions that could guide future research on the link between obesity and cancer, especially breast cancer. The data were cohesively interpreted and synthesized using qualitative synthesis techniques where applicable, ensuring the findings are informative and relevant to future study directions.

The purpose of this review was to go beyond merely aggregating data by providing deeper interpretative insights into obesity's role as a cancer risk factor, with a particular focus on identifying areas where further research could build upon existing knowledge.

Study eligibility criteria

Only peer-reviewed qualitative studies were included in this review. Mixed-methods studies had their qualitative data evaluated for relevance before being considered. Studies conducted over the past twenty years were included to ensure the inclusion of relevant and current research. Only peer-reviewed articles published in English and exploring the connection between obesity and breast cancer were considered.

The studies selected for this review were published between 2002 and October 2022, ensuring the analysis reflected the most up-to-date findings and included emerging issues in the field from a broad range of viewpoints.

Study inclusion and exclusion criteria

The papers included in the review were selected based on their relevance, publication in English, and adherence to a ten-year timeframe. Articles that were duplicates, reviews, or had a primary focus unrelated to the topic were excluded. Any studies not published in English, as well as books, grey literature, or editorials, were also omitted. Only studies that provided qualitative data were considered, excluding others that did not align with the review's focus.

Study selection

The criteria for study selection were aligned with the ENTREQ guidelines for qualitative systematic reviews. To avoid duplication, all relevant studies were first imported into an EndNote library. Following this, the two authors independently reviewed the titles and abstracts of the studies based on the eligibility criteria. Full-text reviews were conducted for the studies that met these criteria.

Any disagreements between the two authors were resolved by consulting a third author. The complete texts of all studies that met the inclusion criteria were thoroughly examined by both authors. If there was a difference of opinion, discussions were held with the third author to reach a consensus. Only the studies that fully met the inclusion standards were included in the final review.

Data extraction

Two authors independently extracted data from the selected studies using a customized data abstraction form. This form included key information about the study population and relevant outcomes. The third author cross-checked the data extraction process to ensure accuracy. Study characteristics, such as the author's name, year of publication, study duration, and geographical location, were recorded. Specific study details, including design, demographic information, sample size, sampling techniques, and data collection methods, were also documented. The focus of the data extraction was to identify the relationship between obesity and cancer as a risk factor.

Data synthesis and analysis

The data was analyzed manually, without the use of software packages, and categorized by thematic areas. The authors organized the themes into an analysis table, which allowed for easy comparison of the results across different studies. The table's columns and rows were structured to summarize the findings, and related themes were compared to identify patterns and variations in the studies' outcomes.

Results and Discussion

Figure 1 outlines the selection and classification process for the studies. Initially, 286 articles were retrieved from the databases, which were then screened by title. After the first screening, 52 studies were excluded, leaving 198 for abstract review. Following this, the full texts of 146 studies were assessed in detail. Out of these, 137 studies were excluded based on their objectives not aligning with the review, while 7 studies were added for the final data analysis **(Table 1)**. The studies included in the review employed a variety of research methodologies.

Table 1 presents details including the authors, countries, publication years, objectives, methodologies, and key findings of the studies.

In a study carried out by Hashemi Madani *et al*. [15], no significant correlation was found between obesity-related factors and the prevalence of gastrointestinal (GI) cancers in men. However, BMI, waist circumference (WC), and waist-to-hip ratio (WHR) were associated with lower risks of esophageal squamous cell carcinoma (ESCC) in women. Additionally, a higher WHR was linked to increased risks for gastric and colorectal cancers in females. The study highlighted statistically significant associations between obesity-related factors and the occurrence of gastric, colorectal, and esophageal cancers among women.

Another study by Diao *et al*. [16] demonstrated a positive association between the obesity-related risk prediction score (ORPS) and breast cancer risk. The ORPS was more effective in predicting breast cancer risk in obese women compared to non-obese women, showing stronger correlations in both premenopausal and postmenopausal women. In premenopausal women, ORPS was particularly associated with triple-negative breast cancer, while also correlating with Luminal breast cancer in other molecular subtypes. This finding suggests that ORPS could serve as a valuable indicator of breast cancer risk in Chinese women.

Yugawa *et al*. [17] observed that obese individuals had higher serum levels of carbohydrate antigen 19-9 compared to those with normal weight. Additionally, they noted a higher intrahepatic metastatic rate and larger tumor sizes in the obese group, along with a poorer prognosis. BMI was positively correlated with increased 18F-FDG uptake in PET/CT scans. The study also found that higher rates of PD-L1 expression, fewer CD8+ tumor-infiltrating lymphocytes (TILs), and more Foxp3+ TILs were present in patients with elevated BMI, suggesting that obesity may influence immune function and metabolic processes in patients with intrahepatic cholangiocarcinoma (ICC), potentially promoting cancer progression.

In research by Loosen *et al*. [18], multivariable regression models revealed a progressive increase in the proportion of obese and overweight patients with colon cancer over the study period. The figures rose from 0.5% and 0.64%

to 0.71% and 0.91% for males and females, respectively. The study indicated a strong link between obesity and colon, rectal, and liver cancers, with sex being a significant factor in this association, particularly in rectal and liver cancers in males.

