DOI: https://doi.org/10.54393/pjhs.v3i07.432

PAKISTAN JOURNAL OF HEALTH SCIENCES

https://thejas.com.pk/index.php/pjhs

Volume 3, Issue 7 (December 2022)

Review Article

Relationship Between Obesity, Menopausal Status and Breast Cancer Risks - A Review

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ARTICLE INFO

Key Words:

Breast cancer, obesity, Risk Factors, Menopausal Status, Adipose tissue Estrogen

How to Cite:

Mehmood, S. ., Yasin, A. ., Ahmad, I. ., Abiha Rabab, S. ., & Muhammad Soomar, A. . (2022). Relationship Between Obesity, Menopausal Status and Breast Cancer Risks - A Review: Obesity, Menopausal Status and Breast Cancer Risks. Pakistan Journal of Health Sciences, 3(07). https://doi.org/10.54393/pjhs.v3i07.432

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Received Date: 12th December, 2022
Acceptance Date: 24th December, 2022
Published Date: 31st December, 2022

ABSTRACT

"Breast cancer" is of the leading malignant neoplasia responsible for high rate of mortality and morbidity. There are many risk factors of "breast cancer" but "obesity" and increased weight have been recognised as the principal risk as well as the prognostic factors causing "breast cancer" especially in "postmenopausal" female. "obesity" possess the complex association with "breast cancer" which varies in menopause status ("premenopausal" and "postmenopausal"). Various hypotheses have been proposed to demonstrate the interaction among "obesity" and high risks of "breast cancer" in "postmenopausal" females. The specific "obesity"-associated factors", such as leptin, insulin, and inflammatory mediators, are involved in progression of "breast cancer" and its prognosis. The adiposity level before menopause, is inversely interrelated to "breast cancer" risk, exhibiting the protective effect, however in "postmenopausal" females, predominantly in elderly women, the association is positively related to cancer, indicating "obesity" as a risk factor of "breast cancer". Positive association is found for higher levels of estrogen production in adipose tissue, resulting in elevated levels of estradiol in systematic circulation, promoting "obesity" related breast carcinogenesis in in "postmenopausal" women. The expression of tumors also effect both progesterone and estrogen receptors. It can be concluded that relation of adiposity and menopausal status is protective effect in younger females (<35 years), before the menopause and negative effects promoting the cancer in older "postmenopausal" women. Therefore, the body composition and "obesity" are highest risk factors for the prognosis of "postmenopausal" breast carcinoma.

INTRODUCTION

Various research studies have demonstrated that increased concentrations of circulating estrogen levels and higher bioavailability leads to the increased risk of "breast cancer" in "postmenopausal" stages [1, 2]. Additionally, several reports also showed the positive relationship among the menopausal hormones, their changes and the adiposity or "obesity" [3, 4]. Although "obesity" is recognised as the higher risk factor for "breast cancer" especially in "postmenopausal" females, the contrary condition embraces aforementioned to the stage of menopause where the "obesity" is linked with the lower risk in younger women [5]. The consequence of "obesity" on the risks of "breast cancer" and the hypotheses regarding the inconsistent effects which are observed in different circumstances in relation to the different status of menopause ("postmenopausal" and "premenopausal"). Despite the fact there are numerous interconnected cellular pathways and mechanisms in which the "obesity" is directly involved in augmenting the risks of developing "breast cancer", predominantly the mechanisms which are directly involved in controlling the actions of insulin and the function of adipokines [6]. The estrogenic and the steroid hormones also effects the bioactivity of menopausal hormones. The production of extra glandular estradiol

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levels is considered to be one of the basic factor which can be enhance the risks of risk of "breast cancer" after the stages of menopause, but the link among the "obesity" and the reduced risks of "breast cancer" in "premenopausal" females of the younger age, is still not clear.

Obesity and Breast cancer

"Obesity" is generally known as the higher concentration of fats deposits in the body which is associated with several disorders including the type 2 diabetes, and endometrial, metabolic syndrome, and "breast cancer" [6]. There are found various epidemiological evidences supporting the correlation among "breast cancer" and "obesity" in females. The major pathway responsible for regulation of homeostasis as well as "AMP-activated protein kinase (AMPK)" responsible of the actions of phosphorylation and inhibition of the actions of "cAMP-responsive element binding protein (CREB)-regulated transcription coactivator 2 (CRTC2)". In the women after menopause ("postmenopausal" stage), the regulation depending on CREB regarding the aromatase is a critical determining factor for the formation of breast tumor through the production of estrogens. It has been also found that the aromatase expression and its regulation in the breast via pathway of CRTC2and AMPK, as a response to the changed adipokine milieu related to "obesity", demonstrates the substantial connotation among "obesity" and risk of "breast cancer" [7]. Additionally, it is noteworthy that the relationship among "obesity", "breast cancer" and total risk seems to be extremely reliant on the status of menopausal. Thus, it is clear that in "postmenopausal" females, "obesity" is involved in increasing the threat of "breast cancer". Conversely, "obesity" acts as a defensive factor against the risks of "breast cancer" in ""premenopausal"" women involving different clinical factors theoretically involved including "estrogen", "adipokines", "mammogram density", activation of "insulin-signalling pathway" as well as "inflammatory pathways" [8]. So, there exists evidence which supports the strong link among metabolic syndrome, "obesity", insulin resistance involving different factors leading to the increased risk of different types of cancers including the colon as well as the "breast cancer".

