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ORIGINAL PAPER

Healthy dietary patterns and risk and survival of breast cancer: a meta-analysis of cohort studies

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Abstract

Purposes Dietary patterns have been found to be associated with the overall cancer risk and survival. However, the associations of healthy dietary patterns and breast cancer remain unclear. We aimed to conduct a meta-analysis of prospective cohort studies to estimate the pooled results of the association of healthy dietary patterns with breast cancer risk and survival.

Methods PubMed, EMBASE, and Web of Science were searched for literature published until June 24th, 2018 that examined the associations between healthy dietary patterns and breast cancer risk and survival. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated by using a random-effects model for meta-analysis.

Results There were 32 articles retrieved for the meta-analysis, with 27 for breast cancer risk and five for breast cancer survival. There was a statistically significant lower risk of breast cancer associated with healthy dietary patterns (RR = 0.93, 95% CI: 0.88, 0.98). Subgroup analysis results suggested that there was an inverse association between breast cancer risk and *posterori*-derived healthy patterns, but no statistically significant associations were found in other stratified subgroups (a priori-derived diet, study region, menopausal status, or breast cancer subtypes). Healthy dietary patterns were associated inversely with all-cause mortality (RR = 0.76, 95% CI: 0.63, 0.92); however, no association was found for breast cancer-specific mortality.

Conclusions The results suggested that healthy dietary patterns might be associated with a reduced risk of breast cancer and all-cause mortality among breast cancer patients. It could be clinically relevant to promote healthy dietary patterns for breast cancer prevention and improve survival among breast cancer patients.

Keywords Dietary patterns · Breast cancer · Risk · Survival · Meta-analysis

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Introduction

Breast cancer is the second leading cause of cancer deaths in women worldwide [1]. Also, there are over 3 million breast cancer survivors in the USA [2]. Diet has been investigated in many breast cancer studies mostly focusing on single nutrients or food groups [3–12]. However, the associations with most nutrients and food groups have been inconclusive [13–16], except for the consistent and positive associations between alcohol and breast cancer [17]. As foods and nutrients are rarely eaten in isolation, the roles of individual dietary components should be considered within the context of overall dietary quality [18]. Moreover, it is advised by American Cancer Society Guidelines for cancer prevention to consume whole foods following an overall healthy dietary pattern, which is characterized as high intake of vegetables, fruits, whole grains, and limited consumption of processed meat and red meat [19]. Several studies have examined the association between dietary patterns and breast cancer risk [20–25], but the evidence is still inconclusive [26]. As results of new research have been published [21, 27–32] since the latest reviews [33–35], we aimed to conduct a meta-analysis to estimate a pooled association of healthy dietary patterns with breast cancer risk to incorporate recently published prospective cohort studies on breast cancer risk and dietary patterns.

The inconsistency of association between dietary patterns and breast cancer risk might be due to that dietary patterns have different effects for populations with varied characteristics. Previous epidemiological studies have reported heterogeneous results on the association between dietary patterns and breast cancer subtypes and menopausal status [22, 36–40]. However, the most recent meta-analysis has only included evidence of *a posterori* dietary pattern with breast cancer risk stratified by menopausal status and breast cancer subtypes [35]. Therefore, we would like to include a priori dietary pattern evidence in the meta-analysis [41], and to examine the association of healthy dietary patterns with breast cancer risk stratified by breast cancer subtypes, menopausal status, study region, and methods to derive dietary patterns. It would be beneficial to know the effects of certain dietary patterns on different subgroups of populations.

There is increasing recognition of the potential significance of nutrition in cancer survival and cancer survivors are likely to have special nutrition requirements [26]. However, only a few studies reported relationships between healthy dietary patterns and breast cancer survival with inconsistent results [42–46]. Recent systematic reviews among breast cancer survivors concluded that no factors were convincing for reducing breast cancer mortality partly due to limited number of studies [43, 47, 48]. Thus, we also conducted a meta-analysis to incorporate the up-to-date evidence on healthy dietary patterns and breast cancer survival.

Methods

Search strategy

For meta-analysis, the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline was followed [49]. Cohort studies that examined diet and breast cancer risk and/or breast cancer survival were systematically searched for in PubMed, EMBASE, and Web of Science until June 24th, 2018. The search terms used in each database are shown in Supplemental Table 1. Additionally, we manually searched for studies listed in review papers, as there may be studies not included in the database. The language of the articles was limited to English.

Data selection and extraction

Study selection was conducted in three steps. First, the titles and abstracts of studies identified in our literature search were independently reviewed by two reviewers (RH, JW). Second, the full texts of studies retrieved in the initial screening were independently reviewed by two reviewers (RH, JW). Any disagreement between the researchers during the study selection period was resolved through discussion with a third researcher (YH). Third, data from studies that met inclusion and exclusion criteria (Supplemental Table 2) were extracted independently by three reviewers (RH, JW, YH), including the first author, year of publication, study name, study's country, sample size, number of cases, diet assessment methods, dietary pattern development methods, labels of the identified dietary patterns and the food components, follow-up years, means and standard deviations of the outcomes, and covariates adjusted in the analysis. If there were multiple articles based on the same cohort, the article with the largest sample size was used for the overall meta-analysis and other articles within the same cohort may be used for subgroup analysis. Corresponding authors of articles with missing information were contacted.

