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Research Article

Obesity influencing Breast Cancer

Obesity as A Risk Factor for Breast Cancer and Its Prognosis: Systematic Review

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Abstract: Obesity is a significant public health issue, particularly in developed countries such as the United States, where more than 36% of adults are obese. Understanding how obesity affects breast cancer is essential for public health because it is the most common cancer and the second leading cause of cancer death among women in developed countries. Numerous studies show a significantly more vital link between increased body mass index (BMI) and breast cancer incidence. Furthermore, obese women with breast cancer have a higher risk of all-cause and breast cancer-specific mortality than non-obese women. A better understanding of the relationship between obesity and breast cancer is critical because this patient population has unique diagnostic and treatment challenges. The study aims to summarize current evidence regarding the association between obesity and breast cancer as a risk factor and its effect on patients' prognosis. For article selection, the PubMed database and EBSCO Information Services were used. All relevant articles relevant to our topic and other articles were used in our review. Other articles that were not related to this field were excluded. The data was extracted in a specific format that the group members reviewed. Our study included nine studies, all of which indicated a positive correlation with different types of breast cancer as a risk factor. One study reported no effect on prognosis.

Keywords: Breast Cancer, Tumor, Obesity, BMI, Overweight, Malignancy

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1. INTRODUCTION

Obesity is a significant public health issue, particularly in developed countries such as the United States, where more than 36% of adults are obese [1]. Obesity and overweight, calculated in the form of body mass index (BMI) [BWI = weight (kg)/height (m2)] or may be estimated by the distribution of fat in the body, is a known risk factor for breast cancer in postmenopausal women, which is associated with the synthesis of estrogen from fat tissues [2]. It has been estimated that about 20% of all cancers are caused by excess weight [3], and the Million Women Study, the most extensive study of its kind on women, has shown that approximately half can be attributed to obesity in postmenopausal women [4]. Many prospective epidemiological studies have demonstrated a direct association between overweight and cancer, even though obesity alone does not apparently heighten cancer risk in all tissues by the same amount [5]. Recent research suggests a link between BMI and breast cancer risk. According to a meta-analysis by Liu et al. [6], a 5 kg/m2 increase in BMI is associated with a 2% increase in breast cancer risk; however, a higher BMI in premenopausal women is associated with a protective effect on breast cancer risk. Iyengar et al. seven also demonstrated that excess adiposity in postmenopausal females is linked to an increased risk of breast cancer, particularly hormone-dependent estrogen/progesterone receptor positive (ER/PR + ve) cancer. Obesity affects the course of breast cancer from the moment it is diagnosed. Overweight and obese women generally have lower compliance with healthy habits and are less likely to follow screening recommendations such as mammography [8]. One could hypothesize that obese women have more fatty tissue in their breasts, reducing breast density and making cancer detection easier on mammography. On the other hand, mammography sensitivity is comparable in obese and non-obese women. Previous studies found that false-positive findings in obese women were 20% higher than in normal- or low-weight women [9]. Howell et al. came to the conclusion that lifestyle changes, such as keeping or lowering BMI to below 25, participating in moderate physical exercise, and limiting alcohol consumption to no more than three drinks per week, can together lower the risk of breast cancer by more than 30% [9]. According to the World Cancer Research Fund, one of these factors—maintaining a healthy weight—could prevent 17% of breast cancer diagnoses in the U.S. [10]. Given the ongoing obesity epidemic, in which two out of every three women in the United States are overweight or obese with a BMI of 25 or higher, this relationship is significant for public health. Understanding how obesity affects breast cancer is essential for public health because it is the most common cancer and the second leading cause of cancer death among women in developed countries. Numerous studies show a significantly more vital link between increased body mass index (BMI) and breast cancer incidence. Furthermore, obese women with breast cancer have a higher risk of all-cause and breast cancer-specific mortality than non-obese women with breast cancer [10].

1.1 Study Objective

The study aims to summarize current evidence regarding the association between obesity and breast cancer as a risk factor and its effect on patients' prognosis.

2. MATERIAL AND METHODS

2.1 Study design

A systematic review of the current evidence on the association between obesity and breast cancer is considered a robust way of identifying and synthesizing the peer-reviewed articles for evidence in this area to define a cohesive empirical research agenda that builds on prior knowledge. This review will include qualitative evidence only to produce an interpretation. Further, a synthesis of qualitative data aims to generate findings that are meaningful, relevant and appropriate to individuals, to inform a research agenda and ultimately to more effective practices on the association between obesity and breast cancer. The review will use qualitative synthesis methods to combine, integrate and interpret, where possible, the evidence from the included papers. The study aims to move beyond the aggregation of available data to provide further interpretive insights into the association between obesity and breast cancer and define where future research can add to what is known.

