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SPECIAL REPORT

Postdiagnosis dietary factors, supplement use and breast cancer prognosis: Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis

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Abstract

Little is known about how diet might influence breast cancer prognosis. The current systematic reviews and meta-analyses summarise the evidence on postdiagnosis dietary factors and breast cancer outcomes from randomised controlled trials and longitudinal observational studies. PubMed and Embase were searched through 31st October 2021. Random-effects linear dose-response meta-analysis was conducted when at least three studies with sufficient information were available. The quality of the evidence was evaluated by an independent Expert Panel. We identified 108 publications. No meta-analysis was conducted for dietary patterns, vegetables, wholegrains, fish, meat, and supplements due to few studies, often with insufficient data. Meta-analysis was only possible for all-cause mortality with dairy, isoflavone, carbohydrate, dietary fibre, alcohol intake and serum 25-hydroxyvitamin D (25(OH)D), and for breast cancer-specific mortality with fruit, dairy, carbohydrate, protein, dietary fat, fibre, alcohol intake and serum 25(OH)D. The results, with few exceptions, were generally null. There was limited-suggestive evidence that predefined dietary patterns may reduce the risk of all-cause and other causes of death; that isoflavone intake reduces the risk of all-cause mortality (relative risk (RR) per 2 mg/day: 0.96, 95% confidence interval (CI): 0.92-1.02), breast cancer-specific mortality (RR for high

Abbreviations: 25(OH)D, 25-hydroxy-vitamin D; ABCPP, After Breast Cancer Pooling Project; AICR, American Institute for Cancer Research; BMI, body mass index; CIs, confidence intervals; CUP Global, Global Cancer Update Programme; CUP, Continuous Update Project; CVD, cardiovascular diseases; HR, hazard ratio; RCT, randomised control trials; RR, relative risk; WCRF, World Cancer Research Fund; WHEL, Women's Healthy Eating and Living; WHI, Women's Health Initiative; WINS, Women's Intervention Nutrition.

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vs low: 0.83, 95% CI: 0.64-1.07), and recurrence (RR for high vs low: 0.75, 95% CI: 0.61-0.92); that dietary fibre intake decreases all-cause mortality (RR per 10 g/day: 0.87, 95% CI: 0.80-0.94); and that serum 25(OH)D is inversely associated with all-cause and breast cancer-specific mortality (RR per 10 nmol/L: 0.93, 95% CI: 0.89-0.97 and 0.94, 95% CI: 0.90-0.99, respectively). The remaining associations were graded as limited-no conclusion.

KEYWORDS
breast cancer survival, diet, evidence grading, food, systematic review

What's new?

To date, there are no evidence-based nutritional guidelines specifically developed for breast cancer survivors due to a lack of knowledge. In this systematic review and meta-analysis, the Global Cancer Update Programme evaluated the associations between postdiagnosis dietary patterns, dietary intakes, and supplements use and breast cancer outcomes among breast cancer survivors. The independent expert panel concluded that the evidence about potential associations remains limited (likelihood of causality: suggestive or no conclusion). Stronger evidence, contributed by intervention trials and/or well-conducted observational studies, is needed before specific dietary recommendations for improving breast cancer prognosis can be made.

1 | INTRODUCTION

Breast cancer was the most commonly diagnosed cancer (2.3 million incident cases, 24.5% of all cancers) and the leading cause of cancer death (684 996 deaths, 15.5% of all cancer deaths) in women worldwide in 2020.[1] Despite its high public health burden, the 5-year relative survival in economically developed countries is approximately 91.2%, in part due to tailored adjuvant treatments, improved surgery and the detection of cases at an earlier stage and detection of more cases.[2-4] With the long survival duration, breast cancer survivors are at risk of disease recurrence, second primary cancer, and other comorbidities, such as cardiovascular diseases (CVD) and diabetes.[5-7]

Despite the breadth of knowledge on the relationship between modifiable lifestyle factors and breast cancer incidence,[8-10] little is known about how these factors might influence breast cancer prognosis. A growing body of evidence suggests that being overweight or obese or physically inactive are associated with a lower overall survival after breast cancer diagnosis,[11,12] but there remains limited data on the role of diet on breast cancer survival. The Third Expert Report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR),[4] which included studies up to 30th June, 2012, suggested that having a healthy body weight, being physically active and following a diet rich in dietary fibre and soy after diagnosis was linked to better overall survival. However, the evidence was graded as limited-suggestive because of the limitations in the design, the few randomised controlled trials (RCTs) available, and the lack of mechanistic evidence. Recommendations specifically for women living with and beyond breast cancer were not developed.[4]

In the previous WCRF/AICR systematic review,[4] breast cancer recurrence was not evaluated as an outcome and the analyses were performed separately by exposure measurement timeframe relative to cancer diagnosis. Since its publication, the number of new studies on

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dietary factors has almost doubled. Importantly, several of these have focused on postdiagnosis exposures such as wholegrains, dairy products, meat, and serum 25-hydroxyvitamin D (25(OH)D) which could not be reviewed previously due to the lack of publications.

This work aimed to systematically review and meta-analyse the accumulated evidence on postdiagnosis diet (foods, food groups, dietary patterns, food components, nutrients, and dietary supplements) and breast cancer outcomes (survival, disease recurrence and secondary primary cancers), and update the findings and the Expert Panel's conclusions of the previously published systematic review and meta-analysis by WCRF/AICR.[4]

This article presents the evidence on dietary factors and supplement use and breast cancer outcomes, whereas evidence on body fatness, physical activity, and the overall summary is presented in the accompanied papers.[13-15]

2 | METHODS

The present systematic review was conducted as part of the ongoing Global Cancer Update Programme (CUP Global), formally known as WCRF/AICR Continuous Update Project (CUP).[16] The protocol is available online.[17] Details on the complete search strategy, data extraction, outcome definition, statistical analysis, and the PRISMA checklist are available in Supplementary Material (Tables S1 and S2 and Appendix S2).

2.1 | Search strategy, selection criteria and data extraction

PubMed and Embase were searched from inception to 31 October 2021. The reference lists of relevant articles were hand searched.

Inclusion criteria were: (1) RCTs with study period of at least 6 months; longitudinal observational studies, or pooled analyses thereof; (2) With at least 100 participants; (3) Investigated postdiagnosis dietary factors (dietary patterns, foods, beverages, macro- and micronutrients intakes and supplements) and breast cancer outcomes (all-cause mortality, breast cancer-specific mortality, breast cancer recurrence [as defined in studies], any second primary cancers, CVD mortality; Table S2).

Among publications with overlapping samples, the publication with the greater number of outcome events was selected.

Relevant data, including participants' characteristics and results of analyses, were extracted in the CUP Global database. Study selection and data extraction was checked by a second reviewer. Any disagreements were resolved by consensus. The quality of individual studies was not graded using a specific tool. Instead, relevant study characteristics that could be used to explore potential sources of bias were included into the CUP Global database. For all the included studies, information on potential for selection bias, information bias of exposure and outcome assessment, and residual confounding by cancer stage and treatment was retrieved after identifying the most likely influential sources of bias in cancer survival studies[18,19] (Appendix S2 and Table S3). Details on how the study authors addressed the potential biases were also included. In the Expert Panel meeting, whether the studies had serious quality issues were discussed when judging the evidence for each exposure-outcome association.

2.2 | Statistical methods for meta-analysis

Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using the random-effects model by DerSimonian-Laird.[20] When at least three (additional) studies were identified in the updated search, a linear dose-response meta-analysis[21,22] was conducted (or updated if reviewed previously in WCRF/AICR Third Expert Report with evidence up to 30 June, 2012[4]) if the studies reported sufficient information for analysis. For evidence that was judged as limited-suggestive or above in the previous systematic review or was related to the WCRF/AICR Cancer Prevention Recommendations, the accumulated evidence was summarised in an updated meta-analysis regardless of the number of studies identified during the CUP Global update.