The classification of healthy dietary patterns was based on the authors' description from selected published articles. When two or more healthy dietary patterns were presented, researchers generally considered a healthy pattern that mostly include protective foods, such as vegetables, fruits, fish, legumes, whole grains, and low-fat dairy products. When multiple dietary guideline indices were used to derive dietary patterns, we chose Mediterranean diet for European studies as it might be more appropriate for the European population, and Dietary Approaches to Stop Hypertension (DASH) diet for U.S. studies as it ranks as top overall healthy diets by U.S. News and World Report compared to Alternative Healthy Eating Index (AHEI) or Healthy Eating Index (HEI) [50, 51]. All discrepancies were resolved through discussion by three reviewers (RH, JW, YH) for the choices of healthy dietary patterns into the meta-analysis.

Quality assessment

The Newcastle–Ottawa Scale was used for quality assessment [52]. The Newcastle–Ottawa Scale evaluates quality of cohort studies in three domains: selection of exposed and unexposed cohorts (representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure, and demonstration of absence of outcome at the beginning of studies), comparability of exposed and unexposed cohorts (analysis appropriately adjusted for potential confounding factors, including the most important and additional factors), and outcome ascertainment (adequacy of outcome assessment, length of follow-up, and adequacy of follow-up). A study was given a maximum of 1 point for selection and outcome domains and a maximum of two points for comparability for a possible maximum total score of 9, with higher scores indicating higher quality. Three independent reviewers (RH, JW, YH) assessed the quality of all included studies. All reviewers agreed on the score of quality assessment.

Statistical analysis

Estimates of associations such as hazard ratios (HRs), odds ratios (ORs), and risk ratios (RRs) of breast cancer and their corresponding 95% CIs were derived from included studies after full adjustment. HR and OR were considered equivalent to RR. To combine the results, a meta-analysis was conducted where we evaluated breast cancer risk or survival by comparing the highest category with lowest category of healthy dietary pattern. Random-effects meta-analysis models were used for included studies. The pooled RR is considered statistically significant if 95% CI did not contain 1. Publication bias was evaluated by Egger's test [53]. Heterogeneity between studies was assessed using I^2 tests. I^2 statistic was calculated to quantify the proportion of between-study heterogeneity attributable to variability in the association rather than sampling variation. An I^2 of > 50% was considered an indicator of substantial heterogeneity across studies. If results showed significant heterogeneity, potential sources of heterogeneity were explored by sensitivity analysis. Sensitivity analysis was conducted by excluding one study each time from the analysis, if evidence of significant heterogeneity across studies existed.

Subgroup analysis was also undertaken using random-effects model based on menopausal status, breast cancer subtypes (estrogen receptor negative (ER-) and ER-/progesterone receptor negative (PR-)), methods to identify dietary patterns (a priori and a posteriori), and regions (Europe and North America). We also conducted analysis for Mediterranean diet as five studies used this diet to derived healthy pattern. No subgroup analysis based on the type of a posteriori methods used was conducted as most studies used factor analysis [including principal component analysis (PCA)]. Also, other breast cancer subtypes was not analyzed due to limited number of studies (< 5). No subgroup analysis was conducted for survival due to limited total number of studies.

Stata 14 (Stata Corp, College Station, TX) was used to conduct meta-analysis and Egger's test for publication bias.

Results

Baseline characteristics for included studies

Initial database search yielded a total of 5130 records as shown in the flow chart (Supplemental Fig. 1). After excluding letters or reviews and eliminating duplicates, 3197 remained. After the abstract screening, 2813 studies were not relevant and therefore excluded. The 384 remaining reports were retrieved in full-text. Finally, a total of 32 articles were included in the meta-analysis, including 27 for risk (19 cohorts) and 5 for survival (5 cohorts), and ten of them were published after 2012. In total, the 19 cohorts for overall breast cancer risk meta-analysis included 1,143,395 women with 38,098 incident cases of breast cancer (Supplemental Table 3) and the five studies for breast cancer survival meta-analysis included 13,443 women diagnosed with breast cancer (Supplemental Table 4).

Among the 27 included articles for breast cancer risk, there were 19 cohorts in total for overall meta-analysis. Out of the 27 published literature (19 cohorts), 11 cohorts were evaluated for pre-menopausal and 11 cohorts were for post- menopausal women; 7 were identified as *priori* and 15 as *posterior* dietary patterns; six were from Europe, eight from North America, and the other five cohorts were not grouped together for analysis due to the heterogeneity in food culture and diet; five reported ER- breast cancer and five reported ER-/PR-breast cancer.

Quality

The quality of each study regarding selection, comparability, and outcome is summarized in Supplemental Table 5. Overall quality of included studies was adequate, with a range of score from 7 to 9. For selection, eight studies were scored "0" for cohort representation, with 6 of them using Nurses' Health Study (NHS) [31, 38, 54–56] or NHS-II [57], one recruited teachers in California [58] and another one study only recruited participants from one province in Italy [59]. Five studies did not specifically mention that breast cancer was not present at the start of the study [21, 24, 55, 59, 60]. The overall comparability for all studies was good with only two studies scores "1" for adjusting only major covariates [21, 61]. For outcome, three studies have not reported statement about their follow-up adequacy but all studies have appropriate length of follow-up and outcome assessment methods [32, 62, 63].