Obesity and Postmenopausal Breast cancer

In "postmenopausal" females, "obesity" has been identified as the major risk factor of "breast cancer" [3, 9]. Additionally, there is strong association with the increase in adiposity with the passage of time after menopause, and the effect of "obesity" is consistent with the expression of adipose tissue-derived estrogens to promote the prognosis of cancer. According to the study by Brandt *et al.* (2000) values of BMI greater than 28.4 kg/m^2 showed adequate risks of "breast cancer" in the age group of females among 50 years to 69 years, and this association become even stronger when the age exceeds 70 years [9]. Howell *et al.* (2009) reported after summarizing various research studies, and demonstrated that which the increased weight gains after 18 years of age, particularly after 29 years of age up to the age of menopause, is even the strongest indicator and risk factor of developing "postmenopausal" "breast cancer". It was also indicated that increase in weight usually is more rapid after the menopause [10]. Most of the studies claimed that the relationship of adiposity and "postmenopausal" "breast cancer" applies more specifically to "obesity" of upper parts of body and high waist hip ratio is also one of the risk factor [6, 11]. The study by Huang *et al.*, (1999) also reported a strong and affirmative link of waist circumference and the WHR with "breast cancer" risk, more specifically in those "postmenopausal" women who never get any estrogen replacement therapy [12].

"Obesity" and "postmenopausal" estrogen production

Estrogens is produced by conversion of androgenic steroids due to the action of influence of aromatase enzyme and their complexation. Ovaries are the chief organs responsible for the expression of aromatase in "premenopausal" women, but after the stage of menopause, the adipose tissue is the principal site for the production of estrogen, where androstenedione undergoes aromatization, that is secreted by adrenal glands as well as the ovaries in "postmenopausal" women, resulting in production of estrone. Both the production of androstenedione and the activity of aromatase enzymes are increased in over weight and "obesity", so there exist a positive relation among production of estrogen and the "postmenopausal" adiposity [4, 6]. Various studies reported that the concentration of both estrone and estradiol are increased in obese "postmenopausal" females [3, 13, 14]. Furthermore, the menopausal hormonal changes also contribute towards augmented risk of emergent "breast cancer" in "postmenopausal" obese females especially related to the estrogen levels. A study by Baglietto *et al.* conducted on "postmenopausal" women also showed a positive correlation among free estradiol and the BMI [14]. According to a research the relation among the risks of "breast cancer" and BMI becomes even stronger in elderly "postmenopausal" females with the age of more than 70 years [15]. The research by Kaaks *et al.* also found the positively correlated of BMI with the estradiol and estrone concentrations in the serum, demonstrating that the total estrogen concentration in free form were significantly higher in the patients of "breast cancer" implying that free form of estradiol in serum is the strongest factor of "breast cancer" especially in obese females [2].

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"Obesity", Estrogens and "premenopausal" "breast cancer"

The frequency of "breast cancer" usually began to intensify after the age of 50 years as a reflection of "postmenopausal" as well as "premenopausal" women "breast cancer" [16]. Different biological differences has been observed in patterns of "breast cancer" arising in females of premenopause and postmenopause demonstrating the clinical expression is highly prevalent in tumors which are hormone-independent, and prognosis related to "premenopausal" "breast cancer" [4, 17]. "Postmenopausal" women depict the positive relationship among "obesity" with the risk of "breast cancer" risk, however some studies also reported that "obesity" act as a protective factor in "premenopausal" females after individual case control studies suggesting reduced risks of "breast cancer" in "premenopausal" females [9, 18]. Generally, an inverse association was found in the young females similar findings were reported by EPIC study conducted in "premenopausal" females [4, 19-21]. One of the determining factor for this association is estrogens level which is controlled by homeostatic regulation so in "premenopausal" females estrogen is not influenced by body fat or adipose mass. However, according to previous study the relationship among estradiol levels and adiposity in "premenopausal" female, is inverse demonstrating reduced risk of "breast cancer" but the study by Emaus *et al*. found opposite results representing the positive association among "obesity" and estradiol but these results are not supported by any other study which may be due to cyclic nature and changes of steroid concentrations occurring in "premenopausal" women during various follicular phases [22, 23]. According to another study there exist a positive relationship among concentration of circulating estradiol and risks of "breast cancer" [24]. Eliassen *et al*., found that the levels of estradiol level significantly high in women has greater risks of "breast cancer" in consistent with the findings of Sturgeon *et al*. showing inverse relationship of BMI and serum estradiol [24, 25]. Sturgeon *et al*. demonstrated that the total estradiol concentrations in early phase of follicular phase was higher in the patients of "breast cancer" [24]. It was also found that in obese women the ovulatory menstrual cycles have increased frequency and the mechanism suggested in "premenopausal" women regarding "obesity" supressing carcinogenesis is the loss of normal functioning of ovary along with impaired production of progesterone and estrogen [16, 26-28]. A study by Terry *et al* also found an inverse relationship among infertility occur because of ovulatory irregularities and "premenopausal" "breast cancer" [28]. The study by Michells *et al* also established the opposite relationship among the occurrence of "breast cancer" and adiposity in "premenopausal" females. So it can be summarized as "obesity" is definitely related with reduced risks of "breast cancer" in females before menopause, but the mechanism is still not clear [29].

