

Original Research Article

Adulthood dietary and lifestyle patterns and risk of breast cancer: Global Cancer Update Programme (CUP Global) systematic literature review

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ABSTRACT

Background: An increasing number of studies in recent years investigate various dietary and lifestyle patterns and associated breast cancer (BC) risk. **Objectives:** This study aimed to comprehensively synthesize and grade the evidence on dietary and lifestyle patterns and BC risk. **Methods:** Databases were systematically searched up to 31 March, 2022, for evidence from randomised controlled trials and prospective cohort studies on adherence to a dietary pattern alone or in combination with lifestyle behaviors and incidence of or mortality from primary BC in adult females. Findings in all, premenopausal, and postmenopausal females were descriptively synthesized instead of meta-analyzed due to patterns heterogeneity. An independent Global Cancer Update Programme Expert Panel graded the strength of the evidence. **Results:** A total of 84 publications were included. Results for patterns reflecting both a healthy diet and lifestyle were more consistent than for patterns that included diet only. There was strong-probable evidence that a priori World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and American Cancer Society (ACS) dietary and lifestyle scores may reduce BC risk in all and postmenopausal females, whereas in premenopausal females, less evidence was found contributing to limited-suggestive grade. There was also a limited-suggestive evidence that adherence to the Healthy Lifestyle Index and other diet and lifestyle scores may reduce BC risk in postmenopausal females; a posteriori Western/Meat/Alcohol dietary patterns may increase BC risk in postmenopausal females; and Prudent/Vegetarian/Mediterranean dietary patterns may reduce BC risk in all females. For the remaining patterns, evidence was graded as limited-no conclusions. **Conclusions:** Advice to adopt combined aspects of a healthy diet and lifestyle according to WCRF/AICR and ACS scores, encouraging a healthy weight, physical activity, alcohol and smoking avoidance, and a healthy diet rich in fruits, vegetables, (whole)grains and cereals and discouraging red and processed meat, can be proposed to females to lower BC risk. This review was registered at PROSPERO as ID CRD42021270129 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021270129) on 28 August, 2021, and further updated on 4 May, 2022, in order to extend the search period.

Abbreviations: ACS, American Cancer Society; AHEI, alternate Healthy Eating Index; BC, breast cancer; CUP, Cancer Update Programme; DASH, Dietary Approaches to Stop Hypertension; DGA, Dietary Guidelines for Americans; HEI, Healthy Eating Index; HI, Health Index; HLI, Healthy Lifestyle Index; PCA, principal component analysis; RoB, risk of bias; RR, relative risk; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; WHI-DM, Women's Health Initiative Dietary Modification.

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Keywords: dietary and lifestyle patterns, breast cancer incidence, evidence grading, systematic review, a priori dietary patterns, a posteriori dietary patterns, hybrid dietary patterns

Introduction

Breast cancer (BC) is a leading public health problem owing to its high incidence (2.3 million new cases in 2020) and mortality (684,996 deaths) in females worldwide [1]. It is known that healthy diet and lifestyle may play an important preventive role [1–4]. During recent decades, several studies on BC risk have assessed its relationship with the intake of single nutrients and food groups (eg, fruits and vegetables, soy food, fiber, meat, saturated fat, and alcohol) [5,6]. However, this approach presents several limitations, as the totality of diet is likely to have interactive, synergistic, and combined effects [7]. Moreover, it is becoming more evident that an important impact on BC risk may result from an overall pattern of a healthy diet, physical activity, and maintenance of a healthy weight [8]. Thus, a clearer assessment of the complexity of various dietary and lifestyle patterns and associated BC risk is warranted.

The 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Third Expert Report [9] concluded that the evidence on the relationship of dietary patterns and the risk of BC was inconclusive. Although the literature on dietary patterns and BC was abundant (the report was based on 45 articles published up to the 31 December, 2015), a variety of methods had been used to derive the patterns, which hindered the validity of summarizing the evidence by conventional meta-analytical methods [10]. As such, the Global Cancer Update Programme (CUP) commissioned a group of international experts to establish a systematic literature review protocol [11] to synthesize the evidence following clear eligibility criteria and instructions for grouping diet and/or lifestyle patterns by deviation methods.

This work aimed to systematically review the literature on dietary and lifestyle patterns and BC incidence and mortality using improved methodologic approaches for reviewing and synthesizing the evidence and update previous WCRF/AICR systematic reviews [9]. We further aimed to identify commonalities across different patterns to classify all the patterns into groups and to synthesize the evidence separately for risk of overall, premenopausal, and postmenopausal BC.

Methods

This systematic literature review was conducted as part of the ongoing CUP Global, formally known as the WCRF/AICR CUP [12], according to the protocol available at <https://osf.io/z9naw/> [11]. The present review was registered in PROSPERO (https://www.crd.york.ac.uk/prospéro/display_record.php?ID=CRD42021270129) on 28 August, 2021, and further updated on 4 May, 2022, in order to extend the search period. Details on the methods used [search strategy, study selection, data extraction, risk of bias (RoB) assessment, and data synthesis] are available in [Supplemental Text 1](#).

Search strategy, selection criteria, and data extraction

PubMed and Embase were searched for relevant publications from inception to 31 March, 2022. Details on search terms used and the inclusion and exclusion criteria are provided in [Supplemental Text 1](#) and [Supplemental Table 1](#). Briefly, the inclusion criteria were as follows: 1) randomised controlled trials (RCTs), prospective cohort studies, nested case–control studies, case–cohort studies, and pooled

analyses of studies with these designs; 2) studies on incidence of or mortality from primary BC in adults (18 y or older); 3) studies that examined consumption of and/or adherence to a dietary pattern alone or in combination with lifestyle behaviors (ie, physical activity, smoking, and body adiposity) as assessed by indices or scores driven from data by statistical methods or predefined; and 4) studies that provided a complete description of the components of the dietary or lifestyle pattern being investigated, as well as the cutoff points used to categorize or assign scores to the participants. Studies that examined a labeled dietary pattern, but did not describe the foods and beverages consumed, and those patterns that are based solely on nutrient intakes, were excluded. The reference lists of reviews were hand-searched for any potential missed articles. To avoid duplication of the results from the same study population, the publication with the higher number of cases and longer follow-up was selected. Publications from the same cohort but reporting different outcomes or using different patterns or components were maintained. Data required for the analysis (study characteristics, participants, exposure, outcomes, and results) were extracted and incorporated into the CUP Global database. Study selection and data extraction was checked in a random sample of publications (10%) by a second reviewer. Discrepancies were discussed and resolved by consensus.

RoB assessment

RoB was assessed using a modified version of the tool for nutrition observational studies tool ([Supplemental Table 2](#)) or version 2 of the Cochrane RoB tool for RCTs (RoB2) (<https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2>). To ensure accuracy, 10% of publications were checked by 2 independent reviewers (J.K., G.M.), and the percentage of agreement between them was high (78%–100% depending on the domain). For observational studies, 7 domains of bias were assessed: 1) confounding; 2) selection of participants into the study; 3) classification of exposure(s); 4) departure from the intended exposure(s); 5) missing data; 6) measurement of outcome(s); and 7) selection of reported results. Within each domain, RoB was judged as low, moderate, serious, critical, or no information. For RCTs, the following domains of bias were evaluated: 1) randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome(s); and 5) selection of the reported results. An overall bias was also graded, and risk was judged as low, some concerns, or high.

Data synthesis

Patterns were grouped considering the type (dietary only or dietary and lifestyle pattern) and derivation method used (a priori, a posteriori, or hybrid). A priori dietary patterns (or hypothesis-oriented) include indexes or scores constructed according to combinations of different foods, drinks, and nutrients, based on previous knowledge regarding the association of individual foods and nutrients with health or disease or reflecting adherence to existing dietary patterns perceived to provide health benefits. In turn, a posteriori (also named data-driven or empirical) dietary patterns are derived empirically from dietary data in the study populations using data-reducing methods, such as principal component analyses (PCAs) or cluster analyses. Patterns can be also derived using hybrid methods, such as reduced rank regression, a 2-step process to derive data-driven patterns that explain the highest

variability of a priori selected intermediate factors such as nutrients or biomarkers [13]. In this review, 4 main groups of patterns were distinguished (Supplemental Table 3). Dietary patterns were derived with a priori, a posteriori, and hybrid methods, whereas dietary and lifestyle patterns were mainly derived with a priori methods (only 1 pattern was obtained using a hybrid method) [14]. To obtain more homogenous patterns, further classification into subgroups was performed based on the pattern's origin and detailed study of included components (Table 1 and Supplemental Table 4). A priori dietary and lifestyle patterns were divided into those that were based on specific recommendations for cancer prevention or general recommendations to follow a healthy lifestyle. Furthermore, a priori dietary patterns were divided into those based on culturally defined dietary habits or dietary guidelines. A posteriori dietary patterns were divided into Western-/Meat/Alcohol, which comprised less healthy dietary patterns; Prudent/Vegetarian/Mediterranean, which was associated with healthier diets; or traditional/ethnic/mixed, which included patterns that did not fit into any of these 2 groups. Hybrid dietary patterns were divided depending on whether the intermediate response variables were biological markers or nutrients.

Meta-analysis was not used to summarize the results because patterns within groups were heterogeneous in terms of components and cutoff points. Instead, a descriptive synthesis with vote counting based on number of studies showing positive [relative risks (RRs) > 1], inverse (RR < 1) or null (RR = 1) direction of effects/associations was used. Neither statistical significance nor the size of the effect was considered in the vote counting procedure [15]. To aid the interpretation of associations, forest plots were created for patterns, which were assessed in ≥ 3 studies. For this, RRs with 95% CIs comparing extreme (highest with lowest) exposure categories were plotted, with additional information such as total number of cases, without calculating an overall summary effect. Studies that reported only continuous associations were reported in tables and in the text.