Overall breast cancer risk

The overall results of 19 cohorts from quality-effects model suggested that there was a statistically significant lower risk of breast cancer associated with healthy dietary patterns (RR = 0.93, 95% CI: 0.88, 0.98) (Fig. 1). There was no apparent evidence of heterogeneity and no indication of publication bias for the meta-analysis (Egger's $p = 0.90$).

Breast cancer survival

All-cause mortality

The meta-analysis of 5 cohort studies indicated that there was an inverse association between healthy dietary patterns and all-cause mortality (RR = 0.76, 95% CI: 0.63, 0.92), with no evidence of heterogeneity (Fig. 2). Egger's test suggested that possible publication bias for all-cause mortality existed among studies (Egger's $p = 0.04$).

Breast cancer mortality

No statistically significant association was found between dietary patterns and breast cancer mortality (RR = 0.91, 95% CI: 0.65, 1.28) and there was evidence of high heterogeneity (Fig. 3). With sensitivity analysis, the heterogeneity is still high (Supplemental Table 6). It might suggest that limited number of research is available and more studies are needed. Egger's test suggested no potential publication bias for breast cancer mortality (Egger's $p = 0.86$).

Subgroup analysis

Subgroup analysis results are shown in Table 1. We found an inverse association between healthy dietary patterns and breast cancer risk in cohorts using *posteriori* methods to

