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Risk-benefits assessment of tamoxifen or raloxifene as chemoprevention for risk reduction of breast cancer among *BRCA1* and *BRCA2* carriers: a meta-analysis

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Background: Breast cancer is a major global health burden, with hereditary factors such as *BRCA1/2* mutations significantly increasing the lifetime risk. This meta-analysis aimed to evaluate the outcomes of selective estrogen receptor modulators (SERMs), tamoxifen, and raloxifene as chemopreventive agents for breast cancer risk reduction in *BRCA1/2* mutation carriers. Methods: A meta-analysis was conducted according to the PRISMA guidelines. PubMed, Cochrane Library, and MEDLINE databases were searched for relevant studies published between 2000 and 2024. Case-control studies and observational cohort studies examining the use of tamoxifen/raloxifene in *BRCA1/2* carriers were included. Data on the incidence and risk ratios of breast cancer were also extracted. Quality was assessed using the Newcastle-Ottawa Scale (NOS). A random-effects meta-analysis was performed using Review Manager (version 5.4.0). Results: Nine studies (13,676 women) were included. Two studies had low risk, and the remaining seven studies had moderate risk, as assessed by the NOS checklist. Pooled analysis showed tamoxifen/raloxifene decreased breast cancer risk compared to controls (RR 0.80, 95% CI 0.72–0.88, $p = 0.04$). The risk ratio of breast cancer incidence among BRCA1/2 carriers was reduced after tamoxifen use (RR 1.82, 95% CI 1.48–2.23, $p < 0.00001$). Subgroup analysis revealed reduced breast cancer risk with SERM use in both *BRCA1* (RR 1.51, 95% CI 1.48–1.51) and *BRCA2* carriers (RR 1.48, 95% CI 1.40–1.58). The heterogeneity ranged from 51 to 85%, representing high significance and variation in true effect sizes underlying the different included studies. Whereas the heterogeneity among subgroups *BRCA1* and *BRCA2* was 98%, and the difference was 0%, showing no difference in response to SERM for risk reduction of breast cancer. Conclusion: This meta-analysis provides evidence that tamoxifen and raloxifene significantly reduce the breast cancer risk in women with *BRCA1/2* mutations. Chemoprevention efficacy was similar for both *BRCA1* and *BRCA2* carriers. Further research is needed to validate these findings and to optimize their use in high-risk populations.

Keywords Breast cancer, *BRCA1/2*, Tamoxifen, Raloxifene, Chemoprevention, Selective estrogen receptor modulators

Breast cancer is the most frequent malignancy among women and is a major global burden on the healthcare system[1]. Approximately 2.3 million new cases and 685,000 deaths due to breast cancer were reported in women in 2020[2]. Hereditary factors play a significant role in the development of breast cancer among women. Some of these genetic predispositions pose a significant lifetime risk of breast cancer[3]. Among these mutations, *BRCA1* and *BRCA2* are the most well-known and can lead to breast cancer[4,5]. The lifetime risk of breast cancer among women who carry the *BRCA1* mutation is 45–85%, and the *BRCA2* mutation is 40–70%, depending on various environmental as well as genetic factors[6,7]. The increasing incidence of these genetic mutations (especially *BRCA* mutations) in the general population, which occurs in 2.5 out of 1000 individuals, emphasizes the need for emergent cancer prevention strategies[8]. Among these preventive strategies, chemoprevention is an effective

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method that involves the use of medications for risk reduction in women carrying *BRCA* mutations[9,10]. Various chemoprevention therapies are used to reduce breast cancer risk, including aromatase inhibitors (anastrozole and exemestane) and selective estrogen receptor modulators (SERMs) (tamoxifen and raloxifene)[11,12]. In this study, our key emphasis was on SERMs as a chemopreventive strategy for breast cancer risk reduction.

Two major SERMs, tamoxifen and raloxifene, have long been examined for their role in breast cancer prevention. Both drugs play a pathogenic role by blocking the proliferative effects of estrogen in breast tissue, thus reducing the probability of pathogenesis in hormone receptor-positive breast cancers[11,13,14]. Among the general population at high risk of breast cancer, tamoxifen has been reported as an effective chemopreventive agent in clinical trials, such as the NSABP P-1 study[15,16]. Raloxifene is another SERM agent that reduces breast cancer risk; however, it is the least used medication owing to its development for the prevention and treatment of osteoporosis[17–19].

The use of chemopreventive agents poses a significant challenge for *BRCA* mutation carriers. In breast cancer prevention, adherence to chemopreventive strategies may be disturbed due to the adverse effects of aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs), which lead to high risks of osteoporosis and thromboembolism among patients. Since *BRCA*-carrier women who are BRCA carriers are at a higher risk of developing breast cancer than the general population. Therefore, SERMs agents such as tamoxifen and raloxifene are effective because of their preventive outcomes. Few previous cohorts and randomized controlled trials (RCTs) have reported the effectiveness of these SERMs among *BRCA1* and *BRCA2* mutation carrier populations for risk reduction of breast cancer[20–22]. Tamoxifen and Raloxifene inhibit the formation of tumors stimulated by estrogen by blocking estrogen receptors in the breast tissue. In comparison to tamoxifen, raloxifene decreased the risk of advanced breast cancer by 44–49% in the MORE and STAR trials. It also has fewer adverse effects such as a lower risk of endometrial cancer[23,24]. However, there is a lack of comprehensive analysis on the effectiveness of tamoxifen or raloxifene in reducing breast cancer risk among women who are *BRCA1* and *BRCA2* mutation carriers. Therefore, this meta-analysis aimed to evaluate the efficacy of tamoxifen and raloxifene as chemopreventive agents for breast cancer risk reduction among *BRCA*1 and *BRCA*2 mutation carriers, focusing on both their potential benefits and associated risks. This study aimed to provide a thorough summary of the role of these drugs in the treatment of women with a high genetic risk of breast cancer by analyzing data from studies published between 2000 and 2024.

