Fruit and vegetable intake and breast cancer prognosis: a meta-analysis of prospective cohort studies

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Abstract

The effect of fruit and vegetable intake on breast cancer prognosis is controversial. Thus, a meta-analysis was carried out to explore their associations. A comprehensive search was conducted in PubMed, Web of Science, OVID, ProQuest and Chinese databases from inception to April 2016. The summary hazard ratios (HR) and 95 % CI were estimated using a random effects model if substantial heterogeneity existed and using a fixed effects model if not. Subgroup analyses and sensitivity analyses were also performed. In total, twelve studies comprising 41 185 participants were included in the meta-analysis. Comparing the highest with the lowest, the summary HR for all-cause mortality were 1·01 (95 % CI 0·72, 1·42) for fruits and vegetables combined, 0·96 (95 % CI 0·83, 1·12) for total vegetable intake, 0·99 (95 % CI 0·89, 1·11) for cruciferous vegetable intake and 0·88 (95 % CI 0·74, 1·05) for fruit intake; those for breast cancer-specific mortality were 1·05 (95 % CI 0·77, 1·43) for total vegetable intake and 0·94 (95 % CI 0·69, 1·26) for fruit intake; and those for breast cancer recurrence were 0·89 (95 % CI 0·53, 1·50) for total vegetable intake and 0·98 (95 % CI 0·76, 1·26) for cruciferous vegetable intake. This meta-analysis found no significant associations between fruit and vegetable intake and breast cancer prognosis.

Key words: Fruits and vegetables: Breast cancer: Recurrence: Mortality: Meta-analyses

Breast cancer is the most prevalent cancer among women; it is increasing globally and is the most common cause of cancer-related death in women on all continents[1]. Breast cancer affects about 12 % of women worldwide[2]. It was reported that 1·7 million new cases were diagnosed worldwide in 2012, accounting for about 25 % of total cancer cases in women[3]. Moreover, breast cancer is the leading cause of cancer deaths in women. It has the highest mortality of any cancer in women (12·9 per 100 000), accounting for approximately 14·7 % of all cancer-related mortalities among women worldwide[4]. However, advances in early detection and in types of therapies and their application have resulted in prolonged survival among women diagnosed with breast cancer[5]. Thus, it is very important to research the prognostic factors of breast cancer given the increasing number of breast cancer survivors.

Fruits and vegetables may offer potential protective effects against breast cancer occurrence and prognosis. Various biochemical compositions found in a diet high in fruits and vegetables kill breast cancer cells *in vitro* and prevent and suppress breast cancer progression in various preclinical animal models[6]. Chatterjee *et al.*[7] found that carotenoids, consisting largely of α-carotene, β-carotene and β-cryptoxanthin, are typical constituents of orange-, red- and yellow-coloured fruits and green vegetables. β-Ionone, an end-ring analogue of β-carotenoid, inhibits 7,12-dimethylbenz-(α)anthracene (DMBA)-induced mammary carcinogenesis by inhibiting cell proliferation and inducing apoptosis[8]. Liu *et al.*[9] also documented the chemopreventive effects of varied doses of dietary β-ionone on the development and growth of DMBA-induced rat mammary tumours and the biologically relevant plasma antioxidant status. Cruciferous vegetables are also major sources of glucosinolate-derived bioactive compounds such as isothiocyanates, which have been shown in animal and *in vitro* studies to inhibit cancer growth and progression[10]. Sulforaphane is an isothiocyanate that elicits both pro-apoptotic and anti-proliferative properties[11]. Azarenko[12] found that sulforaphane stabilised microtubules in breast cancer cells by suppressing microtubule dynamic instability at concentrations that inhibited cell proliferation and induced mitotic arrest. It has also been reported that high consumption of brassicaceous vegetables is regularly associated with low cancer risk, with its extracts regulating the progression of cancer through anti-inflammatory effects, effects on signal transduction, epigenetic effects and modulation of the colonic microflora[13]. At present, interest in a number of fruits high in polyphenols has been heightened because of their reported chemopreventive and chemotherapeutic potential[14]. Many fruits

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such as pomegranate have been shown to exert anticancer activity, which is generally attributed to their high polyphenol content[15]. Therefore, high consumption of fruits and vegetables might play an important role in breast cancer prognosis.

To clarify the effects of the consumption of fruits and vegetables on the prognosis of breast cancer survivors, several studies have investigated the association of fruit and vegetable intake with all-cause mortality or breast cancer-specific mortality or recurrence[10,16–26]. The majority of these studies have reported a non-significant inverse association of fruit and vegetable intake with all-cause mortality[17,22,24–26], and two studies also found this same non-significant association with breast cancer recurrence[10,25]. Moreover, among survivors of early-stage breast cancer, adoption of a diet that was very high in vegetables, fruits and fibre and low in fat did not reduce additional breast cancer events or mortality during a 7·3-year follow-up period[27]. However, two studies reported an inverse association of fruit and vegetable intake with all-cause mortality[16,21], and one study reported that vegetable intake is inversely associated with breast cancer recurrence[18]. Hauner *et al.*[28] found that a low-fat diet rich in fruits, vegetables and fibre seems to be weakly associated with a better prognosis. To our knowledge, the findings on the effects of fruit and vegetable intake on breast cancer prognosis are not conclusive. Therefore, a meta-analysis of prospective cohorts is required to quantitatively evaluate the overall effect of fruit and vegetable intake on the prognosis of breast cancer.

Methods

Literature search

A comprehensive search of PubMed, Web of Science, OVID, ProQuest and Chinese databases from June 1955 to April 2016 was conducted. The structured search strategy included the following format of key terms: [(vegetable OR fruit OR diet OR nutrition)] AND [(breast cancer OR breast neoplasm OR breast carcinoma)] AND [(prognosis OR disease progression OR disease-free survival OR mortality OR survival rate OR survival analysis OR medical futility OR treatment outcome OR treatment failure OR causes of death OR fatal outcome OR recurrence)]. We also carried out manual searches of the reference lists of eligible articles and pertinent reviews. Only full-length, original articles were considered, and no attempt was made to include abstracts or unpublished results. No language restrictions were imposed. The titles and abstracts of all identified articles were screened by one investigator (C. P.) for eligibility. Two investigators (C. P. and W.-P. L.) independently reviewed the full texts of the remaining articles to identify eligible studies, with differences in opinion resolved by consensus.

Study selection criteria

Studies were eligible for the analysis if (i) the study design was a prospective cohort study; (ii) data related to the dietary consumption of fruits and vegetables were available; (iii) prognostic indicators were restricted to recurrence, all-cause mortality and breast cancer-specific mortality[29]; and

(iv) the study provided OR, relative risk (RR) or hazard ratio (HR) and CI data associating fruit and vegetable intake with breast cancer prognosis[30–32]. When multiple publications covered the same population, only the most recently published report was included in the analysis. Case reports, reviews, articles without full text, animal studies and *in vitro* studies were also excluded.

Data extraction and quality assessment

Two reviewers (C. P. and W.-P. L.) independently reviewed and extracted the data. Any discrepancies between the two reviewers were resolved by discussion until a consensus was reached. The study characteristics were recorded using a standardised data collection form, which included the name of the first author, publication year, country or region, study design, number of cases, length of follow-up, dietary assessment, exposure or outcome, comparison, OR, RR or HR from the most fully adjusted model for the highest *v.* the lowest fruit and vegetable intakes and their corresponding 95 % CI; confounders were adjusted for in the multivariate analysis.