Multivariable adjusted estimates were used in the meta-analyses. Between-study heterogeneity was assessed by the Cochran's Q test and I^2 statistic.[23]

The Egger's test and visual inspection of funnel plots were used to assess presence of small study effects when there were 10 or more studies in analyses.[24]

Nonlinear dose-response meta-analysis was conducted using restricted cubic spline regression with three knots at 10%, 50%, and 90% percentiles of the exposure distribution, which were combined using multivariate meta-analysis when there were more than five studies with at least three exposure categories.[25,26] Likelihood ratio test was used to compare between the linear and nonlinear models.[27]

When linear and nonlinear dose-response meta-analyses were not possible, we performed a descriptive synthesis, where the findings of the individual studies were systematically gathered, tabulated, and descriptively summarised by type of dietary exposure and outcome analysed. A forest plot for the RR comparing extreme exposure categories was presented to aid results interpretation.

Statistical analyses were conducted using Stata 13.1 (StataCorp, College Station, TX).

2.3 | Evidence grading criteria

An independent WCRF/AICR Expert Panel (ELG, MJG, AAJ, EK, VL, SKC, AMT) graded the quality of the evidence for all dietary exposures as strong (subgrades evaluating likelihood of causality: convincing or probable or substantial effect on risk unlikely) or limited (subgrades evaluating likelihood of causality: limited-suggestive or limited-no conclusion) according to the predefined criteria listed in Table S4, which cover the quantity, consistency, magnitude and precision of the summary

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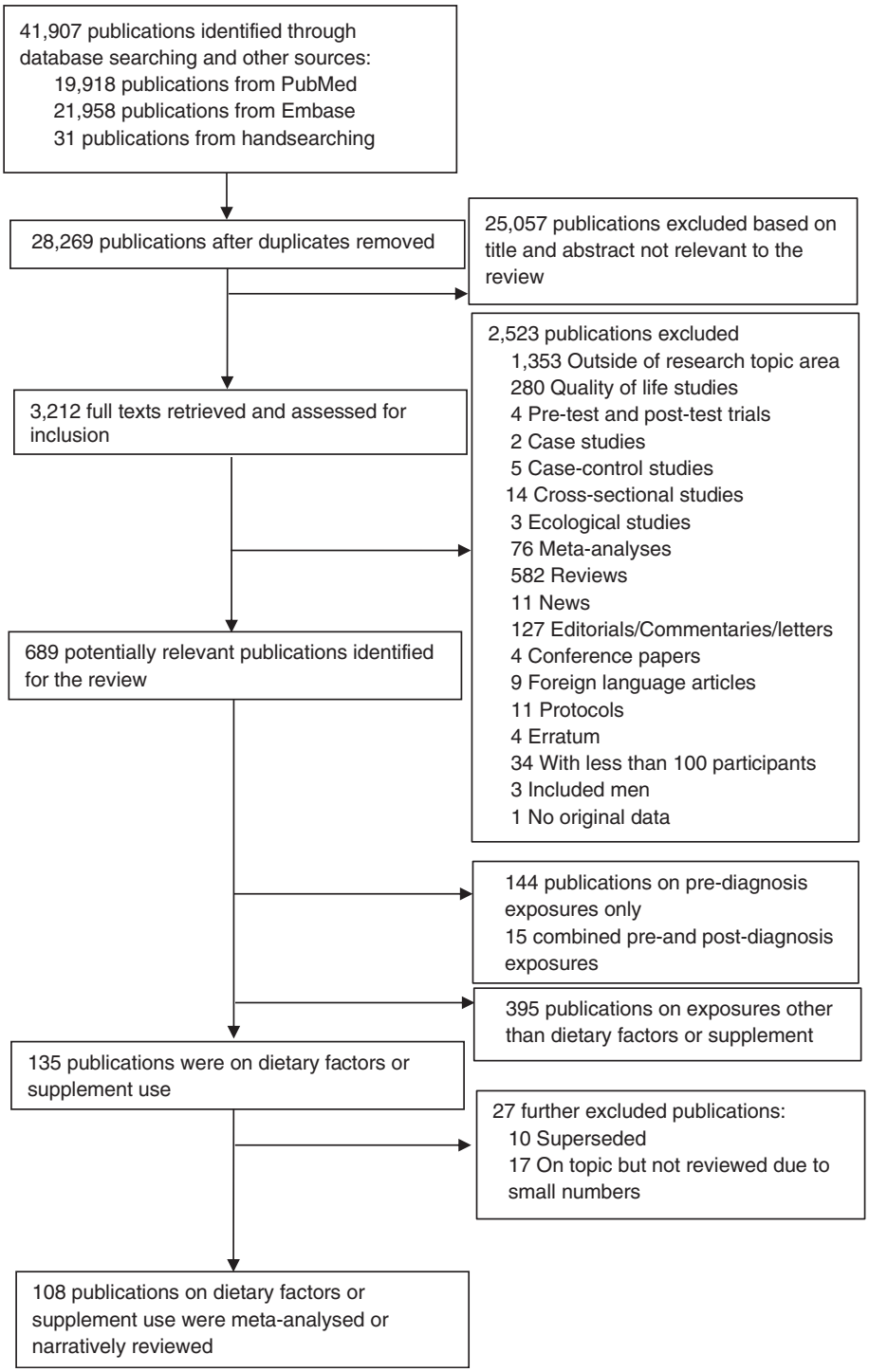

FIGURE 1 Flowchart of study selection process

estimates, existence of a dose-response, risk of bias, study design and limitations, generalisability and mechanistic plausibility of the results.

3 | RESULTS

3.1 | Screening and study characteristics

Figure 1 shows the study selection process. One hundred and eight publications (four from RCTs, 104 from observational studies) comprising more than 14 900 all-cause deaths, 5900 breast cancer deaths and 6000 breast cancer recurrence events among more than 151 000 breast cancer survivors were included.

Studies reporting results on dietary patterns, fruits and vegetables, wholegrains, meat, fish and eggs, milk and dairy products, soy foods (including isoflavones and soy protein), fibre, alcohol, dietary supplements and 25(OH)D met the review criteria, among which meta-analysis was only possible for intakes of fruits, dairy products, isoflavones, carbohydrates, proteins, fat, dietary fibre, alcohol, and serum 25(OH)D. Characteristics of the reviewed studies are presented in Tables S5-S23.

The summary findings and the Expert Panel judgement are shown in Table 1 and explained below for each dietary factor.

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TABLE 1 Evidence grades and main findings from the meta-analyses and narrative reviews of postdiagnosis dietary patterns, food intake, and supplements use

	Diet and survival in women with breast cancer				
		Decreases risk			
2020		Exposure	Outcome	Summary of findings RR (95% CI)	Conclusions
Strong evidence	Convincing	–	–	–	–
	Probable	–	–	–	–
Limited evidence	Limited suggestive	Predefined healthy dietary and lifestyle patterns	All-cause mortality	Sixteen publications (12 studies; 18 different scores), no meta-analysis RR ranged from 0.32 to 1.03, and in eight out of 17 patterns showing inverse associations, the 95% CI did not include 1	The evidence is substantial, and generally consistent in the direction of an inverse association
			Other causes of death	Seven publications (4 studies, 10 patterns), no meta-analysis RR ranged from 0.44 to 0.95, and in 7 out of 10 patterns the 95% CIs did not include 1	
		Soy foods	All-cause mortality	RR = 0.96 (0.92-1.02) I^2 = 66%, 5 studies	The evidence is sparse, but it is suggesting that high isoflavone intake after diagnosis may reduce the risk of all-cause mortality, breast cancer mortality and recurrence
			Breast cancer-specific mortality	Pooled analysis (3 prospective studies), no meta-analysis RR = 0.83 (0.64-1.07) Test for heterogeneity not statistically significant	
			Breast cancer recurrence	Pooled analysis (3 prospective studies), no meta-analysis RR = 0.75 (0.61-0.92) Test for heterogeneity not statistically significant	
		Dietary fibre	All-cause mortality	RR per 10 g/day = 0.87 (0.80-0.94), I^2 = 0%, 4 studies	The evidence is sparse but is suggestive of inverse association
		Vitamin D status (blood levels)	All-cause mortality	RR per 10 nmol/L = 0.93 (0.89-0.97) I^2 = 62.8%, 6 studies	The evidence is sparse but is suggestive of inverse association
			Breast cancer-specific mortality	RR per 10 nmol/L = 0.94 (0.90-0.99) I^2 = 24%, 5 studies	
	Limited—no conclusion	Low-fat diet, predefined healthy dietary and lifestyle patterns (for breast cancer-specific mortality and cardiovascular disease death), data-driven dietary patterns, high-fat dietary pattern, alcoholic drinks, fruit and vegetables, cruciferous vegetables, dietary fibre (for breast cancer-specific mortality and recurrence), wholegrains, red and processes meats, fish, eggs, milk and dairy products, nutrients (fats, carbohydrate, animal protein, plant protein), supplements (multivitamins, antioxidants, vitamins, carotenoids), vitamin D (blood levels on recurrence)			The evidence is sparse and inconsistent