Findings were synthesized separately for all (menopausal status unspecified), premenopausal, and postmenopausal females. Heterogeneity was explored using subgroup analysis within each pattern and according to menopausal status (if possible), when there were ≥ 2 studies in each stratum. Sources of heterogeneity examined were as follows: cancer outcome subtypes (molecular and morphologic); geographic location by continent (North America, South America, Europe, Asia, Australia, Africa, and Antarctica); number of cancer cases (<100, 100–500, and >500); length of follow-up (≤ 5 , 5–10, and >10 y and unknown); study design (RCTs and observational studies); presence of specific components in a pattern (ie, alcohol and smoking); or RoB (low, moderate, serious, critical, or no information). Constructed forest plots were visually explored based on the consistency in the direction (mainly) and magnitude of associations across studies, without using statistical tests. The presence of small-study effects as an indication of publication bias was also assessed using the Egger test and visual inspection of funnel plots [16]. All analyses were conducted using Stata software, version 17 (StataCorp).

Evidence grading

Members of the independent CUP Global Expert Panel judged the evidence according to predefined criteria, including the quantity, consistency, magnitude and precision of the effect estimates, the presence of a dose–response relationship, study design, RoB, generalizability, and mechanistic plausibility of the results (Supplemental Table 5), with preliminary judgments made by the CUP Global Expert Committee on Cancer Incidence. The evidence was graded as strong (subgrades

evaluating likelihood of causality: convincing, probable, or substantial effect on risk unlikely) or limited (subgrades: limited-suggestive or limited-no conclusion). Details on grading criteria and judgment are available at <https://www.wcrf.org/diet-activity-and-cancer/global-cancer-update-programme/judging-the-evidence/>.

RESULTS

Screening and study characteristics

In total, 3024 distinct publications were screened and 84 included (flowchart in Figure 1). There were 77 publications from observational studies and 7 from 3 RCTs, reporting data from different lengths of follow-up or BC subtypes. Most of the studies were conducted in North America and Europe and included large study populations (median: 48,835 participants), with a large number of cases (median: 1477) and follow-up (median: 12 y). Almost all studies addressed total (invasive and in situ) or invasive BC as an outcome. Only 7 studies reported results on BC mortality using a variety of patterns [17–23], limiting the possibility to synthesize these findings. Similarly, evidence synthesis for molecular or morphologic BC subtypes was hampered by a limited number of studies within each subtype.

RoB assessment

Overall, RoB was low-to-moderate for most domains of observational studies (Supplemental Figure 1). Most of the studies (78%) adjusted for all important confounders (age, adiposity, and reproductive factor(s) (including ≥ 1 of the following: age at menarche, age at menopause, parity, and lactation) but in half of them (47%) reliability or validity of measurement of key confounders could not be evaluated or was low, resulting in an overall moderate-to-serious RoB from confounding. Although the majority of the patterns were not validated, the tools used to capture individual components were mostly validated, resulting in an overall moderate RoB in classification of exposure (68%). For the departure of intended exposures, RoB was rated predominantly as critical (84%), given that most studies measured diet and lifestyle only once, hence incurring measurement error due to intra-individual variation [24]. None of the studies reported findings based on a preregistered protocol or statistical analysis plan, as it is quite uncommon for observational studies; hence, risk of reporting of selective findings is unclear. Most studies from RCTs were considered to have low RoB (Supplemental Figure 2).

Results by exposure

Main findings with evidence grading conclusions are available in Table 2. Studies reporting associations for the highest compared with the lowest category of adherence to the pattern are shown in Figures 2–4; results from both categorical and continuous associations can be seen in Supplemental Tables 6–10.

A priori dietary and lifestyle patterns

Twenty-five observational studies (23 prospective cohorts, 1 pooled analysis of 2 cohorts [22], and 1 case–cohort [35] examined associations between a priori dietary and lifestyle scores and BC risk (mostly incidence, mortality was addressed only in 2 studies) [22,23]. Findings on these patterns are available in Supplemental Table 6.

A priori dietary and lifestyle patterns based on specific recommendations for cancer prevention. Eighteen publications were identified. The WCRF/AICR score or its modifications was used in 15 studies

TABLE 1
Summary of components of dietary and lifestyle patterns.

Pattern subgroup	Pattern name	No. of publications	Score versions	Foods and Lifestyle factors																							
				Adiposity	Physical activity	Smoking	Alcohol	Fruits	Vegetables	Nuts/seeds	Potatoes	Legumes	Grains and cereals/fibre	Poultry	Red meat/processed meat	Eggs	Cream/butter/margarine/lard	Dairy products	Fish and seafood	Snacks/sweets/ultra-processed foods	Sugar-sweetened beverages	Olive/veg oil or high-unsat/low sat fatty acids	Sodium	Coffee/tea	Added sugar		
“A Priori” dietary and lifestyle patterns																											
Based on specific recommendations for cancer prevention	WCRF/AICR score	15	15	Dark red	Dark green	Light red	Light red	Dark green	Dark green			Light green	Dark green		Dark red						Dark red		Light red				
	American Cancer Society (ACS) guidelines	4	4	Dark red	Dark green	Light red	Light red	Dark green	Dark green						Dark red												
Based on general recommendations for a healthy lifestyle	Healthy Lifestyle Index (HLI) (and modifications)	5	5	Dark red	Dark green	Light red	Light red	Dark green	Dark green				Dark green		Dark red												
	Dietary Guidelines for Americans (DGAs)	1	1	Dark red	Dark green	Light red	Light red	Dark green	Dark green						Dark red							Dark red		Dark red			
	Health Index (HI) (French recommendations and WHO)	1	1	Dark red	Dark green	Light red	Light red	Dark green	Dark green						Dark red												
	PNNS-Guideline Score (PNNS-GS)	1	1	Dark red	Dark green	Light red	Light red	Dark green	Dark green				Dark green		Dark red							Dark red		Dark red			
Hybrid*	Estrogen-related lifestyle pattern*	1	1	Dark red	Dark green	Light red	Light red	Dark green	Dark green						Dark red												
“A priori” dietary patterns																											
Based on culturally-defined dietary habits	Mediterranean diet score (MDS and modifications)	15	23				Yellow	Dark green	Dark green			Dark green	Dark green	Dark red	Dark red			Dark red	Dark green			Dark green					
	Pro-vegetarian/plant-based diets	3	3					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark green	
	Healthful pro-vegetarian/plant-based diets	2	2					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark green	
	Unhealthful pro-vegetarian/plant-based diets	2	2					Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Palaeolithic diet	1	1				Light red	Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Mexican diet	1	1					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
Based on dietary guidelines	Healthy Eating Index (HEI) and alternate HEI (AHEI)	7	12				Yellow	Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Dietary Approaches to Stop Hypertension (DASH)	5	5					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Recommended Food Score (RFS)	2	2					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Diet Quality Index (DQI)	1	1					Dark red	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Diabetes Risk Reduction Diet (DRRD)	1	1					Dark green	Dark green		Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Healthy Diet Index (HDI) (WHO guidelines)	1	1					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Nordic diet	2	2				Light red	Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	Cumulative risk factors (UK and European guidelines)	1	1					Dark green	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	PNNS diet score	1	1					Dark red	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	The 2015 Dutch dietary guidelines	1	1					Dark red	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
	WCRF diet	2	2					Dark red	Dark green			Dark green	Dark green	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	Dark red	
“A posteriori” dietary patterns																											
	Prudent/Vegetarian/Mediterranean	18	24					Dark green	Dark green			Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	Dark green	
	Western/Meat/Alcohol	17	24					Light green	Light green			Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	
	Traditional/Ethnic/Mixed	12	18					Light green	Light green			Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	Light green	

Dark green colour is used to indicate a higher intake/positively loaded food groups in most of the patterns; light green colour is used to indicate a higher intake/positively loaded specific food groups in some of the patterns; dark red is used to indicate a lower intake of food groups in most of the patterns; light red is used to indicate a lower intake of specific food groups and yellow is used to indicate moderate intake.

Abbreviations: AICR – American Institute for Cancer Research; PNNS – French National Nutrition Health Program; UK – United Kingdom; WCRF – World Cancer Research Fund; WHO – World Health Organization.

*The dietary component of this lifestyle pattern is obtained using reduced rank regression (hybrid).

