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Adherence to Mediterranean Diet and Breast Cancer Risk: A Meta-Analysis of Prospective Observational Studies

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ABSTRACT

Background and Aim: The Mediterranean diet (MD) is widely recognized for its health benefits and potential protective effects against various chronic diseases such as cardiovascular conditions and cancer. This meta-analysis evaluates the association between MD adherence and breast cancer risk in women.

Methods: A comprehensive search of major databases was conducted until November 2024 to identify cohort or case-control studies. The meta-analysis employed a random-effects model to pool multivariable-adjusted effect sizes, reporting them as hazard ratios (HR) while evaluating heterogeneity using the I^2 statistic and assessing publication bias.

Results: The pooled analysis of 31 studies indicated a significant association between adherence to the MD and a 13% risk reduction in risk of breast cancer (HR: 0.87, 95% CI: 0.82–0.92; $I^2 = 70\%$). Specifically, postmenopausal women exhibited a 12% significant reduction in the risk of breast cancer (HR: 0.88; 95% CI: 0.84, 0.92), while premenopausal women showed no significant effect (HR: 0.98, 95% CI: 0.90, 1.06). Geographically, the effect was most pronounced in Asia (OR: 0.59, 95% CI: 0.50, 0.68), while from America (OR: 0.92, 95% CI: 0.82, 1.02) and Europe (OR: 0.90, 95% CI: 0.83, 0.97) showed moderate associations. Subgroup analysis suggested a stronger significant association in case-control studies (HR: 0.77, 95% CI: 0.70, 0.85), whereas no significant association was observed in cohort studies (HR: 0.96, 95% CI: 0.90, 1.02).

Conclusion: Adherence to the Mediterranean diet is associated with a significant reduction in breast cancer risk, particularly among postmenopausal women and in regions such as Asia. These findings suggest that the Mediterranean diet may be an important dietary factor in reducing breast cancer risk, especially in certain populations. However, further research is needed to confirm its impact in different study designs and geographical areas.

1 | Introduction

Breast cancer remains a significant global health challenge, accounting for a substantial proportion of cancer diagnoses among women [1]. The search for effective prevention strategies is therefore critical, with particular attention to lifestyle factors, especially diet, that might modulate cancer risk [2, 3]. Among dietary patterns, the Mediterranean diet (MD) has garnered considerable interest in research due to its association with numerous health benefits, including potential protective effects against cardiovascular and cancer [4–7]. A clear understanding of how the MD might influence breast cancer risk is essential, as it could refine public health recommendations, thereby empowering individuals to adopt lifestyle practices that promote long-term health and potentially mitigate cancer risk.

The MD emphasizes a high intake of plant-based foods such as fruits, vegetables, whole grains, and legumes, paired with healthy fats from sources like olive oil and nuts [8]. This diet is distinctively rich in antioxidants, fiber, and monounsaturated fats, all of which are linked to anti-inflammatory and anti-carcinogenic effects that could be especially pertinent to reducing cancer risks [7]. Adherence to the MD has been associated with a reduced risk of chronic diseases, including cardiovascular diseases, Type 2 diabetes, and various forms of cancer [4–7, 9, 10]. Importantly, breast cancer has emerged as a primary focus within this body of research.

Numerous observational studies and clinical trials have investigated the relationship between adherence to the MD and breast cancer risk, frequently uncovering an inverse association. Although previous research suggests that following this diet may contribute to a reduced risk of developing breast cancer, some inconsistencies remain [11–14]. These variations can be attributed to differences in study populations, levels of adherence to the diet, and potential confounding factors.

This highlights the urgent need for updated, large-scale analyses to better clarify the MD's influence on breast cancer risk. Conducting a systematic review and meta-analysis involving more extensive and diverse populations is essential to validate these findings and address the ongoing controversies surrounding this issue. To address these discrepancies, this systematic review and meta-analysis compile and examine the available evidence on the MD's relationship with breast cancer risk. By analyzing data across diverse observational studies, this study aims to clarify whether an MD pattern significantly reduces the risk of breast cancer and to what extent.

2 | Methods

2.1 | Study Design and Protocol

This systematic review and meta-analysis of observational studies was conducted to investigate the association between MD and breast cancer, based on the Cochrane Collaboration [15], and was written in accordance with reporting items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

2.2 | Search Strategy

A thorough literature search was carried out using major databases, including MEDLINE/PubMed, ISI Web of Science, and Scopus, to identify studies published from their inception until November 2024. The search strategy utilized Medical Subject Headings (MeSH) terms along with relevant synonyms related to MD and breast cancer. The keywords included ("Mediterranean" OR "Mediterranean diet" OR "Mediterranean dietary" OR "Mediterranean adherence") AND ("Breast cancer" OR "breast tumor" OR "breast malignancy" OR "breast neoplasm" OR "breast carcinoma" OR "breast adenocarcinoma"). To enhance the comprehensiveness of the review, supplementary searches were conducted on Google Scholar, and reference lists of pertinent studies were manually examined to identify additional relevant articles, including gray literature. No language restrictions were imposed to ensure a broad scope of study inclusion. A detailed outline of the search strategy and database-specific search queries is available in Supporting Information S1: Tables S1 and S2.

2.3 | Eligibility Criteria

Studies were included based on the following criteria: (1) cohorts or case-control studies; (2) examined adherence to the MD (as reported in the original study); (3) assessed the association between MD adherence and risk of breast cancer in women; (4) reporting of risk estimates using a hazard ratio (HR), relative risk (RR), or odds ratio (OR) and corresponding 95% confidence intervals (CI); (5) written in English. Moreover, all variations of MD were considered eligible for inclusion. Exclusion criteria were as follows: (1) articles not published in English, (2) studies involving exposures to other dietary patterns, (3) non-original studies such as reviews or meta-analyses, and (4) articles lacking quantitative data or sufficient details.

2.4 | Data Extraction

Two reviewers (A.A.S. and K.K.) independently extracted relevant data to ensure accuracy and consistency. The extracted data included the first author's name, year of publication, study design (e.g., cohort, case-control), country of the study, sample size, duration of dietary exposure assessment, and the number of cases and controls. Additional extracted variables included participants' age, menopausal status, the method used for dietary assessment (e.g., food frequency questionnaire or dietary recall), and alcohol consumption as a potential confounding factor. Furthermore, multivariable risk estimates, such as ORs, RRs, or HRs, were collected along with the corresponding 95% CIs, specifically comparing the highest and lowest adherence to the MD groups. This detailed extraction aimed to facilitate robust analysis across studies, capturing comprehensive information on study characteristics and risk metrics.

2.5 | Quality Assessment

The quality assessment of the included studies was investigated according to Newcastle-Ottawa Scale (NOS) criteria [17]. The

NOS is a tool used to assess the risk of bias in observational studies, assigning a quality score from zero to nine points based on the identified biases. Studies scored greater than 6 out of 9 points were considered to be high-quality studies.

2.6 | Statistical Analysis

The meta-analysis was performed by pooling the multivariable-adjusted RRs, HRs, or ORs comparing the highest and lowest categories of MD adherence based on a random-effects model using the Der Simonian-Laird method [18]. We calculated the standard errors for the logarithm of the RR/OR/HR, interpreted as an estimated variance (ER) of the logarithm of the RR/OR/HR to determine the weight of each study [18]. Heterogeneity across studies was evaluated by using the I^2 statistic, with values above 50% indicating a substantial statistical heterogeneity [19]. Therefore, subgroup analysis by menopausal status, study design, and regions was performed to assess whether these variables modify the overall risk estimate. Potential publication bias was examined by graphical evaluation of the Funnel plots and Begg's test for the overall, premenopausal, and postmenopausal categories. All analyses were conducted in R version 4.4.

3 | Result

3.1 | Study Selection

A comprehensive search across major databases—PubMed ($n = 428$), ISI Web of Science ($n = 908$), and Scopus ($n = 853$)—yielded a total of 2189 records. After eliminating 724 duplicates, 1465 unique records remained for an initial screening based on titles and abstracts. At this stage, 1422 documents were excluded for various reasons, including being review articles, non-human experimental studies (such as in vitro and in vivo research), letters to the editor, or other unrelated study types. This resulted in 43 studies advancing to full-text evaluation for eligibility in the meta-analysis. During this review, 12 studies were excluded due to insufficient data, incomplete reporting, or failure to meet the cohort study design criteria. In the end, 31 studies met all inclusion criteria and were included in the final quantitative synthesis (meta-analysis). The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

3.2 | Study Characteristics

The detailed characteristics of the included studies are presented in Table 1. This systematic review and meta-analysis incorporated 31 observational studies, comprising 12 cohort studies and 19 case-control studies, with a total of 36 effect sizes published between 2006 and 2023. The follow-up duration for cohort studies ranged from 8 to 33 years. The age of the women studied varied from 20 to 104 years. Geographically, nine studies were conducted in the Americas, four in Asia, and 26 in Europe, with the majority originating from the United States and Spain.