The quality of the included studies, including selection of the study population, the comparability of the study groups and the outcome or exposure assessment, was assessed on the basis of the Newcastle–Ottawa Quality assessment scale (NOS) for assessing the quality of non-randomised studies in meta-analysis[33]. Studies were considered to be of high quality if they scored seven or higher of a possible nine points[34,35].

Statistical analysis

Summary HR were calculated for recurrence and death (all-cause and breast cancer-specific mortality) using generic inverse variance. The generic inverse variance method in RevMan can be used for ratio measures such as HR or RR[36]. High *v.* low meta-analysis was performed with ratio data from the most fully adjusted model for the highest *v.* the lowest fruit and vegetable intakes. HR is used to represent ratio measures of effect, including RR. Adjusted HR estimates are summarised using a fixed or random effects model. The random effects model was used to consider both within-study and between-study variations. Assessment of heterogeneity among the studies was performed by using Q and I^2 statistics. *P*-values of <0·05 or I^2-values over 50 % indicate substantial heterogeneity[37]. If substantial heterogeneity exists, the random effects model is appropriate; otherwise, the fixed effects model is preferred[38]. Pre-specified stratified analyses were performed to assess the effects of the various study characteristics. Subgroup analyses were carried out by comparing summary HR in each stratum, including menopausal status, number of patients, countries, timing of dietary intake and the use of tamoxifen, on outcomes. Because of the small number of studies reporting on recurrence or breast cancer-specific mortality, the subgroup analyses were mainly carried out for the association between fruit and vegetable intake and all-cause mortality.

Population-based study cohorts were defined as highly representative[39]. In contrast, studies that selected groups of users, for example, nurses and volunteers, and studies with no

description of the derivation were categorised as poorly representative[39]. To assess the stability of the findings, sensitivity analyses to rule out poorly representative results from a single study in the meta-analysis were carried out by excluding each study individually and using both fixed and random effects models to evaluate the robustness of the results. Tests for publication bias were performed by constructing and assessing funnel plots. A symmetric inverted funnel shape arises from a 'well-behaved' data set, in which publication bias is unlikely[40].

Results

Results of the literature search

According to the search criteria, 4493 records were identified, of which 96 % were excluded from the meta-analysis after reviewing the title and abstract. After reviewing the full text of the remaining 146 articles, twelve articles[10,16–26] were included in the meta-analysis. The most common reasons for exclusion were lack of data on fruit and vegetable intake, breast cancer recurrence, all-cause mortality or breast cancer-specific mortality. A flow chart of the procedure used to select studies is shown in Fig. 1.

Characteristics of studies

The characteristics and quality scores of the included studies are summarised in Table 1. In total, twelve included studies involving 52 962 women were identified, which included 29 295 breast cancer patients from eleven studies[10,16–22,24–26] and 23 667 women from one study[23]. The studies had three outcomes: all-cause mortality in ten studies[10,16,17,19–22,24–26], breast cancer-specific mortality in four studies[17,19,23,26] and recurrence in three studies[10,18,25]. The twelve studies included prospective cohort studies published between 1999 and 2013. In total, seven studies were conducted in the USA[17,18,20–22,24,25], one in China[16], one in Japan[23], one in Germany[26], one in Italy[19] and one in both the USA and China[10].

The number of participants in each study ranged from 149 to 23 667, and the median length of follow-up ranged from 3 to 18 years. Most of the individual studies adjusted for a wide range of potential confounders, including age, BMI, stage of disease, age at diagnosis, hormone-replacement therapy use, alcohol use and physical activity. Most studies used a validated FFQ to assess the consumption of fruits and vegetables; eleven studies were of high quality (NOS score ≥7), with an average NOS score of 8·0.

All-cause mortality

As shown in Fig. 2(a), three included studies[19,20,22] with four groups of patients investigated the association between the highest $v.$ the lowest intake of fruits and vegetables combined and all-cause mortality among breast cancer patients. The summary HR (highest $v.$ lowest) from the three studies for all-cause mortality was 1·01 (95 % CI 0·72, 1·42) with moderate heterogeneity ($P_{\text{for heterogeneity}} = 0.09$, $I^2 = 54$ %). No significant association was found between fruit and vegetable intake and all-cause mortality among the breast cancer patients. The funnel plot was symmetrical, and there was no evidence of publication bias.

In all, seven included studies[16,17,21,22,24–26] with eight groups of patients were eligible for the meta-analysis of the association between highest $v.$ lowest total vegetable intake and all-cause mortality among breast cancer patients. The summary HR (highest $v.$ lowest) from the eight groups of breast cancer patients for all-cause mortality was 0·71 (95 % CI 0·43, 1·17) with evidence of high heterogeneity ($P_{\text{for heterogeneity}} < 0.00001$, $I^2 = 91$ %). However, in the funnel plot, one study[16] deviated far from the vertical axis, and an asymmetrically inverted funnel shape indicates potential publication bias. Therefore, as shown in Fig. 2(b), this study[16] was excluded, and the summary HR (highest $v.$ lowest) from the remaining six studies was 0·96 (95 % CI 0·83, 1·12) with no significant heterogeneity ($P_{\text{for heterogeneity}} = 0.11$, $I^2 = 42$ %). No significant association was found between total vegetable intake and all-cause mortality among the breast cancer patients. There was no evidence of small-study bias from the funnel plot.

As shown in Fig. 2(c), three included studies[10,17,22] with four groups of patients investigated the association between highest $v.$ lowest cruciferous vegetable intakes and all-cause mortality. The summary HR (highest $v.$ lowest) for all-cause mortality was 0·99 (95 % CI 0·89, 1·11) with no significant heterogeneity ($P_{\text{for heterogeneity}} = 0.84$, $I^2 = 0$ %). No significant association was found between cruciferous vegetable intake and all-cause mortality among the breast cancer patients. The funnel plot was symmetrical, and there was no evidence of publication bias.

As shown in Fig. 2(d), six included studies[16,17,21,22,25,26] with seven groups of patients investigated the association between highest $v.$ lowest fruit intake and all-cause mortality. The summary HR (highest $v.$ lowest) from the six studies for all-cause mortality was 0·88 (95 % CI 0·74, 1·05) with no heterogeneity detected ($P_{\text{for heterogeneity}} = 0.11$, $I^2 = 43$ %). Thus, no significant association was found between fruit intake and all-cause mortality. The funnel plot was symmetrical, and there was no evidence of publication bias.

Breast cancer-specific mortality

As shown in Fig. 3(a), three included studies[17,23,26] investigated the association between highest $v.$ lowest total vegetable intake and breast cancer-specific mortality. The summary HR (highest $v.$ lowest) for breast cancer-specific mortality was 1·05 (95 % CI 0·77, 1·43), with no evidence of heterogeneity ($P_{\text{for heterogeneity}} = 0.82$, $I^2 = 0$ %). Thus, no significant association was found between total vegetable intake and breast cancer-specific mortality. The funnel plot was symmetrical, and there was no evidence of publication bias.

