

Healthy Eating Index/Alternative Healthy Eating Index and Breast Cancer Mortality and Survival: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: Breast cancer is the most common cancer in women worldwide. The effects of overall diet quality instead of single nutrients after breast cancer diagnosis on mortality have been a growing area of research interest. The aim of this systematic review was to investigate the relationship between the Healthy Eating Index (HEI)/the Alternative Healthy Eating Index (AHEI) and risk of breast cancer mortality or survival rates as a primary outcome, and some related inflammatory factors, as secondary outcomes among postdiagnosed women. **Methods:** This study methodology was performed based on the Preferred Reporting Item for Systematic Review and Meta-analysis statement recommendation and had been registered at PROSPERO (registration number:

CRD42015015605). The systematic search was conducted in the electronic databases including PubMed, ISI, Scopus, Cochrane, and Google before July 2016. Researches that had not reported risk of breast cancer mortality or survival rates separately were excluded from the study. Similarly, this review excluded studies which only had examined the HEI or AHEI without reporting their association with the risk of mortality or survival rates. **Results:** After primary search, of 643 studies identified, 4 studies including eligible criteria were selected for the final assessment. All selected studies had been conducted in the USA and used self-report food-frequency questionnaire for diet quality assessment. In two studies HEI-2005, in one study AHEI, and in another study AHEI-2010 were applied.

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Meta-analysis result showed no significant association between these indexes and risk of breast cancer mortality/survival among women with this malignancy [relative risk: (RR) 1.04; 95% confidence interval (CI): 0.69–1.56; $P = 0.87$]. **Conclusions:** Regarding the adherence HEI/AHEI, we found no association between mentioned indexes and risk of mortality or survival from breast cancer in women with breast cancer. However, evidence in this field is limited and inconsistency and further studies are needed.

Key words: Breast cancer, mortality, survival

Introduction

Breast cancer is the most common cancer in women worldwide and the second cause of cancer-related mortality among them.^[1,2] Moreover, more than half million deaths of women occur from this malignancy per year.^[3]

Among different factors could be affected on breast cancer survival and mortality, diet may play an important role.^[4-7] Most of the previous studies have focused on impact of nutrients^[8-11] or single dietary component on mortality or survival.^[12,13] However, nutrients or foods were not consumed individual.^[14] Thus, investigators become more interested to assess whole diet quality, and dietary patterns have been applied to summarize the overall dietary exposure and variations.^[15]

To assess the diet quality, the Healthy Eating Index (HEI) was developed by the US Department of Agriculture’s Center based on the dietary guidelines for Americans.^[16,17] The HEI has ten components scale, including grains, vegetables, fruits, milk, meat, total fat, saturated fat, cholesterol, sodium, and variety with 0–100 overall scoring range.^[18] The Alternative Healthy Eating Index (AHEI) is a changed HEI and has nine components scale, including vegetables, fruit, nuts and soy protein, white meat to red meat ratio, cereal fiber, trans fat, polyunsaturated-to-saturated fat ratio, duration of multivitamin use, and alcohol with overall scoring range of 2.5–87.5.^[19] Within each of the five major food groups, some foods are more nutrient dense than others. The selection of the most nutrient dense foods within food groups leads to a dietary pattern with a higher HEI or AHEI.^[20]

The HEI and AHEI are useful for evaluating the changes in diet quality over the time and relationship between nutrient and dietary pattern with disease or health.^[21]

The epidemiologic studies reported positive association between the HEI and breast cancer mortality and survival,^[22] but others showed a non-significant relationship.^[23-25] Since the conflicting data, this systematic review and meta-analysis conducted to summarize the existing evidences and clarify the relationship between Healthy

Eating Index (HEI)/Alternative Healthy Eating Index (AHEI) and risk of breast cancer mortality or survival rates among post diagnosed women.

Methods

This study methodology was performed based on the Preferred Reporting Item for Systematic Review and Meta-analysis statement recommendation^[26] and had been registered at PROSPERO (registration number: CRD42015015605).

Data sources and search strategy

To identify relevant studies, systematic search was conducted in electronic database including PubMed, Scopus, Cochrane, ISI, and Google Scholar before July 2016. Three concepts for search strategy were used. The first concept included “HEI” or “AHEI,” the second concept comprised “breast cancer,” and “the risk of mortality or survival rates” was the third concept. There was no search limitation in this study. The details of search term are shown in Table 1.