2.2 Identification and selection of studies

We have developed a search strategy for case-control and cohort studies on the Cochrane Library, Medline, Embase and Cancer Lit. Bibliographies of included studies and proceedings from the meetings of the American Society of Clinical Oncology, the Conference on Diet Nutrition and Cancer (The American Institute for Cancer Research) and the European Conference on Nutrition and Cancer (International Agency for Research on Cancer) were searched for further studies. Experts were contacted, and there were no language restrictions. The abstracts of all relevant studies were reviewed, and full manuscripts were obtained for those that appeared suitable. Cohort or case-control studies were eligible for inclusion, provided separate analyses of the relationship between BMI and breast cancer risk in pre-and/or postmenopausal women were undertaken. For inclusion in the study, both cohort and case-control studies needed to provide sufficient information or relative risk based on quantiles for BMI. Two reviewers assessed inclusion independently, and differences were resolved by discussion. Data extracted (independently in duplicate) included: study design; participant data (mean age, country of study, menopausal status, mean BMI, and the association between breast cancer and BMI). Study quality characteristics were assessed using some of the criteria of Margetts et al. and Downs et al., plus additional factors specifically relevant to this topic, such as whether cohort studies had updated menopausal status throughout the study. The authors were contacted about needing more information. We used the most recent published data on the largest dataset for studies with multiple publications. Unadjusted relative risks were calculated from the study's number of women diagnosed with breast cancer.

2.3 Study Inclusion and Exclusion criteria

The articles were selected based on their relevance to the project, English and the time restriction of twenty years was considered. All other articles which do not have one of these topics as their primary end or repeated studies and review studies were excluded. The reviewers will exclude any studies not available in English, conference abstracts, books or grey literature and editorial comments. Studies reporting only qualitative data were excluded.

2.4 Search strategy

A systematic search strategy was developed using a combination of Medical Subject Headings (MeSH) and controlled vocabulary to identify peer-reviewed articles on primary dysmenorrhea in Saudi Arabia. The databases were PubMed/MEDLINE, Scopus/Embase (Elsevier), EbscoHost, and Google Scholar.

2.5 Selection of study

The ENTREQ guidelines for reporting systematic qualitative reviews were used to demonstrate the selection processes and results. All retrieved studies will initially be imported into the Endnote library to assist in removing duplicates. After removing the duplicates, the Endnote library was shared between the two reviewers to screen the articles by title and abstract, guided by the eligibility criteria. The studies which the two reviewers would have agreed on were subjected to a full-text review. A third reviewer will adjudicate any discrepancies between the two reviewers. The two reviewers will independently review the full text of all eligible studies. In the case of differences between the two reviewers, a consensus was sought by discussing the differences with the third reviewer. Finally, the full texts of all relevant studies found to meet the inclusion criteria were retained for the final framework synthesis.

2.6 Data extraction

Two reviewers independently extracted data from eligible studies onto a customized data extraction form and populated it with variables about the study population and phenomena of interest. The third review author double-checked and verified extracted articles. Study characteristics that were removed will include the name of the first author and year of publication, data collection period and region in which the study was conducted. Specific details will then be captured, including the study design, population, sample size, sampling procedures and data collection procedures. Association between obesity and breast cancer was systematically identified.

3. STATISTICAL ANALYSIS

No software was utilized to analyze the data. Instead, the reviewers will sort the data by theme and present the themes in an analysis table (chart). The columns and rows of the table will reflect the studies and related themes and enable us to compare the findings of the studies across different themes and subthemes.

3.1 Mapping and interpretation

The reviewers will use charts to define the identified concepts and map the range and nature of the phenomena. Our review will explore associations between the themes to help clarify the findings. Our study will map and interpret findings per the review objectives and emerging themes.

4. RESULTS

As illustrated in (Figure 1), the selection and identification of studies, the search of the mentioned databases returned a total of 314 studies that were included for title screening. Two hundred thirteen of them were included for abstract screening, which led to the exclusion of 67 articles. The remaining 146 publications' full texts were reviewed. The full-text revision led to the exclusion of 137 studies due to differences in study objectives, and nine were enrolled for final data extraction (Table 1). Four studies out of 9 reported an association between obesity and the risk of breast cancer post-menopause 15, 16, 18, 19 and an inverse association in premenopausal women 18. One study regarding breast cancer in men reported that obesity at all adult ages, particularly recent abdominal obesity, is associated with a raised risk of breast cancer in men 17. As for prognosis, one study reported that higher BMI is associated with breast cancer mortality among women with Stage I but not among women with more advanced disease 13. In contrast, another Chinese study reported no association between BMI and prognosis.

