Obesity as a Risk Factor for Different Cancers: Systematic Review

Abstract

According to the World Health Organization (WHO) categorization of Body Max Index, obesity is frequently measured in clinical practice by expressing body weight as a function of height (BMI). There is good evidence that obesity raises the risk of many cancers, such as esophageal adenocarcinoma, postmenopausal breast, pancreatic, colorectal, endometrial, liver cancer and kidney cancer. The study aims to summarize current evidence regarding Obesity as a risk factor for different cancers. The PubMed database and EBSCO Information Services were utilised to choose the articles. In our review, all pertinent articles related to our subject and other publications were used. Other articles that have nothing to do with this subject were not included. The group members looked through a certain format in which the data had been extracted. Obesity is a significant risk factor for the occurrence and progression of many cancer types especially when it comes to GI cancers such as colorectal, gastric, and liver cancer. This has been linked to multiple pathophysiological reasons such as lower immunological response in obese patients. However, it is worth noting that in many cases strong evidence has not been established for obesity as a risk factor, and some studies suggest that sex may play a critical role when it comes to obesity as a risk factor for cancer.

Keywords: *Obesity, Overweight, Cancer, Malignancy*

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Introduction

When calorie intake from meals exceeds energy expended through physical activity and cell metabolism, overweight and obesity result. These conditions are characterized by abnormal and excessive fat deposition. According to the World Health Organization (WHO) categorization of Body Max Index, obesity is frequently measured in clinical practice by expressing body weight as a function of height (BMI).[1, 2] Overweight is distinct as a BMI between 25 kg/m2 and 29.9 kg/m2, whereas higher levels indicate obesity. In 2016, the WHO reported that 13% of individuals were obese and 39% of adults were overweight. Because being overweight is a proven risk factor for developing cardiovascular and metabolic disorders, the impact of obesity on health systems is becoming more and more important. Additionally, it has been discovered that metabolic dysregulations linked to obesity, and more specifically, visceral adiposity, play a crucial role in tumor biology by influencing cell proliferation and spread as well as response to therapy. As a result, these conditions are studied as being linked to cancer in terms of risk, prognosis, and mortality.[1-5]

One of the most widespread cancers, primary liver cancer accounts for 9% of all cancer-related fatalities globally. About 80–90% of all primary liver malignance cases are hepatocellular carcinomas (HCC), which are the most prevalent kind of liver cancer. While Chen *et al.* found no connection between obesity and the development of HCC, other studies have found obesity to be a risk factor for the disease.[6-11]

There is good evidence that obesity raises the risk of many cancers, such as esophageal adenocarcinoma, pancreatic, postmenopausal breast, colorectal, endometrial, liver and kidney cancers. This information comes from the World Cancer Research Fund (WCRF). With respect to this, a recent research by Tahergorabi *et al.* found that the hazard of GI cancer was 3.35 times higher in people with high blood glucose compared to people with normal blood glucose, 2.37 times higher in people with lower HDL, and 10.4 times higher in people who are overweight, all of which are symptoms of metabolic syndrome.[12, 13]

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The aberrations of the insulin growth factor (IGF)-I system and signaling, low-grade chronic inflammation, sex hormone biosynthesis and pathway, oxidative stress, intestinal microbiome and changes in adipokine pathophysiology are among the biological mechanisms that link excess body fat to cancer. When calorie intake exceeds calorie expenditure, EBW and related metabolic changes, such as elevated insulin levels and altered steroid and IGF-I bioavailability, ensue. Obesity raises the level of IL-6, which prompts the liver to produce and secrete C-reactive protein. These changes have carcinogenic effects that are both general and tumor-type-specific.[14]

The anti-cancer effects of several foods, such as allium and broccoli, and micronutrients, such as selenium, vitamin D, and carotenoids, have been researched, however, it has been found that examining dietary patterns as a whole is more advantageous than focusing on specific nutrients. The traditional Mediterranean diet (MD), when compared to other dietary patterns, appears to have a significant positive impact on health. This diet's primary components include primarily vegetarian, lower in meat and dairy items, and moderate alcohol consumption, primarily in the form of wine. But MD is more than just a certain meal combo; it's also a typical way of living and interacting with the world.[1]