Eligibility criteria

Studies were selected based on using HEI or AHEI to assess the relationship between quality of dietary pattern and risk of breast cancer mortality or survival rates. Researches that had not reported risk of breast cancer mortality or survival rates separately were excluded from the study. Similarly, this review excluded studies which only had examined the HEI or AHEI without reporting their association with the risk of mortality or survival rates or related risk factors.

Table 1: Search strategy

Concept 1	Concept 2	Concept 3
“Healthy eating index”	AND “Breast Neoplasms”(Mesh)	AND “Risk of mortality”
OR	OR	OR
“Healthy eating index”[tiab]	“Breast Neoplasms”(tiab)	“Mortality”(Mesh)
OR	OR	OR
“HEI”	“Brest cancer”	“mortality”(tiab)
	OR	OR
	“Brest adenoma”	“Death”
	OR	OR
	“Breast neoplasm”	“survival” (Mesh)

Selection strategy

After primary search (643 articles: PubMed 389, Scopus 168, Cochrane 3, Google Scholar 53, and ISI [Web of Science] 30) and elimination of duplicated articles (423 articles), titles and abstracts of all studies were independently reviewed by Makan Pourmasoumi and Nooshin Vosoughi. Ten articles including eligible criteria in title/abstract screening were selected to be checked by full-text. Most of the excluded articles had assessed either non-cancer outcomes or cancers other than breast cancer or outcomes without assessing the mortality and survival measures. Excluded studies and any disagreement in the selection of studies were reviewed and resolved by the third researcher. In addition, all reference lists of selected studies were assessed manually to identify related articles. Finally, of the total 10 full-text articles reviewed, 4 articles were eligible for data abstraction which met inclusion criteria. Publication search and selection results are shown in Figure 1.

Data extraction

The data extracted from selected studies included first author, published year, study design, sample size, sample tested, age, follow-up, country, dietary pattern identified,

mortality report information, hazard ratio/relative risk (HR/RR), main result, and adjustment. Furthermore, 95% confidence interval (CI) and *P* values were extracted where available. The characteristics of each study are illustrated in Table 2.

Quality assessment

The risk of bias assessment of selected articles was investigated by the Newcastle–Ottawa Quality Assessment Scale Cohort Studies.^[27] The full score of cohort checklist was 9. The mean of star of selected studies was 6.5. The score of each study is shown in Table 2.

Statistical analysis

The main outcome variables were measures of adjusted RR or HR and 95% CI for the estimate of association between breast cancer mortality/survival and HEI/AHEI. Empirical byes method was applied for estimating the overall effect.^[28] Meta-regression (duration and age of patients were considered as covariate) and subgroup analyses (based on type of diet; HEI-2005 or AHEI) were performed to find potential source of heterogeneity. Heterogeneity was evaluated with Cochran's *Q*-test and I^2 ($p < 0.05$ and $I^2 > 0.75$ was considered as meaningful heterogeneity).^[29] Sensitivity analysis was performed to explore the robustness of the combined risk estimates. To examine for possible publication bias, visual inspection of funnel plot and Egger test were used.^[28,30] All data analyses were performed with STATA, version 10.0. (STATA, College Station, TX), and $P < 0.05$ was considered statistically significant.

Results

Four cohort articles with total 9819 women and mean age of 56 ± 9.35 years were included in systematic review and meta-analysis. The mean follow-up of studies was 7.7 ± 1.9 . All included studies used Cox proportional hazards' models for statistical analysis. Of the four articles that fulfilled our selection criteria, two had examined breast cancer survival rates and two assessed the risk of mortality.

All selected studies had been conducted in the USA and used self-report food-frequency questionnaire (FFQ) for diet quality assessment. One study^[22] was multiethnic research performing on the Health, Eating, Activity, and Lifestyle (HEAL Study is a multiethnic prospective cohort study that includes 1183 breast cancer survivors' women with Stage 0–IIIA breast cancer) cohort studies. Two studies^[23,24] had been conducted on the Nurses' Health Study (NHS: Cohort study established in 1976, including 121,700 female nurses with 30–55-year-old from 11 US

