SYSTEmATIC REVIEW

Investigating the relationship between breast cancer and the postmenopausal period: a systematic meta-analysis

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Abstract

One possible explanation for the ongoing debate surrounding breast cancer risk factors is that differences in assessment methodologies lead to conflicting results. One way to address methodological differences in assessment between studies is to use a single standardized assessment to calibrate cancer studies. To achieve this goal, we conducted a meta-analysis, integrating findings from various studies that utilized menopause risk factors in the evaluation of breast cancer cases. We conducted a systematic literature review from 2010 to 2023 and included studies that examined the association between the postmenopausal period and breast cancer. Among the results, we found statistically significant evidence that the postmenopausal period has a positive association with breast cancer. We identified and carefully reviewed 49 articles considered relevant in the literature review and 12 met all of our inclusion and exclusion criteria. The intercept value was 0.768 (positive), indicating a significant degree of heterogeneity between the studies. The standard error (0.209) suggests that the effect size estimation is more precise and reliable across studies. The observed log odds ratios ranged from −0.1716 to 2.0202, with the majority of estimates being positive (92%). The estimated average log odds ratio based on the random-effects model was 0.7679 (95% Confidence Interval (CI): 0.3590 to 1.1768). Therefore, the average outcome significantly differed from zero ($z = 3.6809$, $p < 0.001$). Kendall’s Tau value was 0.455, and the $p$-value was 0.045, indicating a positive, statistically significant and moderate relationship between breast cancer and the postmenopausal period. The results obtained in this study carry significant implications for shaping public health policies and breast cancer screening programs. Understanding breast cancer cases in the postmenopausal period holds substantial importance in devising tailored treatment strategies. These findings can provide valuable insights for the enhancement of clinical practice, allowing for more effective and individualized treatment approaches.

Keywords

Postmenopausal period; Breast cancer; Systematic meta-analysis

1. Introduction

Breast cancer stands as one of the most prevalent types of cancer among women worldwide, representing a substantial public health concern [1]. Breast cancer is a disease that arises as a result of the complex interplay of various factors, including age, genetic predisposition, hormonal changes and lifestyle factors. Many of these factors vary in postmenopausal women [2]. The risk and progression of breast cancer are influenced by a multitude of factors, making it a complex process. Notably, the postmenopausal period plays a crucial role in this intricate equation. Extensive research on the risk of breast cancer during the postmenopausal years has garnered significant attention in the scientific community over many years. This period, characterized by postmenopause, marks a vital transitional phase in women’s lives. The postmenopausal phase has been associated with a potential increase in breast cancer risk, primarily attributed to shifts in hormone levels and age-related factors [3]. While numerous epidemiological studies suggest that the postmenopausal period may increase the risk of breast cancer, the findings in this area are often inconclusive. For instance, Smith et al. [4] proposed that postmenopausal hormonal changes are linked to an increased risk of breast cancer. However, Huang and his team emphasized the complexity of the postmenopausal period’s effect on breast cancer risk, with lifestyle factors also playing a significant role [5]. The postmenopausal phase is characterized by hormonal changes, which can influence breast cancer risk. Specifically, a decrease in estrogen hormone levels tends to reduce the risk of breast cancer, suggesting that the post-menopausal period may
be a factor that lowers the risk of breast cancer [6]. To gain a comprehensive understanding of the relationship between breast cancer and the postmenopausal period and to determine the impact of menopause on breast cancer, it is imperative to conduct a thorough review of existing literature and further explore the intricacies of this relationship. These studies can contribute to a more nuanced comprehension of breast cancer risk and help guide women during this transitional phase of life.

This study aimed to consolidate and clarify the relationship between postmenopausal periods and breast cancer through new meta-analysis findings.

2. Methods

2.1 Literature review

First, keywords such as “breast cancer”, “postmenopausal period”, “relationship”, “correlation” and “risk factors” were selected. Subsequently, PubMed (MEDLINE) and Web of Science database search engines were chosen. The combined keywords using Boolean operators were as follows: (“Breast cancer” OR “Mammalian carcinoma” OR “Breast neoplasms”) AND (“Postmenopausal period” OR “Postmenopausal phase”) AND (“Correlation” OR “Relation”) AND (“Risk” OR “Risk factors”). Original research articles in English published between 2010 and 2023 were included. Additionally, references in the identified papers were reviewed, and those meeting the search criteria were added. The reference lists of retrieved papers were screened, and papers that potentially met the inclusion criteria were retrieved and analyzed. This study relates to data from America, China, India, Brazil, Pakistan, Taiwan and South Korea regions.