3.3 | Quality Assessment

The quality assessment of cohort and case-control studies using the NOS indicated generally high methodological rigor, with

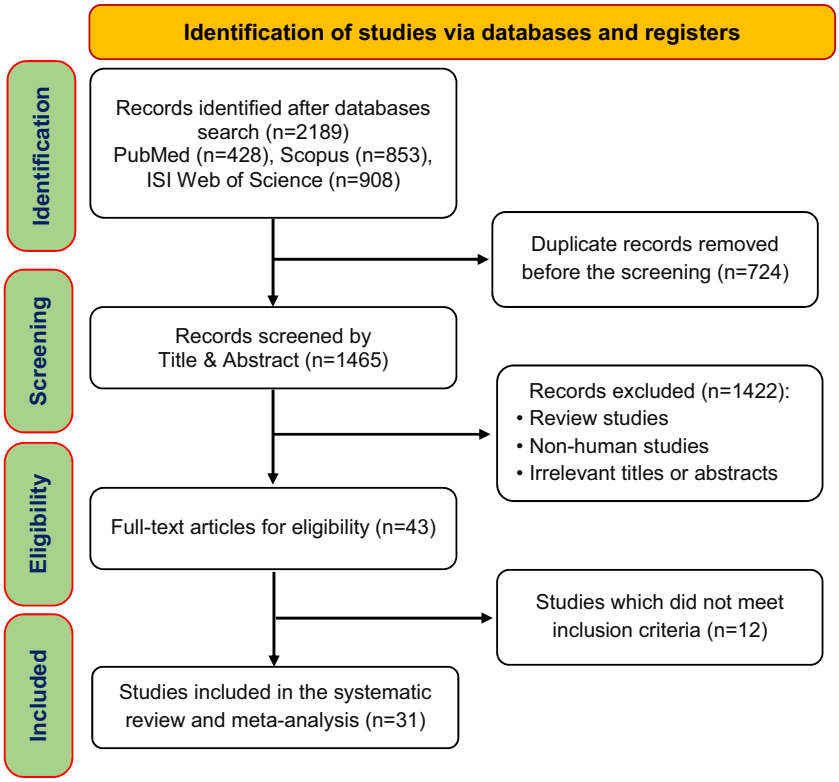


FIGURE 1 | PRISMA flow chart of the study selection process for inclusion studies in the systematic review.

TABLE 1 | Basic characteristics of included cohort and case-control studies.

Study	Country	Study design	Age (y)	Sample size	Cases	Effect size (95% CI)	Adjustment
Fung et al. [2006]	USA	Cohort	30–55	71,058	3580	RR: 0.98 (0.88, 1.10)	Age, BMI, PA, smoking, energy intake, family history, weight change, multivitamin use, history of BBD.
Cottet et al. [2009]	France	Cohort	51–55	65,374	2381	HR: 0.85 (0.75, 0.95)	Age, educational level, region, BMI, height, family history of BC, pregnancy, parity, HRT, history of BBD, OCPs use, lifetime duration of breastfeeding, frequency of Papanicolaou testing at baseline as an indicator of adherence to gynecologic screening, PA, smoking, energy intake, phytoestrogen supplements, vitamin/mineral supplements.
Trichopoulou et al. [2010]	Greece	Cohort	20–86	14,807	240	HR: 0.88 (0.75, 1.03)	Age (at baseline, first delivery), educational level, smoking, BMI, height, metabolic equivalents of task hours per day, energy intake, parity, menopausal, HRT.
Cade et al. [2011]	UK	Cohort	35–69	33,731	828	HR: 0.96 (0.7, 1.32)	Age (age at baseline, menarche), energy intake, menopausal status, calorie-adjusted fat, BMI, PA, OCPs, HRT, smoking, parity, ethanol, breastfeeding, socioeconomic, education.
Wu et al. [2011]	NR	Cohort	50–71	184,932	7182	RR: 0.90 (0.82, 0.99)	NR
Buckland et al. [2013]	European	Cohort	35–70	335,062	10,225	HR: 0.94 (0.88, 1.00)	BMI, height, education, PA, smoking, menopausal, OCPs use, breastfeeding, age (at menopause, menarche), first full-term pregnancy, HRT use, saturated fat intake, alcohol intake, energy intake.
Couto et al. [2013]	Sweden	Cohort	30–49	49,258	1278	RR: 1.42 (0.99, 2.05)	Family history of BC, history of BBD, smoking status, BMI, height, age at first birth, number of children, educational level, age at menarche, energy intake, consumption of beverages, potatoes, sweets, and eggs.
						RR: 1.42 (0.99, 2.03)	Additionally for Alcohol intake
Hirko et al. [2016]	USA	Cohort	30–55	100,643	2372	HR: 1.07 (0.92, 1.25)	BMI at age 18, weight change since age 18, PA, energy intake, parity/age at first birth, HRT, OCPs use, age at menarche, age at menopause, family history of BC, BBD.
van den Brandt et al. [2017]	The Netherlands	Cohort	55–69	62,573	2321	HR: 0.88 (0.73, 1.06)	Age, smoking, height, BMI, non-occupational PA, highest level of education, family history of BC, history of BBD, age at menarche, parity, age at first birth, age at menopause, OCP use, postmenopausal HRT, energy intake
						HR: 0.87 (0.72, 1.06)	Alcohol intake
Haridass et al. [2018]	USA	Cohort	22–104	96,959	3869	Premenopausal women: HR: 1.14 (0.95–1.38) Postmenopausal women: HR: 1.04 (0.87–1.25)	Age (at baseline, menarche), race, BC family history, OCPs use, parity, smoking, socioeconomic, PA, energy intake Additionally for alcohol intake

(Continues)

TABLE 1 | (Continued)

Study	Country	Study design	Age (y)	Sample size	Cases	Effect size (95% CI)	Adjustment
Lavalette et al. [2018]	France	Cohort	≥ 40	30,525	488	HR: 1.13 (0.84, 1.53)	Age, sex, education, smoking, number of 24-h dietary records, height, family history of BC, BMI, PA, energy intake, number of parity, menopausal status, HRT use, OCPs use.
Petimar et al. [2019]	USA	Cohort	35–74	50,884	1700	HR: 0.90 (0.77, 1.06)	Age (at baseline, first live birth, menopause, menarche), energy intake, race/ethnicity, income, smoking, BMI, PA, height, education, family history of BC, parity, HRT, OCPs use, lifetime duration of breastfeeding, and time of last mammogram.
						HR: 0.89 (0.76, 1.05)	Additionally for alcohol intake
Dela Cruz et al. [2020]	USA	Cohort	45–75	101,291	7749	HR: 1.01 (0.94, 1.09)	Age (at baseline, menarche, menopause, first live birth), total energy intake, BMI, smoking status, PA, education, parity, family history of BC, HRT use, DQI depending on the model.
Gardeazabal et al. [2020]	Spain	Cohort	NR	10,713	100	HR: 0.64 (0.30, 1.37)	Age (at baseline, menarche, first live birth, menopause), energy intake, BMI, smoking, PA, education, parity, family history of BC, HRT use, DQI, energy intake, diabetes.
Männistö et al. [2021]	Finland	Cohort	50 <	6374	274	HR: 0.88 (0.59, 1.30)	Age, education, smoking, height, BMI, leisure time exercise, parity, HRT, energy intake
van den Brandt et al. [2023]	The Netherlands	Cohort	55–69	62,573	2321	HR: 0.88 (0.73, 1.08)	Age (at baseline, menarche, first birth, menopause), parity, smoking, height, education, family history of BC, history of BBD, OCPs use, HRT use, energy intake, lifestyle factors.
Yiannakou et al. [2023]	USA	Cohort	30 <	1567	87	HR: 0.91 (0.51, 1.60)	Age (at baseline, menopause), calorie intake, waist-to-height ratio, smoking, PA, diabetes status, supplement use.
Castelló et al. [2024]	Spain	Cohort	29–69	24,892	639	HR: 0.95 (0.72, 1.27)	Alcohol intake, energy intake, BMI, PA, smoking, education, age at first delivery. HRT use, menopausal status, adherence to the Western dietary pattern.
Quartiroli et al. [2024]	Italy	Cohort	35–69	9144	587	HR: 0.76 (0.60–0.97) HR: 0.88 (0.69–1.13)	Age and non-alcoholic energy intake. Further adjusted for age at menarche, parity, age at first birth, smoking status, education, and BMI
Nkondjock et al. [2006]	Canada	Case-control	< 65	183	89	OR: 0.54 (0.17–1.72)	Age, PA, energy intake
Murtaugh et al. [2008]	USA	Case-control	25–79	4746	2281	OR: 0.76 (0.63–0.92)	Age, center, education, smoking, PA, calories, dietary fiber and calcium, height, BMI, parity, HRT, family history of BC, menopausal status
Wu et al. [2009]	USA	Case-control	25–74	2396	1248	OR: 0.65 (0.44–0.95)	Age (at menopause, menarche), Asian ethnicity, education, birthplace, years of residence in the USA, PA, marital status, parity, type of menopause, BMI.