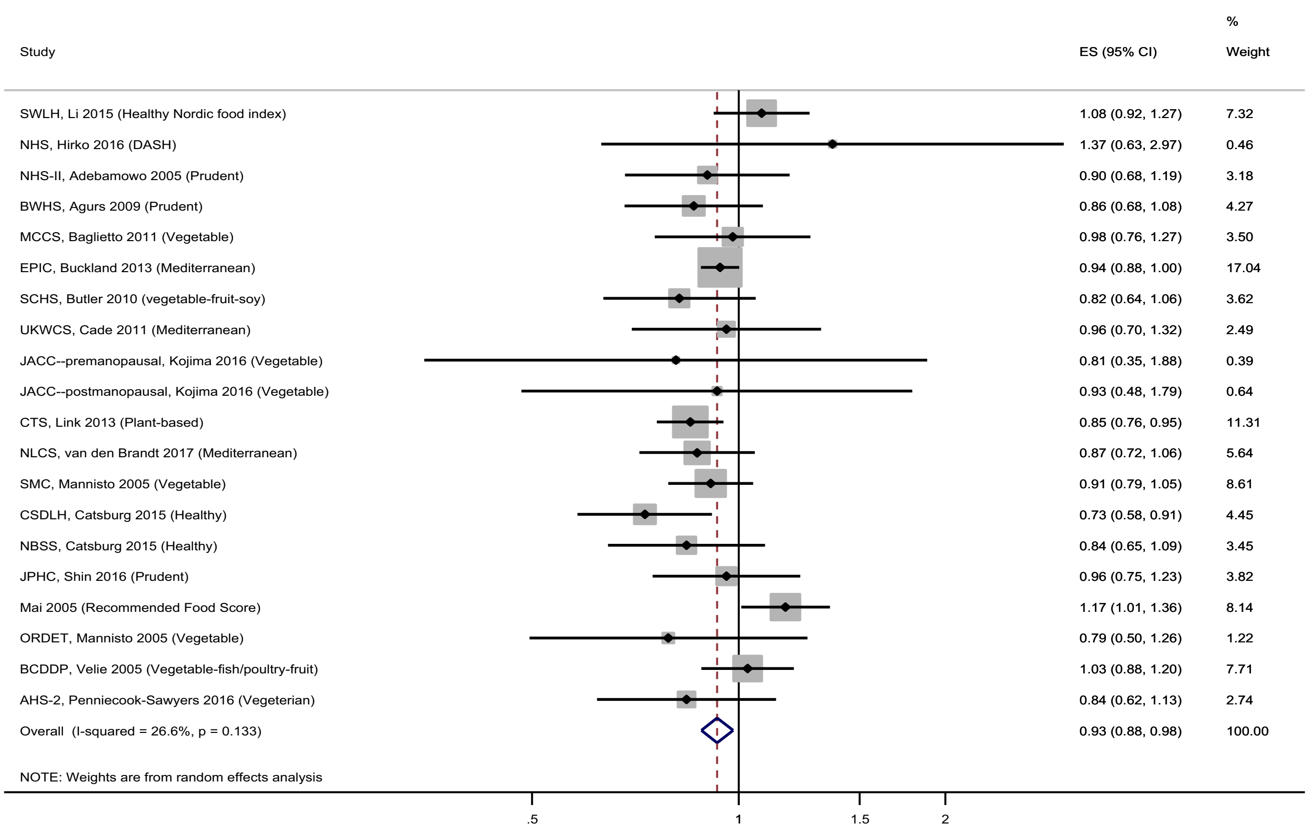

Fig. 1 Forest plot of the highest compared with the lowest categories of intake of healthy dietary patterns and risk of breast cancer. *AHS-2* Adventist Health Study-2, *BCDDP* Breast Cancer Detection Demonstrati on Project, *BWHS* Black Women's Health Study, *CI* Confidence Interval, CSDLH Canadian Study of Diet, Lifestyle and Health, *CTS* California Teachers Study, *EPIC* European Prospective Investigation into Cancer and Nutrition, *ES* Effect Size, *JACC* Japan Collaborative Cohort Study, *JPHC* Japan Public Health Center based on Prospective Study, *MCCS* Melbourne Collaborative Cohort Study, *NBSS* National Breast Screening Study, *NHS* Nurses' Health Study, *NHS-II* Nurse' Health Study II, *NLCS* Netherlands Cohort Study on diet and cancer, *ORDET* Ormoni e Dieta nella Eziologia dei Tumori in Italy, *SCHS* Singapore Chinese Healthy Study, *SMC* Swedish Mammography Cohort, *SWLH* Swedish Women's Lifestyle and Health, *UKWCS* UK Women's Cohort Study

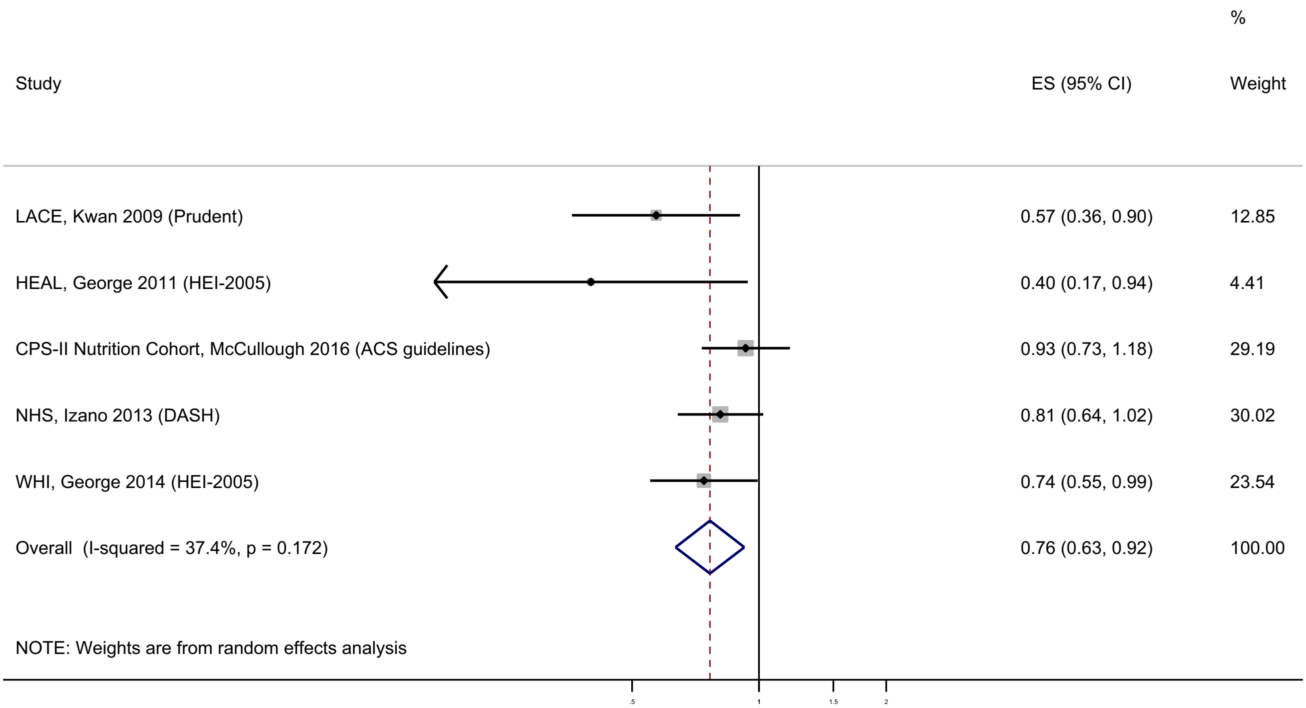

Fig. 2 Forest plot of the highest compared with the lowest categories of intake of healthy dietary patterns and all-cause mortality. *CPS-II* Cancer Prevention Study–II Nutrition Cohort, *ES* Effect Size, *HEAL* Health, Eating, Activity and Lifestyle, *LACE* Life After Cancer Epidemiology Study, *NHS* Nurses' Health Study