Study design

In order to develop a consistent empirical research programme that builds on prior knowledge, a systematic assessment of the current evidence on obesity as a risk factor for various malignancies is observed as a dependable method of locating and synthesising the peer-reviewed papers for evidence in this field. Only an understanding could be made from the qualitative quantifiable in this review. A qualitative data fusion also strives to produce assumptions that are eloquent, pertinent, and proper for persons, to guide a study agenda, and finally to advance behaviours about the link between obesity and breast cancer. The review mutual, cohesive, and, where proper, interpreted the data from the involved studies using qualitative synthesis methods.

The review attempts to go beyond the simple collection of data to offer further interpretive insights into obesity as a risk factor for various malignancies and to identify areas where more research can expand on what is already known.

Study eligibility criteria

Peer-reviewed qualitative study were included in the evaluation. Mixed-methods studies' qualitative data was assessed for applicability before being added if it passed muster. We included those studies that have been conducted over twenty years. All peer-reviewed articles published in English, reporting the association between obesity and breast cancer were included.

For the studies to be included for the review, papers were all published between 2002 and October 2022. This would guarantee the work's currency and allow for the identification of developing issues from a wide range of perspectives.

Study inclusion and exclusion criteria

The papers were chosen for the process focusing on their applicability, English, and consideration of a ten-year time limit. All additional articles, repeated studies, reviews of research, and articles with a primary purpose other than one of these areas were disregarded. The reviewers disqualified any studies that were not published in English, as well as any books, grey literature, or editorial comments. Additionally omitted were studies that solely provided qualitative data.

Selection of study

The choice measures and outcomes were obtainable using the ENTREQ criteria for offering qualitative systematic reviews. To help with repetition removal, all retrieved studies were originally introduced into the Endnote library. After removing the copies, the two authors used a shared Endnote library to independently browse the papers by title and abstract while being led by the qualifying necessities. A full-text review of the studies that the two authors had selected was directed.

Any divergences between the two authors were determined by a third author. The whole texts of all qualifying studies were studied by the two authors autonomously. When the views of the two authors differ, an agreement was sought by conversation about the issues with the third authors. For the final agenda combination, the complete texts of all pertinent study that met the inclusion standards were kept.

Data extraction

Two authors distinctly gathered data from qualifying studies onto a customised data abstraction form, filling it with material about the study population and relevant occurrences. The third review author double-checked and double-verified the pull out articles. The original author's name, the publication year, the duration of the data collection, and the geographical area of the study were all poised as study characteristics. Study-specific data was recorded, including the study's design, demographic, sample size, sampling techniques, and data collection methods. A systematic identification of obesity as a risk factor for many malignancies was made.

Data synthesis and analysis

Data examination was done lacking the use of any software package. The data was organised by theme by the authors, who then provided the themes as an analysis table (chart). The study were epitomized in the table's columns and rows, and related topics allowed us to compare the results of the studies across various themes and subthemes.

Results and Discussion

The choice and categorization of research are shown in **Figure 1**. A total of 286 studies were found after searching the aforementioned databases, which were then used for title screening. 52 of them were excluded after 198 of them were included for abstract screening. The whole texts of the

remaining 146 publications were examined. Due to varying study objectives, 137 studies were excluded after the full-text revision, while 7 were added for the purpose of final data extraction **(Table 1)**. Different study designs were used in the included studies.

Table 1 illustrates the author, country, year of publication, objective, methodology, and outcome.