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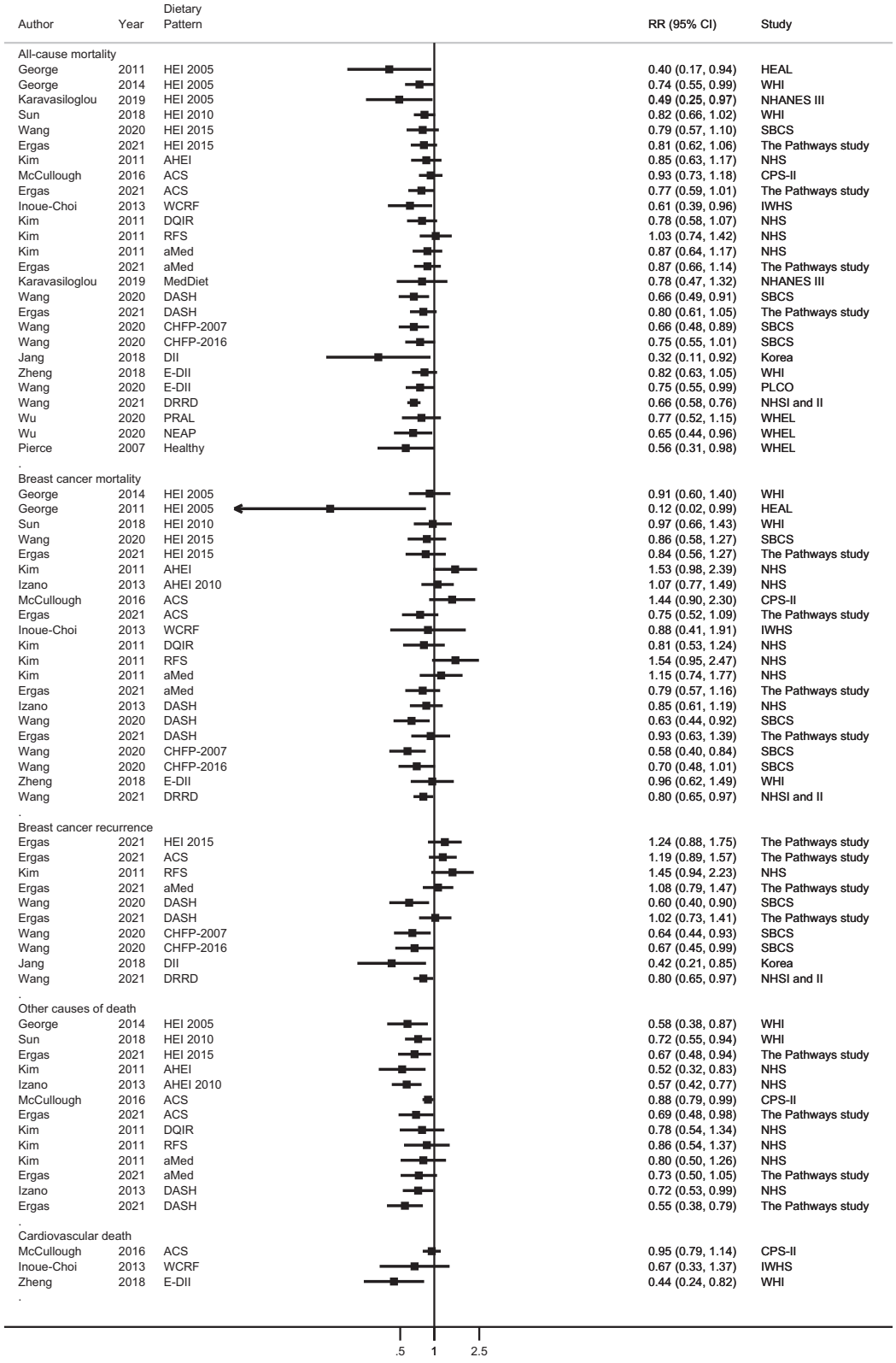

FIGURE 2 Legend on next page.

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3.2 | Postdiagnosis dietary and lifestyle patterns

3.2.1 | Randomised controlled trials

Two RCTs (six publications)[28-33] investigated low-fat dietary pattern (15%-20% of total energy). Two publications[32,33] were superseded by other publications from the same studies.[28,31] The results were inconsistent (Table S5). The low-fat diet intervention did not reduce the all-cause mortality risk in the Women's Intervention Nutrition Study (WINS) or the Women's Healthy Eating and Living (WHEL) study[31] (trials of breast cancer survivors). Breast cancer recurrence risk was reduced by 24% (RR: 0.76, 95% CI: 0.60-0.98) in WINS,[28] but not in WHEL.[31]

3.2.2 | Observational studies

Tables S6 and S7 show the characteristics and main results of the studies identified investigating data driven or predefined dietary and lifestyle patterns.[6,34-56]

Three studies[51-53] investigated the Prudent (healthy) and Western (unhealthy) data-driven dietary patterns. The Prudent diet in the Life After Cancer Epidemiology study, and the Western diet in the Nurses' Health Study were negatively and positively associated, respectively, with all-cause mortality, but not with breast cancer mortality[51,52] or recurrence.[52] Neither of these dietary patterns were associated with breast cancer prognosis in the Hong Kong NTEC-KWC Breast Cancer Survival Study.[53]

Twelve studies (16 publications[6,34-48]) investigated high vs low categories of 18 predefined healthy dietary and lifestyle patterns (Figure 2). Results were generally consistent in the direction of an inverse association with all-cause mortality (only the Recommended Foods Score showed a RR > 1) and in eight (Healthy Eating Index-2005,[35,37,47] WCRF/AICR Cancer Prevention Recommendations,[41] Dietary Inflammatory Index,[39,44] low-fat, high-vegetables, fruit, and fibre diet,[42] Chinese Food Pagoda diet-2007,[43] Dietary Approaches to Stop Hypertension,[43] diabetes risk reduction diet[45] and endogenous acid production diet[48]) out of 17 patterns showing inverse associations, the 95% CIs did not include 1. There was not a clear pattern for breast cancer-specific mortality (RRs ranged from 0.12 to 1.54) and breast cancer recurrence (RRs ranged from 0.42 to 1.45). There were some inverse associations for CVD mortality (three patterns[6,34,41]; RRs: 0.44 to 0.95, in one[6] of which the 95% CI did not include 1) and other causes of death (10 patterns[34,36,37,40]; RRs: 0.44 to 0.95, in seven of which the 95% CIs did not include 1). Only two studies[38,45] assessed changes in pre- to postdiagnosis dietary patterns. In the Women's Health Initiative, a lower risk of mortality from other causes with increased diet quality, but not for all-cause or breast cancer-specific mortality was observed.[38] In the Nurses' Health Study,[45] participants who improved their adherence to the diabetes risk reduction diet showed a lower risk of all-cause and breast-cancer specific mortality compared to those with consistently low adherence. A lower risk of all-cause mortality was also reported among those who maintained a higher adherence after diagnosis.