Methods

Study design

The "Reporting Items for Systematic Review and Meta-Analysis (PRISMA)" guidelines[25] were followed for conducting a recent systematic review and meta-analysis to fulfill research aims of evaluating the risk-benefits of tamoxifen or raloxifene as chemoprevention for risk reduction of breast cancer in women who carry *BRCA1* or *BRCA2* mutations[26]. Our study is a meta-analysis of previously published case-control and observational studies; therefore, there is no need for an additional ethical review.

Search strategy

A comprehensive literature search was conducted using various electronic databases, including PubMed, Cochrane Library, and MEDLINE, to extract and identify related studies published between 2000 and 2024. The relevant research articles were extracted by using MeSH keywords such as ("risk-benefits" OR "risk prevention" OR "risk reduction" OR "risk assessment") AND ("Breast neoplasm" OR "Breast cancer" OR "chemoprevention") AND ("Genetic Predisposition" OR "*BRCA1* Gene" OR "*BRCA2* Gene") AND (Tamoxifen OR Raloxifene). Previous meta-analyses and reviews were manually searched to extract and identify additional studies from reference lists.

Eligibility criteria

The eligibility criteria assisted in the selection and screening of research articles after searching electronic databases. Only studies that met the following inclusion criteria were included: 1). Studies have investigated women carrying *BRCA1* and *BRCA2*, 2). Studies have analyzed the female population receiving chemoprevention with tamoxifen or raloxifene 3). Studies involving the incidence of breast cancer and the associated hazard ratio (HR) or relative risk (RR) among tamoxifen or raloxifene users and non-users 4). Case control and observational cohort studies 5). Studies published in English and in full text are available.

However, these studies were excluded 1). The study population consisted of women who were ER-positive or carried risk genes for other cancer types, 2). Studies involving other drugs for the chemoprevention of breast cancer, rather than tamoxifen or raloxifene 3). Studies have discussed other outcomes such as the incidence of prophylactic bilateral mastectomy 4). Studies based on systematic reviews, meta-analyses, comprehensive reviews, narrative reviews, or editorials were excluded. 5). Studies published in languages other than English, and non-full-text papers were excluded.

Data extraction

Two independent reviewers extracted the data using a prespecified table. Data related to demographic information such as authors, year of study, country, study population, sample size, study design, and study follow-up were extracted (Table 1). Information related to primary outcomes, such as the incidence of breast cancer, hazard ratio of breast cancer, and incidence of breast cancer among *BRCA1* and *BRCA2* carrier women, is shown in Table 2. Discrepancies were resolved by consulting with a third reviewer. The extracted data included the following.

Author, year	Country	Study design	Study population	No. of subjects	Follow-up (years)
Kotsopoulos et al., 2023[29]	Canada	Prospective cohort analysis	4578 unaffected women with *BRCA*1 or *BRCA*2 mutation	Tamoxifen & Raloxifene: 202 Non users: 606	6.8
Gronwald et al., 2014[30]	Poland	Case control study	1,504 women *BRCA*1 or *BRCA*2 mutation	Cases: 411 Control: 1093 Tamoxifen: 331 Non users: 1173	1
Gronwald et al., 2006[31]	Canada	Case control study	1036 women with *BRCA*1 or *BRCA*2 mutation	Cases: 285 Control: 751	2
Philips et al., 2013[32]	Australia	Observational cohort data	2462 women with *BRCA*1 or *BRCA*2 mutation	Tamoxifen; 837 Non users: 1627	6.5
Phillips et al., 2011[33]	Australia	Cohort study	2561 women with *BRCA*1 or *BRCA*2 mutation	Tamoxifen: 818 Non users: 1743	4
Narod et al., 2000[34]	Canada	Case control study	593 women	Cases (tamoxifen users): 209 Control: 384	9.7
King et al., 2001[35]	USA	Randomized clinical trial	19 patients with *BRCA* 1 and *BRCA* 2	Cases; 8 Controls; 11	5.7
Metcalfe et al., 2004[36]	Canada	Case control study	491 women with *BRCA* 1 and *BRCA* 2	T: 244 P: 210	10 years
Anderson et al., 2019[37]	USA	Prospective cohort study	432 women with *BRCA* 1 or *BRCA* 2	Tamoxifen or raloxifene: 24 Non users: 408	9.1

Table 1. Characteristics of included studies. T; treatment & P: Placebo.

Author, Year	Incident of Breast cancer	HR at 95% CI	BRCA 1	BRCA 2
Kotsopoulos et al., 2023[29]	T: 22 out of 232 P: 71 out of 606	0.64 (0.40–1.03)		
Gronwald et al., 2014[30]	T: 15 out of 122 P; 27 out of 112	0.83 (0.44–1.55)	*N* = 719	*N* = 104
Gronwald et al., 2006[31]	T: 35 out of 285 P: 185 out of 751	0.45 (0.29–0.70)	*N* = 204 RR; 0.50 (0.30–0.85)	*N* = 46 RR; 0.42 (0.17–1.02)
Philips et al., 2013[32]	T: 657 out of 1583 P: 426 out of 881		1,583 RR: 0.38 (0.27 to 0.55)	881 RR: 0.33 (0.22 to 0.50)
Phillips et al., 2011[33]	T: 629 out of 1642 P: 412 out of 919		1642 RR; 0.31 (0.22–0.45)	919 RR; 0.24 (0.16–0.35)
Narod et al., 2000[34]	T: 51 out of 209 P: 93 out of 384	0·50 (0·28–0·89).	(RR; 0·38, 0·19–0·74)	(RR; 0·63, 0·20–1·50
King et al., 2001[35]	T: 5 out of 8 P: 8 out of 11		2 out of 8 (RR: 1.67; 0.32–10.70)	3 out of 11 (RR: 0.38; 0.06–1.56)
Metcalfe et al., 2004[36]	T: 151 out of 244 P: 159 out of 210	(0.59; 0.35 to 1.01)	224 out of 327	112 out of 152
Anderson et al., 2019[37]	T; 14 out of 24 P: 359 out of 408	(0.44; 0.18–1.06)		