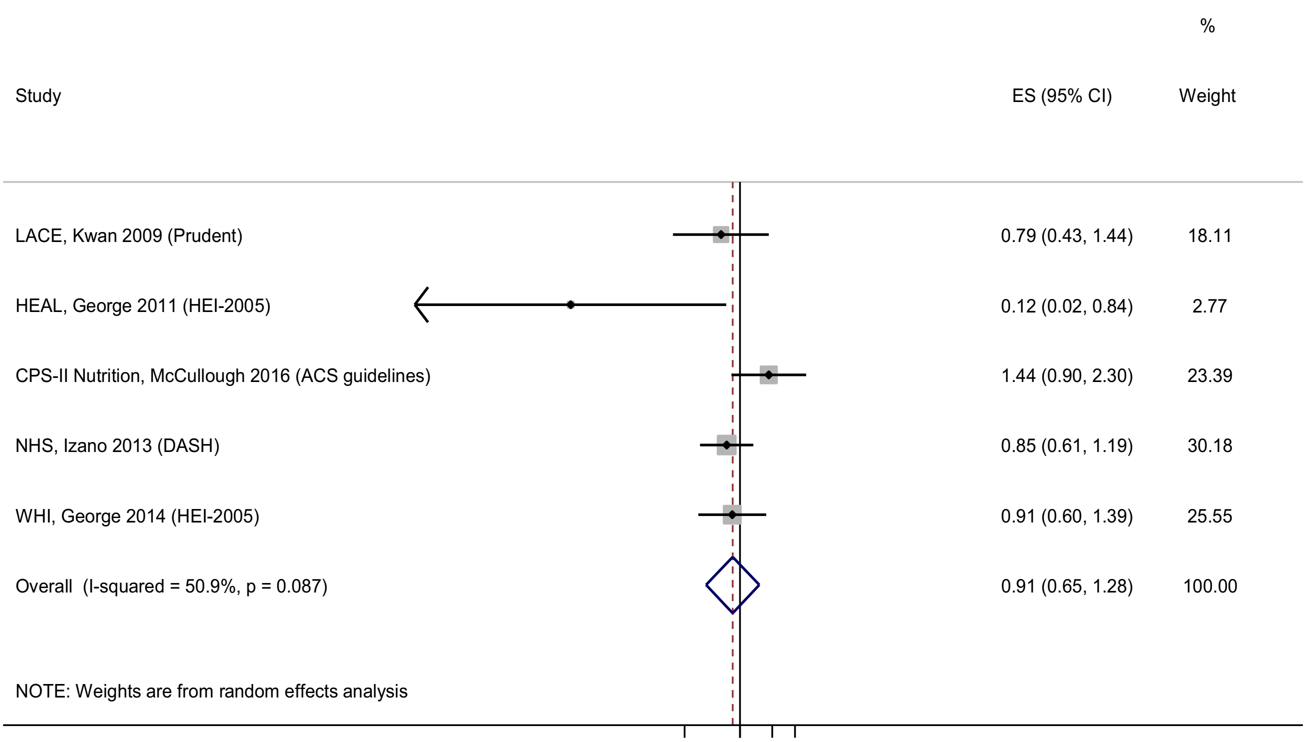

Fig. 3 Forest plot of the highest compared with the lowest categories of intake of healthy dietary patterns and breast cancer mortality. *CPS-II* Cancer Prevention Study–II Nutrition Cohort, *ES* Effect Size, *HEAL* Health, Eating, Activity and Lifestyle, *LACE* Life After Cancer Epidemiology Study, *NHS* Nurses' Health Study

Table 1 Subgroup analysis of the pooled analysis between healthy dietary patterns and risk of breast cancer

	Number of cohorts	Pooled RR (95% CI)	I^2	Studies included in the subgroup meta-analysis
Menopause				
Postmenopausal	11	(RR = 0.97, 95% CI: 0.90, 1.05)	27%	SWLH [27], BWHS [87], EPIC [88], SCHS [62], UKWCS [23], JACC [28], CSDLH [21], NBSS [21], JPHC [30], NHS [89], AHS-2 [32]
Pre-menopausal	11	(RR = 0.92, 95% CI: 0.83, 1.01)	0%	SWLH [27], NHS-II [57], BWHS [87], EPIC [88], SCHS [62], UKWCS [63], JACC [28], CSDLH [21], NBSS [21], JPHC [30], AHS-2[32],
Hormone receptor				
ER-	5	(RR = 0.82, 95% CI: 0.63, 1.06)	63%	SWLH [20], MCCS [25], NLCS [29], SMC [61], NHS [54]
ER-/PR-	5	(RR = 0.86, 95% CI: 0.65, 1.15)	77%	SWLH [20], EPIC [90], CTS [58], NLCS [29], JPHS [30]
Dietary pattern methods				
A posteriori	15	**(RR = 0.90, 95% CI: 0.85, 0.95)**	0%	NHS-II [57], BWHS [87], MCCS [25], SCHS [62], UKWCS [63], JACC [28], CTS [58], NLCS [24], NBSS [21], JPHC [30], NHS [54], ORDET [24], BCDDP [91]
A priori	7	(RR = 0.99, 95% CI: 0.90, 1.09)	48%	SWLH [27], NHS [31], EPIC [88], UK Women's Cohort Study [63], NLCS [29], Mai [92], AHS [32]
Mediterranean diet	5	(RR = 0.96, 95% CI: 0.89, 1.04)	32%	SWLH [20], EPIC [88], UKWCS [63], NLCS[29], NHS [38]
Region				
Europe	6	(RR = 0.94, 95% CI: 0.86, 1.02)	19%	SWLH [27], EPIC [88], UKWCS [23], NLCS [29], SMC [61], ORDET [93]
North America	8	(RR = 0.92, 95% CI: 0.82, 1.05)	64%	NHS [31], NHS-II [57], BWHS [87], MCCS [94], CSDLH [21], Mai [92], BCDDP [91], AHS-2 [32]

Bold indicates statistically significant results

derive dietary patterns. However, no statistically significant associations were found between the risk of breast cancer and a priori healthy dietary patterns or Mediterranean diet. Also, no significant association was found between healthy dietary patterns and risk of breast cancer by study region, breast cancer subtypes (including ER- subgroup or ER-/PR- subgroup), or menopausal status (Figs. 4, 5).