Two studies[54,55] investigated a high-fat diet in relation to all-cause[55] and breast cancer-specific mortality,[54] showing a higher risk.

3.3 | Postdiagnosis fruit, and vegetable intakes

Nine observational studies[31,34,57-63] were identified (Table S8). One publication[61] was superseded by another from the same study.[63] Linear dose-response meta-analysis was only possible for fruit intake and breast cancer-specific mortality. No association was observed per each 100 g/day increase (RR: 1.03; 95% CI: 0.93-1.13, $I^2 = 0\%$, $P_{heterogeneity} = .68$; three studies[60,62,63]; Figure 4A). Studies investigating fruit intake and breast cancer-specific mortality[60,63,64] and cardiovascular death[63] did not show an association. There were inconclusive results for all the other exposures (ie, fruit and vegetables combined, vegetables and cruciferous vegetables) and breast cancer outcomes, with the RRs ranging from 0.69 to 1.44 (Figure S1).

FIGURE 2 Forest plot of prognostic outcomes for the highest compared to the lowest level of predefined dietary or lifestyle patterns after breast cancer diagnosis. Different patterns are represented in the same forest plot to facilitate the visualisation of the data. Also, the same study may be represented more than once if different dietary patterns were investigated. Each square represents the relative risk (RR) estimate for the highest compared to the lowest level of the predefined dietary or lifestyle pattern and the horizontal line across each square represents the 95% confidence interval (CI) of the RR estimate. The figure should not be interpreted as a quantitative summary. The Pathways study which reported the point estimate per each 10-point increase of plant-based dietary index (total, healthy and unhealthy; Anyene 2021)[49] was not included in the figure. Results from Wang 2020[44] and Wu 2020[48] for breast cancer-specific mortality, and from Wu 2020[56] for recurrence were not included because competing risk regression models were employed. Inoue-Choi 2013[41] investigated a score of diet plus lifestyle factors; Pierce 2007[42] investigated the combination of fruit and vegetable intake and physical activity. For comparative purposes, data from Jang 2018[39] and Wang 2020[44] (proinflammatory diet), and Wu 2020[48] (dietary acid load) were recalculated to have higher scores as the reference category. ACS, American Cancer Society; AHEI, Alternate Healthy Eating Index; aMed, alternate Mediterranean Diet Score; CHFP, Chinese Food Pagoda; CPS-II, Cancer Prevention Study II Nutrition Cohort; DASH, Dietary Approaches to Stop Hypertension; DII, Dietary Inflammatory Index; DRRD, Diabetes risk reduction diet; HEAL, Health, Eating, Activity, and Lifestyle Study; E-DII, energy-adjusted Dietary Inflammatory Index; HEI, Healthy Eating Index; IWHS, Iowa Women's Health Study; NEAP, Net endogenous acid production; NHANES; National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; MedDiet; Mediterranean Diet; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; PRAL, Potential renal acid load; RFS, Recommended Food Score; SBCS, Shanghai Breast Cancer Study; WCRF, World Cancer Research Fund; WHEL, Women's Healthy Eating and Living Study; WHI, Women's Health Initiative

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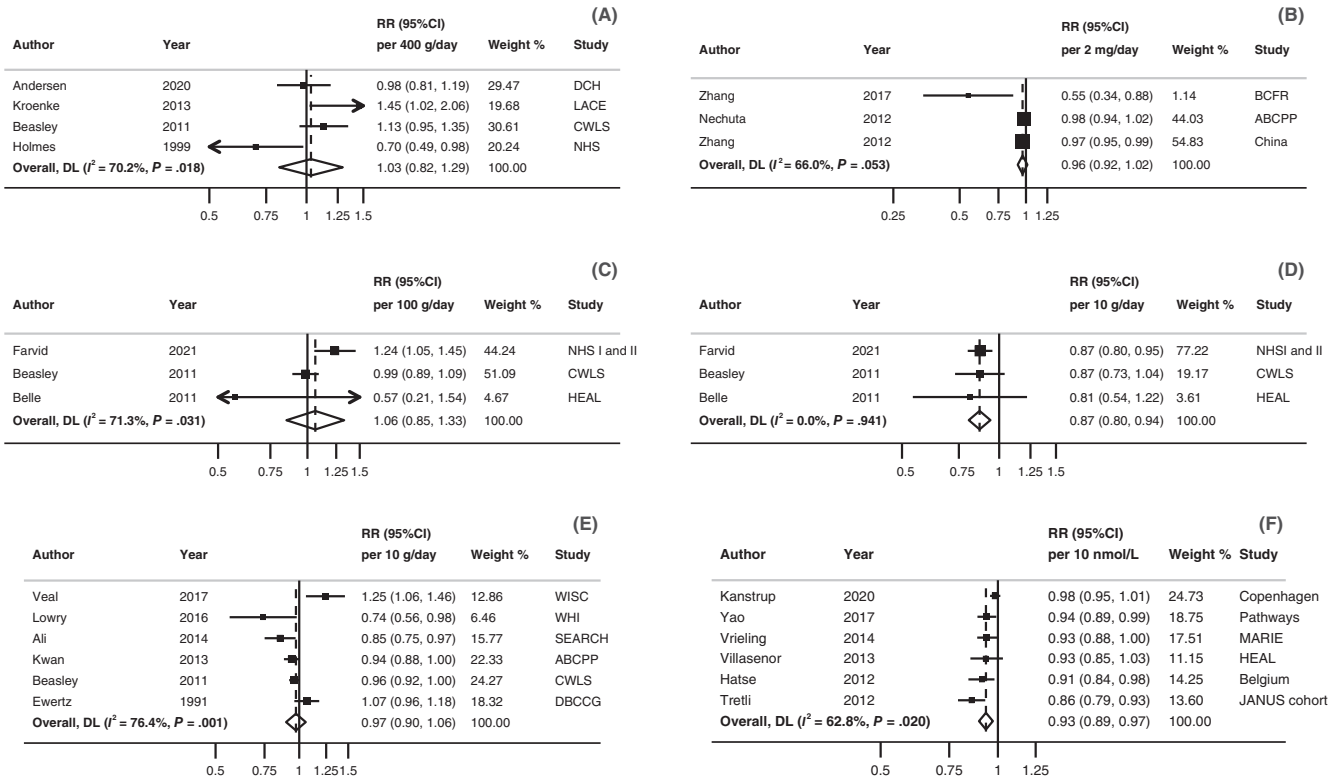

FIGURE 3 Linear dose-response meta-analyses on (A) dairy product intake, (B) isoflavone intake, (C) carbohydrate intake, (D) fibre intake, (E) alcohol intake and (F) serum 25(OH)D and all-cause mortality. Forest plots show the linear dose-response results from the inverse variance DerSimonian-Laird random-effects models. Diamonds represent the summary relative risk (RR) estimates. Each square represents the RR estimate of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the RR estimate. The increment units were (A) 400g/day, (B) 2 mg/day, (C) 100g/day, (D) 10 g/day, (E) 10 g/day, and (F) 10 nmol/L. ABCPP, After Breast Cancer Pooling Project; BCFR, Breast Cancer Family Registry; CI, confidence interval; CWLS, Collaborative Women's Longevity Study; DBCCG, Danish Breast Cancer Cooperative Group; DCH, Danish Diet, Cancer, and Health Study; HEAL, Health, Eating, Activity, and Lifestyle Study; MARIE, Mammary carcinoma risk factor Investigation; NHS, Nurses' Health Study; RR, Relative risk; SEARCH, Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study; WHI, Women's Health Initiative; WISC, Wisconsin In Situ Cohort Study. [Correction added after first online publication on 29 November, 2022: In Figure 3 legend, there were repeated text and have been removed.]