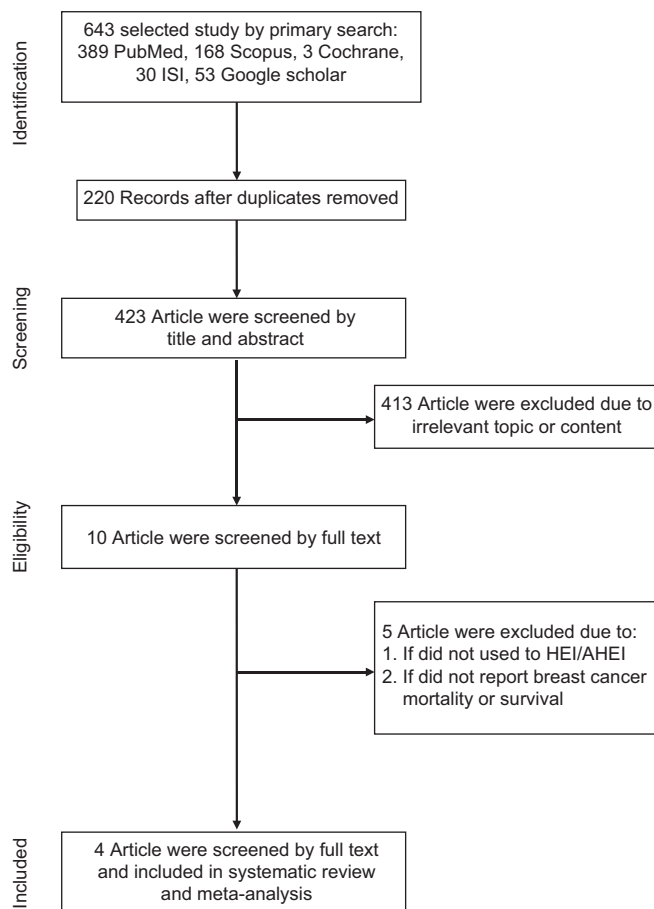


Figure 1: The flow diagram of study selection

Table 2: Characteristics of included studies

Author/ year/ Country	Study design (study name)	Sample size	Age range (years)	Follow up	Questionnaire, Dietary pattern identified	Assessment of mortality	Cause of death	HR/RR (CI)	Main result	adjustment	Quality assessment
Stephanie M. George 2014 USA	Cohort (WHI)	2317	50-79	Median length of follow up was 9.6 years.	FFQ (included 122 composite and single food line items) HEI-2005 (11 component including: total fruit; whole fruit; total vegetables; dark-green vegetables, orange vegetables, and legumes; total grains; whole grains; milk; meats and beans; oils; saturated fat; sodium; calories from solid fat, alcohol, and added sugar)	Through clinical center follow-up of participants, surrogates and periodic searches of the National Death Index.	Determined by medical record and death certificate review.	HR: 0.91 (0.6-1.40)	Better post diagnosis diet quality was not associated with breast cancer death.	age at screening visit (continuous), WHI component (WHI-DM-intervention, WHI-DM-control, or OS), ethnicity (White non-Hispanic, Black/African American, Hispanic/Latino, other, missing), income, education, stage, estrogen receptor status, progesterone receptor status, time since diagnosis, energy intake in kcal, physical activity in MET-h/wk, servings of alcohol per week (continuous), and use of postmenopausal hormone therapy.	7
Izano.MA and <i>et al</i> 2013 USA	Cohort (NHS)	4103	30-55	Median length of follow up was 9.3 years.	FFQ (include 61 item in 1980 and 116 item thereafter until 2002) 7 times used AHEI-2010 (11 component including: vegetables, fruits, nuts and legumes, whole grains, trans fats, long-chain (n-3) fats (EPA + DHA), polyunsaturated fats, sugar-sweetened beverages and fruit juice, red or processed meat, sodium, and alcohol)	By family members, the postal service, or searches in the National Death Index.	Ascertained by physicians' review of death certificates and medical records.	RR: 1.07 (0.77-1.49)	Adherence to AHEI-2010 diet was not significantly associated with breast cancer mortality.	Stratified by time since diagnosis (months), adjusted for age at diagnosis (years), quintiles of energy intake, body mass index, body mass index change, age at first birth and parity, oral contraceptive use, menopausal status and HRT use, smoking, stage of disease, radiation treatment, chemotherapy and hormonal treatment, and physical activity	7

(Continued)

Table 2: (Continued)