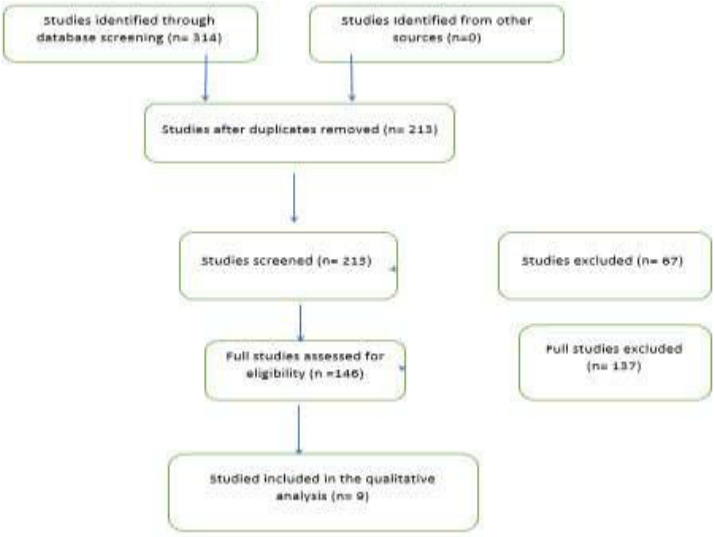

Fig (1): PRISMA chart of included studies

Table 1: Summarization of included articles

Author, Publishing Year	Methodology	Outcome
Nattenmüller, Cina J et al. (2018) [11].	Tumour tissues from 657 incident breast cancer cases were formalin-fixed and paraffin-embedded (FFPE) for histopathological analysis. In addition, Multivariable Cox regression models stratified by menopausal status and hormone therapy (H.T.) use were used to examine the associations between BMI and breast cancer risk across subtypes.	Obesity is related to the risk of breast tumours with lower aggressiveness
Alim, Nural Erzurum, and Gul Kiziltan. (2016) [12]	Data from 525 breast cancer patients diagnosed between 2003 and 2010 in a multi-centre in China were retrospectively analyzed. Following the application of the exclusion criteria, 315 patients with complete data were retained. The chi-square test was used to compare their clinical and pathological characteristics. The Kaplan-Meier method was used for survival analysis. Cox regression was used in univariate and multivariate analyses to calculate the hazard ratios for hormone receptor status, HER-2 status, lymph node status, age, BMI, and tumour size (H.R.).	BMI of breast cancer patients is related to age but not prognosis.
Moore, A Holliston et al. (2018) [13]	Women diagnosed with AJCC Stage I, II, or III breast cancer in 2004 (n = 5394) were identified from a population-based National Program of Cancer Registries (NPCR) patterns of care study (POC-BP) drawing from registries in seven U.S. states. Differences in overall and breast cancer-specific mortality were investigated using Cox proportional hazards regression models that accounted for demographic and clinical covariates and age- and stage-based subgroup analyses.	Higher BMI was associated with breast cancer mortality among women with Stage I disease but not among women with more advanced disease.
Al Jarroudi, Ouissam et al. (2017) [14]	The Regional Oncology Center Hassan II-Oujda is conducting a descriptive and analytical retrospective cohort study. We found 115 patients with triple-negative breast cancer who met the inclusion criteria and were treated between January 2009 and December 2011. The Kaplan-Meier and Cox models collected clinicopathological characteristics to assess the relationship between BMI and overall survival and disease-free survival at five years.	Being overweight is an independent prognostic factor for O.S. and DFS at five years in all patients with triple-negative breast cancer, and menopausal status may be a mitigating factor. However, premenopausal women with overweight are at greater risk of death and progression than women with normal weight.
Gravena, Angela Andréia França et al. (2018) [15]	A case-control study was conducted on 100 newly diagnosed breast cancer patients and 400 age-matched controls. The women were divided into two groups: pre- and postmenopausal.	There is an association between obesity and the risk of breast cancer postmenopause; moreover, there is an association between the occurrence of the positive E.R. subtype in postmenopausal women and pre-diagnostic obesity according to BMI.
Neuhouser, Marian L et al. (2015) [16]	The WHI clinical trial protocol in 40 U.S. clinical centres included measured height and weight, baseline and annual or biennial mammography. It adjudicated breast cancer endpoints in 67 142 postmenopausal women ages 50 to 79 years. The women were enrolled between 1993 and 1998, with a median of 13 years of follow-up until 2010; 3388 invasive breast cancers were discovered.	Obesity is associated with increased invasive breast cancer risk in postmenopausal women.
Swerdlow, Anthony J et al. (2021) [17]	The study was a population-based case-control study of breast cancer in men in England and Wales, including 1998 cases diagnosed between 2005 and 2017 at ages under 80 and 1597 male controls, with questions about various anthropometric variables at multiple generations. All statistical significance tests were two-sided.	Obesity at all adult ages, particularly recent abdominal obesity, is associated with a raised risk of breast cancer in men, probably because of the conversion of testosterone to estrogen by aromatase in adipose tissue. The association is influential for HER2-expressing tumours.
Park, Jae Won et al. (2021) [18]	Using the Korean National Health Insurance System Cohort, the researchers identified 6,467,388 women.	There was a positive relationship between obesity and breast cancer in postmenopausal