As presented in Fig. 3(b), three included studies[17,23,26] investigated the association between highest $v.$ lowest fruit intake and breast cancer-specific mortality. The summary HR (highest $v.$ lowest) for breast cancer-specific mortality was 0·94 (95 % CI 0·69, 1·26), with no evidence of heterogeneity ($P_{\text{for heterogeneity}} = 0.54$, $I^2 = 0$ %). Thus, no significant association was found between fruit intake and breast cancer-specific
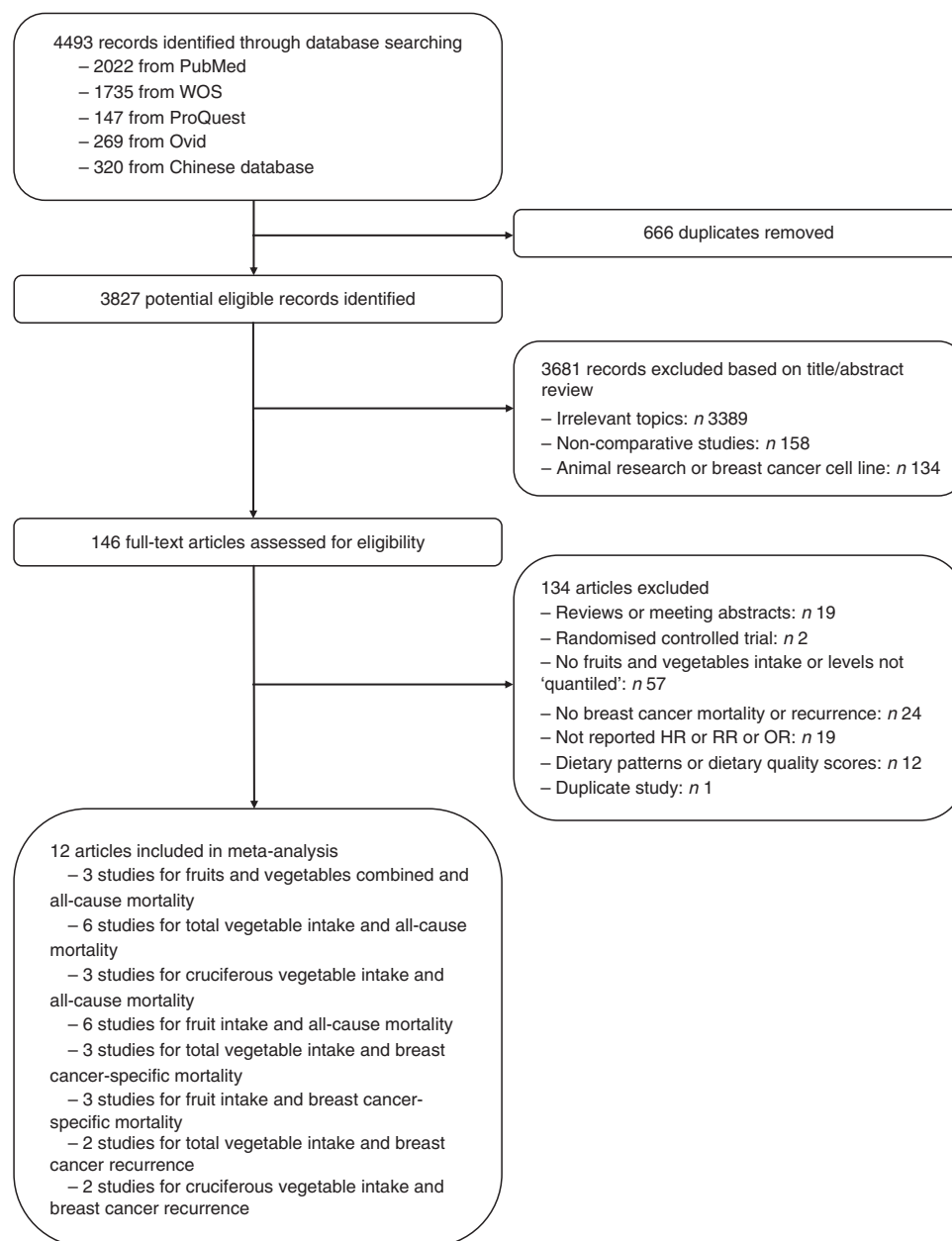
Fig. 1. Flow chart of the selection of studies included in the meta-analyses. WOS, Web of Science; HR, hazard ratio; RR, relative risk.

mortality. The funnel plot was symmetrical, and there was no evidence of publication bias.

Breast cancer recurrence

Two included studies[18,25] investigated the association between highest *v.* lowest total vegetable intake and breast cancer recurrence. The summary HR (highest *v.* lowest) from these two studies for breast cancer recurrence was 0·89 (95 % CI 0·53, 1·50) with substantial heterogeneity shown ($P_{\text{for heterogeneity}} = 0·003$, $I_2 = 89\%$) in Fig. 4(a). There was no evidence of small-study bias from the funnel plot.

As presented in Fig. 4(b), two included studies[10,18] investigated the association between highest *v.* lowest cruciferous

vegetable intake and breast cancer recurrence. The summary HR (highest *v.* lowest) was 0·98 (95 % CI 0·76, 1·26) with moderate heterogeneity ($P_{\text{for heterogeneity}} = 0·05$, $I^2 = 73\%$). The funnel plot was symmetrical, and there was no evidence of publication bias.

Subgroup analyses

Subgroup analyses of the associations of fruit and vegetable intake with all-cause mortality and breast cancer recurrence are summarised in Table 2.

Four included studies investigated the association between total vegetable intake[21,22,25,26] or fruit intake[21,22,25,26] and all-cause mortality stratified by menopausal status, respectively.