(Continues)

TABLE 1 | (Continued)

Study	Country	Study design	Age (y)	Sample size	Cases	Effect size (95% CI)	Adjustment
Demetriou et al. [2012]	Cyprus	Case-control	40–70	2286	935	OR: 0.99 (0.70, 1.40) OR: 0.63 (0.77, 1.53)	Age (age at FFTP, menarche), family history, HRT use, exercise, height, BMI in post-menopausal women only.
Bessaoud et al. [2012]	France	Case-control	25–85	1359	437	OR: 0.97 (0.63–1.48)	Energy intake, education, parity, breastfeeding age at first full-term pregnancy, duration of ovulatory activity, BMI, PA, family history of BC.
Castelló et al. [2013]	Spain	Case-control	NR	2038	1019	OR: 0.44 (0.30–0.65)	NR
Mourouti et al. [2013]	NR	Case-control	56 ± 12	500	250	OR: 0.923 (0.879–0.968)	Age, socioeconomic level, family history of BC, BMI, PA, smoking.
Castelló et al. [2014]	Spain	Case-control	NR	2034	1017	OR: 0.56 (0.40–0.79) OR: 0.74 (0.46–1.18)	Total calories, alcohol consumption, BMI from self-reported weight and height, average PA in the past year, smoking, education, history of BBD and BC, age (at menarche, first delivery)
Mourouti et al. [2014]	Greece	Case-control	56 ± 12	500	250	OR: 0.92 (0.86–0.97)	Age, education, BMI, smoking, PA, family history of BC, age (at menarche and menopause, HRT use.
Pot et al. [2014]	UK	Case-control	57.2 & 56.6	2501	610	OR: 1.05 (0.77–1.43) OR: 1.02 (0.69–1.52)	Exact age, parity, use of HRT, weight, height, PA, menopausal status, family history of BC, breastfeeding, and education level Additionally, for alcohol intake
Castelló et al. [2017]	Spain	Case-control	20–85	2532	258	OR: 0.90 (0.69–1.17)	Age, education, BMI, age at first delivery, family history of BC, PA, smoking, caloric intake, alcohol intake, province of residence as a random effect term.
Krusinska et al. [2018]	Poland	Case-control	40–79	420	190	OR: 0.52 (0.25–1.07)	Age, BMI, socioeconomic status, PA, smoking, abuse of alcohol, age at menarche, menopausal status, number of children, OCPs use, HRT use, family history of BC, vitamin/mineral supplements use, BC subtypes, 'Metabolic-Syndrome' and 'High-Hormone' Profiles Score, excluding the modeled variable from confounders set, respectively
Lope et al. [2019]	Spain	Case-control	18–70	1946	973	OR: 1.06 (0.96–1.18)	Menopausal status, education, BMI, smoking, age (at first birth, menarche), family history of BC and BBD, HRT use, PA, Mediterranean dietary pattern, Western dietary pattern.
Turati et al. [2018]	Italy	Case-control	23–78	6426	3034	OR: 0.82 (0.71–0.95)	Study center, age, education, BMI, PA, smoking, parity, OCPs use, HRT use, diabetes, family history of BC, non-alcohol energy intake
Cao et al. [2021]	China	Case-control	NR	1753	818	OR: 0.61 (0.50–0.76)	Age (at menarche, at first full-term delivery, menopausal age), area, education, tobacco smoking, PA, OCPs use, HRT, family history of BC and BBD, number of parity, breastfeeding, BMI

(Continues)

TABLE 1 | (Continued)

Study	Country	Study design	Age (y)	Sample size	Cases	Effect size (95% CI)	Adjustment
Torre et al. [2021]	Italy	Case-control	55.8 & 57.9	182	94	OR: 0.29 (0.12–0.69)	NR
Caldas et al. [2022]	Brazil	Case-control	27–76	181	90	OR: 2.136 (0.863–5.287)	Age, first-grader parent with BC, OCPs use, hysterectomy, calories, menopausal status.
Cao et al. [2022]	China	Case-control	< 25	1753	818	OR: OR: 0.64 (0.49–0.84)	Age at diagnosis, area, education, tobacco smoking, PA, OCPs use, HRT, family history of BC and BBD, age (at menarche, at first full-term delivery, menopausal age), number Parity, breastfeeding, BMI.
Djafari et al. [2023]	Iran	Case-control	46.6 ± 10.7	300	150	OR: 0.45 (0.21–0.94)	Age, BMI, energy intake, education, residency, family history of BC, PA, marital status, smoking, alcohol consumption, supplement use, length of breastfeeding, history of HRT
Sadeghi et al. [2023]	Iran	Case-control	< 30	1050	350	OR: 0.43 (0.28–0.67)	Age, energy, region, marital status, education, disease history, PA, family history of BC, menopausal status, smoking, alcohol consumption, socioeconomic status, BMI

Abbreviations: BBD, benign breast disease; BC, breast cancer; BMI, body mass index; DQI, diet quality index; HR: hazard ratio; HRT, hormone replacement therapy; NR, non-reported; OCPs, oral contraceptives; OR, odd ratio; PA, physical activity; RR, risk ratio.

most cohort studies scoring between 6 and 8 (Table 2) and case-control studies ranging from 3 to 9 (Table 3). High-scoring studies demonstrated strong exposure assessment, adequate follow-up, and effective control for confounders, while lower-scoring studies had limitations in follow-up adequacy, control selection, or exposure assessment. Despite some methodological weaknesses, the overall quality of the included studies was robust, supporting the reliability of the findings on the association between MD adherence and breast cancer risk.

3.4 | Meta-Analysis

The findings of our primary analysis are derived from 39 studies included in this meta-analysis. Women were grouped into three categories: overall (combining premenopausal and postmenopausal), premenopausal, and postmenopausal, to evaluate the effect of the MD on breast cancer risk. The overall pooled analysis revealed a significant association between adherence to the MD and a lower risk of breast cancer across all women. The HR was 0.87 (95% CI: 0.83, 0.92), corresponding to a 13% reduction in breast cancer risk. The heterogeneity among the studies was substantial, with an I^2 value of 66.4% (Figure 2).

For premenopausal women, the HR was 0.98 (95% CI: 0.90, 1.06), suggesting no statistically significant decrease in breast cancer risk within this subgroup. The moderate level of heterogeneity ($I^2 = 61.5\%$) points to some variability across the included studies (Figure 3). In postmenopausal women, the HR was 0.88 (95% CI: 0.84, 0.92), indicating a significant reduction in breast cancer risk linked to the MD (Figure 4). The heterogeneity was again moderate, with an I^2 value of 45.2%.

3.5 | Subgroup Analysis

A subgroup analysis based on the study design (cohort vs. case-control) demonstrated that for cohort studies, the HR was 0.96 (95% CI: 0.90, 1.02) with low heterogeneity among studies ($I^2 = 36.8\%$), while in case-control studies showed an HR of 0.77 (95% CI: 0.70, 0.85) with a substantial heterogeneity ($I^2 = 77.2\%$) (Figure 5A). Furthermore, no significant difference was found in breast cancer risk between cohort studies with follow-up durations of less than 20 years compared to those over 20 years (Figure 5B, Table 4).