2.2 Selection criteria

We included original studies that specifically related breast cancer in the postmenopausal period. We applied the following inclusion criteria: (a) original research; (b) use operational definition of subthreshold breast cancer symptoms; (c) subjects are limited to post-menopausal specimens (>45 years); (d) functional results were evaluated and results reported; (e) articles are written in English. Articles were excluded if (a) there was a review or opinion, or (b) the study was not available in English or was not available through PubMed and Web of Science (WOS). A clinician and an associate professor scanned all articles for relevance by reviewing the abstracts and further exploring their relevance by identifying relevant articles as full scans. Articles obtained from different sources in accordance with predetermined criteria were included in the study (n = 2). Studies were excluded for the following reasons: (a) they were unable to include sub-threshold breast cancer as a separate group with operationalized diagnostic criteria (n = 26), (b) they couldn’t incorporate sub-threshold post-menopausal related outcomes (n = 4), and (c) they included young subjects (n = 3).

2.3 Analytic approach

In the etiology of breast cancer, the relationship between the postmenopausal period and the disease was examined. The analysis was carried out using the log risk ratio as the outcome measure. A random-effects model was fitted to the data. The amount of heterogeneity (i.e., $\tau^2$), was estimated using the maximum-likelihood estimator [7]. In addition to the estimate of $\tau^2$, the Q-test for heterogeneity [8] and the $I^2$ statistic are reported. In case any amount of heterogeneity is detected (i.e., $\tau^2 > 0$, regardless of the results of the Q-test), a prediction interval for the true outcomes is also provided. Studentized residuals and Cook’s distances are used to examine whether studies may be outliers and/or influential in the context of the model. Studies with a studentized residual larger than the $100 \times (1 - 0.05/(2 \times k))$th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided alpha = 0.05 for k studies included in the meta analysis). Studies with a Cook’s distance larger than the median plus six times the interquartile range of the Cook’s distances are considered to be influential. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictor, are used to check for funnel plot asymmetry. The random effect model is a type of statistical model used in meta-analysis and takes into account heterogeneity between studies. Heterogeneity refers to the situation where the results of different studies show random variations. The random effect model takes into account this random variation between studies and helps to interpret the results in a more general way. Using a random effect model attempts to achieve a broader result, taking into account heterogeneity between studies. All analyses were implemented in Jamovi 2.4.6 [9–11].

2.4 PICOT

PICOT is a methodological framework frequently used in identifying clinical questions and research topics and in the design of clinical trials [12]. In the study, P (Population): Breast cancer patients in the postmenopausal period, I (Intervention/Exposure): The effect of the postmenopausal period on the risk of breast cancer, C (Comparison/Control): Breast cancer patients in the pre-menopausal period or the non-intervention group, O (Outcome): The relationship between breast cancer and post-menopausal period, T (Time): Refers to studies between 2010 and 2023.

3. Result

As demonstrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Fig. 1), 45 articles that were considered relevant in the literature review were identified and thoroughly examined. Out of these 45 articles, only 10 met all of our inclusion and exclusion criteria. In meta-analyses, the intercept of the random effects model provides important statistical information regarding the results of the meta-analysis and the heterogeneity between studies. This heterogeneity suggests the need for further subgroup analyses to understand the complexity of this relationship. When initially conducting a systematic meta-analysis study, although the average result was estimated to be positive, in some studies, the actual result could actually be negative. Therefore, 2 articles obtained from different sources in accordance with predetermined criteria were included in the study (n = 2). Studies were excluded for the following reasons: (a) they were unable to include sub-threshold breast cancer as a separate group with operationalized diagnostic criteria (n = 26), (b) they couldn’t incorporate sub-threshold post-menopausal related outcomes (n = 4), and (c) they included young subjects (n = 3).
A detailed breakdown is presented in the PRISMA Diagram in Fig. 1. Each of the 12 studies identified in Table 1 includes information about the author’s name, study year, subject’s name, sample source (such as clinic or society), study type, number of incidents in the experimental and control groups, and the country.

