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Meta-analyses

Mediterranean diet and risk of breast cancer: An umbrella review

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SUMMARY

Background: The Mediterranean Diet (MedDiet) is a healthy dietary pattern which has been related to a lower risk of certain chronic diseases, such as some cancers. However, its role in breast cancer development remains unclear. This umbrella review aims to summarize the highest available evidence on MedDiet and breast cancer risk.

Methods: Pubmed, Web of Science, and Scopus electronic platforms were searched for relevant systematic reviews and meta-analyses. The selection criteria included systematic reviews with or without meta-analysis including women aged 18 years or older which evaluated the adherence to a MedDiet as the exposure and incidence of breast cancer as the outcome variable. Overlapping and quality of the reviews using AMSTAR-2 tool were independently assessed by two authors.

Results: Five systematic reviews and six systematic reviews with meta-analysis were included. Overall, 4 systematic reviews – two with and two without meta-analysis – were rated as of high quality. An inverse association was found in 5 of the 9 reviews which evaluated the role of MedDiet on the risk of total breast cancer. The meta-analyses showed moderate-high heterogeneity. The risk reduction seemed to be more consistent among postmenopausal women. No association was found for MedDiet among premenopausal women.

Conclusions: The results of this umbrella review suggest that adherence to a MedDiet pattern had a protective effect on the risk of breast cancer, especially for postmenopausal breast cancer. The stratification of breast cancer cases and conducting high-quality reviews are aspects needed to overcome the current results' heterogeneity and to improve knowledge in this field.

1. Introduction

Worldwide, breast cancer was the most frequently diagnosed cancer in both sexes in 2020. The incidence of breast cancer has surpassed lung cancer, as 2.3 million (11.7% of the total) new cases were estimated worldwide for that year. Moreover, it is the fifth leading cause of cancer mortality worldwide, and was the cause of 685,000 deaths in 2020 [1,2]. In recent decades, the incidence of this cancer has increased rapidly, especially in some regions, such as Europe. As the breast cancer burden is expected to increase in the future, the search for risk factors and primary prevention efforts to decrease their exposure are key aspects to curb this tendency [3].

During recent years, the association between breast cancer and certain foods and nutrients has been studied with inconsistent results [4–8]. For example, consuming non-starchy vegetables or foods containing carotenoids has shown limited evidence in their association with both pre- and postmenopausal breast cancer [9].

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Part of this inconsistency could be explained by the fact that foods are eaten together and act synergistically, and the joint action may be more important than that of any single food or nutrient [10,11]. Thus, the study of dietary patterns could capture the broader picture of the potential effect of diet on chronic diseases and, specifically, breast cancer.

The Mediterranean diet (MedDiet) has been shown to be a healthy dietary pattern with promising health outcomes, including cancer [12]. The MedDiet is a healthy dietary pattern based on the abundant use of extra-virgin olive oil, high consumption of plant-based food (vegetables, fruits, legumes and nuts), moderate to high consumption of fish, whole-grain cereals and red wine (with meals) and limited consumption of sugar-sweetened beverages, processed and red meats, milk, butter, whole-fat diary and sweets [13]. Numerous studies have analyzed the association between MedDiet and breast cancer, with some indicating a protective role of this dietary pattern [14–16]. However, other studies have not found any association [17,18]. These inconsistencies are also observed in systematic reviews and meta-analyses, some of which suggest an inverse relationship between this dietary pattern and risk of breast cancer (18,19), while others do not find statistically significant associations [19]. The singularities of breast cancer cases according to menopausal status or to different molecular subtypes [20] could help explain some of the results' heterogeneity. Thus, an analysis of systematic reviews and meta-analysis published, taking into consideration the potential sources of heterogeneity could help to elucidate this association. However, to date, umbrella reviews published on this topic have focused on MedDiet and multiple health outcomes [21,22], on broad aspects of nutrition (not specifically on adherence to a MedDiet pattern) and the risk of breast cancer [23], or diet and different types of cancers [24]. Therefore, this umbrella review aimed to analyze the existing evidence regarding the association between adherence to a MedDiet pattern and the risk of breast cancer.