Discussion

Our updated meta-analysis indicated that healthy dietary patterns may decrease breast cancer risk, which is in agreement with previously published systematic reviews [33, 34, 64]. Moreover, there was an inverse association for *posteriori*-derived dietary patterns, but no modification effects were found by menopausal status, study regions, and breast cancer subtypes. Among breast cancer patients, an inverse association was found between healthy dietary patterns and all-cause mortality, but no association was observed between the healthy dietary pattern and breast cancer mortality.

The healthy dietary patterns, characterized by high intake of vegetables, fruit, and food with a low fat content, are promoted by the World Cancer Research Fund (WCRF) to reduce cancer risk [26] and align with American Cancer Society Guidelines [19]. These foods contain substances with anti-carcinogenic and anti-inflammation properties, which could have protective functions through antioxidant effects on estrogen metabolism and cell proliferation reduction [65, 66]. One epidemiological study suggested an inverse association between high fruits and vegetables consumption with breast cancer risk [67]. Higher dietary inflammatory potential score was also found to be associated with greater breast cancer, suggesting that modifying inflammatory characteristics of diet can reduce the risk of breast cancer [68]. Other plausible reason that diet plays a role in breast cancer might be due to its contribution to obesity pathways or epigenetic alterations affecting carcinogenesis [69–71].

In a posteriori subgroup analysis, the inverse association between a healthy dietary pattern and breast cancer risk was found, while no association was found in a priori subgroup. It has been found that dietary patterns derived by a posteriori analysis have reasonable reproducibility and validity using data from food frequency questionnaire (FFQ), which could minimize the risk of bias and probably results in the inverse association found [41]. It is also possible that we found no association in a priori subgroup due to the heterogeneity in dietary patterns used across studies and limited number of studies, which suggests the