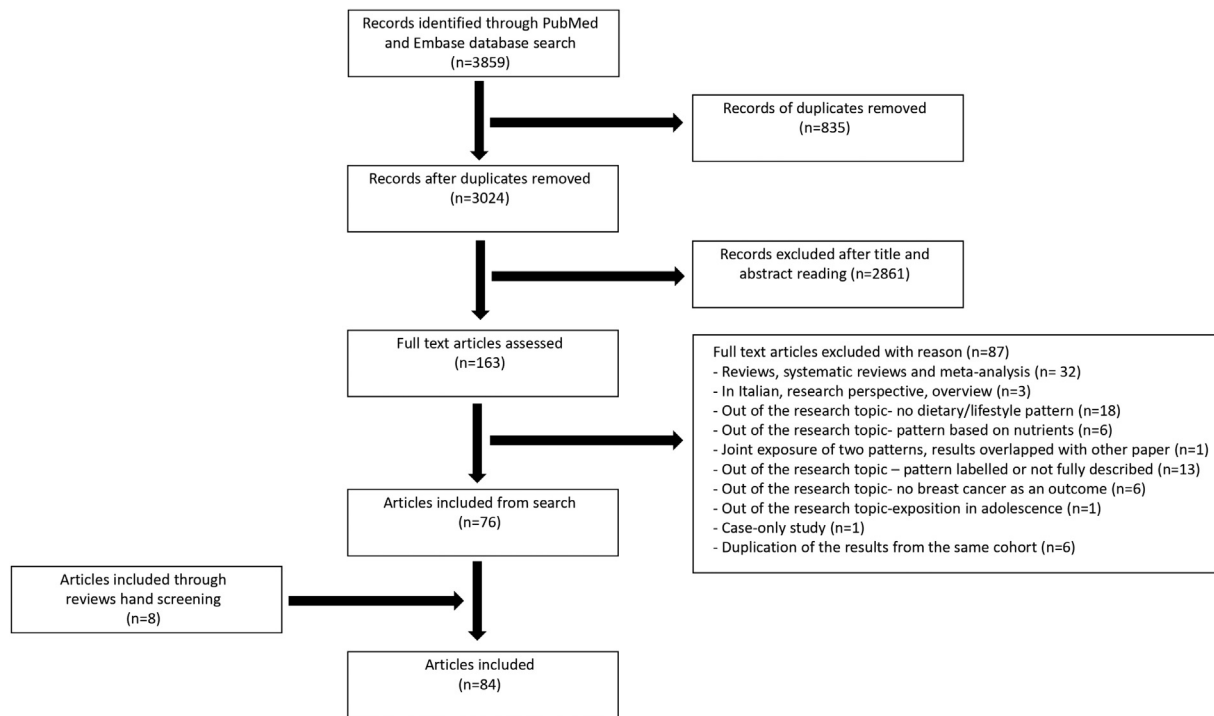


FIGURE 1. Flowchart representing each step of the screening process and inclusion of publications for this review.

[22,25,29,30,31,36–45], and the American Cancer Society (ACS) score in 4 studies [23,37,46,47] (in 1 study both scores were used) [37]. These scores encourage a healthy weight, physical activity, a plant-based diet, and discourage red and processed meat and alcohol consumption [48–50] (see components in Table 1). Notably, results were consistent in the direction of an inverse association independently of menopausal status, with several studies showing strong evidence of an association (Figure 2A and Supplemental Table 6). In particular, all 14 studies (from 13 publications) conducted in all females indicated lower BC risk—RRs: 0.49–0.98; 13 scores assessed categorically [25,30,31,37–40,42–44,46,47] and 1 continuously [29]—of which in 7 [25,30,37,38,42,46,47], 95% CIs did not cross 1. In premenopausal females, 5 studies were identified—RRs: 0.67–1.04; 3 scores assessed categorically [40,43,45] and 2 continuously [30,31]—of which, in 4 [30,40,43,45], an inverse association with BC risk was found, and in 1, the risk of in situ BC was increased (but with CIs including 1) [31]. In postmenopausal females—RRs: 0.27–1.00; 6 scores assessed categorically [23,36,40,41,43,45] and 2 continuously [30,31]—inverse associations were observed in 7 [23,30,31,36,41,43,45] of 8 studies; with 6 of those studies showing strong evidence of association [23,30,36,41,43,45]. Nomura et al. [40] found a null association with BC risk in categorical analyses but an inverse association when the score was analyzed continuously.

A priori dietary and lifestyle patterns based on general recommendations for a healthy lifestyle. Eight publications were identified. Patterns from this group share common lifestyle factors, including BMI, physical activity, smoking, and diet (mostly fruits and vegetables) (Table 1). In 3 studies [26,35,52], the Healthy Lifestyle Index (HLI) score developed by McKenzie et al. [26] was used. The remaining patterns were used in single studies, including other healthy lifestyle scores [27,53], the Health Index (HI) based on French recommendations and World Health organization (WHO) [54], Dietary Guidelines

for Americans (DGA) (fifth edition) [55], and the French National Nutrition Health Program-Guideline Score (PNNS-GS) [30]. In general, an inverse association was identified in all studies regardless of menopausal status with several studies showing strong evidence of association (Figure 2B). In particular, comparison between the highest and the lowest adherence categories showed lower BC risk incidence in 2 studies performed in all females (RRs: 0.65–0.96) [30,53], in 1 study conducted in premenopausal females (RR: 0.80; 95% CI: 0.58, 1.12) [54], and in all 6 studies in postmenopausal females [26,27,35,52,54,55]—RRs: 0.62–0.87, in 5 [26,27,35,52,55] of which CIs did not include 1.

A priori dietary patterns

Associations between a priori dietary patterns and BC risk were examined in 26 observational studies—22 prospective cohorts, 3 pooled analysis cohorts [56–58], and 1 case-cohort study [59]. In this section, 3 RCTs, which used predefined dietary interventions, were also included. Similarities among all these patterns include the combination of high consumption of fruits and vegetables, nuts and seeds, legumes, (whole) grains and cereals or fiber, olive or other vegetable oils or high unsaturated-to-low saturated fatty acids ratio, as well as low consumption of red and processed meat, sugar-sweetened beverages, and sodium. Incidence of BC was a predominant outcome, and mortality was addressed in 3 observational studies [17,18,21] and 1 RCT [19,20]. Components of these patterns derived from observational studies are summarized in Table 1 and findings on risk of BC are shown in Supplemental Table 7. Components and results from the RCTs are tabulated in Supplemental Tables 8 and 9.

A priori dietary patterns based on culturally defined dietary habits. Dietary patterns based on adherence to eating behaviors, traditions, or even fad diets often believed to be inherently healthy were included within this category. These include the Mediterranean dietary pattern,

TABLE 2

Evidence grades and main findings from the descriptive synthesis of dietary and lifestyle patterns and breast cancer risk.

Evidence grades	Pattern	Breast cancer by menopausal status	Summary of findings	Conclusions
Strong evidence	Convincing	—	—	—
	Probable		Decreases risk	
	A priori dietary and lifestyle patterns based on specific recommendations for cancer prevention (WCRF/AICR and ACS score)	In all females	14 RRs (13 RRs for the highest vs the lowest level of adherence ranged 0.49–0.98 and 1 RR: 0.87; 95% CI: 0.74, 1.03 per 1-unit increment in the score) from 13 studies (13 publications): all inverse associations; in 7 studies 95% CIs did not include null value	Evidence based on 14 estimates from cohort studies showed clearly consistent tendency toward inverse associations, without heterogeneity (in effect direction, but little in effect size), supported by plausible mechanistic evidence for pattern components, unlikely influenced by methodologic limitations and publication bias
		In postmenopausal females	8 RRs (6 RRs for the highest vs the lowest level of adherence ranged 0.27–1.00 and 2 RRs per 1-unit increment in the score ranged 0.83–0.94) from 8 studies (8 publications): 7/8 inverse (in 6 studies 95% CIs did not include null value), 1/8 null association	Evidence based on 8 estimates from cohort studies showed a consistent tendency toward inverse associations, without heterogeneity, supported by plausible mechanistic evidence for pattern components, and unlikely influenced by methodological limitations and publication bias
Limited evidence	Limited suggestive		Decreases risk	
	A priori dietary and lifestyle patterns based on specific recommendations for cancer prevention (WCRF/AICR and ACS score)	In premenopausal females	5 RRs (3 RRs for the highest vs the lowest level of adherence ranged 0.67–0.78 and 2 RRs per 1-unit increment in the score ranging 0.98–1.04) from 5 studies (5 publications): 4/5 inverse (in 1 study 95% CIs did not include null value), 1/5 positive associations (95% CIs included null value)	Evidence based on 5 estimates from cohort studies is suggestive of inverse association, without heterogeneity, supported by plausible mechanistic evidence for pattern components, and unlikely influenced by methodologic limitations and publication bias
	A priori dietary and lifestyle patterns based on general recommendations for a healthy lifestyle (HLI, HI, and DGA)	In postmenopausal females	6 RRs from 6 studies (6 publications) ranged 0.62–0.87 for the highest vs the lowest level of adherence: all inverse associations; in 5 studies 95% CIs did not include null value	Evidence based on 6 estimates from cohort studies using 3 different patterns, although showed a general consistent tendency toward inverse associations, supported by plausible mechanistic evidence for pattern components and with no strong evidence of influence by methodologic limitations and publication bias
	A posteriori Prudent/Vegetarian/Mediterranean	In all females	17 RRs from 13 studies (12 publications) ranged 0.64–1.28 for comparison between the highest vs the lowest levels of adherence or clusters: 15/17 inverse (in 3 studies 95% CIs did not include null value); 2/17 positive (in both 95% CIs included null value) associations	The evidence is based on 17 estimates from cohort studies, and generally consistent in the direction of inverse association, but is limited in methodologic quality, supported by plausible mechanistic evidence, and unlikely influenced by publication bias
			Increases risk	
	A posteriori Western/Meat/Alcohol	In postmenopausal females	11 RRs from 10 studies (9 publications) ranged 0.95–1.77 for comparison between the highest and the lowest levels of adherence or clusters: 8/11 positive (in 1 study 95% CIs did not include null value); 3/11 inverse (95% CIs included null value in all) associations	The evidence is based on 11 estimates from cohort studies, and generally consistent in the direction of positive association, but is limited in methodologic quality, supported by plausible mechanistic evidence, unlikely influenced by publication bias

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TABLE 2 (continued)