In research conducted by Hashemi Madani *et al*. Researchers found no links between obesity-related factors and the prevalence of the GI malignancies indicated above in men. BMI, WC, and WHR were linked to significantly lower risks of esophageal squamous cell carcinoma (ESCC) in women.WHR was also linked to notably higher risks for gastric cancer and colorectal cancer in women. In this investigation, statistically significant correlations between obesity-related variables and incidence of gastric, colorectal, and esophageal malignancies were found in females.[15]

In another study conducted by Diao *et al*, ORPS was positively associated with the risk of breast cancer and was a better prognosticator of risk in obese women than in non-obese women in both pre-and postmenopausal in addition to having a favorable correlation with triple-negative breast cancer in premenopausal women, ORPS was favorably connected with Luminal breast cancer among other molecular subtypes. The ORPS may serve as a potential indicator of Chinese women's risk for breast cancer.[16]

According to Yukawa *et al*. In comparison to the normal weight group, the obese group had increased serum levels of carbohydrate antigen 19-9. The intrahepatic metastatic rate and tumor size were also noticeably higher in the obese group. The prognosis of patients in the obesity group was noticeably poorer than that of those in the normal weight group. On 18F-FDG PET/CT, BMI also showed a favorable connection with SUVmax. Higher rates of PD-L1 expression, lower CD8 + tumor-infiltrating lymphocyte (TIL) counts, and higher Foxp3 + TIL counts were all observed in patients with high 18F-FDG uptake. The results of patients with ICC may be predicted by their elevated BMI. Obesity may contribute to the advancement of ICC, presumably by altering immune function and metabolic activity.[17]

In Loosen *et al.* research, Multivariable regression models confirmed that during the observation period, the proportion of obese male and female and overweight patients with colon cancer increased stepwise from 0.5% and 0.64% to 0.71% and 0.91%, respectively. However, obesity was substantially linked to both rectal cancer and liver cancer in males exclusively, according to multivariable regression models. Conclusions: According to research data, obesity is a significant risk factor for the occurrence of the colon, rectal, and liver cancer, with sex being one of the contributing factors.[18]
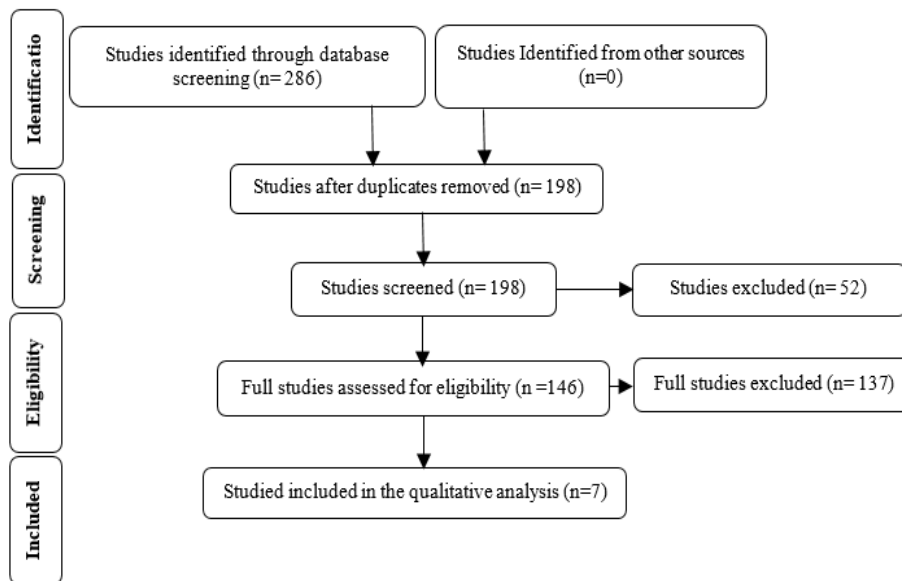

Figure 1. Flow chart representing the data extraction process

Table 1. Extracted data from collected studies		
Author, Publishing Year	**Objective & Methodology**	**Outcomes**
Hashemi Madani et al. 2021[15]	aimed to look into the role of overall and specific obesity indicators in the prophesizing of gastrointestinal (GI) cancer incidents. 47586 cancer-free people who were followed for 12.3 years were included in this study. Researchers looked into the relationship between obesity-related measurements at enrolments, such as BMI, waist	Researchers found no links between obesity-related factors and the prevalence of the GI malignancies indicated above in men. statistically significant correlations between obesity-related variables and incidence of gastric, colorectal, and esophageal malignancies were found in females.