	Adjusted hazard ratios (aHRs) and 95% confidence intervals (C.I.s) for breast cancer risk about BMI and W.C. were calculated using Cox-proportional hazard models.	women and an inverse association in premenopausal women.
Park, Boyoung et al. (2021) [19]	A sample of 3,095,336 postmenopausal cancer-free women aged 40 to 79 years who had their National Health Insurance Service health examination between 2009 and 2010 was included in the study. Invasive breast cancer incidence was tracked until 2018. Obesity (BMI 25 kg/m2), MetS, and each component of MetS were investigated.	Obesity and metabolic syndrome (MetS) were independently associated with an increased risk of breast cancer in postmenopausal women, despite the relationship between MetS and breast cancer appears to result from a partial association with BMI.

Table (2): Demographics of participants

Author	Country	Sample size	Pre and post menopausal	Mean age of pre	Mean age of post	Mean BMI
Nattenmüller, Cina J et al. (2018) 11.	Germany	27,012 women	16207 pre and 10805 post	-	-	24.7
Moore, A Holliston et al. (2018) 13	USA	5394 cases	5394 post		70.2 years	29.1 kg/m2
Al Jarroudi, Ouissam et al. (2017) 14	Morocco	115 patients				
Gravena, Angela Andréia França et al. (2018) 15	Brazil	500 women (100 case group and 400 control)		57.4 years in case group and 52.3 in control		
Swerdlow, Anthony J et al. (2021) 17	England	1998 cases 1597 male controls				
Park, Jae Won et al. (2021) 18	Korea	6,272,367	1,418,180 premenopausal and 4,854,187 postmenopausal women	43.7 years	59.9 years	23.1 kg/m2
Park, Boyoung et al. (2021) 19	Korea	3,095,336 women	All post menopausal	-	60.6	1,159,536 (37.5%) were obese and 1,036,970 (33.5%) had MetS

Table (3): Breast Cancer and BMI determinants among participants

Author	Pre and postmenopausal	Mean BMI	Follow up period	risk of invasive breast cancer (IBC)
Nattenmüller, Cina J et al. (2018) 11.	16207 pre and 10805 post	24.7	13.0 (±3.1) years	obesity is related to the risk of breast tumours with lower aggressiveness
Moore, A Holliston et al. (2018) 13	5394 post	29.1 kg/m2		BMI was not associated with higher overall mortality
Al Jarroudi, Ouissam et al. (2017) 14			3 years	Premenopausal women with overweight are at greater risk of death and progression than women with normal weight.
Gravena, Angela Andréia França et al. (2018) 15	–	—		There is an association between obesity and the risk of breast cancer postmenopause.
Swerdlow, Anthony J et al. (2021) 17	–	–	12 years	Obesity at all adult ages, particularly recent abdominal obesity, is associated with a raised risk of breast cancer in men
Park, Jae Won et al. (2021) 18	1,418,180 premenopausal and 4,854,187 postmenopausal women	23.1 kg/m2	6.2 years	lower in the underweight group (aHR 0.82, 95% CI 0.75–0.89), while it increased linearly in the overweight (1.11, 1.08–1.14), obese (1.28,1.25–1.32), and severely obese groups (1.54,1.47–1.62)
Park, Boyoung et al. (2021) 19	All postmenopausal	1,159,536 (37.5%) were obese, and 1,036,970 (33.5%) had MetS	—	Obesity and MetS were independently associated with an increased risk of breast cancer in postmenopausal women.