Table 1. Characteristics of included studies and quality score

Author, Publication year, Country	Study name	Number of cases	Follow-up period (years)	Dietary assessment	Exposure	Contrast (highest v. lowest)	HR (95 % CI) (highest v. lowest) for mortality or recurrence	Adjustments	NOS score
Beasley et al.[17], 2011, USA	CWLS	4441 breast cancer women	Mean 5·5 (SD 1·1)	Validated 126-item FFQ	Vegetables; Cruciferous vegetables; Fruits	Food group intake (quartiles) (servings/d): Vegetables: Q1 = 0·4; Q2 = 0·8; Q3 = 1·0; Q4 = 2·5 Cruciferous vegetables: Q1 = 0·1; Q2 = 0·2; Q3 = 0·3; Q4 = 0·7 Fruits: Q1 = 0·1; Q2 = 0·4; Q3 = 1·0; Q4 = 2·5	All-cause survival: Vegetables 1·44 (0·91, 2·27); Cruciferous vegetables 1·02 (0·80, 1·30); Fruits 1·38 (0·88, 2·17) Breast cancer survival: Vegetables 0·96 (0·38, 2·45); Cruciferous vegetables 0·95 (0·59, 1·54); Fruits 1·39 (0·64, 2·99)	Factors at diagnosis (age, state of residence, menopausal status, smoking status, breast cancer stage, alcohol intake, history of hormone-replacement therapy), interval between diagnosis and diet assessment, and factors at follow-up (energy intake, breast cancer treatment, BMI, and physical activity)	9
Buck et al.[26], 2011, Germany	Hamburg RNK	2653 post-menopausal breast cancer women	Median 6·4	A self-administered validated 176-items FFQ	Vegetables; Fruits	Vegetables (n/deaths) (median intake) Tertile 1: 875/118 (79 g/d); Tertile 2: 902/100 (118 g/d); Tertile 3: 876/103 (183 g/d) Fruits (n/deaths) (median intake) Tertile 1: 876/122 (79 g/d); Tertile 2: 902/104 (128 g/d); Tertile 3: 876/95 (259 g/d)	Overall mortality: Vegetables 1·09 (0·80, 1·48); Fruits 0·84 (0·61, 1·16). Breast cancer mortality: Vegetables 1·01 (0·70, 1·46); Fruits 0·86 (0·59, 1·25)	Tumour size, nodal status, metastasis, grade, ER/PR status, breast cancer detection type, diabetes, menopausal hormone therapy use at diagnosis, study centre and energy intake	8
Dal Maso et al.[19], 2008, Italy	PACE	1453 invasive breast cancer women	Median 12·6 (maximum 16·8)	Food frequency consumption section (FFQ)	Vegetables and fruits	Vegetables and fruits (servings/d): ≥6; 4 to <6; <4	All-cause mortality: Vegetables and fruits 1·27 (1·00, 1·61). Breast cancer mortality: Vegetables and fruits 1·26 (0·96, 1·64)	Region of residence, age at diagnosis, year of diagnosis, TNM stage and ER/PR status; Total energy intake, using the residual method	9
Fink et al.[22], 2006, USA	LIBCSP	1235 invasive breast cancer women	3	Respondent-completed, modified block FFQ	Any fruits, fruit juices, and vegetables; Any vegetables; Cruciferous vegetables; Any fruits and fruit juices; Leafy vegetables; Yellow vegetables; Citrus fruits	Any fruits, fruit juices and vegetables: 0–18; 19–25; 26–33; 34–45; 46+ Any vegetables: 0–8; 9–13; 14–17; 18–23; 24+ Cruciferous vegetables: 0–1; 2; 3; 4–5; 6+ Any fruits and fruit juices: 0–6; 7–12; 13–16; 17–23; 24+ Leafy vegetables: 0–2; 3; 4–5; 6–8; 9+ Yellow vegetables: 0–4; 5–7; 8–10; 11–15; 16+ Citrus fruits: 0–1; 2–4; 5–7; 8–11; 12+	All-cause mortality: Postmenopausal women Any fruits, fruit juices, and vegetables 0·68 (0·42, 1·09); Any vegetables 0·92 (0·57, 1·48); Cruciferous vegetables 1·07 (0·67, 1·72); Any fruits and fruit juices 0·87 (0·57, 1·35); Leafy vegetables 0·72 (0·41, 1·24); Yellow vegetables 0·90 (0·58, 1·40); Citrus fruits 0·90 (0·56, 1·44). Premenopausal women Any fruits, fruit juices and vegetables 1·38 (0·65, 2·91); Any vegetables 1·40 (0·71, 2·76); Cruciferous vegetables 0·72 (0·34, 1·54); Any fruits and fruit juices 1·10 (0·48, 2·52); Leafy vegetables 0·85 (0·39, 1·85); Yellow vegetables 1·09 (0·52, 2·28); Citrus fruits 1·70 (0·75, 3·89)	Age and energy	7
Holmes et al.[24], 1999, USA	NHS	1982 invasive breast cancer women	18	Validated FFQ	Vegetables	Quantiles of vegetables intake (servings): Q1 ≤ 2·12; Q2 = 2·13–3·12; Q3 = 3·13–4·20; Q4 > 4·20	Multivariate RR for all-cause mortality: Vegetables 0·81 (0·59, 1·11)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, smoking status, age at first birth and parity, postmenopausal hormone use, number of metastatic lymph nodes, tumour size and energy intake	9

Table 1. *Continued*

Author, Publication year, Country	Study name	Number of cases	Follow-up period (years)	Dietary assessment	Exposure	Contrast (highest v. lowest)	HR (95 % CI) (highest v. lowest) for mortality or recurrence	Adjustments	NOS score
McEligot et al.[21], 2006, USA	IRB	516 post-menopausal breast cancer women	Mean 80 months (SD 18)	100-item NCI-block FFQ	Vegetables; Fruits	Vegetables (servings): Tertile 1 = 1·0; Tertile 2 = 2; Tertile 3 = 3·1 Fruits (servings): Tertile 1 = 1·0; Tertile 2 = 1·1; Tertile 3 = 2	All-cause mortality: Vegetables 0·57 (0·35, 0·94); Fruits 0·63 (0·38, 1·05)	Stage of disease, age at diagnosis, BMI, parity, hormone-replacement therapy use, alcohol use, multivitamin use and energy intake	8
Nechuta et al.[10], 2013, USA, China	ABCPP SBCSS LACE WHEL NHS	11 390 invasive breast cancer women	Median 9·0	Validated FFQ	Post-diagnosis cruciferous vegetables intake	Post-diagnosis cruciferous vegetable intake study-specific quartiles (g/d) (Q1; Q2; Q3; Q4): <10·7; 10·7–22·4; 22·4–43·5; 43·5 (LACE) <13·0; 13·0 to <23·8; 23·8–44·6; 44·6 (WHEL) <15·4; 15·4–25·4; 25·4–43·2; 43·2 (NHS) <61·5; 61·5–93; 93–138·0; 138·0 (SBCSS)	Total mortality: Cruciferous vegetables 0·99 (0·86, 1·13). Recurrence: Cruciferous vegetables 1·10 (0·95, 1·28)	Age at diagnosis, ER/PR status, TNM stage, surgery, chemotherapy, radiotherapy, hormonal therapy, smoking status, BMI, exercise, menopausal status, race/ethnicity and education	9
Pierce et al.[20], 2007, USA	WHEL	1490 early-stage breast cancer women	Average 6·7	24-h dietary recalls	Vegetables–fruits/physical activity (VF/PA)	Low VF/low PA (mean, 3·1 VF servings/d; 221 MET-min/week) (reference); Low VF/high PA (mean, 3·4 VF servings/d; 1478 MET-min/week); High VF/low PA (mean, 7·2 VF servings/d; 224 MET-min/week); High VF/high PA category (mean, 7·6 VF servings/d; 1513 MET-min/week)	Mortality: Low VF and low PA (reference); High VF and low PA 0·86 (0·51, 1·45)	Age, alcohol intake, tumour hormone receptor status, and time from diagnosis to study entry	7
Sauvaget et al.[23], 2003, Japan	LSS	23 667 women	Median 16	Validated FFQ	Green-yellow vegetables; Fruits	Green-yellow vegetables and fruit consumption were classified into three frequency categories: C1 'once per week or less'; C2 '2–4 times per week'; C3 'daily or almost daily'	RR for breast cancer mortality: Green-yellow vegetables 1·28 (0·64, 2·54); Fruits 0·91 (0·48, 1·72). RR for total cancer mortality: Green-yellow vegetables 0·92 (0·84, 1·01); Fruits 0·88 (0·80, 0·96)	Sex, age, radiation dose, city, BMI, smoking status, alcohol intake and education level	9
Saxe et al.[25], 1999, USA	IRBSM	149 women with primary breast cancer	Five or more	A National Cancer Institute FFQ	Green and yellow vegetables; Fruits	Green and yellow vegetables (per 3 servings/week) Fruits (per 14 servings/week)	Death (n 26): Green-yellow vegetables 0·97 (0·70, 1·35); Fruits 1·06 (0·69, 1·63). Recurrence (n 28): Green-yellow vegetables 1·17 (0·90, 1·52); Fruits 0·96 (0·63, 1·45)	Energy	6
Thomson et al.[18], 2011, USA	WHEL	3080 breast cancer women	7·3	Pre-scheduled 24-h dietary recalls	Total vegetables; Cruciferous vegetables	Total vegetables: Lowest tertile; middle tertile; highest tertile Cruciferous vegetables: Lowest tertile; middle tertile; highest tertile	Recurrence Vegetables 0·69 (0·55, 0·87); Cruciferous vegetables 0·85 (0·69, 1·06)	Time from diagnosis to study entry, menopausal status, clinical site, intervention status, cancer stage, oestrogen receptor status, chemotherapy, BMI, physical activity, and tamoxifen use in the full model	8
Pan[16], 2003, China	Survival follow-up study	1406 women with primary breast cancer	Average 4·8; Median 5·14	FFQ	Vegetables; Fruits	Vegetables: 2·8 %; 24·6 %; 21·0 % Fruits: 5·3 %; 24·5 %; 31·1 % Significantly reduce: Reference; No changes; Slightly increase; Significantly increase	All-cause mortality: Vegetables 0·06 (0·03, 0·11), P < 0·0001; Fruits 0·47 (0·25, 0·87), P = 0·001	Vegetables: intake of fruits and intake of soya products Fruits: intake of vegetables and intake of soya products	7