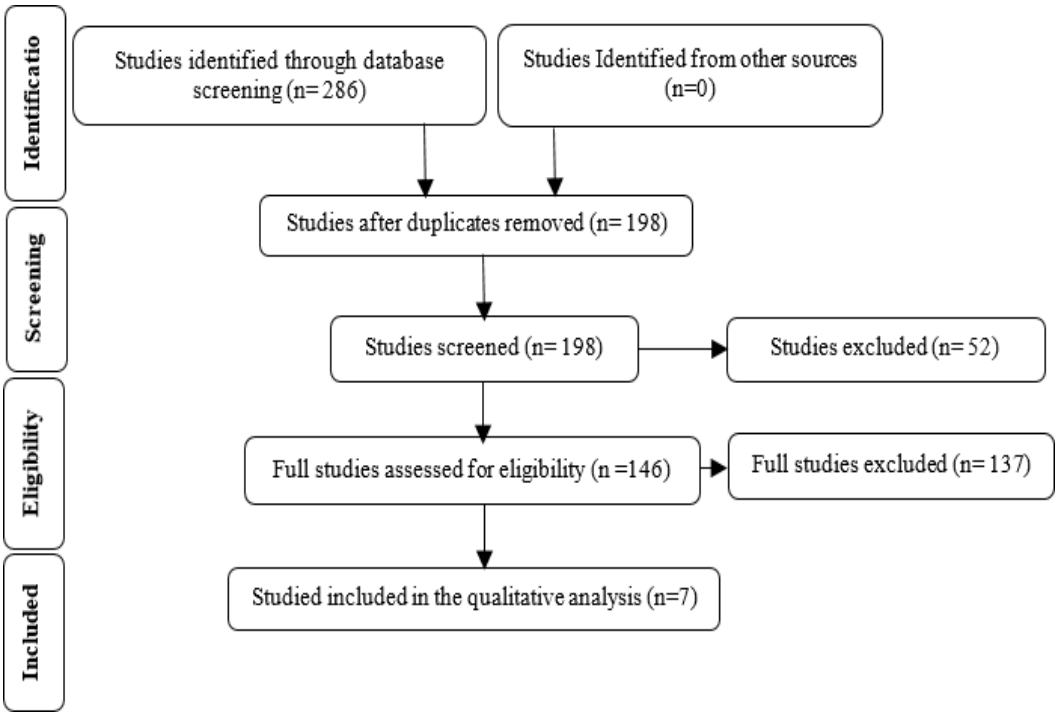

Figure 1. Flow chart representing the data extraction process

Table 1. Extracted data from collected studies

Study	Objective and methodology	Outcomes
Hashemi Madani *et al.* [15]	This research aimed to explore how overall and specific obesity-related factors could predict gastrointestinal (GI) cancer occurrences. A cohort of 47,586 cancer-free participants was followed for an average of 12.3 years. The study examined how obesity metrics such as BMI, waist circumference, and waist-to-hip ratio were associated with the prevalence of pancreatic, esophageal, gastric, and colorectal cancers.	No significant links were found between obesity-related measures and GI cancer prevalence in men. However, in women, BMI, waist circumference, and waist-to-hip ratio were significantly associated with the occurrence of gastric, colorectal, and esophageal cancers.
Diao *et al.* [16]	This study developed an Obesity-Related Protein Score (ORPS) to assess breast cancer risk. Nine proteins were selected based on systematic reviews and population data, and their concentrations were measured via ELISA in a case-control study involving 279 breast cancer cases and 260 controls from Chengdu, Sichuan, China.	ORPS showed a positive correlation with breast cancer risk, with a stronger predictive value in obese women compared to non-obese women, both pre- and postmenopausal. Additionally, ORPS was significantly linked to triple-negative breast cancer in premenopausal women and Luminal breast cancer in other subtypes. This suggests ORPS could be a useful tool for assessing breast cancer risk in Chinese women.
Yugawa *et al.* [17]	The focus of this study was on the metabolic and immune responses, examining the relationships between BMI, clinicopathological features, and patient outcomes.	Compared to individuals with normal weight, the obese group showed significantly higher levels of serum carbohydrate antigen 19-9, larger tumor sizes, and increased intrahepatic metastasis. The obese group also had poorer prognoses. BMI was positively associated with SUVmax in 18F-FDG PET/CT scans, and the results suggest obesity might accelerate intrahepatic cholangiocarcinoma (ICC) progression by altering immune function and metabolism.