Evidence grades	Pattern	Breast cancer by menopausal status	Summary of findings	Conclusions
Limited-no conclusion	<p>A priori dietary and lifestyle patterns based on general recommendations for a healthy lifestyle: HI, PNNS (in premenopausal females)</p> <p>A priori dietary patterns based on culturally defined dietary habits: AHEI (in premenopausal females), healthful provegetarian/plant-based dietary patterns (in premenopausal and postmenopausal females), Paleolithic diet (in premenopausal and postmenopausal females), traditional Mexican diet (in postmenopausal females), unhealthy provegetarian/plant-based dietary patterns (in premenopausal and postmenopausal females)</p> <p>A priori dietary patterns based on dietary guidelines: DASH (in premenopausal females), Dutch Dietary Guidelines (in all females), DQI-R (in postmenopausal females), DRRD (in all, premenopausal, and postmenopausal females), HNFI (in all and premenopausal females), low-fat dietary interventions (in all and premenopausal females), PNNS-GS2 (in all, premenopausal, and postmenopausal females), RFS (in all and postmenopausal females), UK and European dietary guidelines score (in all females), and WHO HDI (in all, premenopausal, and postmenopausal females)</p> <p>Hybrid dietary patterns derived from biological markers: proinflammatory dietary pattern (in all, premenopausal, and postmenopausal females); proestrogen dietary pattern (in all females)</p> <p>Hybrid dietary patterns derived from nutrients: discretionary fats dietary pattern (in all females), fructose dietary pattern (in all females), high-alcohol dietary pattern (in all and postmenopausal females), high-fiber dietary pattern (in postmenopausal females), simplified dietary pattern (in all women), and vitamin D dietary pattern (in all females)</p> <p>Hybrid dietary and lifestyle patterns: estrogen-related lifestyle score (in postmenopausal females)</p>			The evidence is based on 1 estimate from cohort study, pooled analysis, or RCT
	<p>A priori dietary and lifestyle patterns based on general recommendations for a healthy lifestyle: HI and PNNS (in all females)</p> <p>A priori dietary patterns based on culturally defined dietary habits: healthful provegetarian/plant-based dietary patterns (in all females), Mediterranean dietary pattern (in all, premenopausal, and postmenopausal females), provegetarian/plant-based dietary patterns (in all, premenopausal, and postmenopausal females), unhealthy provegetarian/plant-based dietary patterns (in all females)</p> <p>A priori dietary patterns based on dietary guidelines: HEI and AHEI (in all and postmenopausal females), DASH (in all and postmenopausal females), HNFI and mNDI (in postmenopausal females), low-fat dietary interventions (in postmenopausal females), and WCRF/AICR dietary score (in postmenopausal females)</p> <p>A posteriori dietary patterns: Prudent/Vegetarian/Mediterranean (in premenopausal and postmenopausal females), traditional/ethnic/mixed (in all, premenopausal, and postmenopausal females), Western/Meat/Alcohol (in all and premenopausal females)</p> <p>Hybrid dietary patterns derived from biological markers: proestrogen dietary pattern (in postmenopausal females)</p> <p>Hybrid dietary patterns derived from nutrients: high-fiber dietary pattern (in all females)</p>			The evidence is based on 2 or more estimates from cohort studies, pooled analyses, or RCTs but shows inconsistency in the direction of associations

Abbreviations: ACS, American Cancer Society; AHEI, Alternate Healthy Lifestyle Index; CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; DGA, Dietary Guidelines for Americans; DQI-R, Diet Quality Index-Revised; DRRD, Diabetes Risk Reduction Diet; HEI, Healthy Eating Index; HI, Health Index; HLI, Healthy Lifestyle Index; HNFI, Healthy Nordic Food Index; mNDI, modified Nordic Dietary Index; PNNS, French National Nutrition Health Program; PNNS-GS2, French National Nutrition Health Program-Guideline Score 2; RFS, Recommended Food score; RR, relative risk; UK, United Kingdom; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; WHO HDI, World Health Organization Healthy Diet Index.

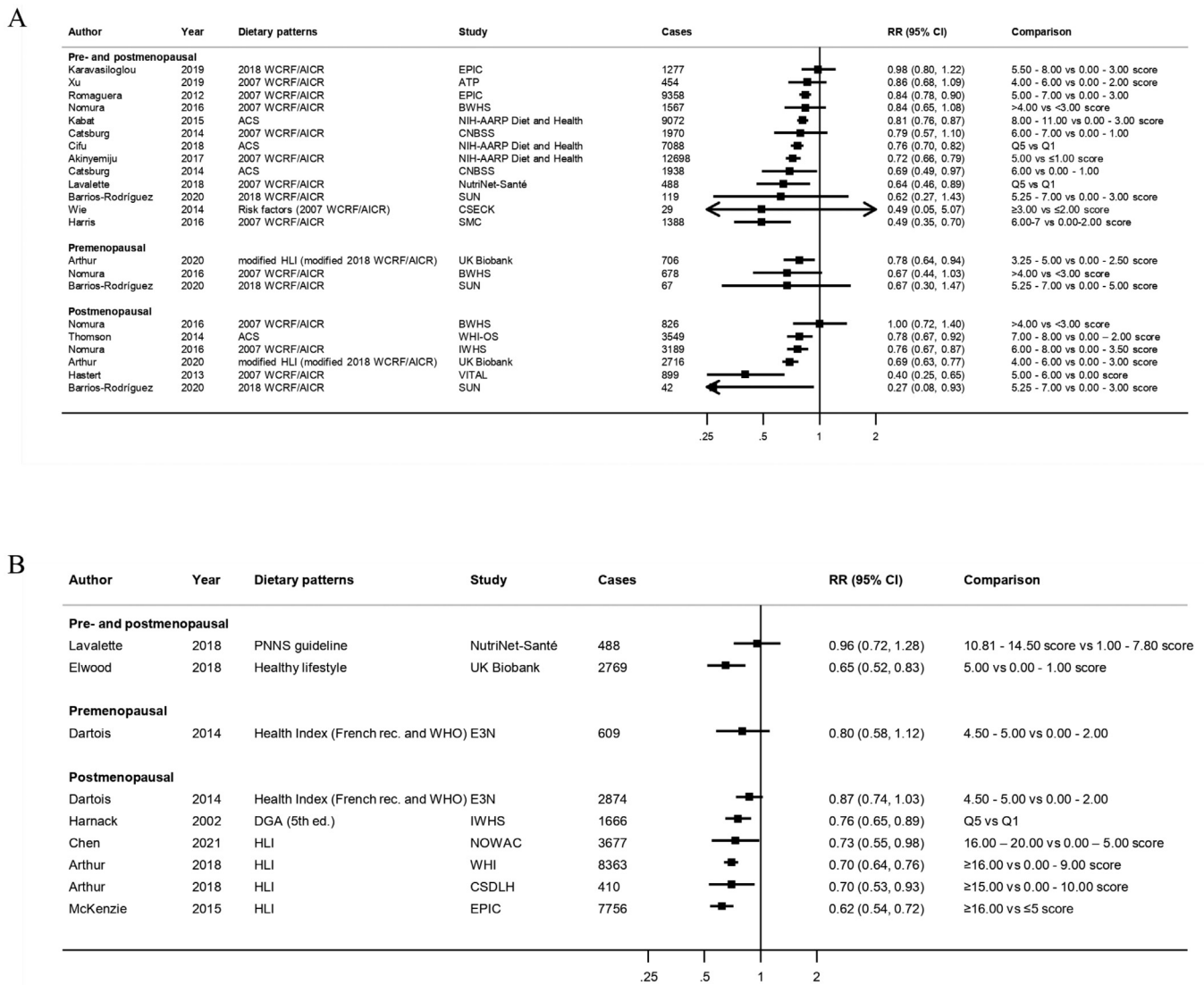


FIGURE 2. Relative risks (RRs) and 95% CIs of breast cancer incidence for the highest compared with the lowest level of adherence to a priori dietary and lifestyle patterns: (A) based on cancer-specific recommendations; (B) based on general recommendations for a healthy lifestyle. For comparability between studies [to show the comparison between the highest (the best) with the lowest (the worst) level of adherence to the pattern] the estimates (95% CI) from the study by Akinyemiju et al. [25] were inverted (A); and those from the studies by McKenzie et al. [26] and Chen et al. [27] were recalculated using an approach implemented in Excel software and described by Hamling et al. [28] (B). Scores analyzed only continuously per 1-unit increment in the WCRF/AICR score: in all females, RR: 0.87; 95% CI: 0.74, 1.03 [29]; in premenopausal females, RR: 0.98; 95% CI: 0.81, 1.17 [30] and RR: 1.04; 95% CI: 0.95, 1.15 [31]; in postmenopausal females, RR: 0.83; 95% CI: 0.75, 0.92 [30] and RR: 0.94; 95% CI: 0.87, 1.02 [31]. AARP, formerly the American Association of Retired Persons) Diet and Health Study; ATP, Alberta’s Tomorrow Project; BWHS, Black Women’s Health Study; CNBSS, Canadian National Breast Screening Study; CSDLH, Canadian Study of Diet, Lifestyle and Health; CSECK, Cancer Screening Examination Cohort of Korea; E3N, Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l’Éducation Nationale (MGEN); EPIC, The European Prospective Investigation into Cancer and Nutrition; IWHS, Iowa Women’s Health Study; NOWAC, Norwegian Women’s and Cancer Study; Q, quintile; SMC, Swedish Mammography Cohort; SUN, Seguimiento Universidad de Navarra Study; VITAL, Vitamins And Lifestyle Study; WHI-OS, Women’s Health Initiative Observational Study.

provegetarian/plant-based diets, and others such as the Paleolithic diet. Overall, the 19 publications retrieved in this category were trending toward lower BC risk with healthy dietary patterns.