3.1 Meta-analysis results

The intercept for the random effect model in meta-analyses provides important statistical information regarding the results of the meta-analysis and heterogeneity between studies. While intercept expresses the estimated effect size of studies, it also reflects heterogeneity. Intercept value = 0.768 (positive), indicating important degree of heterogeneity between studies. That is, the results of the studies differ from each other, and some of these differences are due to random variation. The standard error (0.209) indicates that the effect size estimation is more precise and reliable across studies. The observed log odds ratios ranged from −0.1716 to 2.0202, with the majority of estimates being positive (92%). The estimated average log odds ratio based on the random-effects model was 0.7679 (95% CI: 0.3590 to 1.1768). Therefore, the average outcome differed significantly from zero ($z = 3.6809$, $p \leq 0.001$) in Table 2.

According to the Q-test in Table 2, the true outcomes appear to be heterogeneous ($Q \{11\} = 150.1792$, $p < 0.0001$, $\tau^2 = 0.4567$, $I^2 = 95.5111\%$). A 95% prediction interval for the true outcomes is given by −0.6184 to 2.1542. Hence, although the average outcome is estimated to be positive, in some studies the true outcome may in fact be negative. An examination of the studentized residuals revealed that none of the studies had a value larger than ±2.8653 and hence there was no indication of outliers in the context of this model. According to the Cook’s distances, none of the studies could be considered to be overly influential. Both the rank correlation and the regression test indicated potential funnel plot asymmetry ($p = 0.0447$ and $p = 0.0184$, respectively).

In this case, the results of the studies are closer to each other and the level of heterogeneity is low. A total of $k = 12$ studies were included in the analysis.

The forest graph for 12 studies, which were considered within the framework of the research criteria, is shown in Fig. 2. In this figure, the effect size for the relationship between breast cancer and the post-menopausal period, which each investigator considers separately, can be reached at the lower and upper limits of the effect size at the 95% confidence interval. For example, in the study of Yang et al. [19] (2022), the estimated effect size was found to be 2.02. This may indicate a high positive association between breast cancer and the postmenopausal period. In addition, the confidence interval for this relationship was specified as (1.61, 2.43). Similarly, in the study of Liu et al. [14] (2022), the estimated effect size was found to be 0.25. This may indicate a slight positive association between breast cancer and this particular dietary habit. However, (−0.26, 1.17) may show that the result of the analysis is not statistically significant and the reliability of the...
<table>
<thead>
<tr>
<th>Author</th>
<th>Names of Subject</th>
<th>Sample</th>
<th>Type of study</th>
<th>NIEG</th>
<th>NICG</th>
<th>Country</th>
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<td>Case-control</td>
<td>25</td>
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<td>Xue, H et al. [13] (2021)</td>
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<td>309</td>
<td>260</td>
<td>China</td>
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<td>Paleari, RG et al. [15] (2011)</td>
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<td>Campbell Jenkins, BW et al. [16] (2011)</td>
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<td>Sankar, V et al. [17] (2022)</td>
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<td>Fatima, N et al. [18] (2010)</td>
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<td>Yang, PC et al. [19] (2022)</td>
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<td>Javed, S et al. [20] (2011)</td>
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<td>Oh, H et al. [21] (2016)</td>
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<td>Wang, X et al. [22] (2016)</td>
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<td>Cho, YA et al. [23] (2010)</td>
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Total Experimental sample size: 45
Total control sample size: 95

Total Experimental sample size: 925
Total control sample size: 923

Total Experimental sample size: 134
Total control sample size: 129

Total Experimental sample size: 37
Total control sample size: 3165

Total Experimental sample size: 181
Total control sample size: 858

Total Experimental sample size: 644
Total control sample size: 131

Total Experimental sample size: 100
Total control sample size: 100

Total Experimental sample size: 310
Total control sample size: 552

Total Experimental sample size: 1400
Total control sample size: 1400

Total Experimental sample size: 358
Total control sample size: 360

Total Experimental sample size: 5380
Total control sample size: 89,175

*NIEG: Number of incidents in experimental group; NICG: Number of incidents in control group.*
### Table 2. Heterogeneity statistics of the study.