2. Methods

This umbrella review was conducted following the guidelines for Preferred Reporting Items for Overviews of Reviews (PRIOR) [25]. The protocol was registered within the PROSPERO database (registration number: CRD42021203587).

2.1. Selection criteria

Predefined eligibility criteria were: systematic reviews with or without meta-analysis of individual observational studies (cohort, nested case–control and case–control studies) and randomized controlled trials which examined the association between MedDiet and breast cancer incidence including: (1) women aged 18 years or older; (2) evaluation of the adherence to the MedDiet as the exposure, estimated either with an a priori approach or with an a posteriori approach, as e.g. principal component analysis; and (3) breast cancer as outcome variable.

Exclusion criteria were: (1) narrative reviews; (2) systematic reviews/meta-analyses which evaluated individual food or nutrients or dietary patterns other than the MedDiet pattern; and (3) reviews that evaluated only mortality or prognosis of breast cancer as outcome variables. The year of publication of studies was not an exclusion criterion, and the search was done until June 30, 2022.

2.2. Literature search and study selection

Two researchers independently (C.G.P.T and R.B.-R) did the literature search using three electronic platforms: Pubmed, Web of Science, and Scopus. In case of disagreements and failed consensus, a third reviewer helped making the decision (J.J.J.-M). The used key words were: "breast cancer", "breast carcinoma", "breast neoplasm", "mediterranean diet", "mediterranean", "mediterranean dietary pattern", "mediterranean lifestyle", "dietary pattern", "dietary score", "dietary adherence", "dietary guidelines", "diet index", "nutritional score", "dietary index score", "systematic review", and "meta-analysis". The search strategies are available in Supplementary Table 1.

For the selection of articles, titles and abstracts of the identified articles were initially assessed. The full text was read for those articles considered relevant for inclusion. In addition, a manual search was carried out from the bibliography of the selected reviews to identify possible systematic reviews and/or meta-analyses not previously included. An active search was continued through an alert system in each of the electronic platforms used in the literature search until the date of submission. Finally, the authors were contacted if a selected article's full text or supplementary material was unavailable.

2.3. Overlapping and outdated reviews

To avoid bias in the interpretation of results, the overlapping of the potentially included reviews in this umbrella review was assessed. First, systematic reviews and meta-analyses with both the same exposure and outcome were grouped. Then, the following criteria were also considered: (1) if there were systematic reviews/meta-analyses from the same authors, the last update was chosen; (2) if the reviews were from different author/s and overlapping (see description below) was detected, reviews published before 2017 were excluded, since up to 50% of published systematic reviews are considered outdated after 5.5 years from publication [26]; (3) if overlapping systemic reviews/meta-analyses from different author/s were all published before or after 2017, the degree of overlap was evaluated. For this last step, a graphical cross-tabulation (citation matrix) was performed between the overlapping systematic reviews/meta-analyses (columns) and the included primary studies (rows). Thereby, we estimated the corrected covered area (CCA), which is expressed as a percentage (N = total number of primary studies from all reviews, r = rows, c = columns) and quantifies the degree of overlap:

$$ACC = \frac{(N - r)}{(r \times c - r)} \times 100$$

The overlapping is rated as: very high CCA >15%, high CCA 11%–15%, moderate CCA 6%–10%, and slight CCA 0%–5% [27]. Both reviews were kept if the degree of overlap was slight or moderate. If the degree of overlap was high or very high, the systematic review/meta-analysis with the highest quality according to the AMSTAR 2 tool was selected (see below for the description of this tool). If they had the same quality, the most recent one was included [26,28].

2.4. Data extraction and quality assessment

Data extraction and quality assessment were independently performed by two reviewers (C.G.P.T and R.B.-R). Any disagreement was resolved by consensus. The following information was collected from each selected systematic review: (1) First author's last name, and year of publication; (2) Number and design of the original studies; (3) Number of participants (differentiating participants from cohort studies, case–control studies and clinical trials for each systematic review); (4) Assessment of the dietary patterns; (5) Main results; and (6) Methodological quality (with AMSTAR-2 tool). In meta-analyses, pooled estimations from the random effects model with the 95% confidence interval (CI), both

from global and from stratified analyses, with the percentages of heterogeneity (I^2 coefficient) were indicated as main results.