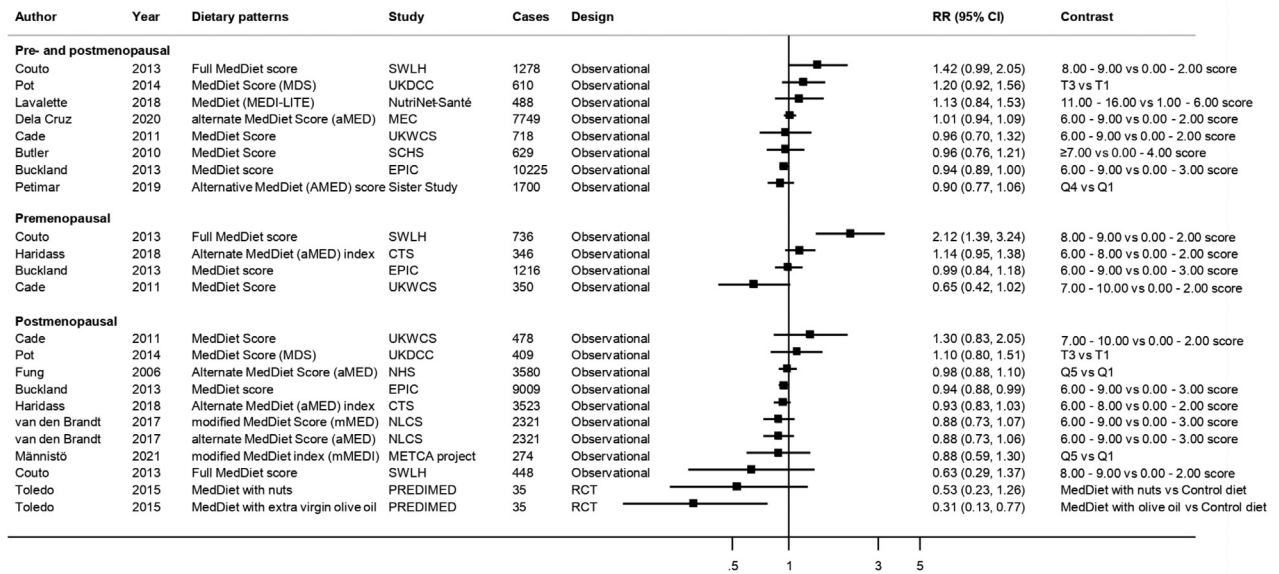
- Mediterranean dietary pattern

Sixteen publications (15 observational studies and 1 RCT) were identified. The traditional Mediterranean diet score or its modifications [60,61] encourages the intake of vegetables, legumes, fruits and nuts, cereals, fish and seafood, unsaturated fats, and a moderate intake of alcohol and discourages the intake of dairy, meat and meat products.

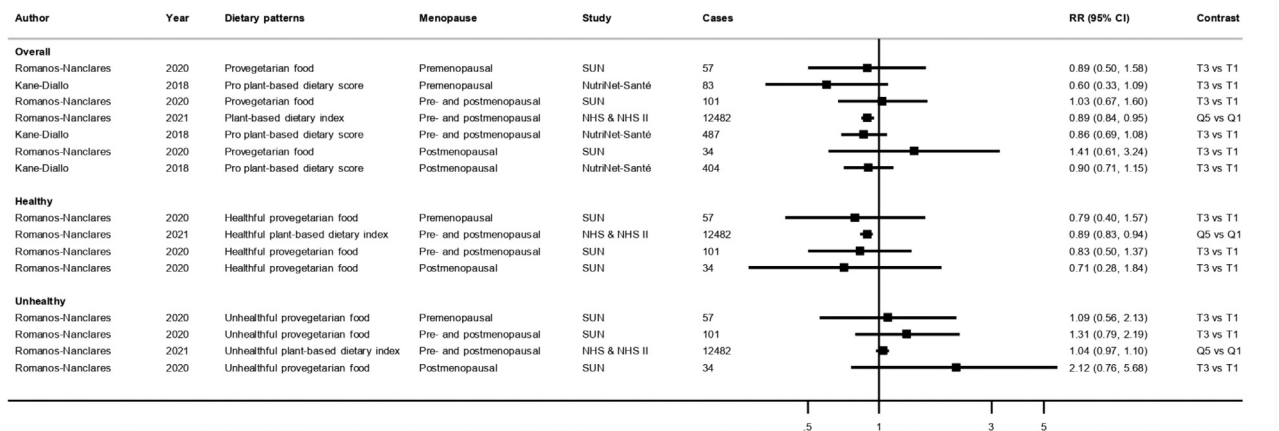
We synthesized the evidence from studies using the traditional scoring system including moderate alcohol intake, albeit it is an established risk factor for BC [2,6,9]. Overall, a tendency toward an inverse association between a higher adherence to the Mediterranean diet and BC risk was observed among postmenopausal females, although 95% CIs included null value in most of those studies (Figure 3A).

Nine studies performed in all females showed inconsistent associations with BC incidence—RRs: 0.90–1.42; 8 scores assessed categorically [30,56,62–67] and 1 continuously [34]. Four of the 9 associations were positive [30,56,62,63] and 5 were inverse [34, 64–67]. A similar pattern of mixed associations was found in

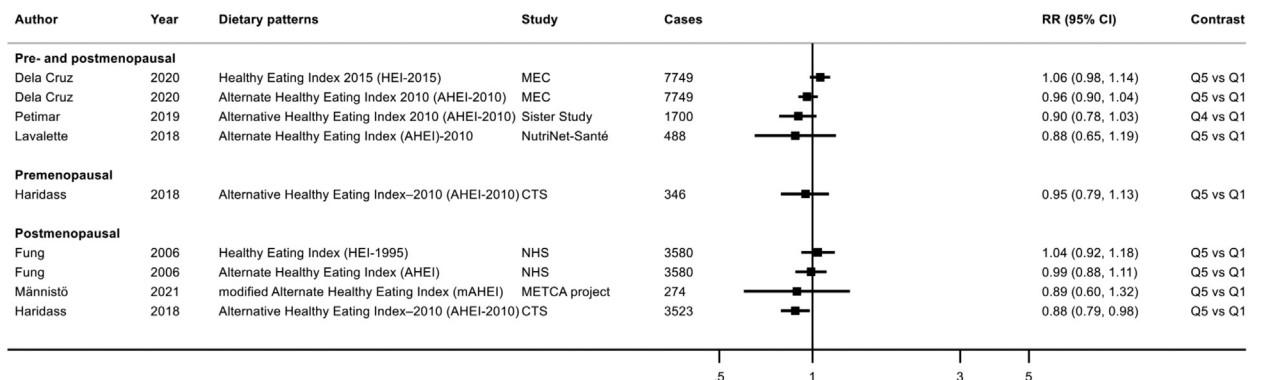
A



B



C



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FIGURE 3. Relative risks (RRs) and 95% CIs of breast cancer risk for the highest compared with the lowest level of adherence to a priori dietary patterns: (A) Mediterranean dietary pattern; (B) provegetarian/plant-based dietary patterns; (C) Healthy Eating Index (HEI) and Alternate Healthy Eating Index (AHEI) scores. Results from the publication by Toledo et al., originally published in 2015 [32], present estimates (95% CI) recalculated accounting departures from the protocol of individual randomization [33]. Scores analyzed only continuously per 1-tertile increment in the Mediterranean dietary score in all women (RR: 0.98; 95% CI: 0.92, 1.05) [34]. CTS, California Teachers Study; EPIC, The European Prospective Investigation into Cancer and Nutrition; MEC, Multiethnic Cohort Study; METCA, The Prospective Meta-Cohort Study of Cancer Burden in Finland; NHS, Nurses' Health Study; NLCS, The Netherlands Cohort Study; PREDIMED, PREvención con Dieta MEDiterránea Clinical Trial; Q, quartile; SCHS, Singapore Chinese Health Study; SUN, Seguimiento Universidad de Navarra Study; SWLH, The Swedish Women's Lifestyle and Health Study; T, tertile; UKDCC, UK Dietary Cohort Consortium; UKWCS, UK Women Cohort Study.

premenopausal females, when comparing extreme categories of the scores (RRs: 0.65–2.12): 2 of the 4 associations were positive [62,68] and the other 2 were inverse [64,66]. Among postmenopausal females (RRs: 0.63–1.30), most (7/9) point estimates from observational studies were <1 [57,59,62,66,68,69], and only 2 were positive [56,64]. The only RCT “Prevencción con Dieta MEDiterránea” (PREDIMED) [32] performed in postmenopausal females demonstrated that a Mediterranean diet supplemented either with extra-virgin olive oil or nuts lowered BC risk in comparison with a low-fat diet (control group). The evidence of an effect was stronger in females supplemented with extra-virgin olive oil. These results were based on 35 incident cases after 4.8 y of follow-up.

- Provegetarian/plant-based dietary patterns

The original provegetarian dietary score positively weighs the consumption of plant-based foods (ie, vegetables, legumes, fruits, cereal products, potatoes, nuts, and vegetable oils) and animal foods (ie, meat/meat products, eggs, animal fat, dairy products, and fish and other sea food) negatively, independently of their quality or type [70, 71]. In some studies, an adherence to healthful or unhealthful versions of diets were assessed [72]. In all females, the estimates for higher compared with lower levels of the provegetarian/plant-based score and BC risk ranged 0.86–1.03 [71,73,74], being negative in 2 [71,73] of 3 studies (Figure 3B). In the 2 studies that performed analysis by menopausal status, the associations were inverted, but weak in premenopausal females (RRs: 0.60–0.89) [71,74] and mixed in postmenopausal females (RRs: 0.90–1.41) [71,74]. In 2 studies [73,74] that addressed the quality and types of foods of the score, a healthful dietary pattern was associated with a lower risk of BC in all females (RRs: 0.83–0.89), whereas an unhealthful plant-based pattern was associated with a higher risk (RRs: 1.04–1.31), albeit CIs included null value in most of those associations.