Table 2. Breast cancer incidences and risks among *BRCA* 1 and *BRCA* 2 mutation carriers. T; treatment & P: placebo.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the case-control and cohort studies[27]. A score of > 7 for included studies was considered low-risk, a score of 5–7 for included studies indicated moderate-risk, and a score of < 5 for included studies indicated high-risk. Any disagreement regarding risk bias assessment was resolved through consensus.

Statistical analysis

All statistical analyses were conducted using Review Manager Software (Cochrane Collaboration, version 5.4.0)[28]. Statistical significance was set at $P < 0.05$. Pooled analysis of data was performed for studies with potential heterogeneity using random effects models. Effect sizes are shown as risk ratios (RR) for dichotomous outcomes (e.g., breast cancer incidence). Heterogeneity was evaluated using the I^2 statistic, I^2 values > 50% indicating significant heterogeneity. Subgroup analyses were conducted according to variables, such as tamoxifen versus non-users and *BRCA1* versus *BRCA2* mutation carriers.

Results

In this study, research articles were selected and screened according to the study aims and title "Risk-benefits assessment of tamoxifen or raloxifene as chemoprevention for risk reduction of breast cancer among *BRCA1* and *BRCA2* carriers" according to the PRISMA guidelines[26]. A total of 6,280 research articles were obtained from the above-mentioned electronic databases by using "MeSH" keywords and 4180 duplicates were removed. In

accordance with the PRISMA guidelines, only 1509 papers were retrieved after excluding 591 research articles. Among them, only 807 met the eligibility criteria. Only nine studies met the inclusion criteria and were included in this study, as shown in Fig. 1.

Characteristics of included studies

Our study analyzed nine research articles (four prospective cohort studies and five case-control studies) and a total of 13,676 women who carried either *BRCA1* or *BRCA2* to evaluate the benefits of tamoxifen or raloxifene as chemoprevention for risk reduction of breast cancer using a meta-analysis approach. The main characteristics of the selected studies are presented in Table 1. All the included studies were published between 2000 and 2024. The sample size for some included studies was limited due to the involvement of case-control studies, ranging from 19 to 1504 *BRCA1* and *BRCA2* female carriers[29–33] while the sample size of cohort studies ranged from 432 to 4578 risk carrier women[34–37]. The follow-up periods in the included studies ranged from 1 to 10 years.

Quality assessment

Among the nine included studies, two were at low risk[30,33] and the remaining seven were at moderate risk[29,31,32,34–37], as shown in Table 3. Most comparisons showed low to moderate evidence quality, and the study's limitations, inconsistencies, indirectness, and imprecision were the key reasons for the decline in confidence.

Primary outcomes

A. Incidence of breast cancer

All nine included studies reported the incidence of breast cancer among *BRCA1/2* carrier women receiving tamoxifen or raloxifene compared to the general population (non-users). The pooled analysis showed that administration of tamoxifen or raloxifene decreased the breast cancer risk as compared to control [RR: 0.80