Only one study investigated individual fruit and vegetable intake and breast cancer outcomes, showing mostly null associations.[63]

3.4 | Postdiagnosis wholegrains

Three studies[34,60,65] were identified (Table S9 and Figure S2). The observed associations were generally null. There was not clear pattern for all-cause (RRs ranged from 0.79 to 1.09) and breast cancer-specific mortality (RRs ranged from 0.83 to 1.24). No association was observed in the only study analysing recurrence (RR per 200 g/day increase: 0.98, 95% CI: 0.83-1.13).[65]

3.5 | Postdiagnosis meat, fish and eggs intake

Six observational studies (seven publications)[34,58,60-62,66,67] were identified (Tables S10 and S11 and Figures S3 and S4). One publication[61] was superseded by a new publication of the same study.[66] Only one[34] out of the three[34,60,66] studies investigating different types of meats and all-cause mortality reported a 36% (HR for high vs low: 0.64, 95% CI: 0.49-0.84) lower risk with lower red and processed meat intake. No associations were observed for breast cancer mortality[34,58,60,62,66,67] or recurrence.[58,66]

Pre- to postdiagnosis changes in different types of meat and fish intake and breast cancer outcomes were assessed in one study, showing mostly null associations.[67]

3.6 | Postdiagnosis milk and dairy product intake

Four observational studies (five publications)[60,61,65,66,68] were included (Table S12). One publication[61] was superseded by another from the same study[66] only for the high vs low forest plots (Figures S5-S7). The linear dose-response meta-analysis showed no association between total dairy product intake and all-cause mortality (RR per 400 g/day: 1.03, 95% CI: 0.82-1.29; I^2 = 70%, $P_{heterogeneity}$ = .02; Four publications[60,61,65,68]; Figure 3A). A pattern

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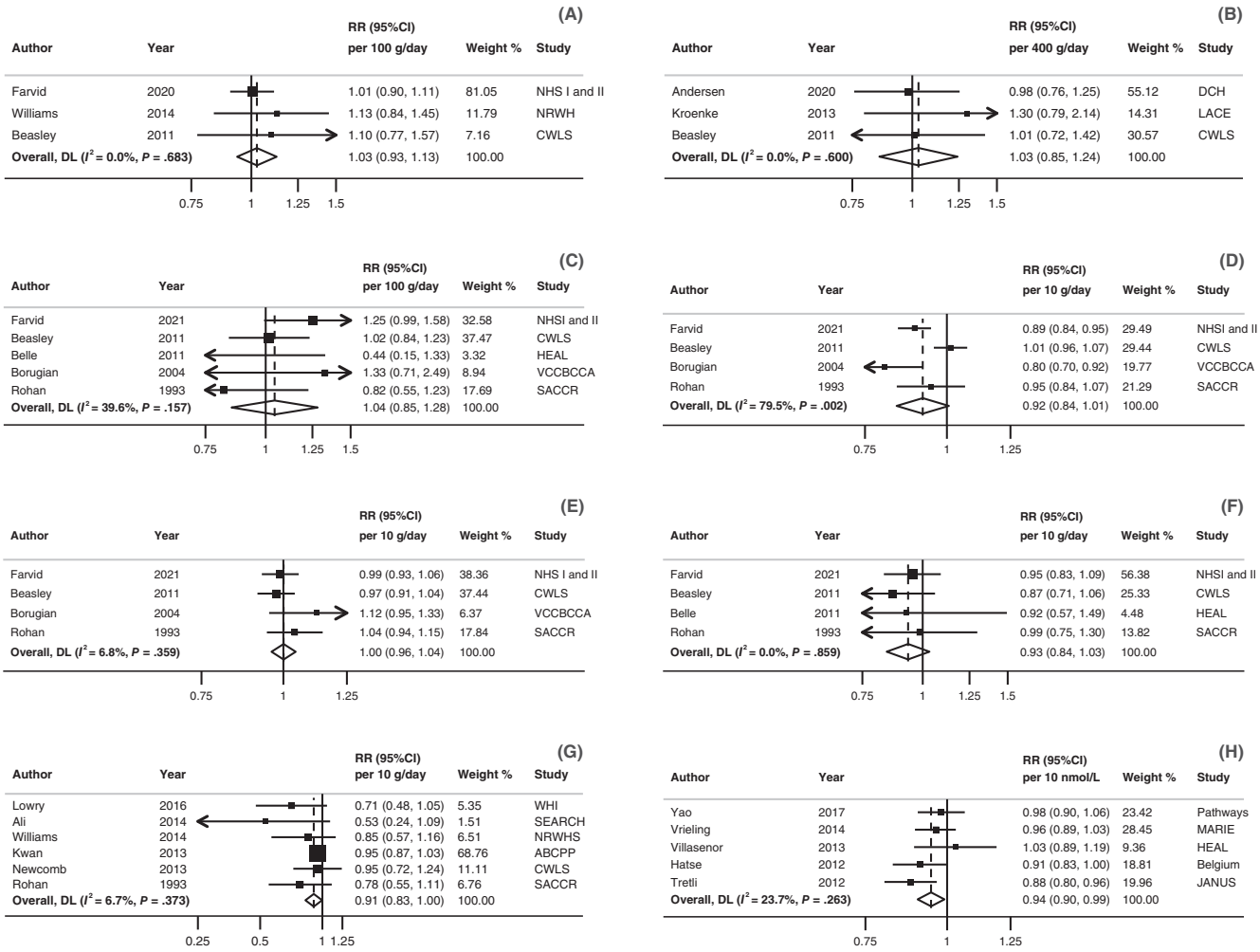

FIGURE 4 Linear dose-response meta-analyses on (A) fruit intake, (B) dairy product intake, (C) carbohydrate intake, (D) protein intake, (E) dietary fat intake, (F) fibre intake, (G) alcohol intake, and (H) serum 25(OH)D and breast cancer-specific mortality. Forest plots show the linear dose-response results from the inverse variance DerSimonian-Laird random-effects models. Diamonds represent the summary relative risk (RR) estimates. Each square represents the RR estimate of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the RR estimate. The increment units were (A) 100 g/day, (B) 400 g/day, (C) 100 g/day, (D) 10 g/day, (E) 10 g/day, (F) 10 g/day, (G) 10 g/day, and (H) 10 nmol/L. ABCPP, After Breast Cancer Pooling Project; BCFR, Breast Cancer Family Registry; CI, confidence interval; CWLS, Collaborative Women's Longevity Study; DCH, Danish Diet, Cancer, and Health Study; HEAL, Health, Eating, Activity, and Lifestyle Study; MARIE, Mammary carcinoma risk factor Investigation; NHS, Nurses' Health Study; RR, Relative risk; NRWHS, National Runner's and Walker's Health study; SACCR, South Australian Central Cancer Registry; SEARCH, Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study; WHI, Women's Health Initiative. [Correction added after first online publication on 29 November, 2022: In Figure 4 legend, there were repeated text and have been removed.]

of positive associations was observed across the two studies on high-fat dairy[66,68] (RRs: 1.12-1.64, in one[68] of which the 95% CIs did not include 1) and all-cause mortality. No associations were observed on low-fat dairy and all-cause mortality.[66,68] Dairy consumption was not associated with breast cancer-specific mortality (RR per 400 g/day: 1.03, 95% CI: 0.85-1.24; $I^2 = 0\%$, $P_{heterogeneity} = .6$; Three publications[60,65,68]; Figure 4B). For high-fat, risk estimates from both studies[66,68] suggested the potential for a higher risk (RRs >1.0), in one[68] of which the 95% CIs did not include the null value (RR for high vs low intake: 1.49, 95% CI: 1.00-2.24).