The subgroup analysis based on the geographical region revealed that studies conducted in Asia showed the strongest association between Mediterranean diet adherence and a reduced risk of breast cancer (HR: 0.59, 95% CI: 0.50, 0.68). In contrast, the association was moderate in Europe (HR: 0.90, 95% CI: 0.83, 0.97) and insignificant in America (HR: 0.92, 95% CI: 0.82, 1.02) (Figure 5C). In addition, the subgroup analysis by alcohol adjustment (inclusion vs. exclusion) showed no significant effect on breast cancer risk in women (Figure 5D, Table 4).

In premenopausal women, cohort studies (HR: 1.05, 95% CI: 0.88, 1.24) did not show any significant effect of the MD on reducing breast cancer risk. Similarly, the marginal association seen in case-control studies (HR: 1.09, 95% CI: 0.95, 1.24)

TABLE 2 | Quality assessment of the cohort studies according to the Newcastle-Ottawa Scale (NOS) criteria.

Cohort studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Score
Fung et al. [2006]	—	*	*	*	*	*	*	*	7
Cottet et al. [2009]	*	*	*	*	*	*	*	*	8
Trichopoulou et al. [2010]	*	*	*	*	*	*	*	*	8
Cade et al. [2011]	—	*	*	*	*	—	*	*	6
Wu et al. [2011]	—	*	*	*	—	*	*	*	7
Buckland et al. [2013]	*	*	*	*	*	*	*	*	8
Couto et al. [2013]	*	*	*	*	*	—	*	*	7
Hirko et al. [2016]	—	*	*	*	*	*	*	*	7
van den Brandt et al. [2017]	—	*	*	*	*	*	*	*	7
Haridass et al. [2018]	—	*	*	*	*	*	*	—	6
Lavalette et al. [2018]	—	*	*	*	*	*	*	—	6
Petimar et al. [2019]	—	*	*	*	*	*	*	*	7
Dela Cruz et al. [2020]	*	*	*	*	*	*	*	—	7
Gardeazabal et al. [2020]	—	*	*	*	*	*	*	—	6
Männistö et al. [2021]	—	*	*	*	*	*	*	*	7
van den Brandt et al. [2023]	*	*	*	*	*	*	*	*	8
Yiannakou et al. [2023]	—	*	*	*	*	*	*	—	6
Castelló et al. [2024]	*	*	*	*	*	*	*	*	8
Quartiroli et al. [2024]	*	*	*	*	*	*	*	*	8

Note: Q1: Representativeness of the exposed cohort. Q2: Selection of the non-exposed cohort. Q3: Ascertainment of exposure. Q4: Demonstration that outcome of interest was not present at start of study. Q5: Comparability of cohorts on the basis of the design or analysis. Q6: Assessment of outcome. Q7: Was follow-up long enough for outcomes to occur (> 5 years). Q8: Adequacy of follow-up of cohorts (loss-to-follow-up < 20%). Q9: Total score.
Q9: Total score.

TABLE 3 | Quality assessment of the case-control studies according to the Newcastle-Ottawa Scale (NOS) criteria.

Case-control studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score
Nkondjock et al. [2006]	*	—	*	*	*	*	*	*	*	8
Murtaugh et al. [2008]	*	*	*	—	*	*	*	*	—	7
Wu et al. [2009]	*	*	*	—	*	*	*	*	—	7
Demetriou et al. [2012]	*	—	*	*	*	*	*	*	*	8
Bessaoud et al. [2012]	*	*	*	—	*	*	*	*	—	7
Castelló et al. [2013]	—	*	*	—	*	*	*	*	—	6
Mourouti et al. [2013]	—	*	*	—	*	*	*	*	—	6
Castelló et al. [2014]	*	*	*	—	*	*	*	*	*	8
Mourouti et al. [2014]	*	*	*	*	*	*	*	*	*	9
Pot et al. [2014]	*	—	*	*	*	*	*	*	*	8
Castelló et al. [2017]	*	*	*	—	*	*	*	*	—	7
Krusinska et al. [2018]	*	—	*	*	*	*	*	*	—	7
Lope et al. [2019]	*	*	*	—	*	*	*	*	—	7
Turati et al. [2018]	*	*	*	*	*	*	*	*	*	9
Cao et al. [2021]	*	*	*	*	*	*	*	*	—	8
Torre et al. [2021]	—	—	*	—	—	—	*	*	—	3
Caldas et al. [2022]	*	*	*	*	*	*	*	*	*	9
Cao et al. [2022]	*	*	*	—	*	*	*	*	—	7
Djafari et al. [2023]	*	—	*	—	*	*	*	*	—	6
Sadeghi et al. [2023]	*	*	*	*	*	*	*	*	*	9

Note: Q1: Is the case definition adequate? Q2: Representativeness of the cases. Q3: Selection of controls. Q4: Definition of controls. Q5: Comparability of cases and controls on the basis of the design or analysis controlled for confounders. Q6: Study controls for any additional factor. Q7: Ascertainment of exposure. Q8: Same method of ascertainment for cases and controls. Q9: Non-response rate.

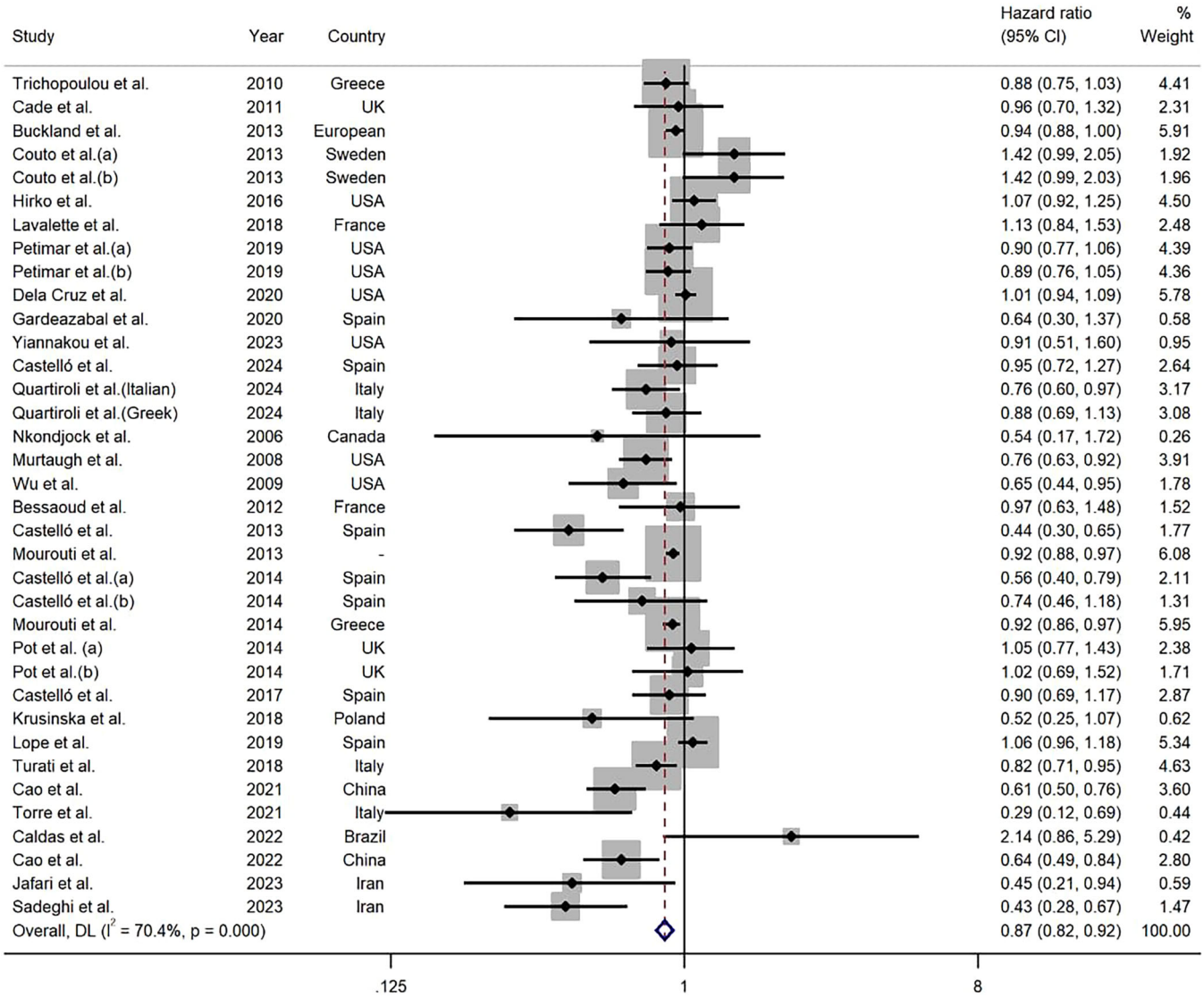


FIGURE 2 | Forrest plot demonstrating the hazard ratio (HR) and 95% confidence interval (95% CI) for the overall association between adherence to the Mediterranean diet (MD) and risk of breast cancer in women.

appears overestimated. The subgroup analysis by region for premenopausal women showed no significant reduction in risk across America (HR: 0.92, 95% CI: 0.82, 1.02), Europe (HR: 0.98, 95% CI: 0.88, 1.10), or Asia (HR: 0.88, 95% CI: 0.63, 1.21). These findings suggest that adherence to the MD in premenopausal women in America and Europe does not significantly reduce breast cancer risk. Likewise, the inclusion or exclusion of alcohol did not result in significant differences in risk. For studies that included alcohol, the HR was 1.12 (95% CI: 0.90, 1.40), while those excluding alcohol had an HR of 0.94 (95% CI: 0.86–1.03) (Table 4, Supporting Information S1: Figure S1).