- Other culturally based dietary patterns

The remaining dietary patterns based on culturally defined dietary habits derived using a priori approaches were used in single studies, such as the Paleolithic [68] or the traditional Mexican diet [75], and were associated with increased and decreased BC risk, respectively (for both patterns, 95% CIs included null value).

A priori dietary patterns based on dietary guidelines. Seventeen publications from observational studies using dietary scores and indices based on country-specific guidelines and on chronic disease prevention guidelines, and 6 publications from RCTs on predefined low-fat dietary interventions were identified. The most studied dietary patterns in this category were the Dietary Approaches to Stop Hypertension (DASH) and the Healthy Eating Index (HEI) and alternate Healthy Eating Index (AHEI) scores. A few other scores were also identified, such as the Healthy Nordic Food Index (HNFI), the

Recommended Food score (RFS), and the WCRF dietary score. Overall, a tendency toward a decrease in BC risk was mostly observed in all and postmenopausal females.

- Dietary Approaches to Stop Hypertension

The DASH dietary index characterizes the adherence to a dietary pattern that encourages the intake of vegetables, fruits, nuts and legumes, whole grains, and low-fat dairy, and de-emphasizes sodium-rich foods, sweetened beverages, and red and processed meats. This diet was originally developed to lower blood pressure and later assessed using a scoring system (based on quintiles of subject's intake) proposed by Fung [76]. Association between extreme categories of the score and BC risk was addressed in 5 publications. The 2 studies conducted in all females (RRs: 0.78–0.95, in 1 study 95% CI did not cross 1) [63,67] and the 2 in postmenopausal females (RRs: 0.91–0.97, in both CIs included null value) [68,77] reported an inverse associations. The only study conducted in premenopausal females showed an RR of 1.03 (95% CI: 0.86, 1.23) [68] (Supplemental Figure 3).

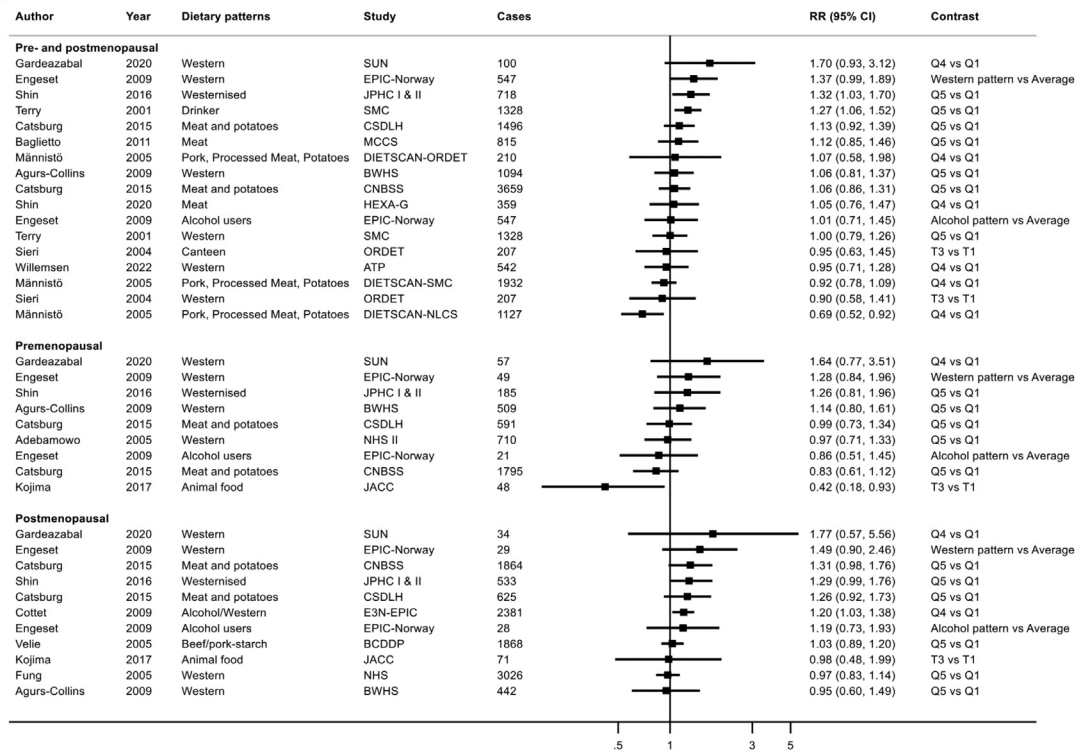
- The HEI and AHEI

The HEI measures diet quality in relation to the DGA, which aim to promote healthy eating in the general population and are updated every 5 years [78]. The AHEI defines diet quality using evidence-based recommendations for chronic disease prevention [79]. Although there are components that are specific to each index and both differ on how components are scored, similarities include that both indices encourage consumption of fruits, vegetables, legumes, wholegrains, and polyunsaturated fats, and discourage sodium and saturated fat [80]. The association between versions of the HEI [63,69] or AHEI [30,63,67,68, 81] scores and risk of BC was assessed in 6 publications. As shown in Figure 3C, estimates <1 (highest compared with lowest category) were found in 3 of the 4 studies in all (RRs: 0.88–0.96) [30,63,67] or postmenopausal (RRs: 0.88–0.99) [57,68,69] females and in 1 single study conducted in premenopausal females (RR: 0.95; 95% CI: 0.79, 1.13) [68], although CIs crossed null value in most of those associations.

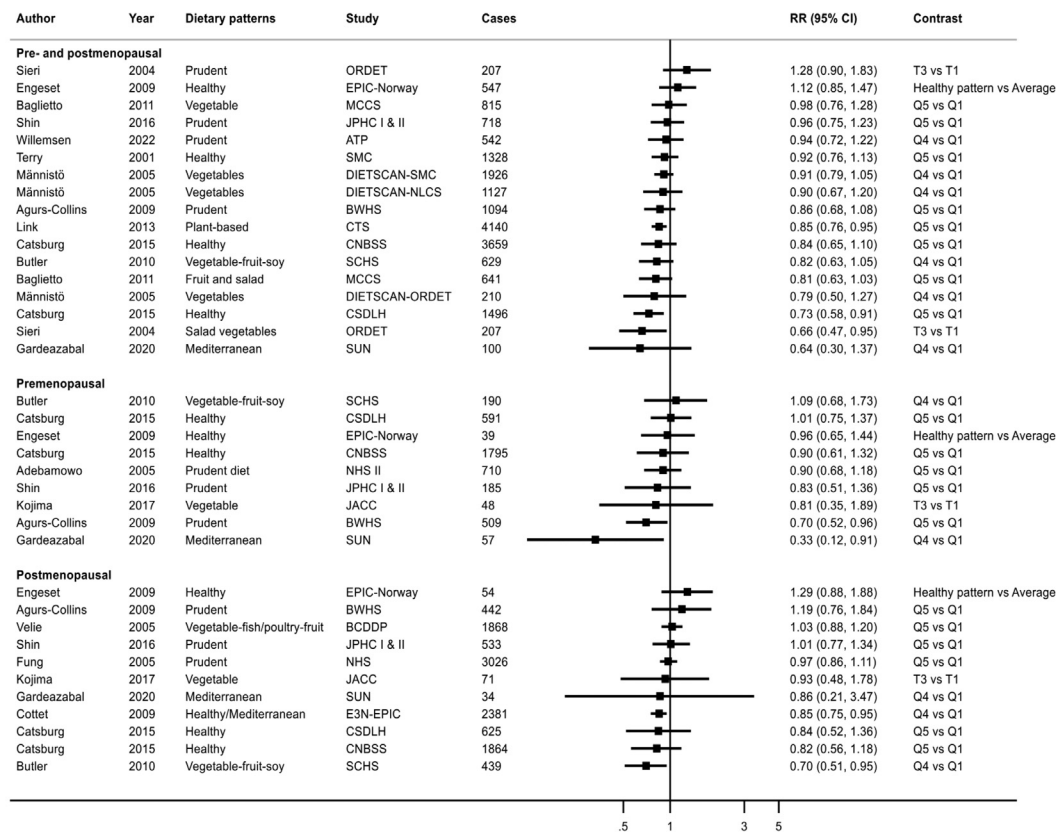
- Other dietary patterns based on dietary guidelines

Some additional a priori dietary patterns based on dietary guidelines were found. Contrasting results on BC risk were found in 2 studies that calculated HNFI or its variants [57,82], RFS [17,69], and WCRF/AICR dietary score [58,59]. Other scores and indices were used in single studies—WHO Healthy Diet Index [64], the 2015 Dutch dietary guidelines [83], the Diabetes Risk Reduction Diet [84], the 2017 PNNS-GS2 [85], the cumulative dietary risk factors score (based on United Kingdom and European dietary guidelines) [21], and the Diet Quality Index-Revised [69]—and showed mostly inverse, but weak, associations with BC risk.