Null associations were reported for breast cancer recurrence.[65,66,68]

3.7 | Postdiagnosis soy foods (isoflavones and soy protein) intake

Five observational studies (six publications)[69-74] on isoflavones and proteins from soy foods were reviewed (Table S13). Three publications[70-72] were superseded by a pooled analysis of three prospective studies.[69]

Five studies (three publications)[69,73,74] were included in the dose-response meta-analysis showing that a 2 mg/day higher isoflavone intake yielded a 4% lower all-cause mortality risk but with CIs crossing the null value (RR: 0.96, 95% CI: 0.92-1.02; $I^2 = 66\%$, $P_{heterogeneity} = .05$; Figure 3B; isoflavone was assessed on average

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69 days to 5 years after diagnosis in the studies). The results from the pooled analysis showed no association between isoflavone intake and breast cancer-specific mortality (HR for high vs low: 0.83, 95% CI: 0.64-1.07), whereas a lower cancer recurrence risk was associated with highest intakes (HR for high vs low: 0.75, 95% CI: 0.61-0.92).[69]

Soy protein intake was inversely associated with all-cause mortality in two[72,74] studies, and a reduced risk was also observed for breast cancer-specific mortality and recurrence combined[72] (Table S13).

3.8 | Postdiagnosis carbohydrate, protein and fat intake

Eight observational studies[60,61,64,75-79] on carbohydrates, five on protein[60,64,66,76,78] and 10 on lipids[42,60,61,64,76,78,80-83] intake were reviewed (Tables S14-S16 and Figures S8-S14). Linear dose-response meta-analysis showed no association per each 100 g/day increase in carbohydrate intake and all-cause mortality (RR: 1.06, 95% CI: 0.85-1.33; $I^2 = 71\%$, $P_{heterogeneity} = .03$; three studies[60,64,75]; Figure 3C). We did not find evidence of linear (RR per 100 g/day: 1.04, 95% CI: 0.85-1.28, $I^2 = 40\%$, $P_{heterogeneity} = .16$; five studies[60,64,75,76,78]; Figure 4C) neither nonlinear association ($P_{nonlinearity} = .33$; Figure S9) with breast-cancer specific mortality. One[77] out of the two studies[75,77] on total carbohydrate and breast cancer recurrence reported a higher risk (RR for stable/increased vs decreased: 2.00, 95% CI: 1.30-5.00). One study analysed carbohydrates from different food sources and all-cause and breast cancer-specific mortality showing mostly null associations.[79]

For total protein, a meta-analysis was only possible for breast cancer-specific mortality, showing limited evidence for an association (RR per 10 g/day: 0.92, 95% CI: 0.84-1.01; $I^2 = 79\%$, $P_{heterogeneity} = .002$; four studies[60,64,76,78]; Figure 4D). Higher animal protein intake was associated with lower risk of breast cancer recurrence in one study (RR for high vs low: 0.78, 95% CI: 0.63-0.95; Figure S12).[66]

The results are limited and inconsistent for total and specific types of fats (Table S15 and Figures S13 and S14). Overall, studies reported no association between dietary fat intake, and all-cause mortality. Only one out[82] of the three[60,64,81] studies on total fat, and one[60] out of the two[60,61] studies on saturated fat and trans fatty acids reported a higher all-cause mortality risk. Marine fatty acids (eicosapentaenoic acid and docosahexaenoic acid combined or alone) were associated with lower risk of all-cause mortality in two studies.[61,80] For breast cancer-specific mortality there was no association per each 10 g/day increase in total fat (RR: 1.00, 95% CI: 0.96-1.04; $I^2 = 7\%$, $P_{heterogeneity} = .36$; five studies[60,64,76,78]; Figure 4E). An increased risk was reported in one[78] out of the three[60,76,78] studies on saturated fat.

3.9 | Postdiagnosis dietary fibre intake

Six observational studies (eight publications)[42,60,61,64,75,76,78,84] on dietary fibre intake were reviewed (Table S17). One publication[61] was superseded by a new publication[64] from the same study. Three studies[60,64,75] could be included in the dose-response meta-analysis, where a lower all-cause mortality risk was observed for every 10 g/day increase in fibre (RR: 0.87, 95% CI: 0.80-0.94; $I^2 = 0\%$, $P_{heterogeneity} = .94$; Figure 3D). On average, fibre was assessed 2 years after diagnosis. No association was observed in the dose-response meta-analysis for fibre and breast cancer-specific mortality (RR: 0.93, 95% CI: 0.84-1.03; $I^2 = 0\%$, $P_{heterogeneity} = .86$; Figure 4F) or for the high vs low comparisons (Figures S15 and S16). Only one study investigated breast cancer recurrence, showing no association.[75]

3.10 | Postdiagnosis alcohol intake

Twenty-nine publications from 22 observational studies were reviewed[60-62,76,78,81,85-107] (Table S18 and Figures S17-S20). The meta-analyses showed little evidence for a linear dose-response association with all-cause mortality (RR per 10 g/day: 0.97, 95% CI: 0.90-1.06; $I^2 = 76\%$, $P_{heterogeneity} = .001$; Figure 3E; 8 studies[60,81,87,89,92,93]; alcohol was assessed >1 year to 5 years after diagnosis); the point estimate was inverse with CIs crossing the null value for breast cancer-specific mortality (RR per 10 g/day: 0.91, 95% CI: 0.83-1.00; $I^2 = 7\%$, $P_{heterogeneity} = .37$; Figure 4G; 8 studies[62,76,89,92-94]; alcohol was assessed on average 4.8 months to 5.8 years after diagnosis). We did not find evidence of nonlinearity for any of the two outcomes ($P_{nonlinearity} > .05$; Figures S21 and S22).

Alcohol intake after diagnosis was not associated with breast cancer recurrence in any of the three[86,91,93] studies that conducted high vs low analyses (RR ranged from 0.68 to 1.04; Figure S19). One[105] out of the three[103,105,107] studies on alcohol intake and second primary cancer showed an increased risk (RR for ≥7 vs 0 drinks/week: 1.90, 95% CI: 1.10-3.20; Figure S20).

In the only study investigating pre- to postdiagnosis changes in alcohol intake and all-cause and breast cancer-specific mortality, no associations were observed.[89]

3.11 | Postdiagnosis dietary supplement use

Fourteen publications[108-121] were reviewed, showing in general null associations of supplements use with breast cancer outcomes (Tables S19-S22).

No associations were observed in the two studies on beta-carotene or lycopene supplement use and breast cancer outcomes.[111,113] Frequent use of combination of carotenoid supplements was positively associated with all-cause and breast cancer-specific mortality but not recurrence.[111]

Evidence regarding other multivitamins and minerals on breast cancer outcomes was reviewed in three studies,[111,113,115] showing an increased risk of all-cause mortality with iron supplement use in one study (HR for user vs never user: 1.60, 95% CI: 1.11-2.31).[113]

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A significant inverse association was observed for antioxidant use and all-cause mortality in one study (HR for yes vs no: 0.84, 95% CI: 0.72-0.99).[112]

No association was observed with breast cancer outcomes in the only study investigating pre- and postdiagnosis combined use of multivitamin/mineral supplements and antioxidants.[121]

Limited studies have analysed the influence of dietary supplements on breast cancer outcomes according to timing of cancer treatment. One publication[120] investigated the association between dietary supplement use before and after chemotherapy and breast cancer prognosis. Results showed that antioxidant supplements, iron, and vitamin B12 use before and during chemotherapy might be associated with an increased risk of all-cause mortality and recurrence (HRs ranging from 1.41 to 2.04). Multivitamin use was not associated with breast cancer prognosis. In another publication, concurrent use of antioxidants with chemotherapy or radiotherapy was associated with an increased risk of all-cause mortality (HR: 1.64, 95% CI: 1.01-2.66) and recurrence (HR: 1.84, 95% CI: 1.26-2.68).[119]

3.12 | Postdiagnosis vitamin D from diet and/or supplements, and serum 25-hydroxyvitamin D (25(OH)D)