To evaluate the methodological quality of the included systematic reviews, the AMSTAR 2 tool was used [29]. It contains ten domains from the previous AMSTAR version (A MeaSurement Tool to Assess systematic Reviews), published in 2007 [30]; two domains are more detailed, and it includes four additional domains. Of the 16 domains, 7 are considered as critical: 1. Protocol registered before commencement of the review; 2. Adequacy of the literature search; 3. Justification for excluding individual studies; 4. Risk of bias from individual studies being included in the review; 5. Appropriateness of meta-analytical methods; 6. Consideration of risk of bias when interpreting the results of the review; and 7. Assessment of the presence and likely impact of publication bias [29]. The quality rating according to the AMSTAR 2 tool is as follows: (1) High quality: no or one non-critical weakness. (2) Moderate quality: more than one non-critical weakness. (3) Low quality: one critical flaw with or without non-critical weaknesses. (4) Critically low: More than one critical flaw with or without non-critical weaknesses.

3. Results

3.1. Literature selection

Figure 1 shows the detailed literature selection. Briefly, 509 articles were initially identified. After removal of the duplicate records, 368 studies were obtained. Based on the abstracts and titles, 281 were excluded. Finally, after reviewing the full text and excluding overlapping articles, a total of 11 systematic reviews were included in this umbrella review: 5 were systematic reviews and another 6 were systematic reviews which also included a meta-analysis (see Supplementary Table 2 for the reasons for excluding manuscripts after full-text review).

3.1.1. Overlapping evaluation

According to the evaluated exposure and outcome, systematic reviews were organized in 5 groups (Supplementary Table 3): (a) MedDiet and risk of breast cancer as well as of other cancers [before this evaluation, we excluded three previous reviews of Morze et al. [31–33]; (b) MedDiet or other dietary patterns, and breast cancer risk; (c) MedDiet and breast cancer risk; (d) MedDiet or other dietary patterns, and risk of breast cancer as well as of other cancers. (e) MedDiet and risk of breast cancer risk as well as of other health outcomes.

3.2. Quality assessment of studies

The evaluation of the methodological quality of each systematic review and meta-analysis according to AMSTAR-2 criteria is shown in Tables 1 and 2. One systematic review was scored as critically low quality [34], one as low [35], one as moderate [36], and only two, Du et al., 2018 [37] and Ubago-Guisado et al., 2021 [38], as high quality. Among the meta-analyses, the quality of one of them was critically low [39], three were scored as low [19,40,41], and two as high: Dianatinasab et al., 2020 [42] and Morze et al., 2021 [43]. Supplementary Table 4 shows the results of each evaluated item.

3.3. Characteristics of included systematic reviews and meta-analyses

The main characteristics of the included reviews are summarized in Table 1 for systematic reviews and in Table 2 for systematic reviews and meta-analyses. Morze et al. [43] was the systematic review with the highest number of included studies (n = 24), and, together with the review of Bloomfield et al. [41], the only one incorporating a clinical trial. The total number of breast cancer cases in primary cohort studies ranged from 1094 to 35,373. For the reviews that included case–control studies, the lowest number of participants were 973 cases and 973 controls [34], and the highest was 2718 cases and 3387 controls [36].

Regarding the types of dietary patterns, 5 reviews included the MedDiet and other dietary patterns [19,35–38]. Due to the lack of unanimity defining the MedDiet pattern, 2 reviews considered in the analysis other dietary patterns (e.g. prudent pattern) along with MedDiet [41,42]. The remaining reviews exclusively included a MedDiet pattern [34,39,40,43]. Regarding the assessment methods, 5 reviews included studies using a priori and a posteriori approach.