Loosen *et al.* [18]	This study assessed how obesity and being overweight affect the risk of GI cancers, considering sex differences in the data from the Disease Analyzer database spanning 2010 to 2019, with 287,357 adult patients.	The study concluded that obesity is a key risk factor for the development of colon, rectal, and liver cancers, with significant differences between sexes observed, particularly for rectal and liver cancer in males.
Ramdass *et al.* [19]	The relationship between obesity and cancer mortality was examined in this study, which retrospectively reviewed medical records of 784 cancer patients.	Among these patients, 43 (5.2%) did not survive, while 741 (94.8%) survived. The cancer non-survivor group had a significantly lower BMI than the survivor group. Patients without peripheral artery disease (PAD) had a 4.9 times greater likelihood of surviving cancer, while those with PAD had a 3.5 times higher cancer mortality risk.
Look AHEAD Research Group *et al.* [20]	This study aimed to investigate whether a rigorous lifestyle intervention for weight loss could lower cancer incidence and mortality. 4,859 cancer-free individuals were enrolled, excluding those with non-melanoma skin cancer.	The results indicated no significant difference in overall cancer incidence, cancers unrelated to obesity, or total cancer mortality between the group that received intensive lifestyle intervention and the control group.
Youssef *et al.* [21]	This pooled study analyzed the effects of BMI and weight change on thyroid cancer development by reviewing data from 24 million cohorts across 31 studies.	The study found that individuals of normal or underweight status had a lower risk of developing thyroid cancer (TC), whereas overweight and obese individuals had a higher risk. Women were more likely to develop TC than men. Furthermore, weight loss reduced the likelihood of TC, while weight gain increased the risk. The study also found no significant gender differences in the effects of weight change on TC risk.

Although obesity-related illnesses, particularly those linked to elevated BMI, have received the most attention, other biomarkers have emerged as indicators of a heightened cancer risk. Both BMI and fasting insulin are correlated with advanced disease stages and unfavorable prognoses, positioning them as key risk factors for breast cancer. Additionally, elevated C-peptide levels, which signal increased insulin production—often seen in insulin resistance—have been associated with a greater likelihood of developing colorectal cancer [1].

Studies examining the relationship between obesity and stomach cancer have shown mixed findings. Earlier research suggested that obesity and excess weight were major risk factors for gastric cancer, primarily in men, while others found both men and women at risk. A recent meta-analysis concluded that BMI alone does not serve as a definitive risk factor for gastric cancer. Nevertheless, some evidence points to central obesity as a potential contributor to gastric cancer development. A specific study even noted a modest increase in stomach cancer occurrence in women with a higher waist-to-hip ratio (WHR). The IARC has classified gastric cancer as an obesity-related malignancy [15, 22-25].

The potential for obesity-related proteins to serve as indicators for breast cancer risk faces several hurdles. Research on the association between various obesity-related proteins and breast cancer risk has yielded inconsistent results. This inconsistency undermines the reliability of using a single obesity-related protein as a risk marker. A meta-analysis of 119 studies found that leptin is positively associated with breast cancer risk, while adiponectin showed an inverse relationship [16].

After curative liver resection, individuals with intrahepatic cholangiocarcinoma (ICC) and high BMI showed poor prognosis and a higher risk of recurrence. There was a strong link between BMI and increased 18F-FDG uptake in PET/CT scans. This high uptake was inversely related to CD8+ TILs but positively correlated with PD-L1 expression and Foxp3+ TILs. These findings emphasize the role of obesity as a risk factor for cancer development in ICC, alongside immune and metabolic changes [17].

In recent years, multiple modifiable risk factors, alongside genetic predispositions, have been identified as contributing to cancer development. Among these, overweight and obesity are particularly prominent risk factors, with prevalence rising in both developed and developing nations. Numerous studies have highlighted the connection between obesity and an increased risk of various cancers, including post-menopausal breast cancer, cervical cancer, ovarian cancer, and renal cell carcinoma. However, the exact mechanisms remain unclear. There

is also increasing evidence linking excess body fat to a higher risk of gastrointestinal (GI) cancers, including colorectal, gastric, and liver cancers. These GI cancers are among the most common and deadly worldwide, underlining their global significance. However, results remain mixed, especially concerning gender-based differences in risk [18].

Obesity also affects metabolic and endocrine pathways, including alterations in sex hormone metabolism, insulin and insulin-like growth factor signaling, and inflammatory pathways. Weight gain leads to increased insulin levels, elevated pro-inflammatory cytokines, reduced abdominal fat, and lower adiponectin levels, all of which contribute to cancer risk by promoting cell growth. Clinical trials in overweight or obese postmenopausal women have shown that calorie restriction, with or without exercise, leads to improvements in insulin resistance, decreased inflammatory markers, reduced oxidative stress, and lowered angiogenesis. These changes provide molecular and endocrine support for the theory that weight loss can decrease the incidence of obesity-related malignancies [20].

Conclusion

Obesity plays a crucial role in the development and progression of various cancers, particularly gastrointestinal (GI) cancers such as gastric, colorectal, and liver malignancies. This association is attributed to several underlying pathophysiological mechanisms, including compromised immune responses in individuals with obesity. However, it is important to recognize that conclusive evidence establishing obesity as a definitive risk factor remains lacking in many instances. Additionally, some studies indicate that sex may influence the relationship between obesity and cancer risk, suggesting that gender could be an important factor in this context.

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