No association was observed for vitamin D from diet and supplements for any of the outcomes across the four identified studies.[60,61,109,122] Dietary vitamin D was also not associated with all-cause mortality (Figure S23) and recurrence.[61,122] Vitamin D supplementation was inversely associated with all-cause mortality in one[117] study out of the four identified[112,113,117,118] (HR for >400 I.U./day vs 1-400 I.U./day: 0.82, 95% CI: 0.69-0.99). Vitamin D supplementation was associated with improved disease-free survival (HR for users vs no users: 0.36, 95% CI: 0.15-0.88) in another study.[118] A decreased risk of recurrence among women diagnosed with oestrogen receptor-positive (HR for use vs no use: 0.64, 95% CI: 0.47-0.87) but not oestrogen receptor-negative tumours was observed in the After Breast Cancer Pooling Project.[112]

Twenty-three publications[122-144] on serum 25(OH)D were reviewed (Table S24). Linear dose-response meta-analyses were conducted for all-cause and breast cancer-specific mortality. Results showed an inverse association between serum 25(OH)D and all-cause (RR per 10 nmol/L: 0.93, 95% CI: 0.89-0.97; $I^2 = 63\%$ $P_{heterogeneity} = .020$; 6 studies[125,128-131,135]; 25(OH)D assessed on average 58 days to 36 months after diagnosis; Figure 3F) and breast cancer-specific mortality (RR per 10 nmol/L: 0.94, 95% CI: 0.90-0.99; $I^2 = 24\%$ $P_{heterogeneity} = .26$; 5 studies[125,128-131]; 25(OH)D was assessed on average 69 days to 36 months after diagnosis; Figure 4H). The relationship with all-cause mortality was somewhat nonlinear ($P_{nonlinearity} = .02$; Figure S24). The risk of death increased sharply below 50 nmol/L and was null with wide CIs above this. Results remained essentially the same when only studies collecting 25(OH)D before treatment initiation were included (Figures S25-S27).

Most studies yielded inverse point estimates for breast cancer recurrence, and in seven of them the CIs did not include the null value (Figure S28).

3.13 | Evidence grading

Table 1 reports the evidence grading for all dietary factors. Evidence was graded as "limited- suggestive" for dietary patterns and lower risk of all-cause and other causes of death and for soy food intake and lower risk of all-cause mortality, breast cancer mortality and recurrence. Additionally, there was limited-suggestive evidence that dietary fibre intake was associated with lower risk of all-cause mortality and that serum 25(OH)D was associated with a lower risk of all-cause and breast cancer-specific mortality.

The evidence on the remaining associations was limited and sparse, thus they were graded as "limited-no conclusion."

4 | DISCUSSION

The improved survival after breast cancer diagnosis has created an urgent need to understand the relationship between dietary intake, dietary patterns and supplements use and subsequent outcomes. Such insights would direct the development of evidence-based nutritional guidelines for breast cancer survivors. In the current updated systematic reviews and meta-analyses, the number of studies for many of the exposures ranged from one to three, often with insufficient information to be included in a dose-response meta-analysis. Therefore, dose-response meta-analyses were only possible for dairy products, carbohydrates, dietary fibre, alcohol intake and serum 25(OH)D with all-cause mortality and breast cancer-specific mortality; for isoflavone intake with all-cause mortality; and for protein, dietary fat, and fruits with breast cancer-specific mortality. In general, data on dietary factors and breast cancer outcomes were limited and inconsistent, and no conclusions could be reached. Evidence was judged by the Expert Panel as limited-suggestive for dietary patterns in association with lower risk of all-cause and other causes of death, intake of soy in association with lower risk of all-cause mortality, breast cancer mortality and recurrence, dietary fibre in association with lower risk of all-cause mortality, and serum 25(OH)D in association with lower risk of all-cause and breast cancer mortality. The remaining exposures reviewed were judged as limited-no conclusion.

In our previous WCRF/AICR review,[4] we presented the results separately according to exposure assessment timepoint relative to the cancer diagnosis. For postdiagnosis dietary exposures, dose-response meta-analysis was only possible for dietary fibre and alcohol intake (all-cause and breast cancer-specific mortality), and for isoflavones (all-cause mortality), assessed 12 months or more after breast cancer diagnosis. In the present work, all postdiagnosis timepoints were pooled, and subgroup analysis was performed, when possible, by timeframe relative to cancer treatment, which is a more accurate

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measurement of the relevant periods in the natural history of cancer survivors.

Despite the differences in the synthesis approach, the current analysis confirmed our previous findings on postdiagnosis dietary fibre, alcohol and isoflavone intake and their corresponding conclusions by the independent Expert Panel (ie, limited-suggestive evidence for a lower risk of outcomes for fibre and isoflavones and limited-no conclusion for alcohol).

For most of the exposures (ie, low-fat dietary patterns (RCTs), data-driven dietary patterns, vegetables, wholegrains, fish, meat, and supplements use), few studies were identified, and their results were not meta-analysed. We descriptively synthetised these studies and found that associations with breast cancer outcomes were mostly null. These results are in line with other recently published meta-analyses in breast cancer survivors.[145-147]

A considerable amount of research has examined the association between postdiagnosis predefined healthy dietary and lifestyle patterns and breast cancer outcomes. Due to the diversity in the methods and cut-off points used to derive the patterns, the identified studies were descriptively synthesised instead of being meta-analysed. Considering the consistency in the direction of an inverse association, the evidence was graded as limited-suggestive reduced risk of all-cause and other causes of death. This beneficial association could be partially explained by the individual and synergistic favourable effect of fruits, vegetables, and wholegrains on overall health.[148,149] The standardisation of the operationalization of the patterns is crucial to strengthen the evidence in this field.

Despite the small number of studies on isoflavone intake from soy foods, we were able to conduct a dose response meta-analysis of three publications[69,73,74] with all-cause mortality as outcome. Soy isoflavones may have a protective association on breast cancer survival through the modulation of the oestrogen receptor β, which has anticarcinogenic and antiproliferative effects.[150] Besides, isoflavones also exert an antioxidative and anti-inflammatory function.[151] In our meta-analysis, there was little evidence to support an association between isoflavone intake from soy foods and all-cause mortality risk (narrow CI crossing the null value, and with substantial heterogeneity). Three out of the five studies comprised women from Western countries, which may limit the ability to detect an association due to their low soy intake compared to Asian countries.[152] In fact, the two[69,74] Chinese studies investigating soy protein intake and all-cause mortality reported inverse associations. The country-specific results may at least partly explain the substantial heterogeneity. A recent published categorical (high vs low intakes) meta-analysis reported a suggestive association between postdiagnosis isoflavone and soy protein intake and overall survival (HR: 0.80, 95% CI: 0.62-1.04),[153] which is in agreement with our findings. Taken together the consistent direction and magnitude of association for soy foods (including isoflavones and soy protein) intake and all outcomes, the evidence was graded as limited-suggestive.

We conducted a linear dose-response meta-analysis of four observational studies (three publications[60,64,75]) on postdiagnosis dietary fibre intake and breast cancer outcomes. Our results demonstrated a 13% lower risk of all-cause mortality for each 10 g/day increase in fibre intake with no evidence of between-study heterogeneity. There was no association with breast cancer-specific mortality. Our findings are in line with a recent categorical meta-analysis that included three studies[60,61,75] and showed a 30% lower risk of all-cause mortality when comparing extreme categories of postdiagnosis fibre intake, but not with breast cancer-specific mortality.[154] The authors rated the quality of the evidence as moderate for all-cause mortality and low for breast cancer-specific mortality based on the NutriGrade scoring system,[155] whereas the evidence of causality using the predefined grading in the present study was graded as limited-suggestive. Dietary fibre has shown beneficially effects on diabetes, CVD and its associated risk factors,[156] which could partially explain the reduced risk of all-cause mortality observed in our meta-analysis. Further studies considering the type of dietary fibre consumed and information on the tumour oestrogen receptor status are needed to thoroughly elucidate the potential association between postdiagnosis fibre intake and breast cancer survival.