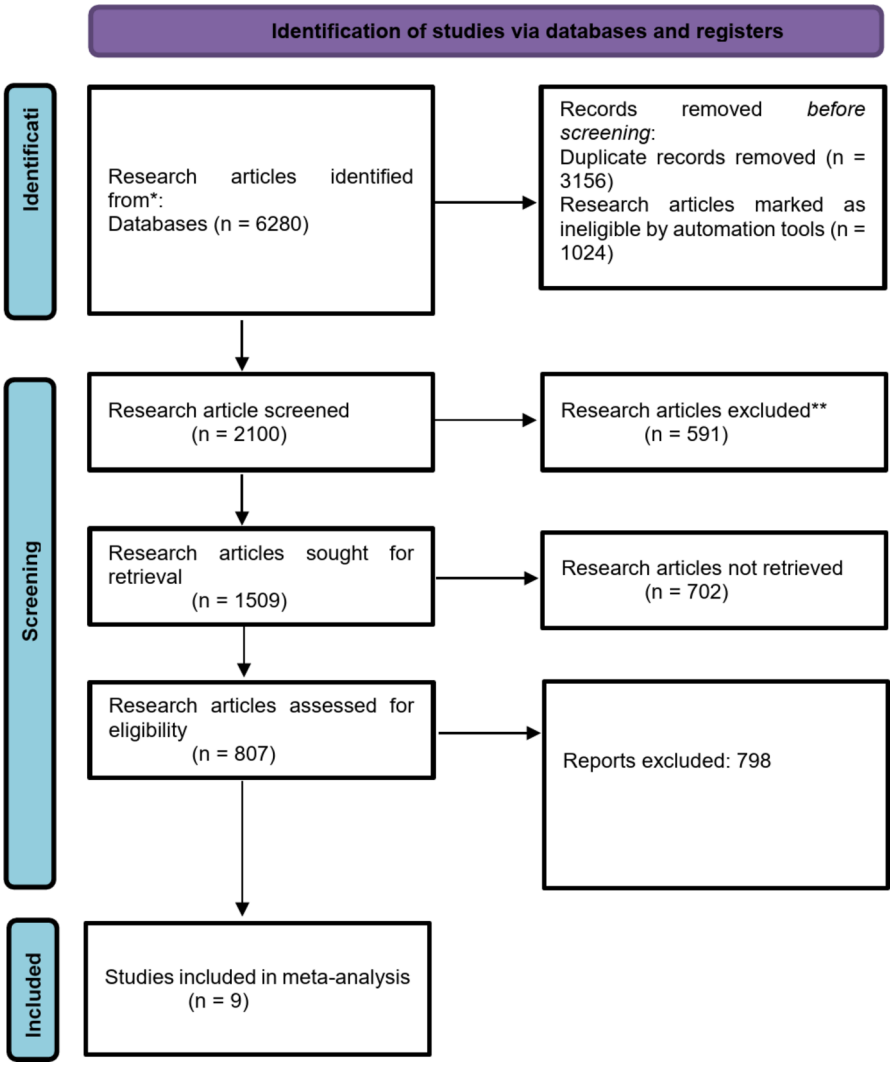

Fig. 1. Screening and selection of included studies by PRISMA Guidelines.

	Selection				Comparability		Outcome			
Study	Representative of the exposed cohort	Selection of external control	Ascertainment of exposure	Outcome of interest not present	Main factor	Additional factor	Assessment of outcome	Sufficient follow up time	Adequacy of follow up time	**Total**
Kotsopoulos et al., 2023[29]	*	0	*	0	*	0	*	*	*	6/9
Gronwald et al., 2014[30]	*	*	*	0	*	0	*	0	0	5/9
Gronwald et al., 2006[31]	*	*	0	*	*	*	*	*	*	8/9
Philips et al., 2013[32]	0	*	*	0	*	0	*	*	*	5/9
Phillips et al., 2011[33]	*	*	0	*	*	0	*	0	0	5/9
Narod et al., 2000[34]	*	0	*	0	*	*	*	*	*	7/9
King et al., 2001[35]	*	*	*	0	*	0	*	0	0	5/9
Metcalfe et al., 2004[36]	*	*	0	*	*	*	*	*	*	8/9
Anderson et al., 2019[37]	*	0	*	*	0	*	*	0	*	6/9

Table 3. Quality assessment of included studies by Newcastle-Ottawa Scale. *= yes, 0 = no.

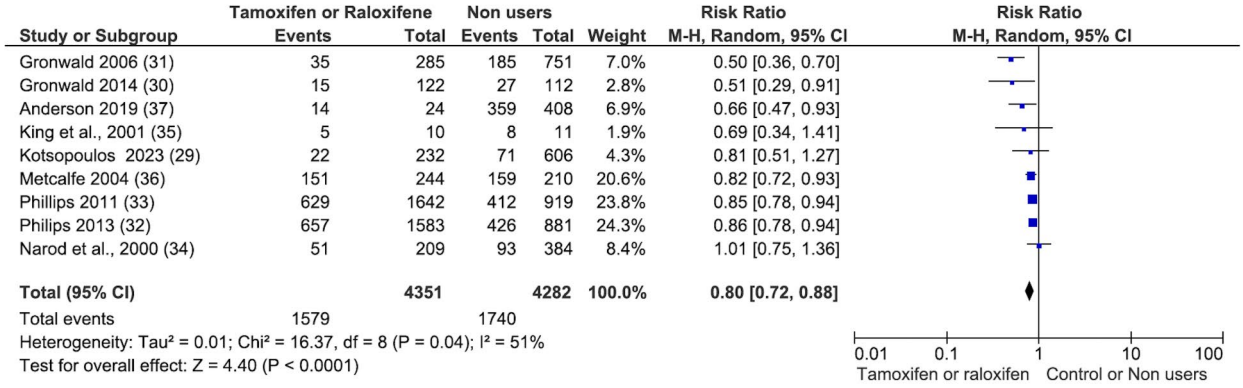

Fig. 2. Forest plot of Risk ratio of breast cancer incidence among tamoxifen or raloxifene and control.

(95%CI; 0.72 to 0.88], $p = 0.04$) and heterogeneity reported ($I^2 = 51\%$), as shown in Fig. 2. The symmetrical distribution of the risk ratios of the included studies revealed the absence of publication bias (Fig. 3).

B. Risk of breast cancer

Among the nine included studies, six reported the risk ratio of breast cancer among *BRCA1/2* carriers receiving tamoxifen or raloxifene. The pooled risk ratio of breast cancer incidence was higher in *BRCA1/2* carriers [RR: 1.82 (95% CI; 1.48 to 2.23), $p < 0.00001$) and heterogeneity reported ($I^2 = 85\%$), as shown in Fig. 4. This indicates that tamoxifen use can significantly reduce the risk of breast cancer among *BRCA1/2* carriers. The symmetrical distribution of the risk ratios of the included studies revealed the absence of publication bias (Fig. 5).

C. Subgroup analysis for BRCA1 and BRCA2 mutation carriers

Five studies demonstrated the risk ratio of breast cancer incidence among *BRCA1* (subgroup 1) and *BRCA2* carriers receiving tamoxifen or raloxifene compared with the control rate. A meta-analysis showed that treatment with tamoxifen or raloxifene had reduced the risk of breast cancer incidence (RR = 1.51, 95% CI = 1.48 to 1.54, $P < 0.00001$) among both subgroups: *BRCA1* [RR: 1.51; 1.48 to 1.51] and *BRCA2* [RR: 1.48; 1.40 to 1.58], and heterogeneity reported (I2 = 98%), as shown in Figs. 6 and 7.