5. DISCUSSION

Obesity is now linked to the development of 13 different types of cancer, including oestrogen receptor-positive breast cancer in postmenopausal women, according to new research. A variety of local and systemic changes, including increased insulin and glucose and adipose tissue-derived oestrogens, adipokines, and inflammatory mediators, are hypothesized to support this relationship. Tumour cells have dysregulated metabolic pathways for energy production and utilization, a newly recognized hallmark of cancer. Non-neoplastic cells in the tumour microenvironment are also thought to have dysregulated metabolism. Obesity-related factors regulate metabolic pathways in breast cancer cells and cells in the breast microenvironment, establishing a molecular link between obesity and breast cancer [20]. In the United States, nearly 35% of premenopausal women aged 20 to 59 were obese between 2011 and 2014 [21]. Breast cancer affects approximately 20% of women under the age of 50. Obesity has been linked to an increased risk of premenopausal breast cancer [22- 25]. A meta-analysis of seven studies involving 337,819 women and 4385 invasive breast cancers found an inverse relationship between BMI and premenopausal breast cancer risk when comparing women with a BMI >31 kg/m2 to those with a BMI 21 kg/m2 [26]. An inverse correlation between premenopausal breast cancer risk and obesity per unit increase in BMI was also found in a meta-analysis of nine studies [27]. A further large meta-analysis of 20 data sets, including >2.5 million women and 7930 premenopausal breast cancers, found that increasing BMI by 5 kg/m2 reduces premenopausal breast cancer risk by about 8%[28]. That meta-analysis included prospective cohort studies with a more robust study design than case-control studies. Obesity does not reduce the risk of premenopausal breast cancer in all studies. A case-control study found a marginally positive relationship between obesity and premenopausal breast cancer risk [29]. Furthermore, the Breast Cancer Prevention P1 trial, which included 5864 premenopausal women, discovered that obesity was associated with an increased risk of premenopausal breast cancer [30]. In the studies described above, differences in the distribution of women with hormone receptor-positive and negative breast cancer may explain the disparities in results. Furthermore, two meta-analyses found ethnic differences, with most groups showing an inverse association between increased BMI and premenopausal breast cancer risk, but the Asian population showed a positive association [28, 31]. Between 2011 and 2014, the prevalence of obesity among U.S. women aged 60 and up was approximately 39% [21]. Metabolic syndrome has become more common as obesity has increased [32] and is associated with an increased risk of postmenopausal breast cancer [33]. Obesity has been linked to an increased risk of postmenopausal breast cancer in numerous studies [34-37]. The Million Women Study followed 1.2 million U.K. women aged 50 to 64 years for an average of 5.4 years, including 45,037 with breast cancer, and discovered that obesity was associated with a nearly 30% increased risk of developing postmenopausal breast cancer [38] Correspondingly, a meta-analysis of 34 studies involving >2.5 million women, including 23,909 postmenopausal breast cancers, found that each 5kg/m2 increase in BMI was associated with an increased risk of postmenopausal breast cancer [28]. Obesity is associated with a higher risk of postmenopausal breast cancer in women who have not used menopausal hormone therapy, and this association may be limited to women who have not used menopausal hormone therapy (H.T.) [39- 41]. Triple-negative breast cancers (TNBCs) are very aggressive and lack expression of E.R., PR, and human epidermal growth factor receptor 2 (HER2). Obesity, in contrast to E.R. positive breast cancers, is linked to an increased risk of premenopausal E.R. negative breast cancer [42,-46]. A strong positive association between BMI and premenopausal TNBC risk was found in the Cancer and Steroid Hormone (CASH) population-based, case-control study of 3432 breast cancers [47]. Obesity and the risk of ER negative breast cancer and TNBC appear to differ before and after menopause. Although obesity is associated with an increased risk of ER negative breast cancer and TNBC before menopause, the risk of ER negative breast cancer and TNBC is minimally or inversely associated with obesity after menopause. Other studies, as well as a Swedish mammography cohort of 51,823 postmenopausal women, found an inverse relationship between obesity and hormone receptor-negative breast cancer [48]

6. CONCLUSION

Our study included nine studies, all of which indicated a positive correlation with different types of breast cancer as a risk factor. One study reported no effect on prognosis. Ongoing research into the multifactorial relationships between obesity and breast cancer outcomes and factors that may modify these relationships was critical in the continuing effort to reduce the disease burden caused by breast cancer.

7. AUTHOR CONTRIBUTION STATEMENT

Dr. Khulud Sughayyer Naif Alanazi conceptualized and designed the study. Dr. Rawan Dubas Alanazi and Dr. Almagd Mtap N Alanzai searched data bases for previous literature. Dr. Ayashah Moulfi Alhazmi and Dr. Rasha zaki A Alruwaili screened and filtered selected studies. Dr. Asma Saleh S Alruwaili and Dr. Eman Mazyad alruwaili wrote the manuscript. Dr. Amjad Mofareh S Alruwaili and Dr. Ghzl Ghazi Alenezi revised the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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