In postmenopausal women, cohort studies indicated a modest reduction in breast cancer risk with MD adherence (HR: 0.91, 95% CI: 0.88, 0.95), while case-control studies suggested a stronger protective effect (HR: 0.82, 95% CI: 0.75, 0.90). Regional subgroup analysis revealed varying associations, with Europe showing a moderate reduction (HR: 0.90, 95% CI: 0.87, 0.93), a weaker and non-significant effect in America (HR: 0.95, 95% CI: 0.89, 1.02), and a notably strong association in Asia (HR: 0.49, 95% CI: 0.37, 0.64), which may be influenced by regional dietary patterns or study limitations. Furthermore, subgroup analysis based on alcohol inclusion demonstrated a significant difference in breast cancer risk reduction. When alcohol adjustment was included in the MD pattern, the risk was more substantially reduced (HR: 0.80, 95% CI: 0.72, 0.90), whereas excluding alcohol resulted in a higher HR of 0.92 (95% CI: 0.88, 0.95), suggesting that moderate alcohol consumption within the MD framework may contribute to its protective effect (Table 4, Supporting Information S1: Figure S2).

3.6 | Publication Bias

Three common methods were used to assess publication bias across these groups. The funnel plots for the overall, premenopausal, and postmenopausal categories displayed a symmetric distribution of studies, suggesting that publication bias was unlikely to be a major concern (Figure 6). This was further supported by Begg's test for the overall group ($p = 0.18$), premenopausal group ($p = 0.76$), and postmenopausal group ($p = 0.06$), indicating minimal risk of publication bias in all

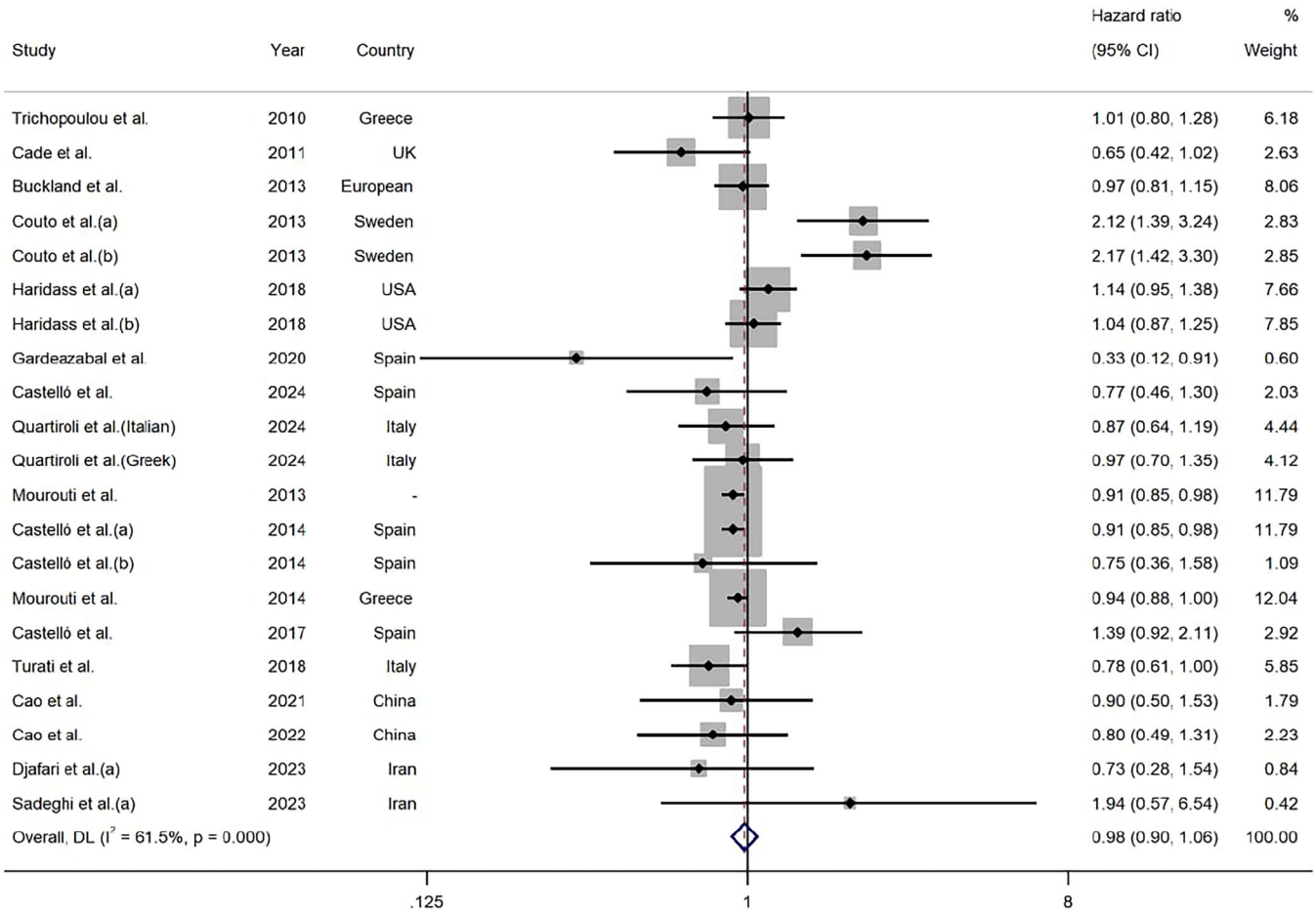


FIGURE 3 | Forrest plot demonstrating the hazard ratio (HR) and 95% confidence interval (95% CI) for the overall association between adherence to the Mediterranean diet (MD) and risk of breast cancer in premenopausal women.

three groups. Additionally, the results of the trim-and-fill method confirmed these findings, reinforcing that publication bias was not significant in any of the groups (Supporting Information S1: Table S3).

3.7 | Sensitivity Analysis

A sensitivity analysis was conducted using the leave-one-out method, revealing that no outlier studies were identified in any of the three groups: overall, premenopausal, and postmenopausal (Supporting Information S1: Figures S3 and S4).

4 | Discussion

This systematic review and meta-analysis examined the association between adherence to the Mediterranean diet and breast cancer risk in women. The findings demonstrated a significant 13% reduction in breast cancer risk, with the protective effect being more pronounced in postmenopausal women, while no significant association was observed in premenopausal women. Geographically, the strongest protective effect was identified in Asian populations, with moderate associations in European and American populations. Additionally, subgroup analysis indicated a stronger association in case-control studies, whereas cohort studies did not show a significant effect, highlighting potential differences in study design and methodological approaches that may influence the observed outcomes. These results emphasize the potential role of the Mediterranean diet in breast cancer prevention, particularly among postmenopausal women, though further research is needed to explore underlying mechanisms and regional variations.

MD is characterized by a high intake of vegetables, fruits, nuts, monounsaturated fatty acids, legumes, and cereals, limited intake of red meat and saturated fat, and moderate consumption of red wine [20], rich in polyphenolic compounds such as carotenoids and flavonoids, along with unsaturated fatty acids, and numerous bioactive agents that function as antioxidant, anti-inflammatory, antiproliferative, apoptotic, and anti-angiogenic agents, all of which contribute to its potential anticancer properties [21–23]. Furthermore, phytoestrogen in plant-based components may reduce breast cancer risk by modulating estrogen activity and decreasing the harmful effects of excess estrogen in developing breast cancer [24]. MD has been reported to play a role in various cancer prevention as well [23, 25]. Moazzen et al. [26], in 2020, reported a notable 28% reduction in upper gastrointestinal cancer risk [26]. Furthermore, significant inverse correlations between MD and lung cancer were observed in several studies [27–29]. Protection was also observed in bladder and colorectal cancer [25, 30, 31], though no prevention was noted in the case of prostate and ovary cancers [29, 32].