Author/ year/ Country	Study design (study name)	Sample size	Age range (years)	Follow up	Questionnaire, how many items and how many use	Dietary pattern identified	Assessment of mortality	Cause of death	HR/RR (CI)	Main result	adjustment	Quality assessment
EhJ.Kim and <i>et al</i> 2011 USA	Cohort (NHS)	2729 Women diagnosed with stages I-III breast cancer	30-55	6 years	FFQ (include 61 item in 1984 and 130 item in 1984 and thereafter until 2004) 5 times used	AHEI (9 components including: vegetables (potatoes were removed), fruits, nuts and soy, cereal fiber, ratio of white to red meat, trans fat, polyunsaturated, saturated fat ratio, and alcohol)	By family members or the postal service, or were service, or were identified from a search of the National Death Index.	Determined by physicians' reviewers.	RR: 1.53 (0.98, 2.39)	No association was found between AHEI and either total or non-breast cancer related death and a higher AHEI did not considerably change the risk of death from breast cancer.	time since diagnosis, age (continuous), energy, body mass index in kg/m2, body mass, index (BMI), weight change (BMI at time of diet minus BMI just prior to diagnosis), oral contraceptive use, age, smoking status, physical activity in METs, stage (I, II, III), categories of treatment, age at first birth and parity, menopausal status and postmenopausal hormone use.	6
George <i>et al.</i> 2011 USA	Cohort (HEAL)	670 Woman with first primary breast cancer	18-64	6 years	FFQ (122-item) 1 time used	HEI-2005 (12 component including:(total fruit (includes 100% juice), whole fruit (not juice), total vegetables, total vegetable, dark green and orange vegetables and legumes, total grains, whole grain, milk, meat and beans, oil, saturated fat, sodium, calories from solid fats, alcoholic beverage and added sugars)	From state mortality files and the National Death Index.	Not mentioned	HR :0.12 (0.2-0.99)	The higher scores of HEI results in reduce breast cancer mortality	energy intake, physical activity, race, stage, tamoxifen use and body mass index	6

states. In this study, the case completed question about medical and lifestyle factors), and on the Women’s Health Initiative (WHI).^[25] The studies on the same cohort had different samples.

Although in two studies^[22,25] HEI-2005 had been used, in the study conducted by Kim *et al.*^[23] AHEI, that adapted from the original HEI based on the 1992 Food Guide Pyramid and the 1995 Dietary Guidelines for Americans,^[31] was used, and another study^[24] applied AHEI-2010. The details of each index component are shown in Table 2.

One study reported highest adherence to HEI compared to lowest, caused reduced risk of mortality, but in other three cohorts, no significant effects were found. The result of meta-analysis on total studies failed to show a significant relation between adherence to HEI/AHEI diet and risk of breast cancer mortality/survival in women with this malignancy (relative risk: (RR) 1.04; 95% confidence interval (CI): 0.69–1.56; $P = 0.87$) [Figure 2]. Also subgroup analyses based on type of diets did not show significant association for none of AHEI and HEI (Figures 3 and 4, respectively). We did not find any significant impact of age and duration

on dependent measures (mortality/survival) in meta regression analysis (regression coefficient (standard error): -0.032 (0.026); $P = 0.43$ for age and 0.086 (0.13); $P = 0.64$ for duration). The observed significant heterogeneity between the studies ($P = 0.002$) was remained significant even after subgroup analysis based on diets’ types (AHEI) assessment and meta-regression based on age and duration.

Sensitivity analysis

Sensitivity analysis showed that removing none of each included studies in meta-analysis did not significant impact on estimated overall effect size [Figure 5]. No evidence of publication bias was seen using funnel plot [Figure 6] and Egger test ($P = 0.3$).

Discussion

To the best of our knowledge, the present study is the first systematic review and meta-analysis investigated the association between the HEI/AHEI and breast cancer

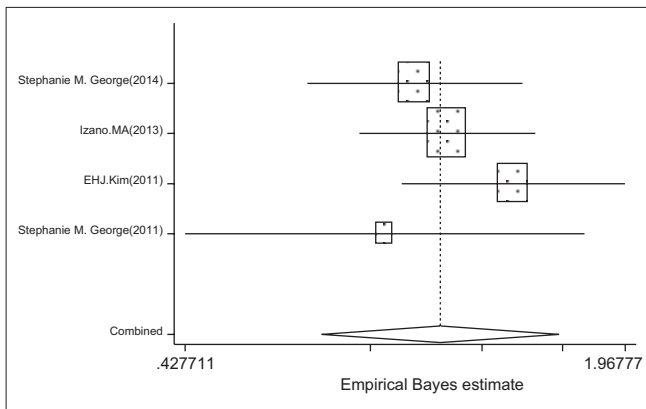


Figure 2: Forest plot illustrating weighted relative risk (RR) using empirical Bayes method