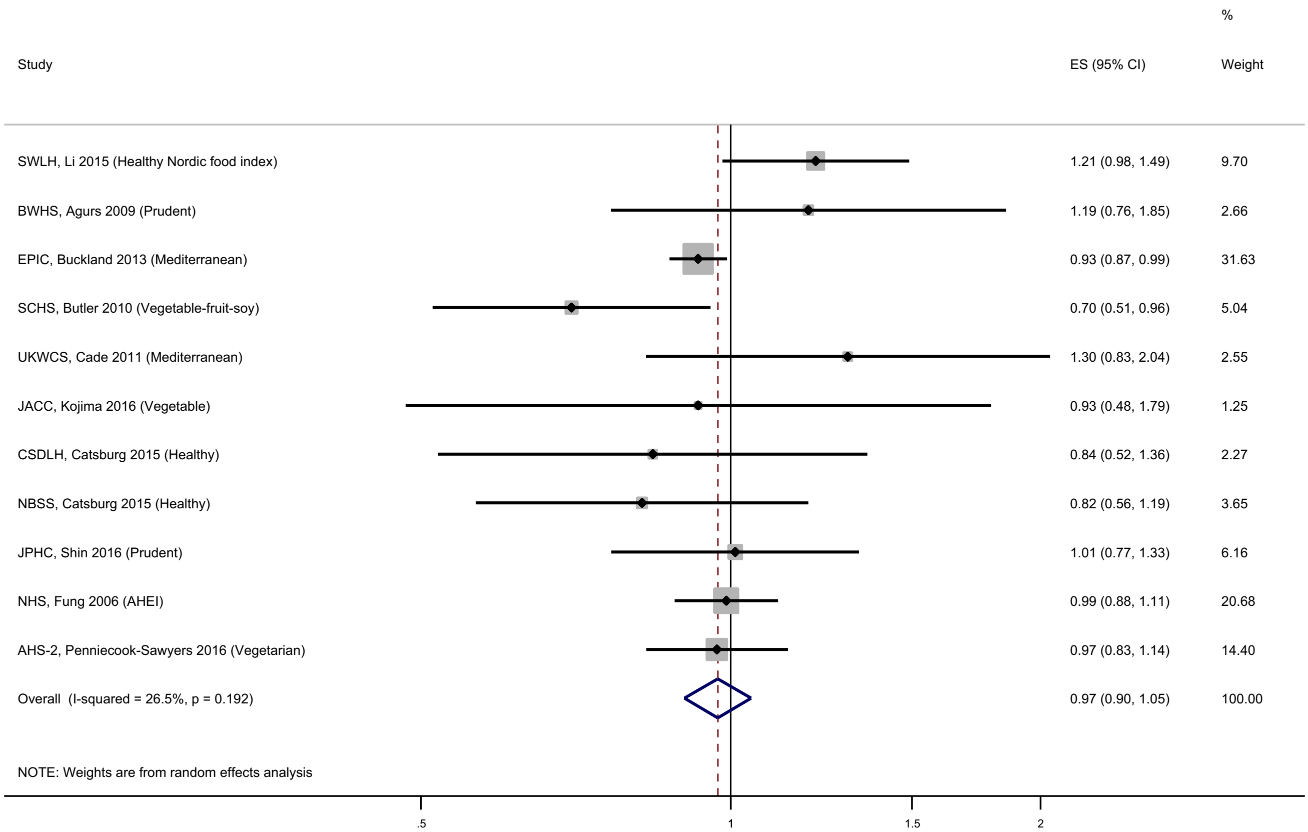

Fig. 4 Forest plot of the highest compared with the lowest categories of intake of healthy dietary patterns and risk of breast cancer in postmenopausal women. *AHS-2* Adventist Health Study-2, *BWHS* Black Women's Health Study, *CI* Confidence Interval, *CSDLH* Canadian Study of Diet, Lifestyle and Health, *EPIC* European Prospective Investigation into Cancer and Nutrition, *ES* Effect Size, *JACC* Japan Collaborative Cohort Study, *JPHC* Japan Public Health Center based on Prospective Study, *NBSS* National Breast Screening Study, *NHS* Nurses' Health Study, *SCHS* Singapore Chinese Healthy Study, *SWLH* Swedish Women's Lifestyle and Health, *UKWCS* UK Women's Cohort Study

need of a more specific dietary guideline created for breast cancer prevention.

Although some studies reported modification effects by menopausal status between breast cancer and foods [36], no significant effects were found in our study, which is consistent with the latest review on dietary pattern and cancer risk [72]. Moreover, no significant associations were found in our analysis for ER- group or ER-/PR- group even though different breast cancers subtypes have different molecular, pathologic, and clinical features [73]. It is possible that we are unable to identify the association due to limited number of studies and the high heterogeneity between studies. These studies were conducted in different regions with different dietary patterns influenced by culture and in different FFQ. Moreover, it is found that different techniques to measure ER and PR have limitations and it is likely to have different techniques in cohorts of different regions [73].

As dietary pattern is strongly related to cultural habits and differs by country or ethnicity and variables like cooking methods may not be captured, subgroup analysis based on the study region was conducted as surrogate since no point estimates were provided by ethnic group in the original articles. However, no association between healthy dietary patterns and breast cancer risk was found in North America or Europe. It is possible that we are underpowered within each region with six studies in Europe and eight studies in North America. We did not conduct analysis in different regions of Asia due to limited number of studies and diverse dietary patterns of various cultures.

For breast cancer survival, an inverse association was found between healthy dietary patterns and all-cause mortality, but no association was shown with breast cancer-specific mortality in our analysis. Our findings are consistent to a recent systematic review, where better overall dietary intake was found to be associated with decreased risk of overall mortality but insufficient to draw conclusions regarding breast cancer-specific survival [48]. One previous study has also shown that healthy diet was not associated with breast cancer-specific mortality but reduces risk of overall mortality in women who had been previously treated for early-stage