3.3.1. Evidence summary of selected reviews

For total breast cancer risk, 5 out of 11 reviews suggested that adherence to the MedDiet pattern reduced the risk of breast cancer [36,38,40,42,43]. This result was found in all the cohort studies and in one of the two case–control studies included in the systematic reviews. However, there was moderate-high heterogeneity in the estimations of the 3 meta-analyses which reached this conclusion (I^2 ranged from 31% to 95.3%) [40,42,43]. The heterogeneity persisted in analyses restricted to cohort studies (n = 5), except in the high-quality review of Morze et al. [43], which found a pooled estimate of RR: 0.97 (95% CI: 0.94–1.00) with null heterogeneity. Again, considering only case–control studies (n = 3), heterogeneity was low only in the study by Morze et al. (I^2: 6%), with a risk reduction of 13% (RR = 0.87, 95% CI: 0.82–0.93). In the analyses with case–control studies, the estimates showed stronger than results based on cohort studies.

A possible source of heterogeneity in the association between MedDiet and breast cancer risk may be menopausal status. This aspect was considered in 7 reviews [19,34,37–40,43], and there was consistency in finding an inverse association among postmenopausal women. It should be taken into account that the heterogeneity was partially or completely solved in three of the four meta-analyses [19,39,43]. Nevertheless, statistical significance was only reached in the high-quality review by Morze et al. (RR: 0.95; 95% CI: 0.92–0.99; I^2: 0%). The three reviews that showed results for premenopausal women consistently found that a MedDiet was non-significantly associated to a lower risk of breast cancer risk [19,40,43], but only Hou et al. showed homogeneity in its result (RR: 0.92, 95% CI: 0.83–1.01, I^2: 0%) [19].

The consideration of the tumor receptor status was not very frequent in the included reviews [34,37–39,43]. Nonetheless, the 3 systematic reviews that did consider it found a stronger risk reduction in ER-tumors, particularly in postmenopausal women. This result was mainly based on cohort studies as only Coughlin et al. [34] included a case–control study. In the same line, Van den Brandt et al. [39] found a significant risk reduction of 23% (RR:0.77 95% CI: 0.63–0.94) and 27% (RR:0.73 95% CI: 0.57–0.93) for ER-/PR- and ER-respectively, with null and low heterogeneity respectively. Morze et al. [43] described a non-significant inverse association with these negative hormonal receptor tumors but with high heterogeneity. Hence, the literature suggests and inverse association between a MedDiet and breast cancer risk for ER-tumors and, specifically, among postmenopausal women but the results were not conclusive.

4. Discussion

In search of potential primary prevention strategies, the objective of the present umbrella review was to synthesize the existing evidence to date on the association between adherence to a MedDiet pattern and the risk of breast cancer.