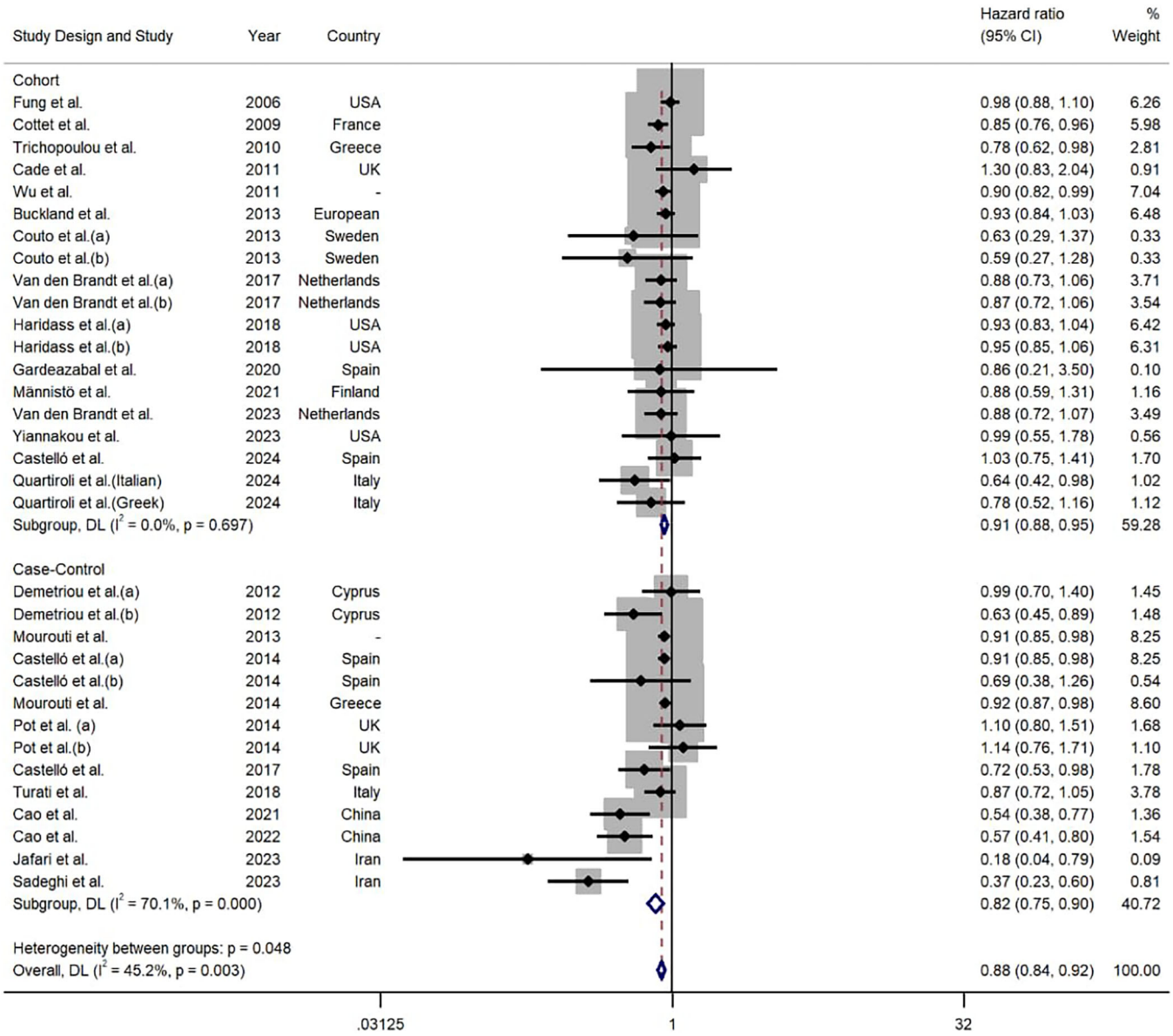


FIGURE 4 | Forrest plot demonstrating the hazard ratio (HR) and 95% confidence interval (95% CI) for the overall association between adherence to the Mediterranean diet (MD) and risk of breast cancer in postmenopausal women.

Our subgroup analysis based on menopause status revealed a considerable association between MD and breast cancer risk in postmenopausal women, whereas no significant association was observed in premenopausal breast cancer risk. In line with our findings, a meta-analysis by Li et al. [33] on 18 cohorts and case-control studies revealed that MD has a direct association with a risk reduction of breast cancer in overall and postmenopausal women but not in the premenopausal population. In a study by Dianatinasab et al. [34], a notable inverse association between adherence to MD and reduced invasive ductal carcinoma and invasive lobular carcinoma was found in case-control studies. However, no such association was found in cohorts. Besides, these subtypes were significantly associated with consumption of the Western diet, characterized by higher intakes of red meat, dairy products, and saturated fat [22]. In combined data from five Finnish cohorts evaluated the protective role of the MD on postmenopausal breast cancer risk, no association was obtained [35]. Similarly, Brandt et al. [36] found no association between MD and breast cancer risk in postmenopausal women, but a significant inverse association was observed in hormone receptor subgroup analyses, particularly for estrogen receptor-negative and estrogen/progesterone receptor-negative breast cancers.

The observed inconsistencies may be attributed to the possibility of a heterogenous association between the MD and various histologic subtypes, hormone-receptor status, and menopause status subgroups of breast cancer. This hypothesis aligns with our findings, demonstrating different associations between MD and menopause status. The stronger inverse association between MD and breast cancer in postmenopausal women was also documented in prior studies as well [33, 37]. This divergence may be explained by several underlying mechanisms. After menopause, estrogen production shifts from ovaries to adipose tissue [38]. MD is proven to play a favorable role in weight management and improving

insulin sensitivity, particularly by reducing visceral fat accumulation, which can lead to decreased estrogen levels post-menopause and lower the risk of breast cancer [39]. Considering that the mechanisms of developing breast cancer before menopause are more complex and rely on several factors, including family history, genetic mutations, lifestyle, reproductive and hormonal factors [40], The current state of knowledge did not come to a conclusion regarding the association between dietary patterns and breast cancer risk in perimenopause age.

The role of alcohol within the MD, particularly red wine, remains a subject of debate. Daily and moderate red wine consumption is noted to exhibit antioxidant effects due to its