HR, hazard ratio; NOS, the Newcastle–Ottawa Quality assessment scale; CWLS, the Collaborative Women's Longevity Study; Q, quartiles; RNK, Rhein-Neckar-Karlsruhe; ER/PR, oestrogen receptor/progesterone receptor; PACE, Prospective Analysis of Case–control studies on Environmental factors and health study group; TNM, tumour node metastasis; LIBCSP, the Long Island Breast Cancer Study Project; NHS, The Nurses' Health Study; IRB, the Internal Review Board of the University of California, Irvine; ABCPP, the After Breast Cancer Pooling Project; SBCSS, the Shanghai Breast Cancer Survival Study; LACE, the Life After Cancer Epidemiology Study; WHEL, the Women's Healthy Eating and Living Study; MET, metabolic equivalent tasks; LSS, the Life Span Study; IRBSM, Institutional Review Board of the School of Medicine, University of Michigan.
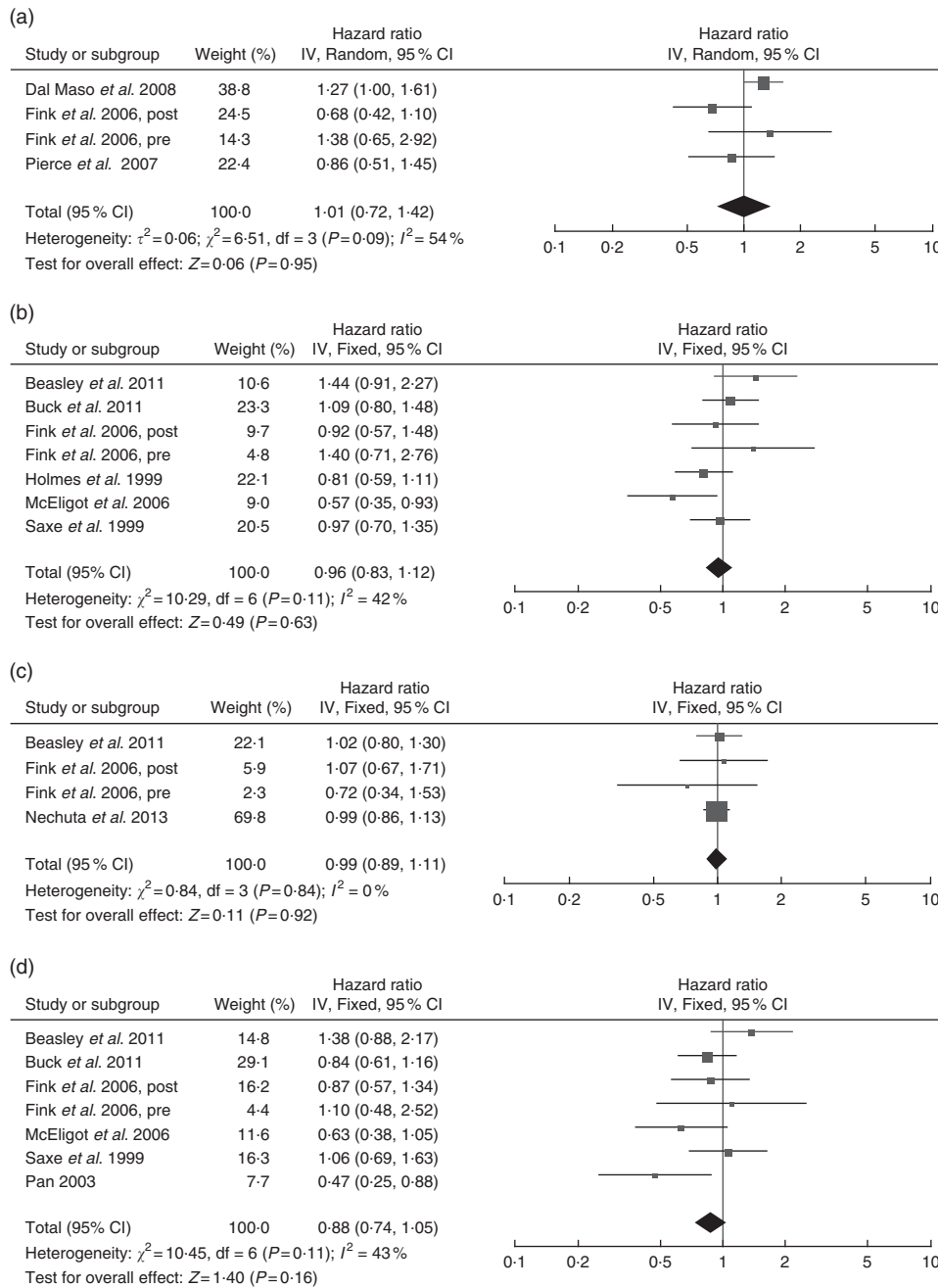
(a)

Study or subgroup	Weight (%)	Hazard ratio IV, Random, 95 % CI
Dal Maso et al. 2008	38·8	1·27 (1·00, 1·61)
Fink et al. 2006, post	24·5	0·68 (0·42, 1·10)
Fink et al. 2006, pre	14·3	1·38 (0·65, 2·92)
Pierce et al. 2007	22·4	0·86 (0·51, 1·45)
Total (95 % CI)	100·0	1·01 (0·72, 1·42)

Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 6.51$, df = 3 ($P = 0.09$); $I^2 = 54\%$
Test for overall effect: $Z = 0.06$ ($P = 0.95$)

(b)

Study or subgroup	Weight (%)	Hazard ratio IV, Fixed, 95 % CI
Beasley et al. 2011	10·6	1·44 (0·91, 2·27)
Buck et al. 2011	23·3	1·09 (0·80, 1·48)
Fink et al. 2006, post	9·7	0·92 (0·57, 1·48)
Fink et al. 2006, pre	4·8	1·40 (0·71, 2·76)
Holmes et al. 1999	22·1	0·81 (0·59, 1·11)
McEligot et al. 2006	9·0	0·57 (0·35, 0·93)
Saxe et al. 1999	20·5	0·97 (0·70, 1·35)
Total (95 % CI)	100·0	0·96 (0·83, 1·12)

Heterogeneity: $\chi^2 = 10.29$, df = 6 ($P = 0.11$); $I^2 = 42\%$
Test for overall effect: $Z = 0.49$ ($P = 0.63$)

(c)

Study or subgroup	Weight (%)	Hazard ratio IV, Fixed, 95 % CI
Beasley et al. 2011	22·1	1·02 (0·80, 1·30)
Fink et al. 2006, post	5·9	1·07 (0·67, 1·71)
Fink et al. 2006, pre	2·3	0·72 (0·34, 1·53)
Nechuta et al. 2013	69·8	0·99 (0·86, 1·13)
Total (95 % CI)	100·0	0·99 (0·89, 1·11)