Despite alcohol being a risk factor for breast cancer incidence in pre- and postmenopausal women,[4] the present analyses did not detect an association between postdiagnosis alcohol intake and all-cause mortality but the point estimate was inverse with CIs crossing the null value for breast cancer-specific mortality, as reported in another published meta-analysis.[92] The included observational studies may be subject to methodological issues as discussed in the limitations paragraph below, and collider-stratification and heterogeneity disease bias might be present. It has been suggested that alcohol intake could differentially impact breast cancer risk depending on the patient's genotype.[157] Whether this is true for breast cancer prognosis warrants investigation.

The current evidence on dietary supplementation use after breast cancer diagnosis was scarce and did not show any overall benefit on breast cancer outcomes. More detailed investigations are needed, as cancer survivors tend to use dietary supplements to aid with treatment side effects.[158] However, there are still concerns about the use of dietary supplements in patients undergoing certain types of cancer treatment due to the potential compromise of the effectiveness of therapy.[2] Future studies should aim to collect comprehensive information that is currently lacking on the types, dosages and duration of use for the supplements before and after cancer diagnosis, the type of cancer treatments, and account for the dietary sources of the nutrients. Given the limitations of the few studies identified and the inconsistent associations, the evidence on dietary supplements was graded as limited-no conclusion.

There were limited studies examining the association of postdiagnosis dietary and/or supplemental vitamin D intake and breast cancer outcomes, and the associations observed were generally null. The linear dose-response inverse association for serum 25(OH)D concentrations and all-cause and breast cancer-specific mortality is in agreement with a previous dose-response meta-analysis.[159]

Experimental evidence suggests a plausible anticancer role of vitamin D mediated by its interaction with the vitamin D receptor.[160]

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Calcitriol, a metabolite of vitamin D3, is involved in oestrogen receptor signalling pathways that could also have a role in reducing the risk of breast cancer mortality.[159] Factors such as BMI,[161] physical activity,[162] or chemotherapy[163] could modify 25(OH)D levels. However, only three of the included studies in our meta-analyses adjusted for BMI[125,129,131] and one for physical activity[129] which could bias the results of the individual studies. When we repeated our meta-analysis including only studies assessing serum 25(OH)D in participants before or without receiving cancer treatment, results remained essentially the same.

The current systematic reviews and meta-analyses have limitations that should be considered in the interpretation of the findings. These were also taken into account by the independent Expert Panel when making the decisions on the evidence grading. There are few intervention studies on diet and outcomes in breast cancer survivors and have substantially different follow-up periods (ranging from 60 months up to 11.5 years), which sometimes might not be large enough before mortality effects are apparent. Moreover, although considered useful in determining causation, intervention studies may be opened to issues such as small sample size, and low adherence to intervention.[164] Most of the data come from observational studies, which are susceptible to several biases, such as reverse causation, survival bias and exposure measurement error. Most of the studies adjusted for breast cancer prognostic factors but had inadequate control for cancer treatment type or completion. In addition, we were unable to conduct subgroup meta-analyses due to the small number of available studies stratified by cancer treatment, hormone receptor status of the tumour, time frame (before, during and after treatment), socioeconomic status and country, among other factors; and examined small-study effects, because of the small number of studies, and with insufficient information for analysis.

Observational studies differed in the dietary assessment method used (food frequency questionnaires, 24 h recalls, diet records, medical records, or other instruments), and the average time of assessment (ranging from 90 days up to 6 years postdiagnosis). Moreover, although in general the dietary assessment tools were validated, with few exceptions, most of the studies measured diet after diagnosis only at one point in time. Results from updated diet assessment during the follow-up, could reduce measurement error due to intraindividual variation.[165] Likewise, only a limited number of studies assessed dietary change from pre- to postdiagnosis,[38,67,77,89] and there were no data on dietary changes over time after breast cancer diagnosis which could bias the observed diet-cancer survival associations.

We also observed variations in the definition of the breast cancer recurrence outcome, which may undermine the quality of the evidence. The clinical trials may use different endpoints as surrogate measures of overall survival. Some studies referred to recurrence as "*disease-free survival*," "*progression-free survival*," "*additional breast cancer events*" and other studies included different events or combination of events under the term recurrence. Despite these heterogenous definitions, all were reviewed under the general term of recurrence, as the number of studies was small to allow subgroup analyses.

Breast cancer survivors involved in research studies are healthy enough to participate. These women are likely more health-conscious and may come from a higher socioeconomic background compared to nonparticipants. Therefore, selection bias, when not accounted for, may have an unpredictable impact on study results.

Despite these limitations, the present updated systematic reviews and meta-analyses are the most comprehensive scientific investigation of postdiagnosis dietary factors and breast cancer outcomes. Each diet-related exposure was evaluated for all-cause mortality, breast cancer-specific mortality and breast cancer recurrence and the evidence was examined and judged by the independent Expert Panel following the standardised evidence grading criteria, as part of the work for the on-going CUP Global that aims to systematically collect and synthesise the evidence for making lifestyle recommendations and research recommendations.[16]

5 | CONCLUSIONS

In conclusion, the current assessment of the evidence indicates that the associations between postdiagnostic dietary factors, dietary patterns, and supplement use and breast cancer outcomes in women with breast cancer remains inconclusive, and further research is needed before specific dietary recommendations for improving breast cancer prognosis can be made. Breast cancer survivors are still advised to follow the guidelines developed for the public on cancer prevention once their treatment is completed,[166] which is in line with the general recommendations to cancer survivors recently released by the American Cancer Society.[167] In some specific situations survivors may be advised otherwise by their health care professional.[166] More large, well-designed RCTs of dietary interventions and observational studies with long follow-up and repeated measures of dietary exposures and confounders, in diverse populations, and studies exploring the underlying biological mechanisms may strengthen the evidence for specific dietary recommendations for breast cancer survivors.

AUTHOR CONTRIBUTIONS

Konstantinos K. Tsilidis and Doris S. M. Chan are coprincipal investigator of CUP Global at Imperial College London. Konstantinos K. Tsilidis was part of the Expert Panel but was not involved with judging the evidence after becoming a coprincipal investigator of CUP Global. Teresa Norat and Doris S. M. Chan wrote the protocol based on the advice from the Protocol Expertise Group and implemented the study with Konstantinos K. Tsilidis. Doris S. M. Chan and Neesha Nanu did the literature search. Leila Abar, Katia Balducci, Margarita Cariolou, Neesha Nanu, Rita Vieira and Nerea Becerra-Tomas did the study selections and data extraction. Leila Abar, Katia Balducci, Margarita Cariolou and Nerea Becerra-Tomas checked, analysed, and interpreted the data. Dagfinn Aune and Georgios Markozannes were CUP Global team members who revised the manuscript. Darren C. Greenwood was statistical adviser. Anne McTiernan, Steven K. Clinton, Edward L. Giovannucci, Ellen Kampman, Alan A. Jackson, Konstantinos K. Tsilidis, Marc J. Gunter, and Vivien Lund (lay member)

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were the Expert Panel members who provided judgements on the evidence and advised on the interpretation of the review. Elio Riboli and Amanda J. Cross were Expert Panel observers. Kate Allen, Nigel T. Brockton, Helen Croker, Daphne Katsikioti, Deirdre McGinley-Gieser, Panagiota Mitrou, and Martin Wiseman were the CUP Global Secretariat members who provided overall coordination for the work and convened and facilitated discussions with the Expert Panel. Katia Balducci and Nerea Becerra-Tomás drafted the original manuscript. All authors reviewed and provided comments on the manuscript. Doris S. M. Chan is the guarantor and has full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The work reported in the study has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study. Data sources and handling of these data are described in the Materials and Methods section. Further details are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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