Discussion

This study aimed to evaluate the risk benefits of tamoxifen or raloxifene as a chemoprevention for breast cancer risk reduction among *BRCA1* and *BRCA2* carriers by adopting a meta-analysis approach. Through the analysis of nine research articles (four prospective cohort studies and five case-control studies) and 13676 women who carried either *BRCA1* or *BRCA2*, this study reported that tamoxifen or raloxifene as chemoprevention strategies reduced breast cancer risk among *BRCA1* and *BRCA2* carriers. The primary outcomes of this study were the incidence of breast cancer risk and the risk ratio of breast cancer among *BRCA1/2* carrier women receiving tamoxifen or raloxifene compared to controls. The pooled analysis showed that administration of tamoxifen or raloxifene decreased the breast cancer risk [RR: 0.80 (95%CI: 0.72 to 0.88], $p = 0.04$) and risk ratio of breast cancer incidence among BRCA1/2 carriers after tamoxifen use [RR: 1.82 (95% CI: 1.48 to 2.23], $p < 0.00001$). The findings of subgroup analysis reported that treatment by tamoxifen or raloxifene had reduced the risk of breast

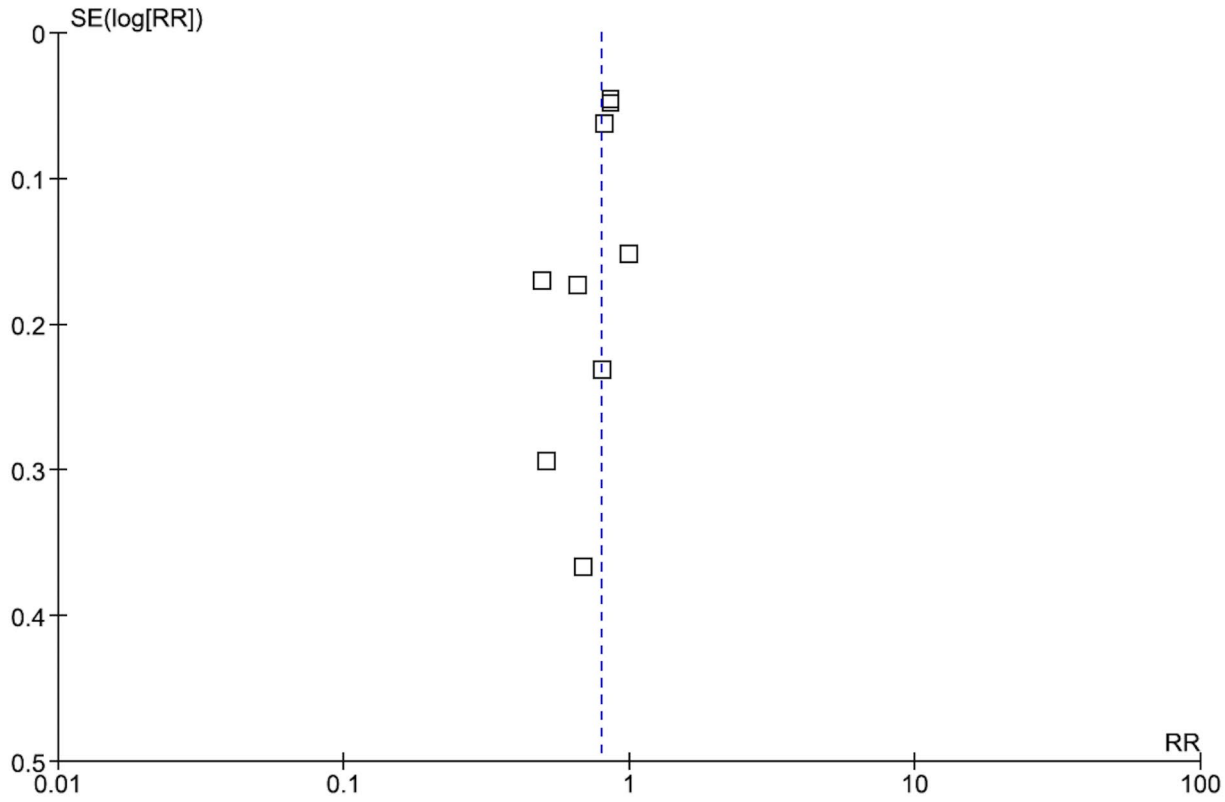

Fig. 3. Funnel plot of Risk ratio of breast cancer incidence among tamoxifen or raloxifene and control.