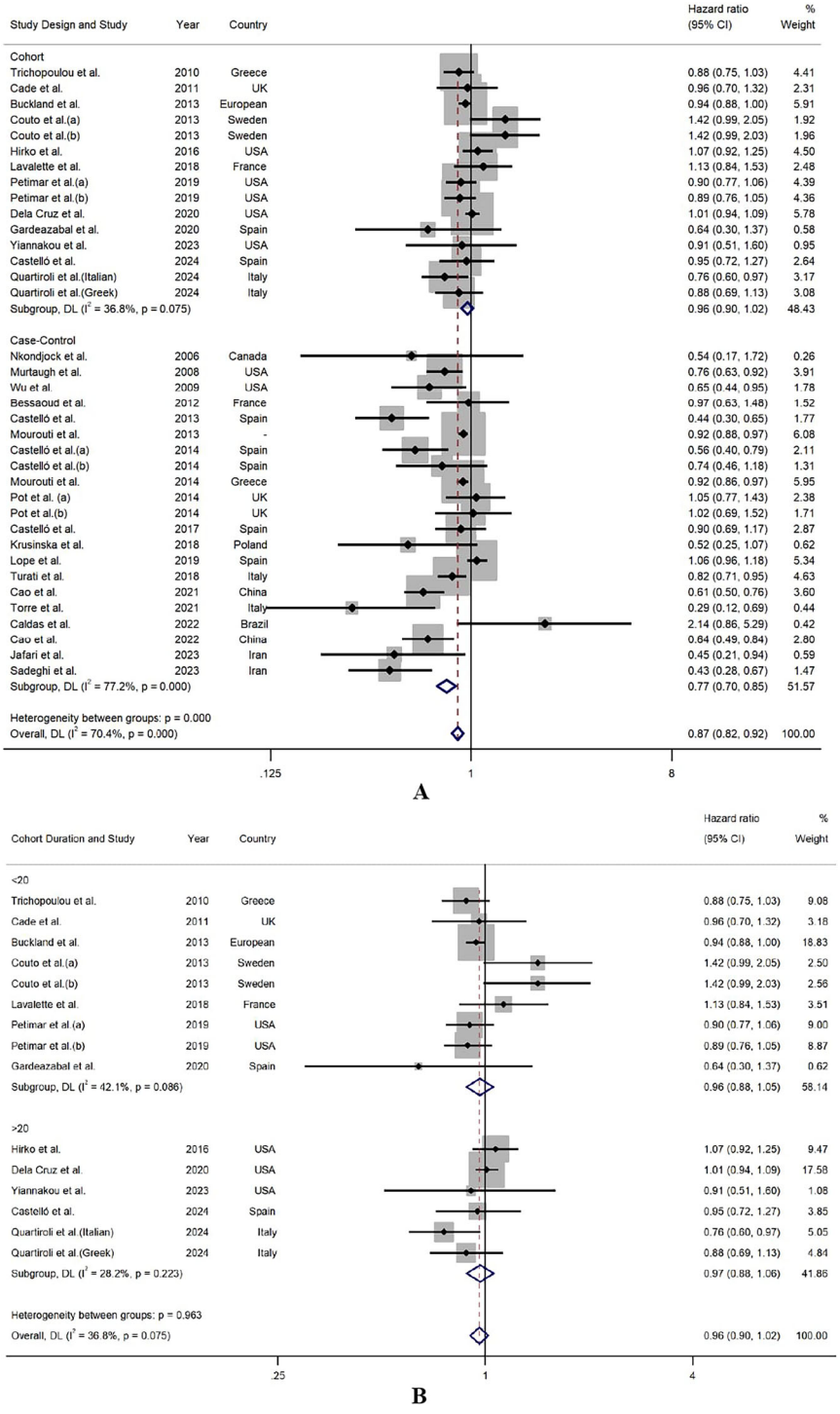
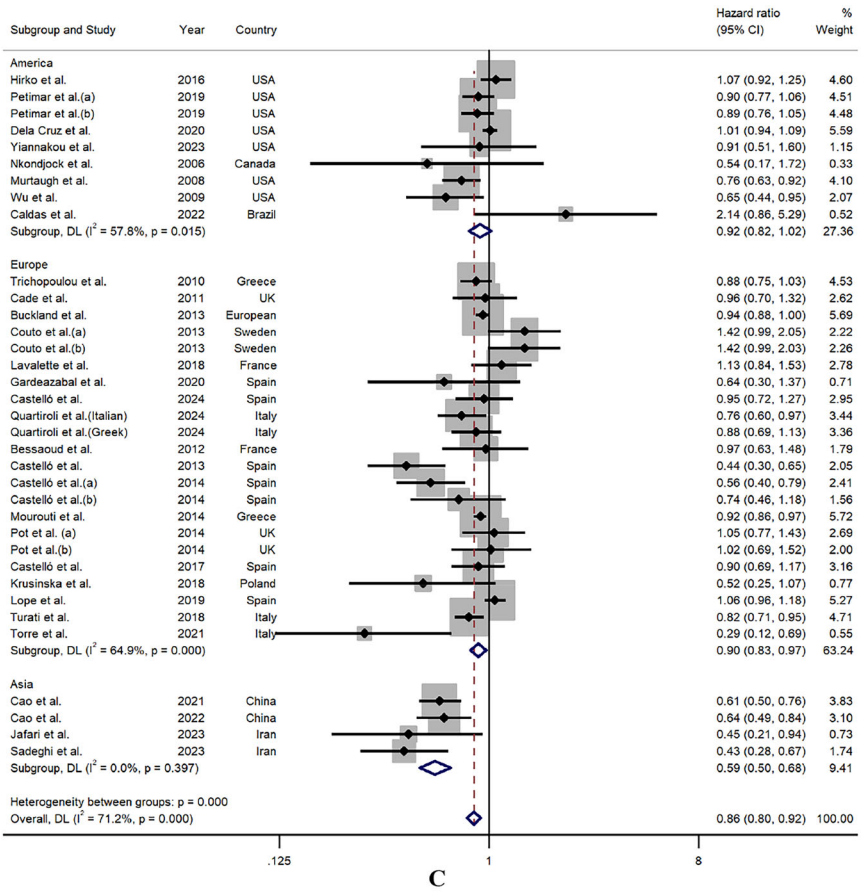


FIGURE 5 | Forrest plot demonstrating the hazard ratio (HR) and 95% confidence interval (95% CI) for the overall association between adherence to the Mediterranean diet (MD) and risk of breast cancer in women, based on the subgroup analysis based on thr study design (A), follow-up duration of cohort studies (B), geographical population (region) (C), and alcohol adjustment (D).



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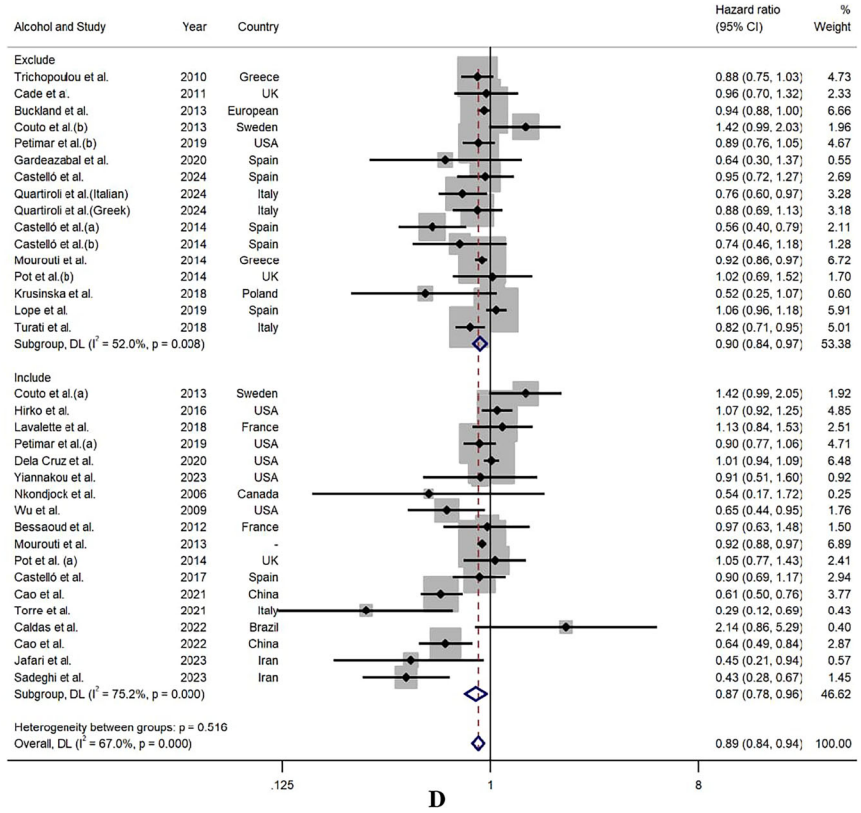

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FIGURE 5 | (Continued)

TABLE 4 | Meta-analysis findings of the association between the Mediterranean diet and the risk of breast cancer.