Reference	Study type	Comparative arms	Measure of association
"Studies supporting a negative correlation between obesity and breast cancer risk in premenopausal women			
van den Brandt 2000 [9]	Pooled analysis [7 cohorts; 337,819 women and 4385 incident cases of invasive BC]	BMI >31 kg/m^2 vs.≤ 21 kg/m^2	RR: 0.54; 95% CI, 0.34 -0.85
Bergstrom 2001 [30]	Meta-analysis [Premenopausal (17 studies); postmenopausal (27 studies)]	Unit increase in BMI	RR: 0.98; 95% CI, 0.97 -0.99
Michels 2010 [29]	Prospective [113,130 premenopausal women]	BMI ≥30 kg/ m^2 vs. 20.0-22.4 kg/m^2	HR: 0.81; 95%CI, 0.68 -0.96
Berstad 2010 [31]	Case-control [2097 premenopausal women, 1900 postmenopausal women, and 4041 case controls]	BMI ≥35 kg/ m^2 vs. <25 kg/ m^2	OR: 0.81; 95%CI, 0.61-1.06
Harris 2011 [32]	Prospective [45,799 premenopausal women]	BMI ≥27.5 vs. <20.5*	HR: 0.74; 95%CI, 0.57-0.96
Renehan 2008 [33]	Meta-analysis [Premenopausal (20 studies); postmenopausal (31 studies)]	5 kg/m^2 increase in BMI	RR: 0.92; 95% CI, 0.88 -0.97
Premeno-pausal breast Cancer Collaborative Group 2018 [34]	Pooled analysis [19 cohorts: 758,592 premenopausal women]	5 kg/m^2 difference in BMI	1.9- to 4.2-fold increased risk for lower BMI, depending on age"
"Studies supporting a positive association between obesity and breast cancer risk in postmenopausal women			
Reference	**Study type**	**Comparative arms**	**Measure of association**
Rosenberg 2006 [35]	Population-based study [3345 postmenopausal women and 3455 matched controls]	≥30 kg vs. <10 kg weight gain	OR: 1.5; 95% CI, 1.2-1.8[a]
Reeves 2007 [36]	Prospective cohort study [1,222,630 women: Premenopausal BC 1179 cases, postmenopausal BC 5629 cases]	Obese women	RR: 1.29; 95% CI, 1.22 -1.36
Renehan 2008 [33]	Meta-analysis [Premenopausal (20 studies); postmenopausal (31 studies)]	5 kg/m^2 increase in BMI	RR: 1.12; 95% CI, 1.08 -1.16
Neuhouser 2015 [37]	Extended follow-up from the WHI Clinical Trial. [67, 142 postmenopausal women]"	BMI >35 kg/m^2	HR, 1.86; 95% CI, 1.60 -2.17[a]"

Table 1: "Summary of analyses investigating correlation of obesity with breast cancer (BC) based on menopausal status"

CONCLUSIONS

After all this discussion it is concluded that adiposity as well as "obesity" has adverse effect on the projection of "breast cancer", with small differences the effects are

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almost comparable in both menopausal conditions ("premenopausal" and "postmenopausal" stages) in women. "obesity" and the etiology of breast cancer as well as the elevated levels of estrogen and its activity are well established in women after menopause, but the resultant relations is still unclear for "premenopausal" types of cancers. It must be noted that before the menopause, the influence of adiposity on the production of estrogen and estradiol is unclear and there is not any acceptable and substantial mechanism proving the defence action of "obesity" in women before the menopause stage relative to "breast cancer". So further investigation is necessary. Moreover, obese patients of "breast cancer" irrespective of the age have high risk for potentially fatal conditions, which must be considered in survivals of "breast cancer"

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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