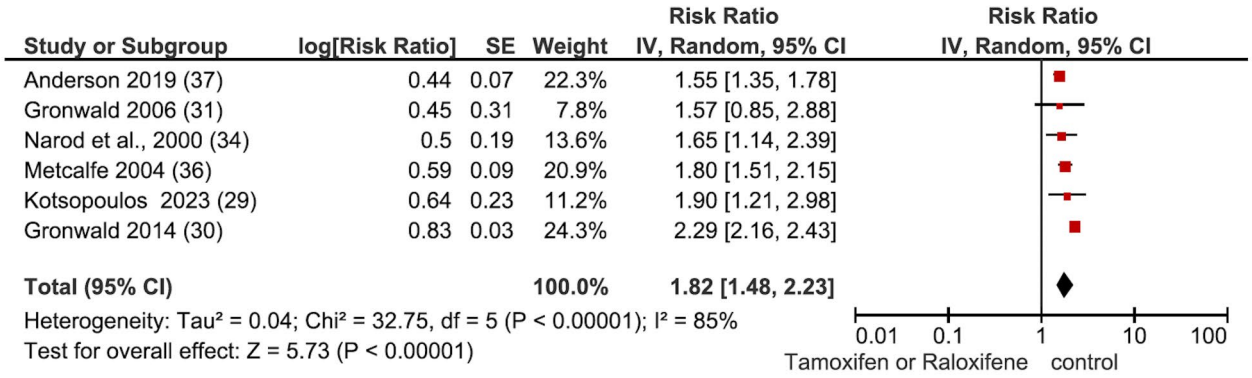

Fig. 4. Forest plot of the risk ratio of breast cancer among *BRCA1/2* carriers.

cancer incidence (RR = 1.51, 95% CI = 1.48 to 1.54, $P < 0.00001$) among both subgroups; *BRCA1* [RR: 1.51; (95% CI; 1.48 to 1.51)] and *BRCA2* [RR: 1.48 (95% CI: 1.40 to 1.58)]. Among the nine included studies, two were at low risk[30,33], and the remaining seven were at moderate risk[29,31,32,34–37], as assessed by NOS.

The findings of this study are consistent with those of previous studies that have demonstrated tamoxifen as an effective chemopreventive strategy for breast cancer in women with *BRCA1* and *BRCA2* genetic mutations. However, raloxifene, unlike tamoxifen has originally been used for the prevention of osteoporosis in postmenopausal women[18,38]. Thus, few cohort or case-control studies have reported the outcomes of raloxifene in breast cancer risk reduction among *BRCA1* and *BRCA2* carrier women[39,40]. Collectively, the findings of this meta-analysis support the use of SERMs among high-risk populations, especially *BRCA1* and *BRCA2* carriers[41]. For instance, Sestak et al.[42] reported that tamoxifen reduced the risk of breast cancer in women with *BRCA1* and *BRCA2* mutations. Furthermore, research on raloxifene in comparable populations has indicated that it is

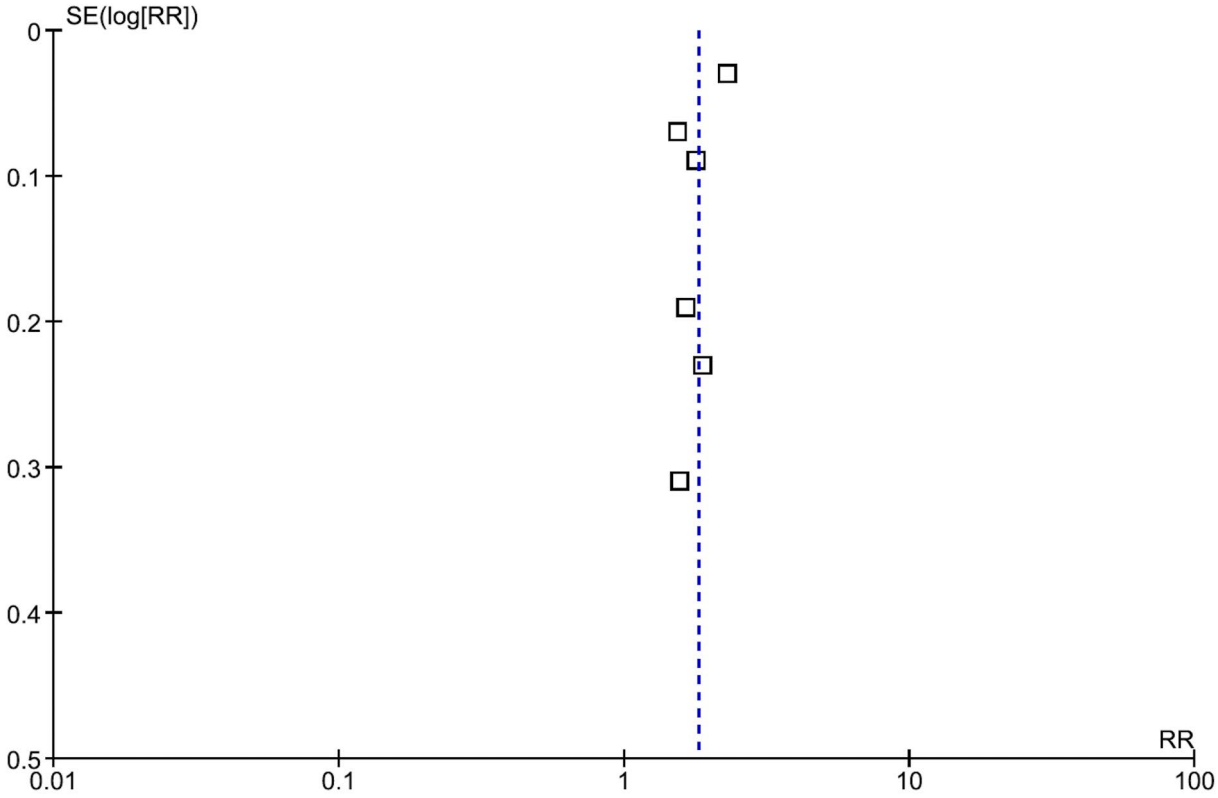

Fig. 5. Funnel plot of the risk ratio of breast cancer among *BRCA1/2* carriers.

effective in lowering the incidence of breast cancer, although with weaker evidence than that for tamoxifen[18,24]. The evidence supporting tamoxifen and raloxifene as effective chemopreventive strategies for *BRCA1* and *BRCA2* carriers was strengthened by the pooled analysis conducted in this study.