Heterogeneity: $\chi^2 = 0.84$, df = 3 ($P = 0.84$); $I^2 = 0\%$
Test for overall effect: $Z = 0.11$ ($P = 0.92$)

(d)

Study or subgroup	Weight (%)	Hazard ratio IV, Fixed, 95 % CI
Beasley et al. 2011	14·8	1·38 (0·88, 2·17)
Buck et al. 2011	29·1	0·84 (0·61, 1·16)
Fink et al. 2006, post	16·2	0·87 (0·57, 1·34)
Fink et al. 2006, pre	4·4	1·10 (0·48, 2·52)
McEligot et al. 2006	11·6	0·63 (0·38, 1·05)
Saxe et al. 1999	16·3	1·06 (0·69, 1·63)
Pan 2003	7·7	0·47 (0·25, 0·88)
Total (95 % CI)	100·0	0·88 (0·74, 1·05)

Heterogeneity: $\chi^2 = 10.45$, df = 6 ($P = 0.11$); $I^2 = 43\%$
Test for overall effect: $Z = 1.40$ ($P = 0.16$)

Fig. 2. Forest plots of observational studies investigating the association of all-cause mortality with (a) fruit and vegetable intake, (b) total vegetable intake, (c) cruciferous vegetable intake and (d) fruit intake. Highest v. lowest intake.

No significant association was found between total vegetable intake or fruit intake and all-cause mortality when stratified by menopausal status. The summary HR of total vegetable intake were 0·92 (95 % CI 0·76, 1·12) for those who were postmenopausal and 1·18 (95 % CI 0·71, 1·95) for those who were premenopausal. Those of fruit intake were 0·88 (95 % CI 0·72, 1·08) for postmenopausal patients and 0·90 (95 % CI 0·41, 1·97) for premenopausal patients.

Six included studies with seven groups of patients were eligible for the meta-analysis of the association between total vegetable intake[17,21,22,24–26] or fruit intake[16,17,21,22,25,26] and all-cause

mortality stratified by number of patients. Three studies included 4441[17], 1982[24] and 2563[26] breast cancer patients for total vegetable intake, and three studies included 1264[16], 4441[17] and 2563[26] cases for fruit intake, whereas three other studies with four groups of patients included 516[21], 376[22], 834[22] and 149[25] breast cancer patients for total vegetable or fruit intake. Stratified by number of patients, the summary HR of total vegetable intake were 1·05 (95 % CI 0·78, 1·42) for studies with more than 1000 patients and 0·89 (95 % CI 0·66, 1·22) for those with less than 1000 patients. The summary HR of fruit intake were 0·85 (95 % CI 0·51, 1·42) for those with more than
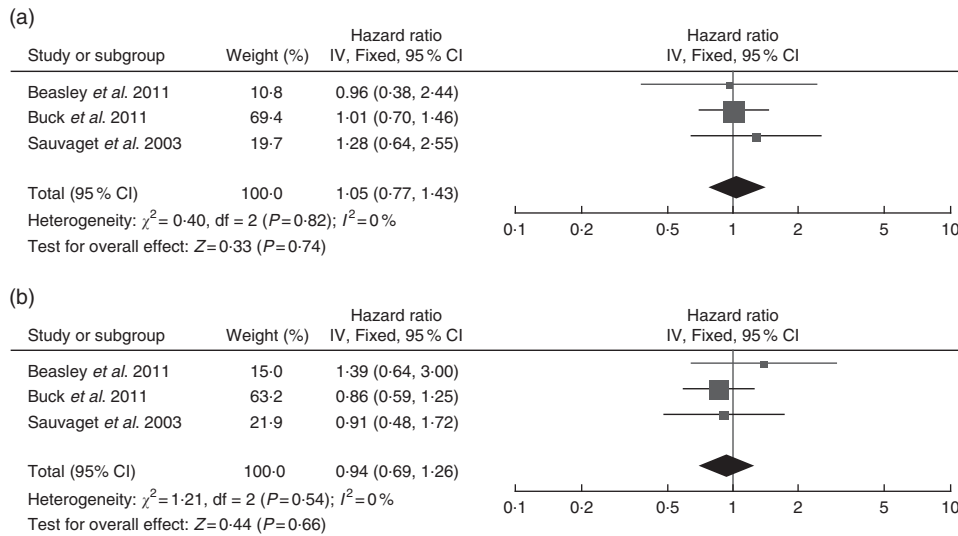
(a)

Fig. 3. Forest plots of observational studies investigating the association of breast cancer-specific mortality with (a) total vegetable intake and (b) fruit intake. Highest *v.* lowest intake.
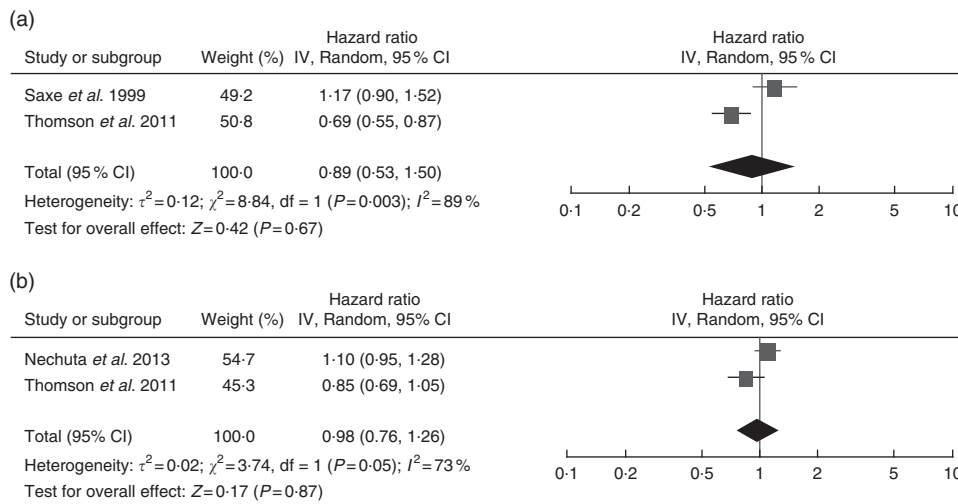
(a)

Fig. 4. Forest plots of observational studies investigating the association of breast cancer recurrence with (a) total vegetable intake and (b) cruciferous vegetable intake. Highest *v.* lowest intake.

1000 patients and 0·88 (95 % CI 0·68, 1·13) for those with less than 1000 patients.

Six included studies with seven groups of patients were eligible for the meta-analysis of the association between total vegetable intake[17,21,22,24–26] or fruit intake[16,17,21,22,25,26] and all-cause mortality stratified by timing of dietary intake information. Four studies[21,22,25,26] were based on information on diet collected before diagnosis or dietary habits before diagnosis and three studies collected after diagnosis[16,17,24]. The summary HR of total vegetable intake were 0·95 (95 % CI 0·75, 1·20) for those whose information on diet was collected before diagnosis[21,22,25,26] and 1·05 (95 % CI 0·60, 1·85) for those collected after diagnosis[17,24]. The summary HR of fruit intake were 0·86 (95 % CI 0·71, 1·05) for those collected before diagnosis[21,22,25,26] and 0·82 (95 % CI 0·29, 2·36) for those collected after diagnosis[16,17].

Six included studies[16,17,21,22,25,26] were eligible for the meta-analysis of the association between fruit intake and all-cause mortality stratified by countries. No significant association was found between fruit intake and all-cause mortality among breast cancer patients in the studies from the USA and the study from Germany, respectively. In the study data from the USA, the summary HR for all-cause mortality was 0·98 (95 % CI 0·79, 1·21). Of the single study from Germany and that from China, only the HR from the study in China indicated statistical significance.