	circumference, and waist-to-hip ratio, and the prevalence of pancreatic, esophageal, gastric, and colorectal malignancies.	
Diao *et al.* 2021[16]	The objective of this study was to develop a reliable obesity-related protein score (ORPS) that could be applied to determine the risk of breast cancer. Researchers chose nine such proteins that are stable in vitro based on data from high-quality systematic reviews and population studies, and they measured their circulating concentrations by ELISA in a case-control study carried out in Chengdu, Sichuan, China, with 279 breast cancer cases and 260 healthy controls..	ORPS was positively correlated with the risk of breast cancer and was a better predictor of risk in obese women than in non-obese women in both pre-and postmenopausal In addition to having a favorable correlation with triple-negative breast cancer in premenopausal women, ORPS was favorably connected with Luminal breast cancer among other molecular subtypes. The ORPS may serve as a potential indicator of Chinese women's risk for breast cancer.
Yugawa *et al.* 2021[17]	This study focused on metabolic activity and immunological status as it explored the connections between BMI and clinicopathological traits and patient outcomes.	In comparison to the normal weight group, the obese group had increased serum levels of carbohydrate antigen 19-9. The intrahepatic metastatic rate and tumor size were also noticeably higher in the obese group. The prognosis of patients in the obesity group was noticeably poorer than that of those in the normal weight group. On 18F-FDG PET/CT, BMI also showed a favorable connection with SUVmax. The results of patients with ICC may be predicted by their elevated BMI. Obesity may contribute to the advancement of ICC, presumably by altering immune function and metabolic activity.
Loosen *et al* 2022[18]	Sex differences in obesity and overweight influence the risk for gastrointestinal cancer. From 2010 to 2019, the Disease Analyzer database yielded a total of 287,357 adult outpatients with a BMI value that was accessible (IQVIA).	Obesity is a significant risk factor for the occurrence of the colon, rectal, and liver cancer, with sex being one of the contributing factors.
Ramdass 2022[19]	Obesity and Cancer Mortality Association. 784 adult patients with cancer had their medical records retrospectively reviewed.	Among the patients, 43 (5.2%) did not survive cancer, while 741 (94.8%) did. Patients in the cancer non-survivors group had an average body mass index (BMI) that was considerably lower than that of the cancer survivors group.. Patients who were not clinically obese had 4.9 times higher cancer mortality chances..In comparison to individuals without peripheral artery disease (PAD), those with PAD had 3.5 times higher risks of dying from cancer.
Yeh *et al.* 2020[20]	to ascertain if a rigorous lifestyle intervention for weight loss reduces the incidence and death of cancer. The goal of the study was to determine whether those assigned to the intensive lifestyle intervention would have experienced lower rates of overall cancer, cancer-related obesity, and cancer mortality. 4,859 people in this research were cancer-free at baseline, except for non-melanoma skin cancer.	Incidence of all cancers, incidence of cancers unrelated to obesity, and total cancer mortality, did not significantly vary between the two groups.
Youssef *et al.* 2021[21]	Obesity and the prevention of thyroid cancer: Pooled findings from 24 million cohorts on the effects of BMI and weight change on thyroid cancer development. A thorough search was conducted up until February 25, 2020. Fixed and random models were used to evaluate the pooled relative risk (RR). Using the Q-test and I2 index, heterogeneity between publications was investigated. Egger's regression test was used to evaluate publication bias.	There were a total of 31 studies with 24,489,477 cohorts that qualified. A combined study showed that cohorts that were normal and underweight had a lower risk of TC. On the other hand, cohorts that were overweight or obese had a higher risk of developing TC. Women were more likely to acquire TC if they were than males were. Additionally, weight loss lowered the chance of acquiring TC whereas weight gain increased the risk of doing so. Results indicated that weight change effects were similar for both males and females.