Our meta-analysis reported a lower relative risk reduction of 20% in comparison to 40–50% risk reduction of included randomized controlled trials (RCTs) that emerged due to differences in patient populations and study designs. Due to the inclusion of diverse populations from observational studies and case-control studies, the results varied in follow-up durations and baseline risk factors for breast cancer. Additionally, strict eligibility criteria, controlled environments, and higher patient compliance in RCTs resulted in greater risk reduction. Given the variations in breast cancer risk linked to each mutation, subgroup analysis also examined the effectiveness of tamoxifen and raloxifene in carriers of *BRCA1* and *BRCA2* mutations. The study discovered that, after using tamoxifen or raloxifene, the risk of breast cancer decreased in both *BRCA1* and *BRCA2* carriers. This result is consistent with earlier studies that found that carriers of *BRCA2* mutations also benefit from chemoprevention, even though they have a higher overall chance of developing breast cancer[43,44]. However, the small variation in risk reduction between the two groups might indicate variable efficacy, which calls for greater research in larger, more focused trials.

In this case, the reported heterogeneity ranging from 51 to 85% indicated a moderate to high level of variability in the effect sizes across the included studies. This suggests that the true effect sizes or the actual impact of the intervention (Selective Estrogen Receptor Modulators, or SERMs) for breast cancer risk reduction vary significantly across different studies. Such variation could be due to differences in the study design, population, or other factors affecting the outcomes. In contrast, the heterogeneity within the *BRCA1* and *BRCA2* subgroups was reported at 98%, indicating almost complete variability between these two genetic groups. However, the statement that the "difference was 0%" indicates that despite the high heterogeneity, there was no difference in the response to SERMs between women with *BRCA*1 and *BRCA*2 mutations in terms of risk reduction for breast cancer. Essentially, the response to SERMs was similar between the two genetic subgroups, although the individual studies contributing to the analysis were highly variable.

The quality of the studies included in the meta-analysis was a crucial factor to consider when evaluating the findings. Based on the Newcastle-Ottawa Scale (NOS), the study found that six of the nine included studies had a moderate risk of bias, whereas two had a low risk. The existence of moderate risk in multiple studies indicates that the results should be carefully observed even though the overall quality of the research is generally good. The stability of the observed effect sizes may be affected by potential biases, particularly in case-control studies.

With enormous benefits, there are a few limitations in this study. First, the number of included studies was limited, which could have affected the reliability and credibility of the findings. Furthermore, not all studies

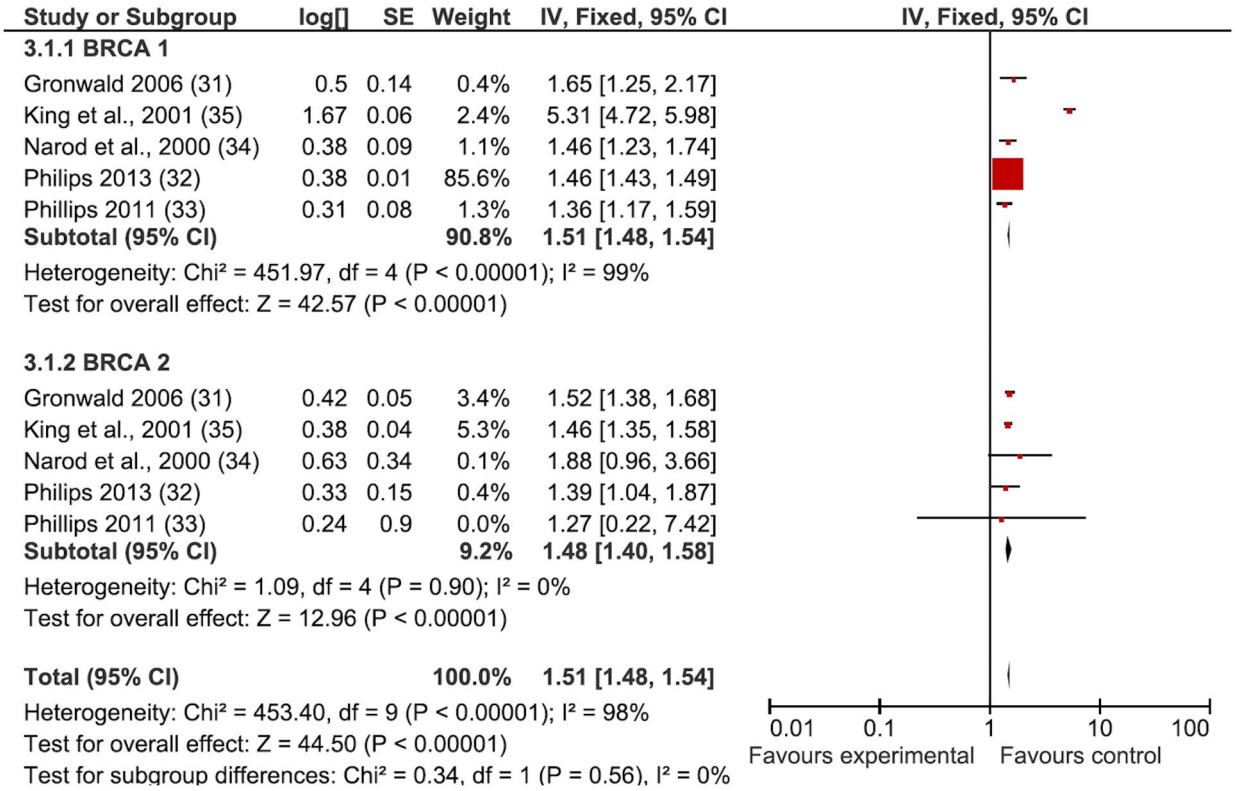

Fig. 6. Forest plot of the risk ratio of breast cancer incidence among *BRCA1* and *BRCA2* subgroups.