Two included studies[10,18] investigated the association between cruciferous vegetable intake and breast cancer recurrence stratified by the use of tamoxifen. No significant association was found between cruciferous vegetable intake and breast cancer recurrence when stratified by tamoxifen use. In the group of patients taking tamoxifen, the summary HR was

Table 2. Summary of subgroup analyses of the effects of fruit and vegetable intake on all-cause mortality and breast cancer recurrence
(Hazard ratios (HR) and 95 % confidence intervals)

Outcomes	Groups	No. of studies	Summary HR	Summary 95 % CI	Heterogeneity I^2 (%)	Heterogeneity P	P for difference*
All-cause mortality							
Total vegetable	Menopausal states	4					0·37
	Postmenopausal	4	0·92	0·76, 1·12	38	0·19	
	Premenopausal	2	1·18	0·71, 1·95	0	0·47	
	No. of patients (*n*)	6					0·46
	>1000	3	1·05	0·78, 1·42	55	0·11	
	≤1000	3	0·89	0·66, 1·22	41	0·16	
	Timing of dietary intake	6					0·73
	Before diagnosis	4	0·95	0·75, 1·20	35	0·19	
	After diagnosis	2	1·05	0·60, 1·85	76	0·04	
Fruit	Menopausal status	4					0·95
	Postmenopausal	4	0·88	0·72, 1·08	24	0·27	
	Premenopausal	2	0·90	0·41, 1·97	52	0·15	
	No. of patients (*n*)	6					0·90
	>1000	3	0·85	0·51, 1·42	74	0·02	
	≤1000	3	0·88	0·68, 1·13	0	0·45	
	Timing of dietary intake	6					0·93
	Before diagnosis	4	0·86	0·71, 1·05	0	0·61	
	After diagnosis	2	0·82	0·29, 2·36	87	0·006	
	Countries	6					0·09
	USA	4	0·98	0·79, 1·21	29	0·23	
	Germany	1	0·84	0·61, 1·16			
	China	1	0·47	0·25, 0·88			
BC recurrence							
Cruciferous vegetable	Use of tamoxifen	2					0·24
	Yes	2	1·12	0·88, 1·43	0	0·70	
	No	2	0·83	0·53, 1·29	82	0·02	

HR, hazard ratio; BC, breast cancer.
* *P*-values were obtained using test for subgroup differences to compare each group.

1·12 (95 % CI 0·88, 1·43), whereas in the group of patients not taking tamoxifen the summary HR was 0·83 (95 % CI 0·53, 1·29).

Sensitivity analyses

Sensitivity analyses to examine the effects of outliers were performed by using both fixed and random effects models and excluding each study individually and re-calculating the summary HR. Most of the results showed that the summary HR of each meta-analysis remained statistically non-significant. Only the sensitivity analysis excluding one study[17] yielded a different result, showing that the summary HR for the association of fruit intake with all-cause mortality was 0·82 (95 % CI, 0·68, 0·99) with no heterogeneity ($P_{\text{for heterogeneity}} = 0.30$, $I^2 = 17$%), which may indicate the instability of the finding of the association between fruit intake and all-cause mortality (data not shown).

Discussion

The studies included in this meta-analysis examined four types of fruit and vegetable intakes including fruits and vegetables combined, total vegetable intake, cruciferous vegetable intake and fruit intake. The studies had three outcomes, including all-cause mortality, breast cancer-specific mortality and breast cancer recurrence. In this meta-analysis, no significant association was found between fruits and vegetables combined, total vegetable intake, cruciferous vegetable intake or fruit intake and all-cause mortality, breast cancer-specific mortality or breast cancer recurrence, respectively.

To our knowledge, this is the first meta-analysis to assess a possible association between fruit and vegetable intake and breast cancer prognosis. The ability of this meta-analysis to evaluate the effect of fruit and vegetable intake on breast cancer prognosis might be limited because the types of fruit and vegetable intake or the outcome indicators of breast cancer prognosis were investigated differently among the included studies. Some studies mainly investigated the association of total vegetable or fruit intake with all-cause mortality or breast cancer-specific mortality[17,21,23,24,26], whereas others focused only on breast cancer recurrence[10,18,25]. Only one included study evaluated the association between fruits and vegetables combined[19] or cruciferous vegetable intake[17] and breast cancer-specific mortality, respectively. Similarly, only one or no included study investigated the association between fruit intake[25] or fruits and vegetables combined and breast cancer recurrence, respectively. Thus, the types of fruit and vegetable intake and the outcomes of breast cancer prognosis were inconsistent; therefore, this meta-analysis mainly evaluated the summary analysis on all-cause mortality.

The dose–response relationship of fruit and vegetable intake with all-cause mortality might be impossible to estimate in the present meta-analysis due to inconsistent assessment. Some studies used servings per day[17,19,20,21,24] or quartiles with gram

per day[10], and others indicated a rough assessment criteria[16,18,23]. Furthermore, some studies assessed the intake with quartiles[10,17,24] and some with tertiles[21,26]. Most of the included studies indicated the HR of intake with highest *v.* lowest, but one study reported the HR with the highest quartile as the reference[19]. Although these factors constrained the ability to find a dose–response relationship and might slightly have influenced the summary HR investigated in this meta-analysis, sensitivity analyses were carried out. Most of them confirmed the robustness of the findings. Only the sensitivity analysis excluding one study[17] investigating the relationship between fruit intake and all-cause mortality yielded different results, which showed that the excluded one[17] might be poorly representative. However, no heterogeneity was detected on the summary HR for the association of fruit intake with all-cause mortality, which indicated that there is no difference among the included studies. Thus, this study[17] was included for the meta-analysis.

The findings of this meta-analysis reported a non-significant association between fruit and vegetable intake and breast cancer prognosis, probably because the consumption of fruits and vegetables may not be a strong dietary determinant of breast cancer mortality but has an indirect effect on breast cancer prognosis[41,42]. Many related articles regarding the association of fruit and vegetable intake with breast cancer prognosis mainly focus on the association between fruit and vegetable intake and weight change among breast cancer patients[43–47]. Thomson et al.[48] indicated minimal short-term changes in body weight in response to a high-vegetable, low-fat diet in breast cancer survivors. However, several studies have implicated obesity as being positively associated with breast cancer mortality[49–53]. Stokes et al.[54] indicated that an unhealthy body weight is an important modifiable risk factor for the recurrence of breast cancer. Hauner & Hauner[55] found that obesity is a potent risk factor for both cancer development and prognosis, increasing the risk for overall and breast cancer-specific mortality by approximately 30 %. On the whole, it is suggested that a healthy dietary pattern that increases fruit and vegetable intake and reduces dietary fat intake and is associated with modest weight loss may influence breast cancer prognosis. Thus, it is likely that the association of fruit and vegetable intake with breast cancer prognosis should be investigated with weight change among breast cancer patients.