A



B



(caption on next page)

FIGURE 4. Relative risks (RRs) and 95% CIs of breast cancer risk for the highest compared with the lowest level of adherence to a posteriori dietary patterns: (A) Western/Meat/Alcohol; (B) Prudent/Vegetarian/Mediterranean. ATP, Alberta's Tomorrow Project; BCDDP, The Breast Cancer Detection Demonstration Project; BWHS, Black Women's Health Study; CNBSS, Canadian National Breast Screening Study; CSDLH, Canadian Study of Diet, Lifestyle and Health; CTS, California Teachers Study; DIETSCAN, A common approach for analyzing dietary patterns; E3N, Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale (MGEN); EPIC, The European Prospective Investigation into Cancer and Nutrition; HEXA-G, Health Examinees-Gem Study; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; MCCS, Melbourne Collaborative Cohort Study; NHS, Nurses' Health Study; NLCS, The Netherlands Cohort Study; ORDET, Hormones and Diet in Etiology of Tumors Study; Q, quartile; SCHS, Singapore Chinese Health Study; SMC, Swedish Mammography Cohort; SUN, Seguimiento Universidad de Navarra Study; T, tertile.

- Low-fat dietary interventions

Low-fat diets (independently of fat quality) were promoted in dietary guidelines for BC prevention for decades. Two interventional trials that tested a low-fat diet (15%–20% of total energy) were identified (Supplemental Tables 8 and 9). These trials were the Women's Health Initiative (WHI) Dietary Modification (DM) Trial (WHI-DM) [19,20,51,86,87], carried out in postmenopausal females, and the Canadian Diet and Breast Cancer Prevention (CDBCP) trial [88] in premenopausal and postmenopausal females with high mammographic densities. For WHI-DM, different follow-up periods or BC outcomes were reported in 5 publications [19,20,51,86,87]. The incidence of invasive BC was reduced, albeit 95% CIs included null value, in females on a low-fat diet compared with control diet from the WHI-DM trial after an average of ≤ 8.5 y of follow-up (intervention) and ≤ 19.6 y for the cumulative (intervention+postintervention) period [19,20], but opposite direction of findings (CI crossed 1) were revealed in the CDBCP trial after an average of 10 y of follow-up [88].

A posteriori dietary patterns

Twenty-one publications from observational studies—20 prospective cohorts, 2 case cohorts [89,90], 1 nested case control [91], and 1 pooled analysis [56]—identified 66 different patterns conducted in 27 study populations. Most studies used PCA or factor analyses to derive a posteriori dietary patterns, except for 1 study in which cluster analyses was used [92].

- Western/Meat/Alcohol dietary patterns

We identified associations between 24 dietary patterns and BC incidence (from 17 publications, 20 study populations). Overall, Western/Meat/Alcohol patterns were characterized by high consumption of red and processed meats, snacks, sweets, and ultraprocessed foods, potatoes, eggs, (refined) grains and cereals, and some of them also included sugar-sweetened beverages, alcohol, dairy, poultry, and animal fats (Table 1). Even though the results were inconsistent, a tendency for an association between a higher consumption of Western/Meat/Alcohol patterns and increased overall and postmenopausal BC risk was observed, albeit with 95% CIs crossing null value in most of those associations (Figure 4A and Supplemental Table 10). In all females, RRs ranged from 0.69 to 1.70, when comparing the highest with the lowest adherence category (or comparing the patterns obtained using cluster analyses with the reference pattern). Most of the associations (11/17) were positive [89,90,92–98]; in 1 study, the association was null [96], and in 5 studies, it was inverse [90,99,100]. In premenopausal females, RRs for the risk associated with 9 different patterns ranged from 0.42 to 1.64. Four associations were positive [92,93,95,98], and 5 other were inverse [89,92,101,102]. The RRs for the 11 associations with postmenopausal BC ranged from 0.95 to 1.77. For most patterns (8/11), positive associations were observed [89,92,93,95,103,104], although weak evidence of inverse associations were found in the remaining 3 studies [98,102,105].

- Prudent/Vegetarian/Mediterranean dietary patterns

Twenty-four dietary patterns (from 18 publications, 21 study populations) were retrieved. Major food groups in these patterns included fruits, vegetables, legumes, fish and seafood, and some of them also included (whole) grains and cereals, potatoes, poultry, dairy products, and olive or other vegetable oils (Table 1). A tendency for an inverse association between Prudent/Vegetarian/Mediterranean dietary patterns and BC risk was observed, and particularly among all and premenopausal females, albeit 95% CIs crossed null value in most of those associations (Figure 4B and Supplemental Table 10). Risk estimates for all 17 patterns comparing the highest with the lowest level of adherence (or comparing the patterns obtained using cluster analyses with the reference pattern) in all females ranged from 36% lower risk to 28% higher risk. Nearly all studies (15/17) found an inverse association [65, 89,90,93,95–100,106], although 2 other found positive associations [92,99]. In premenopausal females, 9 Prudent/Vegetarian/Mediterranean dietary patterns were evaluated, reporting RRs from 67% lower risk to 9% higher risk. An inverse association was reported in most (7/9) of the studies [89,93,95,98,101,102], and in another 2 studies, estimates were >1 [65,89]. In postmenopausal females, estimates for 11 different patterns and BC risk ranged from 30% lower to 29% higher risk. Most of the studies (7/11) reported an inverse association [65,89,93,102,103,105], but 4 other studies found positive associations [92,95,98,104].

- Traditional/Ethnic/Mixed dietary patterns

Eighteen different patterns (from 12 publications, 16 study populations) were explored in relation to the risk of BC incidence (total, invasive, or hormone receptor subtypes). These patterns were named traditional [91,95,97,104] or ethnic [89,106]; high-protein, high-fat, high-carbohydrate, salad, and wine [106]; fish eaters; bread eaters [92]; dairy product [102]; white rice [94]; meat-dim sum [65]; sugar, fruit, and dairy [100]; other (vegetable, fish, and legumes) [94], and PCA factor 1 (dairy, crisps, and plant foods) [56]. These patterns were comprised of foods that are considered healthy (i.e. mostly vegetables, grains and cereals, and fish and seafood) and unhealthy (ie, red and processed meat) (Table 1). There was inconsistency in the direction of associations with BC risk (RRs: 0.84–1.35, 0.79–1.22 and 0.85–1.51 in all, premenopausal, and postmenopausal females, respectively) (Supplemental Figure 4 and Supplemental Table 10).

Hybrid dietary patterns

In 8 studies (from 8 publications, 11 study populations), the hybrid method (reduced rank regression) was used to derive 12 different patterns. Patterns for which biological markers were used as the response variables were the inflammatory dietary pattern, assessed in 1 study [107], and the estrogenic dietary pattern, examined in 4 studies [108–111]. Patterns for which the derivation was based on nutrients included a simplified dietary pattern associated with intake of all types of fatty acids [112], as well as patterns characterized by the intake of

alcohol [56], fiber [56,100], vitamin D [100], fructose [100], and discretionary fats [100], which were mostly used in single studies. Components of these patterns and findings on BC risk are shown in Supplemental Tables 4 and 11, respectively. The association between an estrogen dietary pattern (high consumption of red/processed meat, legumes, ultraprocessed foods, and alcohol, and low consumption of coffee, and nuts and seeds) and BC risk was evaluated predominantly among postmenopausal females, showing contrasting results across 4 studies (RRs: 0.95–1.26) [108–111] (Supplemental Figure 5). Similarly, estimates of mixed directions were found for patterns associated with fiber intake in 2 studies performed in all females (RRs: 0.89–1.08) [56,100].

Additional analyses

Details on the results from stratified and sensitivity analyses can be found in Supplemental Text 2 and Supplemental Figures 6–23. Overall, little evidence of heterogeneity between studied subgroups was found. Only Western/Meat/Alcohol dietary patterns that included high alcohol consumption, or studies with less RoB due to confounding and missing data, were slightly more consistently associated with increased BC risk in all and postmenopausal females, than studies without alcohol component in the pattern, or the ones with more RoB in these domains. Furthermore, a tendency toward an inverse association between Prudent/Vegetarian/Mediterranean and BC risk seemed to be more consistent in studies with longer follow-up among all and postmenopausal females. Finally, we found that studies showed greater evidence of lower BC risk when patterns included several lifestyle components compared with patterns based solely on diet. There were few studies within each of the molecular subtypes or histologic variants, limiting the synthesis of the evidence considering BC subtypes. Even though the results were inconclusive, there was a slight tendency toward an inverse association between higher adherence to healthy dietary patterns and hormone negative tumors, when combining studies among all and postmenopausal females.

Evidence grading

Evidence was graded as strong probable for a priori WCRF/AICR and ACS lifestyle scores based on specific recommendations for cancer prevention and lower risk of BC in all and postmenopausal females, whereas in premenopausal females the evidence was limited suggestive. Similarly, limited-suggestive evidence of a lower risk of BC was found for a group of dietary and lifestyle patterns based on general recommendations for a healthy lifestyle (HLI, HI, and DGA) in postmenopausal females only. There was also limited-suggestive evidence that a posteriori Western/Meat/Alcohol dietary patterns were associated with higher BC risk in postmenopausal females and that a posteriori Prudent/Vegetarian/Mediterranean dietary patterns were associated with lower risk in all females. The evidence for associations with remaining patterns was graded as limited-no conclusion. The rationale for the Expert panel judgment is provided in Table 2 and Supplemental Table 12.

Discussion

This systematic review encompasses 84 publications, mainly from prospective cohort studies. Patterns were divided into 4 groups: a priori dietary and lifestyle patterns, and dietary only patterns derived with a priori, a posteriori, or hybrid methods. The evidence for risk of BC was synthesized overall and by menopausal status, if possible. Very few studies reported results on BC mortality and within each BC subtype

(molecular/morphologic), limiting the possibility to synthesize these findings. Owing to the heterogeneity of the patterns in terms of components and cutoff points, evidence was descriptively synthesized using vote counting. The independent CUP Global Expert Panel judged the strength of the evidence. Overall, higher adherence to healthy patterns that included diet and other lifestyle factors—such as adiposity and physical activity—consistently showed inverse associations with BC risk, and the evidence for these patterns was graded as strong-probable. Results from studies on dietary patterns only were less consistent and more heterogeneous, depending on their method of derivation and across menopausal statuses, hence the evidence for these patterns was graded as limited suggestive or limited-no conclusion.