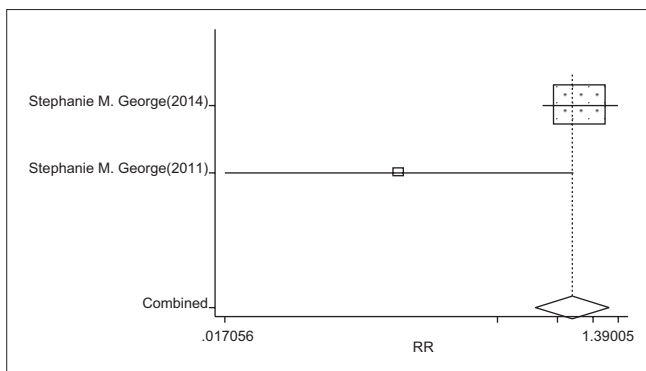


Figure 4: Forest plot illustrating weighted relative risk (RR) using fixed effect method for HEI diets subgroup

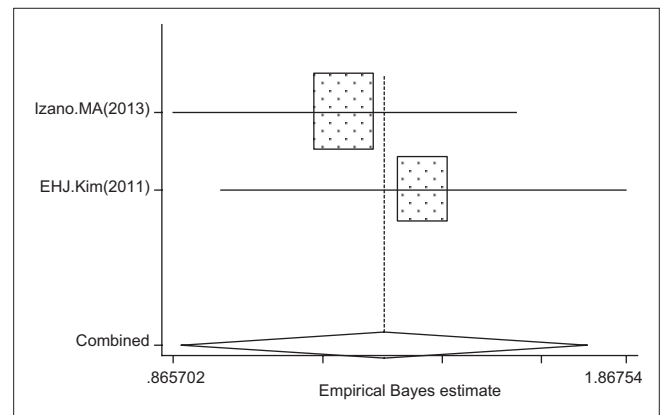


Figure 3: Forest plot illustrating weighted relative risk (RR) using empirical Bayes method for AHEI diets subgroup

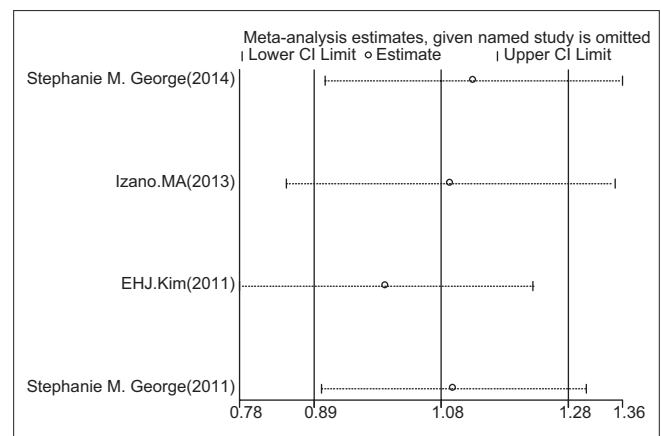


Figure 5: Results of sensitivity analysis for detecting influential studies on estimated overall effect in meta-analysis

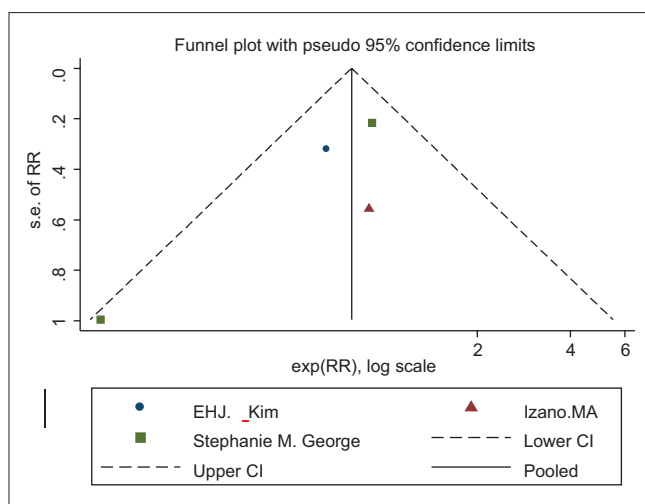


Figure 6: Begg's funnel plots (with pseudo 95% confidence intervals) for detection of publication bias

mortality/survival. Our result failed to show a significant effect of HEI/AHEI on risk of breast cancer mortality in women with breast cancer prognosis.