were of high quality or low risk, and several studies were rated as having a moderate risk of bias. This may have affected the outcomes, especially regarding the precision and applicability of the findings. Moreover, the observed heterogeneity among studies may have been caused by differences in the patient characteristics and outcomes of tamoxifen or raloxifene. Lastly, there is a lack of subgroup analyses based on age, postmenopausal and reproductive phases, and other genetic risk factors that may affect the efficacy of tamoxifen for breast cancer risk reduction among *BRCA1/2* carrier women.

Because participants may have differing degrees of knowledge regarding their genetic status or treatment history, case-control studies are frequently vulnerable to recall bias, which could affect the accuracy of the reported results. When considering the therapeutic use of these drugs, one should consider the risk profiles of each individual, potential side effects, and long-term effects on quality of life[45]. Further research is required, particularly in the form of larger randomized controlled trials, to validate these findings and more precisely define the optimal patient populations for each chemoprevention strategy.

Conclusion

Overall, the findings of this meta-analysis showed that tamoxifen or raloxifene can significantly reduce breast cancer risk among women with *BRCA1* and *BRCA2* mutations. The effectiveness of tamoxifen and raloxifene was similar across the *BRCA1* and *BRCA2* subgroups in women. Individual risk profiles, the possibility of adverse effects, and long-term implications on quality of life should all be considered when making therapeutic decisions to utilize these medications. More research is required, especially in larger randomized controlled trials, to clearly define suitable patient populations for each chemoprevention approach and to validate these findings.

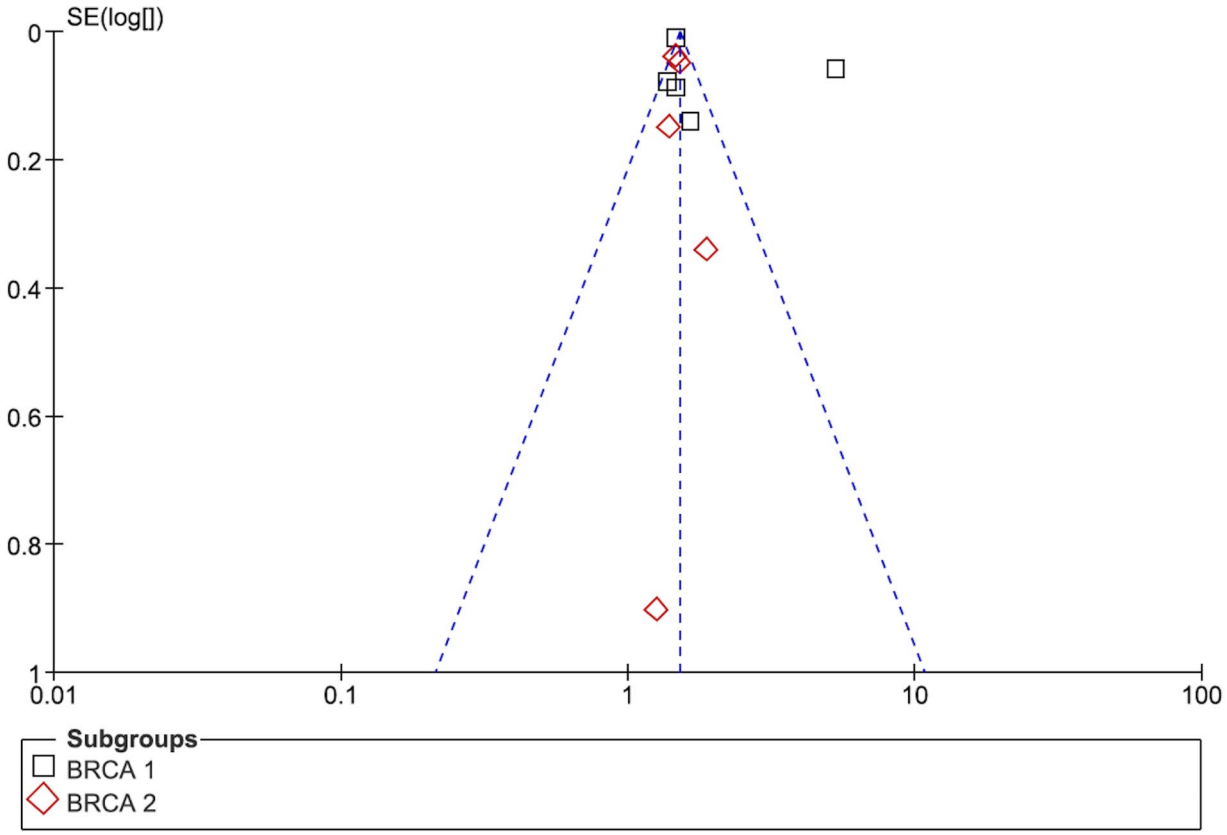

Fig. 7. Funnel plot of the risk ratio of breast cancer among *BRCA1* and *BRCA2* risk ratio.

Data availability

The manuscript includes all the necessary data; related data may be provided on request from the corresponding author/s.

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Author contributions

ASSA and NUK did the literature search, extracted the data, analyzed it, and wrote the manuscript. NUK and TC oversaw the data extraction and review of the final manuscript. All authors revised it for important intellectual content.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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