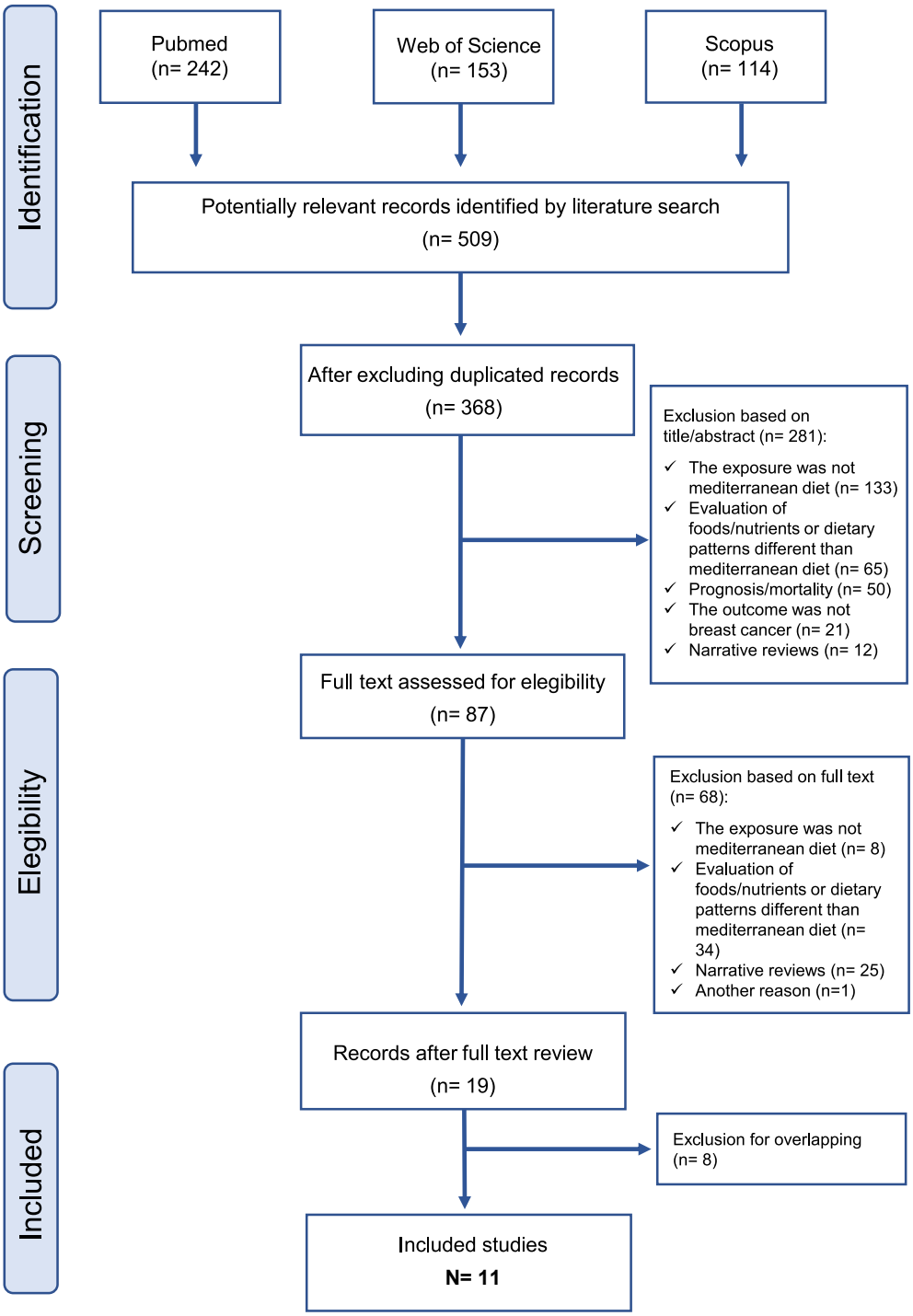

Fig. 1. Flowchart of the selection process in the umbrella review.

There was a lack of high-quality research among most of the selected reviews, which could be a source of their inconsistency. In addition, the heterogeneity of the included primary on the association between MedDiet and total breast cancer was maintained after stratification by type of design in most of the meta-analyses. The reviews analyzing only case–control studies reflected a higher inverse association between adherence to the MedDiet and total breast cancer risk than those analyzing only cohort studies [40,42,43]. The former showed a significant risk reduction of breast cancer of up to 13% (95% CI 7–18%) with low heterogeneity in one of the high-quality meta-analyses [43]. However, it should be considered that the use of odds ratio could overestimate the risk ratio estimations [44]. Moreover, case–control studies are particularly susceptible to some biases [45]. Thus, although all reviews pointed to the existence of an inverse association, the uncertainty about the relationship between the MedDiet and global breast cancer risk continues, mainly due to the lack of high-quality research in this approach and the presence of high heterogeneity.

Table 1
Characteristics of the systematic reviews included in the umbrella review.