<table>
<thead>
<tr>
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<th>Estimate</th>
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<th>p</th>
<th>CI Lower</th>
<th>CI Upper</th>
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<tr>
<td>Intercept</td>
<td>0.768</td>
<td>0.209</td>
<td>3.680</td>
<td>&lt;0.001</td>
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<td>1.177</td>
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<td>Tau</td>
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<td>&lt;0.001</td>
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CI: Confidence Interval.

### Table 3. Rank correlation test for funnel plot asymmetry.

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<th></th>
<th>Kendall’s Tau</th>
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<td></td>
<td>0.455</td>
<td>0.045</td>
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</table>

#### 3.2 Publication bias findings

In a meta-analysis study, the researcher states only the studies with statistically significant results; however, intentionally or deliberately hiding or not stating the results that are not statistically significant will cause the effect size to be obtained as a result of the meta-analysis to be larger or smaller than it should be.

In Fig. 3, Examining the statistically significant ones, and eliminating the insignificant ones and not taking them into account, reveals the danger that all the studies done in that field cannot be represented [25]. Such a situation may cause publication bias. Publication bias can be tested using the funnel scatterplot and the Classic fail-safe N statistic. As seen in the graph, almost all of the 12 studies included in the study are at the top of the graph. According to graph, a slow-level image of publication bias can be said. In the classic fail-safe N statistic, the power of the study and the number of studies that must be included in the analysis for the p value to be greater than the alpha value can be learned. The number of additional studies required for the p value to be greater than 0.05 is 605.

### 4. Discussion

The postmenopausal period is characterized by significant changes in hormone levels as a natural part of women’s aging process. In particular, a decrease in estrogen levels has been associated with breast cancer risk [26]. It has been postulated that this decrease may lead to structural and hormonal changes in breast tissue during the postmenopausal period [27]. However, the results of research on this topic in the literature are quite contradictory.

More research on this topic is needed because breast cancer is a significant threat to women’s health. It is important for postmenopausal women to understand this risk and take precautions when necessary. For example, some epidemiological studies have found a strong link that postmenopause...
FIGURE 3. Funnel scatterplot for publication bias.

may increase the risk of breast cancer [28]. However, other studies suggest that this relationship is complex and not fully understood [29]. These conflicting results reflect the complexity of understanding the relationship between postmenopause and breast cancer.

In a study investigating the relationship between breast cancer and the postmenopausal period, based on the results of a meta-analysis conducted with 12 original articles, the intercept estimate is 0.768, RE (Random Effects) is 0.77, and Kendall’s Tau is 0.45. The obtained results from the meta-analysis provide significant insights for evaluating the association between postmenopause and breast cancer. These results indicate that there is heterogeneity among the study samples when utilizing the random effects model, suggesting that the relationship between postmenopause and breast cancer may vary in different subgroups. This heterogeneity suggests the necessity of further subgroup analyses to comprehend the complexity of this relationship. Similarly, the articles in the study seem to be in agreement with each other, possibly implying that postmenopausal women may be at an increased risk of breast cancer. This underscores the need for additional research and the importance of breast cancer screening programs for this age group.

The results obtained are crucial for shaping public health policies and breast cancer screening programs. Postmenopausal women may require additional information and resources to comprehend and mitigate their risk of breast cancer. Furthermore, breast cancer cases during the postmenopausal period are significant in determining treatment strategies. These findings can inform clinical practice by enabling more effective personalization and direction of treatment approaches.

In conclusion, this meta-analysis study has made a significant contribution both in the realm of scientific research and clinical practice by scientifically establishing the connection between postmenopause and breast cancer. These findings hold importance in guiding breast cancer research and shaping healthcare policies. Future research endeavors may delve more deeply into this relationship to further elucidate risk factors and protective measures.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

MK, DN—conceptualization, resources, supervision; formal analysis, investigation; methodology, software, visualization; writing-original draft; writing-review & editing; MK—data curation; project administration; validation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

REFERENCES