Among the 5 included studies, 1 study reported the positive effects^[22] and 3 ones could not find any significant relationship.^[25-27] Some possible reasons have been suggested for these conflicting findings. The reason is the use of the HEI and AHEI together that may cause this heterogeneity. Among studies using the HEI, the consumption of red and processed meat did not assess,^[22,25] in contrast to other researches evaluating by AHEI.^[23,24] Thus, the additional factors in AHEI may cause different results compared to HEI.

The heterogeneity of results has also attributed to the varied number of confounders that were controlled in these studies.^[22-25] Furthermore, in the HEAL study,^[22] women who may have been receiving treatment for subsequent recurrences or new primaries that occurred before their 30-month assessment were excluded. While in the NHS, assessment during active treatment were avoided and only measurements taken at least 2 years after diagnosis, were considered.^[23,24] In the WHI, they did not have data of cancer treatment.^[2]

One possible reason for different results is physical activity that plays a role to categorize the participants, and it has done in Kim *et al.*'s study.^[23] As the impact of measurement error of FFQ, physical and psychological characteristics of participants play an important role in the observed reporting bias in the dietary intake assessment.^[32] Moreover, sample size^[23-25] follow-up duration in cohort studies^[24,25] and stage of breast cancer^[23] are the important factors that may change the results.

High amounts of healthy foods such as fruits and vegetables and low amounts of unhealthy foods such as alcohol, total and saturated fats may reduce breast cancer recurrence and mortality.^[13,33-36] The potential protection against breast cancer mortality by a healthy diet may be considered as anti-inflammatory^[37] and anti-oxidative effects, principally due to increased intake of protective nutrients, and lower intake of pro-inflammatory nutrients.^[38,39] However, results among studies assessing overall dietary pattern were not as much positive as researches evaluating individual dietary components. Proverbially, in the life after cancer epidemiology, healthy diet not associate with breast cancer mortality in women had been previously treated for early-stage breast cancer. However, it reported that healthy eating reduces risk of overall mortality.^[14] In addition, it might be due to protective effect of adherence to the healthy diet on cardiovascular disease among these women and via this way linked to reduced mortality.^[40-42] Furthermore, consumption of healthy foods is associated with improved quality of life, physical and cognitive function in breast cancer survivors.^[43]

The positive effect of the healthy eating pattern may also associate with lower C-reactive protein (CRP).^[44] Inflammation can increase the breast tumors through the chronic activation of humoral immunity, infiltration of Th2 cells, and polarized inherent inflammatory cells.^[45] Thus, higher concentration of CRP may associate with lower rates of survival.^[46] In addition, high-quality diets with high content of fruits and vegetables may affect cancer mortality through many biological mechanisms. Magnesium, fiber, potassium, and flavonoids may have a beneficial effect on inflammation.^[20] It was also found that unhealthy foods consumption is associated with breast cancer mortality.^[47]

In all reviewed studies, there were not control groups. However, in the HEAL^[22] and WHI^[25] studies, diet quality was measured with the HEI, and for each participant, they scored each component, calculated total score, and classified HEI scores into quartiles to best separate those with better quality diets (Q4), mixed quality diets (Q2-Q3), and poor quality diets (Q1), and this is the comparison of their analysis. While in the NHS^[24,25] AHEI was used, women were categorized into quintiles of dietary scores and compared.

In this study, potential limitations should be considered. Our review was based on the available data; relatively few studies, that have examined HEI and AHEI among breast cancer patients, were available. The heterogeneity of these studies was a significant consideration in the results interpretation. Furthermore, since only English-language

studies were included, some studies may have been excluded.

Conclusion

The meta-analysis findings show no association between HEI/AHEI and risk of breast cancer mortality/survival among women with breast cancer medical history. Further prospective cohort studies and clinical trials with long follow-up time and reliable method for collecting data are required to reach a definite conclusion among different populations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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