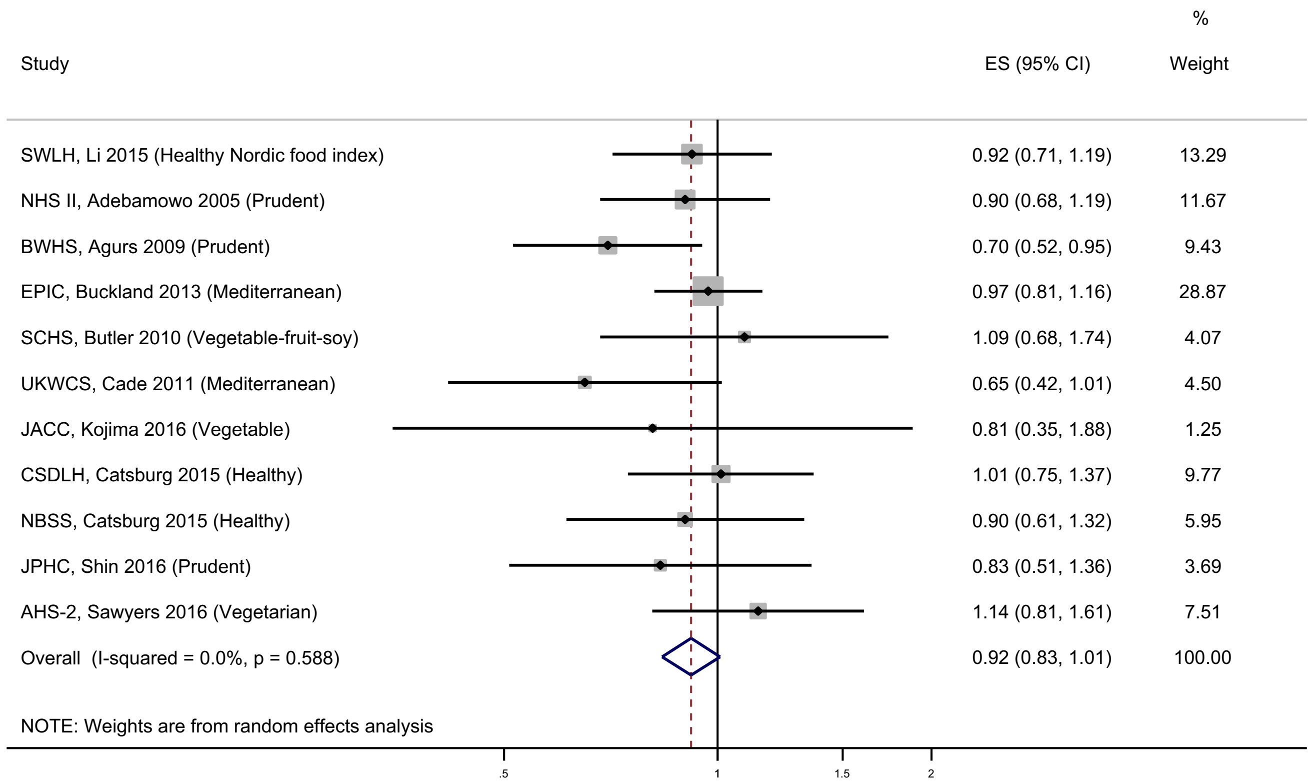

Fig. 5 Forest plot of the highest compared with the lowest categories of intake of healthy dietary patterns and risk of breast cancer in pre-menopausal women. *AHS-2* Adventist Health Study-2, *BWHS* Black Women's Health Study, *CI* Confidence Interval, *CSDLH* Canadian Study of Diet, Lifestyle and Health, *EPIC* European Prospective Investigation into Cancer and Nutrition, *ES* Effect Size, *JACC* Japan Collaborative Cohort Study, *JPHC* Japan Public Health Center based on Prospective Study, *NBSS* National Breast Screening Study, *NHS-II* Nurse' Health Study II, *SCHS* Singapore Chinese Healthy Study

breast cancer [43]. It could indicate that although dietary habits may not influence breast cancer-related outcomes for breast cancer patients, they could still play an important role in etiology of overall health [74–76]. Moreover, better diet quality is associated with improved physical functioning and vitality in cancer survivors [77]. Furthermore, sample size, follow-up duration, measurement errors in dietary assessment, and stage of breast cancer may also affect the results [78–81]. Our results are consistent with dietary guidelines directed towards the general population for overall chronic disease or cancer prevention [40, 82, 83], which indicates that women diagnosed with breast cancer may benefit from healthy dietary patterns and improve their survival rates. Five cohorts were used between healthy dietary patterns and breast cancer survival meta-analysis, and the small number of studies underscores the limited publications on the research topic. Therefore, representativeness of the findings cannot be ensured.

Our meta-analysis has several strengths. First, we only included evidence from prospective cohort studies as case–control studies are more likely to be influenced by recall bias and less adept at showing a causal relationship compared to prospective cohort studies [84]. Second, we examined the association based on menopausal status, breast cancer subtypes, methods to derive dietary and region, which could provide novel knowledge to the relationship between dietary patterns and breast cancer. There are also some limitations. First, the findings are directly driven by the included studies, and those studies have their own strengths and limitations in terms of study design, e.g., measurement errors for individual intake or no dietary pattern data in childhood which could miss a critical period for breast cancer prevention. Also, not including alternate studies in the same cohort (those with smaller sample size than the included ones) may lose some information and affect the results. Second, we only compared the risk estimates or mortality between the highest and lowest categories of healthy dietary patterns. The middle categories were not considered in the current analysis and the highest category of one study could be considered as low in another study; therefore, we cannot recommend an absolute intake/category to achieve the beneficial effects of healthy diet. However, the relative categories within the same study could still provide useful information about relative effects of healthy dietary patterns. Moreover, the dietary assessment methods were different among studies although the majority of studies used FFQ, which could introduce heterogeneity. This tool is known to be subject to substantial amounts of random and systematic variability [85, 86]. It is possible that the associations shown in this analysis was attenuated to the null due to non-differential misclassification. However, FFQs are commonly used in nutrition studies and mostly validated in the studies. Additionally, only single time-point measurements of dietary patterns were examined in the included studies, and these do not account for changes in eating habits over time, which might be especially relevant to cancer development. More studies with multiple measurements of dietary patterns are needed to better address the effects of diet on breast cancer risk. Lastly, we have only included published studies and studies published in English.

In conclusion, our results provide evidence of an overall inverse association between a healthy dietary pattern and breast cancer risk. An inverse association between a healthy dietary pattern and all-cause mortality was found among breast cancer patients. It could be clinically relevant to promote healthy dietary patterns for breast cancer prevention and provide guidance for nutritional care of breast cancer patients. Further investigation is needed to better understand the mechanism between dietary patterns and breast cancer and how dietary patterns affect people differently by menopausal status and breast cancer subtypes. Future studies involving large scale randomized controlled trials or carefully designed observational studies are required to get more definitive conclusions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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