First author, year	Number and epidemiologic design of included studies	Number of participants	Assessment of the dietary patterns				Main results	AMSTAR-2
			Types of dietary patterns	Tools for dietary information	Assessment methods			
Albuquerque, 2014 [36]	1 cohort 2 C-C	Cohort: 65,374 total 2,381 cases C-C: 2,718 cases, 3,387 controls	MD	2 FFQ 1 dietary history questionnaire	PCA Factor analysis	A posteriori	MD was associated with a risk reduction of breast cancer	Moderate
Coughlin, 2018 [34]	6 cohorts 1 C-C	Cohorts: 679,550 total, 22,157 cases. C-C: 973 cases, 973 controls	MD	Unspecified	MD scale by Trichopoulous Factor analysis PCA	2 a priori 2 a posteriori 1 both 2 unspecified	A risk reduction was found in postmenopausal women, and stronger for ER- tumors.	Critically low
Dandamudi, 2018 [35]	2 C-C 2 nested C-C	C-C: 1,267 cases, 1,267 controls. Nested C-C: 1,888 cases	MD, other healthy dietary patterns and unhealthy dietary patterns	3 FFQ 1 food diary (4-7 days)	aMED (0-8 points) MDS (0-9 points) MDS (0-55 points) MDS (0-8 points) PCA	3 a priori 1 a priori and a posteriori	There was no consensus. An inverse association was found in only one study with a priori approach	Low
Du, 2018 [37]	4 cohorts	513,533 total, 15,358 postmenopausal cases (1758 ER- cases)	MD, DASH, HEI, AHEI, DII, E-DII, LCD	3 FFQ 1 FFQ and dietary history questionnaire	aMED arMED score (0–16 points) MedS (0–9 points) aMedr (0–8 points)	A priori	The most consistent results were found with MD pattern, showing a risk reduction of ER- tumors in postmenopausal women	High
Ubago-Guisado, 2021 [38]	2 cohorts	339,404 total, 10,465 incident cases	MD, FSA-NPS DI, Vegetarian diet	FFQ	MDS arMED (0–16 points)	A priori	A risk reduction in overall and postmenopausal women, and stronger for PR- and ER- tumors.	High

Abbreviations: C–C: case–control study; MD: mediterranean diet; FFQ: food frequency questionnaire; PCA: principal component analysis; ER-: estrogen receptor negative; aMED: alternate mediterranean diet; DASH: dietary approaches to stop hypertension; HEI: healthy eating index; AHEI: alternate healthy eating index; DII: dietary inflammation index; E-DII: energy-adjusted dietary inflammation index; LCD: low-carbohydrate diet; arMED: adapted relative mediterranean diet; Meds/MDS: mediterranean diet score; aMedr: alternate mediterranean diet II; FSA-NPS DI; Food Standards Agency nutrient profiling system dietary index; PR-: progesterone receptor negative.

Table 2
Characteristics of the systematic reviews with meta-analysis included in the umbrella review.