Even while elevated BMI is the obesity-related illness that has been examined the most frequently, additional biomarkers have been identified as indicators of a higher risk of developing cancer. Fasting insulin and BMI are both linked to late-stage illness and a poor prognosis, making them risk factors for breast cancer. Additionally, a greater blood level of C-peptide, a marker of insulin production that is often raised in conditions of insulin resistance, has been linked to an increased risk of developing colorectal cancer.[1]

Data on the link between stomach cancer risk and obesity are inconsistent. Previous research indicated that obesity and overweight were only significantly linked to a higher risk of gastric cancer in males, whereas another reported that both men and women were positively affected. A more recent meta-findings analysis revealed that an increase in BMI is not a definite risk factor for stomach cancer. There is some evidence—albeit a few meta-analyses that central obesity may play a part in the development of gastric cancer. Similarly, one study found a weakly significant increase in the incidence of stomach cancer in women who had WHR. IARC has identified gastric cancer as an obesity-related malignancy.[15, 22-25]

Although it has been proposed that proteins associated with obesity may be useful as indicators of the risk of breast cancer, several significant obstacles must be addressed. Since the relationships between different obesity-related proteins and breast cancer are inconsistent, the evidence to date, for example, shows that utilising a single obesity-related protein as a risk indicator for breast cancer is undependable. Using leptin and adiponectin as illustrations, a meta-analysis of data from 119 investigate found that leptin concentration is favourably associated to breast cancer risk while adiponectin is negatively linked.[16]

After curative hepatic resection, individuals with ICC had a poor prognosis and a higher probability of recurrence when their BMI was high. Importantly, there was a strong correlation between BMI and the buildup of ^{18}F-FDG on PET/CT. Furthermore, high ^{18}F-FDG uptake was inversely connected with CD8 + TIL counts but positively correlated with PD-L1 expression and Foxp3 + TIL counts. These findings point to obesity as a risk factor for the development of cancer in ICC, together with changes to immune function and metabolic activity.[17]

In recent decades, several modifiable risk factors for cancer have been found, in addition to genetic changes linked to an elevated risk for cancer development. A significant risk factor for the development of cancer among them is overweight and obesity, which is sharply increasing in both high and less-developed countries of the world. Numerous papers have demonstrated a link between obesity and an augmented risk for the advance of various cancer entities, including post-menopausal breast cancer, cervix, ovarian, and renal cell carcinoma. However, the underlying pathophysiological mechanism is still not fully understood. Additionally, a growing body of research indicates a link between excess body fat and a higher risk of GI malignancies such as colorectal, gastric, and liver cancer. The majority of these GI malignancies are among the most prevalent tumor entities globally and are linked to relatively high death rates, which supports their significant global importance. Results, however, have been mixed, especially in terms of sex-dependent impacts.[18]

Among other metabolic and endocrine disorders, obesity is associated with alterations in the metabolism of sex hormones, insulin and insulin-like growth factor signalling, and inflammatory pathways. Gaining weight increases insulin and pro-inflammatory cytokines, lowers intra-abdominal fat, and levels of the endogenous insulin sensitizer adiponectin, all of which increase the risk of cancer through reducing cell proliferation and cancer risk factors. According to data from clinical studies in overweight or obese postmenopausal women, calorie restriction diets with or without exercise had positive effects on insulin resistance, decreased inflammatory biomarkers, oxidative stress, and angiogenesis in addition to improving insulin sensitivity. These underlying processes offered molecular and endocrine proof in favor of the theory that losing weight may lower the incidence of malignancies linked to obesity.[20]

Conclusion

Obesity is a significant risk factor for the occurrence and progression of many cancer types especially when it comes to GI cancers such as colorectal, gastric, and liver cancer. This has been linked to multiple pathophysiological reasons such as lower immunological response in obese patients. However, it is worth noting that in many cases strong evidence has not been established for obesity as a risk factor, and some studies suggest that sex may play a critical role when it comes to obesity as a risk factor for cancer.

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