	No. of effect sizes	Hazard ratio (HR) (95% CI)	I^2 (%)	*p*-Heterogeneity
Overall	**36**	**0.87 (0.82, 0.92)**	**70.4%**	**< 0.001**
Study design				
Cohort	15	0.96 (0.90, 1.02)	36.8%	0.075
Case-control	21	0.77 (0.70, 0.85)	77.2%	< 0.001
Study location				
Asia	4	0.59 (0.50, 0.68)	0.0%	0.397
Europe	22	0.90 (0.83, 0.97)	64.9%	< 0.001
America	9	0.92 (0.82, 1.02)	57.8%	0.015
Cohort duration				
> 20 years	6	0.97 (0.88, 1.06)	28.2%	0.223
< 20 years	9	0.96 (0.88, 1.05)	42.1%	0.086
Alcohol adjustment				
Include	18	0.87 (0.78, 0.96)	75.2%	< 0.001
Exclude	16	0.90 (0.84, 0.97)	52.0%	0.008
Premenopausal	21	0.98 (0.90, 1.06)	61.5%	< 0.001
Study design				
Cohort	11	1.05 (0.88, 1.24)	72.3%	< 0.001
Case-control	10	0.92 (0.89, 0.96)	0.0%	0.499
Study location				
Asia	4	0.88 (0.63, 1.21)	0.0%	0.583
Europe	14	0.98 (0.88, 1.10)	70.4%	< 0.001
America	2	1.09 (0.95, 1.24)	0.0%	0.489
Alcohol adjustment				
Include	8	1.12 (0.90, 1.40)	70.7%	< 0.001
Exclude	13	0.94 (0.86, 1.03)	56.4%	0.007
Postmenopausal	33	0.88 (0.84, 0.92)	45.2%	0.003
Study design				
Cohort	19	0.91 (0.88, 0.95)	0.0%	0.697
Case-control	14	0.82 (0.75, 0.90)	70.1%	< 0.001
Study location				
Asia	4	0.49 (0.37, 0.64)	27.1%	0.249
Europe	23	0.90 (0.87, 0.93)	0.0%	0.461
America	4	0.95 (0.89, 1.02)	0.0%	0.928
Alcohol adjustment				
Include	15	0.81 (0.74, 0.90)	68.8%	< 0.001
Exclude	17	0.91 (0.88, 0.94)	0.0%	0.704

polyphenolic compounds [41]. Resveratrol can reduce estrogen production and decrease aromatase levels in Breast cancerous cells. However, the potential advantages should not obscure the harmful effects of ethanol in ROS production and the generation of DNA-damaging acetaldehyde in cancer development [29]. Additionally, alcohol inhibits the activity of 2-hydroxylase and sulfotransferase enzymes, which are involved in estrogen metabolism and can lead to higher estrogen levels [42]. The inclusion of alcohol in our study resulted in no significant risk reduction in premenopausal women but rather a greater reduction in breast cancer risk in the postmenopausal subgroup. Although evidence regarding alcohol's role in cancer prevention is currently inconclusive, future research should focus on determining whether alcohol consumption within MD offers protective effects and, if so, how much daily intake is effective in cancer prevention.

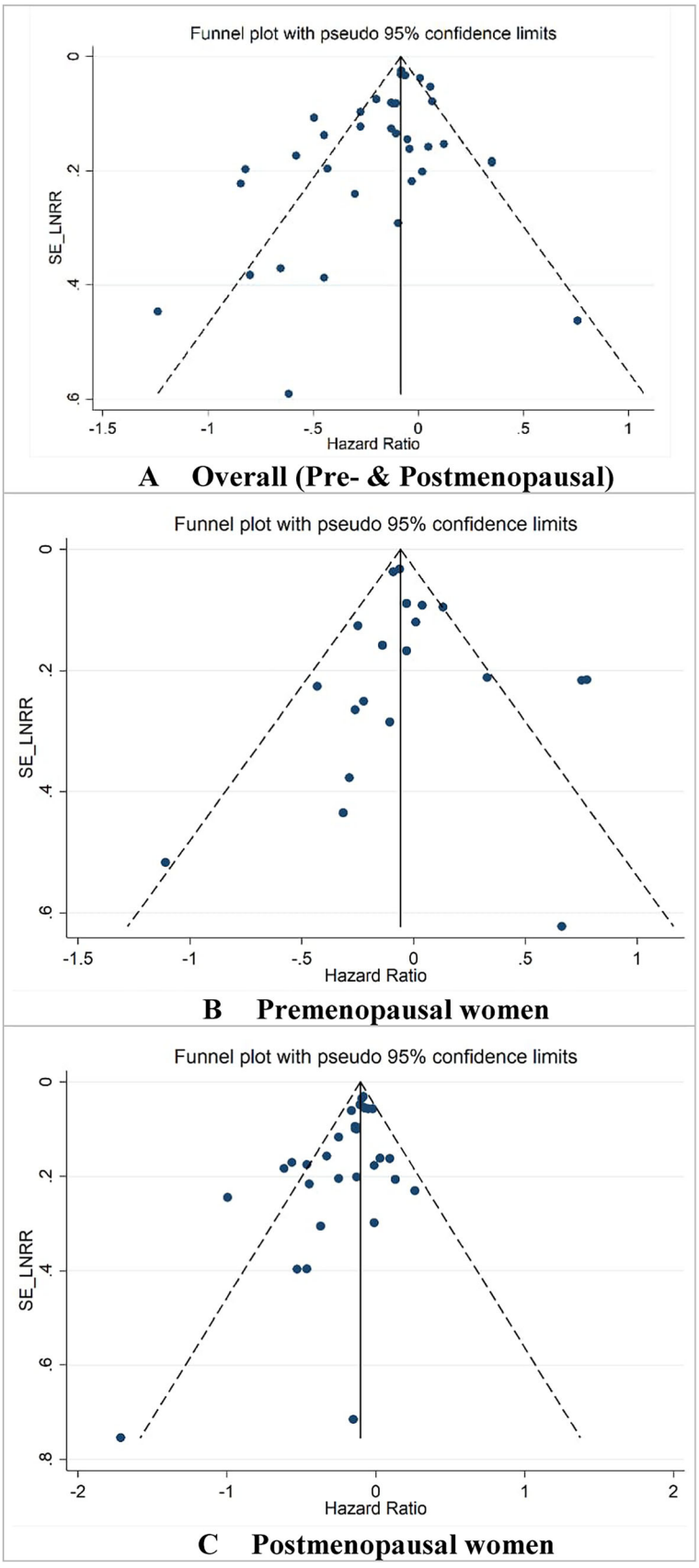

FIGURE 6 | Funnel plot for assessing publication bias in (A) Overall women (pre- and postmenopausal), (B) premenopausal, and (C) postmenopausal.

4.1 | Strength and Limitations

A particular strength of our study is the inclusion of a large number of observational and experimental studies, enabling us to perform subgroup analyses of some important risk factors. Furthermore, no publication bias was detected, as confirmed by the funnel plot and Begg's and Egger's tests. Nevertheless, some limitations should be acknowledged. In the subgroup analysis of study design, cohort studies indicated a non-significant association between MD and breast cancer risk, whereas case-control studies demonstrated a significant association but with higher heterogenicity. Since observational studies often indicate stronger evidence, this inconsistency can be explained through the possibility of recall bias and challenges in maintaining participant compliance in case-control studies. The Contradictory results in regional subgroup analysis could be attributed to variations in study designs and differences in MD content, which are mainly a cultural matter and need to be standardized in different regions. Future well-designed studies should consider breast cancer risk factors and subgroup analyses based on genetic predispositions, hormone receptor status, histological subtypes, and lifestyle to draw more definite conclusions regarding whether the MD can reduce the risk of various types of breast cancer in women.

5 | Conclusion

This meta-analysis highlights a significant association between adherence to the MD and a 13% reduction in breast cancer risk. The protective effect was particularly evident in postmenopausal women, whereas no significant impact was observed in premenopausal women, suggesting potential differences in the diet's influence based on hormonal and life-stage factors. Geographically, the strongest protective association was found in Asia, with moderate effects in Europe and America. Subgroup analysis indicated a more pronounced association in case-control studies, while cohort studies did not show significant effects, emphasizing the potential influence of study design on detecting the MD's benefits. These findings suggest that the MD may serve as a promising dietary strategy for breast cancer prevention, particularly for postmenopausal women. However, further research is necessary to explore its impact across diverse populations, different study designs, and various geographical regions.

Author Contributions

Mehdi Karimi: conceptualization, investigation, funding acquisition, writing – original draft, methodology, validation, visualization, writing – review and editing, formal analysis, software, project administration, data curation, supervision, resources. **Omid Asbaghi:** investigation, writing – review and editing, visualization, supervision, software, formal analysis. **Farnaz Hooshmand:** conceptualization, writing – original draft, writing – review and editing, investigation, funding acquisition, resources. **Amir Hossein Aghayan:** software, formal analysis, data curation, validation, methodology, writing – original draft, investigation. **Amir Ahmad Shariati:** data curation, software, resources, writing – original draft, funding acquisition, investigation. **Kimia Kazemi:** resources, writing – original draft, validation, visualization, investigation. **Mahdi Amirpour:** investigation, visualization, software, resources. **Sayed Hosein Davoodi:** supervision, investigation, methodology, validation, project administration. **Bagher Larijani:** visualization, project administration, supervision, investigation.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used in this meta-analysis were extracted from publicly available published studies. All relevant data supporting the findings of this study are included within the article and its supporting materials. For any further inquiries, please contact the corresponding author.

Transparency Statement

The lead author Mehdi Karimi, Sayed Hosein Davoodi, Bagher Larijani affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.