First author, year	Number and epidemiologic design of included studies	Number of participants	Assessment of the dietary patterns				Risk estimations (95% IC), I^2	AMSTAR-2
			Types of dietary patterns	Tools for dietary information	Assessment methods			
Bloomfield, 2016 [41]	12 cohorts 1 RCT	Cohorts: 984,584 total RCT: 4152 total	MD (considered along with: healthy pattern, salad and wine pattern, prudent pattern, and other vegetable patterns)	Unspecified	arMED MDS aMED	3 a priori 10 unspecified	Cohorts: 0.96 (0.90–1.03), 53%	Low
Van den Brandt, 2017 [39]	5 cohorts	Unspecified	MD	4 unspecified 1 FFQ	4 unspecified 1 mMEDr and aMEDr	A priori	Postmenopausal: 0.94 (0.88–1.01), 13.2% ER+: 0.98 (0.82–1.17), 47.6% ER-: 0.73 (0.57–0.93), 6% ER-/PR-: 0.77 (0.63–0.94), 0% MD with alcohol: 1.03 (0.83–1.28), 29.3% MD without alcohol: 0.92 (0.87–0.98), 0%	Critically low
Li, 2018 [40]	10 cohorts 8 C–C	Cohorts: 809,521 total C–C: 7041 cases, 8964 controls	MD	14 FFQ 4 unspecified	MDS (0–9 points) arMED (0–16 points) Factor analysis MDS by Panagiotakos PCA aMED (0–8 points) MDS (0–10 points) MDS (0–8 points) MDS (0–55 points)	14 a priori 3 a posteriori 1 unspecified	Global: 0.92 (0.86–0.99), 69.9% Postmenopausal: 0.91 (0.85–0.97), 59.9% Premenopausal: 0.93 (0.83, 1.05), 67.5% Cohorts: 0.95 (0.88, 1.03), 71.3% C–C: 0.85 (0.73, 0.99), 61.0%	Low
Hou, 2019 [19]	5 cohorts	493,095 total, 18,232 cases	MD and other healthy dietary patterns	FFQ, one also used a diet-history questionnaire or food record	1 aMED 4 unspecified	A priori	MD: 0.96 (0.89–1.04), 32% Including MD in healthy patterns Overall: 0.93 (0.88–0.98), 26.6% Premenopausal: 0.92 (0.83–1.01), 0% Postmenopausal: 0.97 (0.90–1.05), 26.5%	Low
Dianatinasab, 2020 [42]	2 cohorts 5 C–C	Cohorts: 106,555 total, 3704 cases (3085 ductal and 619 lobular) C–C: 1677 cases (1642 ductal, 35 lobular), 2136 controls	MD (considered along with prudent and healthy pattern) and Western pattern	6 FFQ 1 diet history questionnaire	MDS (0–9 points) PCA Factor analysis	6 a posteriori 1 a priori	Global IDC: 0.77 (0.72–0.82), 95.3% Cohorts IDC: 0.98 (0.92–1.05), 88.8% C–C IDC: 0.47 (0.39–0.55), 85.1% Global ILC: 0.76 (0.64–0.87), 89.2%	High
Morze, 2021 [43]	12 cohorts 11 C–C 1 RCT	Cohorts: 35,373 cases C–C: 10,615 cases, 13,593 controls	MD	Unspecified	Factor analysis PCA aMED (0–9 points) aMED (0–8 points) MEDI-LITE (0–18 points) Polish-aMED (0–8 points) MDS (0–8 points) Polish-aMED (0–8 points) MDS (0–55 points) MDS (0–9 points) MDS (0–10 points)	21 a priori 3 a posteriori	Global: 0.94 (0.90–0.97), 31% Premenopausal: 0.99 (0.71–1.37), 81% Postmenopausal: 0.95 (0.92–0.99), 0% Cohorts: 0.97 (0.94–1.00), 0% C–C: 0.87 (0.82–0.93), 6% RCT: 0.41 (0.19–0.87) Fung MD: 0.98 (0.93–1.02), 0% Trichopoulou MD: 0.99 (0.97–1.13), 38% Mediterranean countries: 0.95 (0.57–1.59), 46% Non-mediterranean countries: 0.98 (0.94–1.02), 0% ER+: 0.98 (0.89–1.06), 30% ER-: 0.86 (0.64–1.15), 73% PR+: 1.00 (0.91–1.09), 0% PR-: 0.91 (0.61–1.36), 82% ER+/PR+: 0.95 (0.88–1.02), 21% ER-/PR-: 0.81 (0.66–1.20) 76%	High

Abbreviations: RCT: randomized controlled trials; MD: mediterranean diet; arMED: adapted relative mediterranean diet; MDS: mediterranean diet score; aMED: alternate mediterranean diet; FFQ: food frequency questionnaire; mMEDr modified mediterranean diet score excluding alcohol; aMEDr: alternate mediterranean diet score excluding alcohol; ER+: estrogen receptor positive; ER-: estrogen receptor negative; PR-: progesterone receptor negative. C–C: case–control study; MD: mediterranean diet; FFQ: food frequency questionnaire; MDS: mediterranean diet score; arMED: adapted relative mediterranean diet; aMED: alternate mediterranean diet; PCA: principal component analysis. C–C: case–control study; MD: mediterranean diet; FFQ: food frequency questionnaire; MDS: mediterranean diet score; PCA: principal component analysis; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma. C–C: case–control study; RCT: randomized controlled trial; MD: mediterranean diet; PCA: principal component analysis; aMED: alternate mediterranean diet; MEDI-LITE: mediterranean diet based on the literature; MDS: mediterranean diet score; ER+: estrogen receptor positive; ER-: estrogen receptor negative; PR+: progesterone receptor positive; PR-: progesterone receptor negative.