Subgroup analyses stratified by menopausal states, number of patients and use of tamoxifen showed no different effects in each group. First, hormone-related factors such as late menopause or use of postmenopausal hormone therapy have been known to be associated with an increased risk of breast cancer[56]. Bernstein & Ross[57] found that endogenous sex hormones play a role in the development of breast cancer. Further, of the natural forms of oestrogen in women, oestrone (E1) is predominately found in postmenopausal women, whereas oestradiol (E2) is the major form in women of reproductive age[58]. In addition, the clinical implications of oestrogen receptor and progesterone receptor are different between premenopausal and postmenopausal patients with breast cancer[59]. Some constituents mainly present in fruits and vegetables, such as phyto-oestrogens, may either have similar effects as oestrogen (agonistic) or block oestrogen's effects (antagonistic)[60]. These compounds structurally resemble oestrogen and exert their effects primarily through binding to the oestrogen receptor[61]. However, not all included studies so far published had enough information on hormonal receptor breast cancer subtypes. Therefore, analysis stratified by hormonal receptor status cannot be conducted. The findings of the subgroup analyses stratified by menopausal status also did not show any statistical significance. More epidemiological studies are needed to further investigate the influence of sex hormone levels on which fruit and vegetable intake may impact in promoting breast cancer. Second, analysis stratified by the number of patients was conducted to determine potential sources of heterogeneity and to see whether this factor influences the results. No significant difference in the subgroup was found. Therefore, the number of patients did not seem to be relevant to explain variability between studies, which confirmed the robustness of the effects of total fruit or vegetable intake on all-cause mortality. Finally, tamoxifen is an important oestrogen receptor antagonist used successfully for the treatment and prevention of breast cancer[62]. One included study[18] suggested that baseline vegetable intake may be associated with a reduction in the risk of breast cancer recurrence, particularly for those using tamoxifen, whereas another study[10] found no significance in the presence or absence of tamoxifen. However, existing mechanistic evidence suggests a synergistic anti-carcinogenic action of combinational interventions with selected bioactive constituents in cruciferous vegetables and both tamoxifen and oestrogen receptor-α[63–65]. Thus, these findings encourage future investigations of the possible effects of fruits or vegetables on breast cancer prognosis.

In the subgroup analysis stratified by countries, the HR in the single study from China indicated a significant association between fruit intake and all-cause mortality. However, no significant association was indicated by the summary HR in the studies from the USA or in the study from Germany. Although breast cancer mortality rates have steadily increased in recent years, one study also found that east Asian countries have a lower rate, which may be associated with their low-fat diet and higher intake of fruits and vegetables when compared with their Western counterparts[3]. However, epidemiological studies evaluating the association of fruit and vegetable intake with breast cancer prognosis in Asia were limited in that only two included studies were from Asian countries[16,23] in this meta-analysis. Thus, more epidemiological studies examining regional differences in diet are expected to explore the association between fruit intake and all-cause mortality among breast cancer patients, especially in Asian countries.

No significant association was found between total vegetable or total fruit intake and all-cause mortality when stratified by timing of collection of dietary intake information. Some researchers suggested that antioxidant supplements provided during treatment could repair cellular oxidative damage to cancer cells caused by treatments such as radiation therapy and chemotherapy[66,67], which probably explain why fruit and vegetable intake following diagnosis may not be beneficial to breast cancer patients. However, Velentzis et al.[68] reported that patients were likely to make significant changes to their diet

and adopt healthier food choices after diagnosis of breast cancer, potentially decreasing their risk of breast cancer recurrence and reducing the risk of developing other co-morbidities including diabetes and heart disease, which probably account for all-cause mortality. Izano et al.[69] indicated that healthy dietary choices after breast cancer diagnosis did not change the risk of breast cancer death and recurrence but were associated with a reduced risk of non-breast cancer mortality. Studies included in the present meta-analysis also indicated that high post-diagnostic fruit and vegetable intake decreased the risk of mortality following breast cancer[24,25]. Moreover, it is possible that pre-diagnosis diets may have reflected taste or appetite changes resulting from breast cancer[25]. Some studies indicated that pre-diagnosis diet associated with risk of breast cancer may be related to progression following the diagnosis of breast cancer and among the determinants of tissue characteristics that influence prognosis[70,71]. Dal et al.[19] found that women eating <4 servings of fruits and vegetables/d before diagnosis showed higher risk for all-cause and breast cancer mortality compared with those who consumed 6 or more servings/d. Therefore, to pay more attention to post-diagnosis dietary changes and pre-morbid dietary habits in relation to breast cancer prognosis, more studies are needed to evaluate fruit and vegetable intake before and after diagnosis and its effects on breast cancer prognosis.

Although this meta-analysis provided no evidence that a higher fruit and vegetable intake decreased the risk of all-cause mortality among breast cancer patients, several studies indicated that dietary intakes of nutrients common in fruits and vegetables seem to be associated with a better prognosis among breast cancer patients. Fruits and vegetables are common sources of many candidate protective substances, including ascorbic acid and carotenoids[32]. Harris et al.[72] suggested that post-diagnosis dietary vitamin C intake was statistically significantly associated with a reduced risk of total mortality and breast cancer-specific mortality. Plasma total carotenoid concentration was reported to be inversely associated with breast cancer recurrence in a cohort of 1551 women who had been diagnosed with early-stage breast cancer[73]. Dietary fibre was found to be inversely associated with overall mortality among breast cancer patients[21]. Moreover, some phytochemicals such as monoterpenes, resveratrol and lignans present in fruits and vegetables are also protective[74]. Some in vitro studies and animal models have also shown that nutrients from fruits and vegetables may inhibit the metastasis of breast cancer cells. Kim et al.[75] found that a non-toxic, small-molecule constituent of edible cruciferous vegetables (benzyl isothiocyanate) inhibits mammary cancer development in mouse mammary tumour virus-neu transgenic mice by causing epithelial tumour cell apoptosis. Koh et al.[76] reported the significant inhibitory effect of lycopene on the invasive and migratory phenotypes of two highly aggressive breast cancer cell lines. Xu et al.[77] evaluated the effects of cyanidin-3-glucoside (C3G), an anthocyanin present in many fruits and vegetables, on ethanol-induced breast cancer cell migration/invasion and found that C3G blocks ethanol-induced activation of the ErbB2/cSrc/FAK pathway, which is necessary for cell migration and invasion.

There are some potential limitations to this meta-analysis. First, only twelve articles[10,16–26] with inconsistency in the types of fruit and vegetable intake and the prognostic indicators were included. Thus, the number of included articles might be too small to yield reliable summary results of breast cancer-specific mortality or breast cancer recurrence. Second, this meta-analysis did not estimate the dose–response relationship of fruit and vegetable intake with breast cancer prognosis and subgroup analysis stratified by other factors, such as pre- and post-diagnosis diet, because of lack of data. Finally, two funnel plots for the subgroup analyses stratified by menopausal state showed some asymmetry, indicating the risk of publication bias. However, the present meta-analysis also has several strengths. As all the included studies were prospective cohorts, we have effectively avoided recall and selection bias. Our clear delineation of the research questions and selection criteria, the comprehensive search strategy used and the objective assessment of the quality of the studies may have increased the validity of the findings. Moreover, with one exception, all the studies were high-quality cohorts. All but one of the sensitivity analyses yielded similar results, thus suggesting the stability of the findings. Most funnel plots were symmetrical, indicating that the results were unlikely to be due to publication bias.

In conclusion, no significant associations were found between fruit and vegetable intake (fruits and vegetables combined, total vegetable intake, cruciferous vegetable intake and fruit intake) and breast cancer prognosis (all-cause mortality, breast cancer-specific mortality and breast cancer recurrence). More studies are needed to determine whether the consumption of fruits and vegetables plays an important role in improving breast cancer prognosis. Additional studies on weight change, regional differences in diet, pre-diagnosis diet and dietary changes made after diagnosis are needed to confirm the effects of fruit and vegetable intake on breast cancer prognosis.

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