Combined dietary and lifestyle patterns were based on advice to maintain a healthy weight, be physically active, consume moderate-to-zero alcohol, and follow a healthy diet. Patterns based on an overall healthy lifestyle (ie, HLI, HI, and DGA) were more likely to include smoking as a component, whereas patterns specific for cancer prevention (ie, WCRF/AICR and ACS scores) included specific dietary components associated with lower cancer risk [ie, high consumption of fruits, vegetables, (whole) grains and cereals, and low consumption of red and processed meat]. Inverse associations with BC were found for all these patterns independently of menopausal status and other plausible sources of heterogeneity. However, a considerable number of cohort studies consistently showing inverse associations and presence of mechanistic evidence for pattern components was found only for the WCRF/AICR and ACS scores in all and postmenopausal females, and thus, the evidence was graded as strong probable. Fewer studies were found for these patterns in premenopausal females and on HLI and other indices based on general healthy recommendations in postmenopausal females, and the evidence was judged as limited-suggestive. These findings are in line with those from categorical meta-analysis of observational studies that evaluated associations between BC risk and adherence to WCRF/AICR guidelines, either in its 2007 [113] or 2018 [114] version, or the great diversity of healthy lifestyle indices combined [8]. It is to note that this group of patterns was heterogeneous in terms of components and cutoffs, and their results were not meta-analyzed for this review. Future standardization of the operationalization of dietary and lifestyle patterns is warranted to strengthen the evidence in this field.

The associations between BC risk and a group of a posteriori less healthy Western/Meat/Alcohol dietary patterns [high intake of red and processed meats, snacks, sweets, and ultraprocessed foods, potatoes, eggs, and (refined) grains and cereals] were generally consistent in the positive direction, but the evidence was graded as limited-suggestive in postmenopausal females due to potential confounding resulted from self-reported or lack of information in the assessment. In all and premenopausal females, the findings were inconclusive. We found that patterns including high alcohol consumption were slightly more consistently, than studies without alcohol component, associated with a higher BC risk, which is in accordance with the evidence showing alcohol is a risk factor for BC [9]. Recent meta-analyses of case-control and cohort studies also found a positive association between a Western dietary pattern and BC risk, with an association being strong only among postmenopausal females in subgroup analysis [115]. In turn, in former reviews and meta-analyses, no overall association was shown for a Western/unhealthy dietary pattern, but risk of BC was increased with better adherence to drinker/alcoholic dietary patterns [116,117].

Adherence to healthier empirically derived dietary patterns, labeled as Prudent/Vegetarian/Mediterranean, which included vegetables, legumes, and fish and seafood, tended to be inversely associated with BC

risk, particularly among all females. However, study quality issues mostly due to confounding were raised by Expert Panel, hence the evidence was judged as limited-suggestive. In particular, most of these studies did not provide information on how the confounders were assessed, and some of them did not adjust for relevant confounders, such as reproductive factors, age or adiposity. In premenopausal and postmenopausal females, the findings were less consistent and inconclusive. Our findings support those from previously published systematic reviews and meta-analyses on this topic [115–117]. However, patterns derived with an a posteriori approach are population specific. Hence, any advice on food behaviors that might emerge from a posteriori patterns should be interpreted with caution.

The evidence on a priori dietary patterns was broadly heterogeneous and inconclusive due to the inclusion of the variety of scores, incomparable cutoff points, and the small number of studies by outcome groups, hence it was graded as limited-no conclusion. Despite the studies using a variety of dietary scores, similarities in food components were found, in line with a healthy diet [higher intake of fruits and vegetables, nuts and seeds, legumes, (whole) grains and cereals, olive or other vegetable oils, and lower intake of red and processed meat, sugar-sweetened beverages, and sodium]. Studies investigating a Mediterranean diet (with or without moderate alcohol consumption), healthy vegetarian/plant-based diets, as well as DASH, HEI/AHEI or other scores based on healthy dietary recommendations, were trending toward inverse associations with BC risk among postmenopausal females. However, more epidemiologic data are warranted to strengthen these observations.

Different biological mechanisms have been proposed to explain observed associations. Most likely biological processes linking dietary patterns to BC include the reduction of inflammation and oxidative stress and improvement of insulin resistance. Several meta-analyses of both observational studies and RCTs reported inverse associations between adherence to healthy dietary patterns such as the Mediterranean diet, DASH, HEI, or the Paleolithic diet and proinflammatory markers or insulin [118–120]. Adherence to a Western diet was, on the contrary, associated with elevated levels of proinflammatory and oxidative stress markers. Both inflammation and insulin have been associated with BC risk in observational prospective studies or Mendelian randomization studies [121,122].

To our knowledge, this updated systematic review was the first to conduct a comprehensive critical synthesis of a variety of dietary and lifestyle patterns derived using different methodologic approaches through a wide time frame (22-y period based on publication dates) in relation to BC risk. Moreover, the evidence was synthesized by menopausal status, and potential sources of heterogeneity for important factors were assessed. Included studies were conducted in relatively large cohorts with a long follow-up. Unlike previous works on the topic, RoB was assessed in this review for each included study following standardized criteria. Finally, an independent Expert Panel examined and judged the evidence using the standardized grading criteria.

A potential limitation is the fact that only few intervention studies were identified. Consequently, most of the evidence came from observational studies, which are susceptible to several biases, such as exposure measurement error and confounding. In fact, identified patterns were mostly based on tools validated for capturing specific components, not on the patterns themselves. Moreover, reliance on self-reported questionnaires to collect data on dietary intake, as well as physical activity and adiposity (as is the case of dietary and lifestyle patterns), is subject to potential measurement error. Although included studies adjusted for relevant confounders, in half of them reliability or

validity of measurement of key confounders could not be evaluated or was low. Moreover, most studies assessed patterns only once at baseline and did not consider possible fluctuations that may have occurred during follow-up. Furthermore, most cohorts were mainly from North America and Europe, potentially affecting generalizability of the results. Neither the synthesis method based on vote counting does not provide information on the magnitude of the effects/associations nor it takes into account differences in the relative sizes of the studies [15]. Moreover, we could not assess the clinical relevance of the results, as these were not comparable in terms of magnitude of effect (different contrasts were used across studies) but were still comparable in terms of direction. This aspect also justifies that the used approach (vote counting) might be the most sensible method in case of this review. Finally, new evidence may emerge after our literature search (31 March, 2022). However, we performed a quick search that resulted in only 1 new publication with data corroborating our results on the association between greater adherence to WCRF/AICR score and lower BC risk [123].

In conclusion, there was strong-probable evidence that a higher adherence to the WCRF/AICR and ACS dietary and lifestyle scores decreases BC risk in all and postmenopausal females. The associations with the remaining dietary patterns were less conclusive. This work sheds light on dietary and lifestyle behaviors to adopt for BC protection. Thus, besides not smoking, recommendations to maintain a healthy weight, be physically active, consume moderate-to-zero alcohol, and follow a healthy diet rich in fruits, vegetables, (whole) grains, and cereals and low in red and processed meat, could be given to females as a strategy to lower BC risk. It is to highlight that the greatest benefits may be achieved when these recommendations are followed simultaneously (healthy diet, body weight, and physical activity). The evidence from this review may form the basis of guidance developed by the CUP Global for reducing BC risk. However, it should be acknowledged that the evidence for most of the patterns did not support associations being causal. This suggest the need for more large and well-conducted RCTs and observational studies (including trial emulation studies and pooled analyses applying standardized methods) with repeated measures of exposures and confounders and validated tools to reduce exposure misclassification. It is also critical for future research to assess BC risk in premenopausal females and within (molecular/morphologic) tumor subtypes, reflect greater demographic diversity (eg, race, ethnicity, and socioeconomic status), and address the issue of clinical relevance in order to better evaluate the strength of the aforementioned associations.

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Author contributions

The authors' responsibilities were as follows—KKT, DSMC: are coprincipal investigators of CUP Global at Imperial College London; DR, DSMC: were among the coauthors to the development of the protocol for this work; JK, IP-G: did the literature search, study selections, and data extraction and assessed risk of bias; AC: did data extraction; DR, DSMC: checked the data; GM, KKT: prepared the tool, training session, and checked data related to risk of bias assessment; JK, DR: synthesised and interpreted the data and wrote the draft of manuscript; NB-T: assisted with evidence synthesis; GM, NB-T, AC: critically revised the manuscript; DSMC, DR: supervised the study; MLB: was the Chair of the CUP Global Expert Committee on Cancer Incidence and Expert Panel member; YP: was the Deputy Chair of the CUP Global Expert Committee on Cancer Incidence; JK, MPW, EC, SJL, JCS, RC, LH: were the CUP Global Expert Panel members; all members of the Expert Panel: provided input into the judgments on the evidence and advised on the interpretation of the review, with the Expert Committee providing the preliminary evidence interpretation, the public representative (LH) did not contribute to the final decisions made by the Panel; LD, EMG-G: were the CUP Global collaborators on biological processes and provided input into the biological mechanism citations in the manuscript; HC: was the Head of the CUP Global Secretariat; Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/WHO; and all authors: revised and approved the manuscript.

Conflict of interest

The authors report no conflicts of interests.

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Data availability

For this review, only publicly published data were used. All information on data sources and handling is described in Methods section and supplementary material. Further details could be available from the corresponding author upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajcnut.2024.10.003>.

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