Breast cancer is not a single entity (e.g., menopausal status or molecular subtypes), and this circumstance could underlie this lack of homogeneity in the global case results.

The stratified results by menopausal status suggested a small protective effect of the adherence to a MedDiet pattern on the risk of breast cancer in postmenopausal women. The results were scarcer for premenopausal women, but no significant effect was consistently found. This difference could be due to the MedDiet having a different behavior according to the menopausal status of women as it occurs with the body mass index [9] which would difficult the observation of an effect in global analysis. Of note, there was unresolved heterogeneity in some of the included reviews addressing premenopausal breast cancer risk in this umbrella review. Also, the role of a MedDiet has not yet been sufficiently investigated in premenopausal women [46], and it may also affect the results.

Another characteristic that should be considered in evaluating breast cancer etiology and developing prevention strategies is the variability of tumor receptor subtypes [47]. The results of the included reviews pointed toward an inverse association between a higher adherence to a MedDiet and the risk of ER-, highlighting this effect among postmenopausal women. The contribution of other factors in the risk of breast cancer according to hormone receptor subtypes may affect the implication of diet in its appearance. Thus, dietary factors could have a higher importance in ER-tumors, where there is less influence of hormonal factors [48,49]. Nevertheless, authors of the included reviews acknowledged insufficient research in this line, probably due to the impossibility of presenting stratified results by receptor with a more limited statistical power to detect associations. In any case, more research should be carried out to confirm this finding as ER-tumors continue to be a challenge in terms of prevention, prognosis, and treatment [50,51].

The potential protective effect found for a MedDiet, especially for postmenopausal breast cancer and ER-tumors, could be explained by (1) the suggested benefit of MedDiet components, e.g., its lipid-lowering effect, the protection against oxidative stress, inflammation, and platelet aggregation, or the modification of hormones and growth factors involved in breast cancer pathogenesis [52], and/or (2) the potential contribution of other associated healthy behaviors in women with a higher adherence to a MedDiet [53]. In any case, it would be beneficial to encourage women to follow a MedDiet pattern taking into account the results of this study and its demonstrated benefits on other health outcomes [54].

Regarding the strengths of this umbrella review, we highlight: (1) To our knowledge, it is the first umbrella that exclusively studies the relationship between a MedDiet and the risk of breast cancer. (2) It was conducted following the PROSPERO protocol. (3) The selection of reviews was made without restriction of publication date in three important electronic databases to minimize the selection bias. (4) The overlapping was assessed to eliminate double counting and avoid bias in the results.

This umbrella review has potential limitations that should be considered when interpreting the results. First, several reviews showed low quality. To establish a protocol prior to the conduct the review and to evaluate the risk of bias of studies are some of the items to be considered in future systematic reviews and meta-analysis to improve the quality of the summary evidence. Second, the findings came from observational studies, as there was only one RCT among the included primary studies [16]. This points out the need for further experimental studies to better control biases and interpret results. Third, the heterogeneity was not solved in most of the results. The evaluation of the level of adherence to a MedDiet pattern of a population is complex and there is high variation in the assessment methods (a priori based on different indexes/a posteriori) as well as in the cut-off points used to define the highest vs. the lowest category [55]. To determine the real impact of the MedDiet pattern on breast cancer risk, a uniform assessment with harmonized components of a MedDiet and cut-off points could be useful, as previously suggested [56].

5. Conclusion

Adherence to a MedDiet seems to have a protective effect for breast cancer risk, especially among postmenopausal breast cancer. This umbrella review has highlighted the necessity for a stratified approach in the etiology research for breast cancer and conducting high-quality reviews.

Author contributions

RB-R, JJJ-M and CM-B contributed to the study design; RB-R and CG-PT conducted the literature search and study selection, extracted the data and assessed the methodological quality, any disagreement was solved by JJJ-M; RB-R and CG-PT, wrote original draft preparation; ET, TD and JJ-M got funding acquisition; ET, TD, CM-B and JJJ-M critically reviewed and edited the manuscript; all authors read, approved the final version and agreed on the submission of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.02.012.

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