Lead Article

Dietary phytoestrogens and biomarkers of their intake in relation to cancer survival and recurrence: a comprehensive systematic review with meta-analysis

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Context: *Recent studies have outlined the potential role of dietary factors in patients who have survived cancer.* ***Objective:*** *The aim of this study was to summarize the evidence of the relation between dietary intake of phytoestrogens and their blood biomarkers and, overall, cancer-specific mortality and recurrence in patients with cancer.* ***Data Sources:*** *A systematic search of PubMed, EMBASE, and Web of Science databases of studies published up to September 2019 was performed. Databases were searched for prospective and retrospective cohort studies reporting on dietary phytoestrogen intake and/or blood biomarkers and the outcomes investigated.* ***Data extraction:*** *Data were extracted from each identified study using a standardized form.* ***Data analysis:*** *Twenty-eight articles on breast, lung, prostate, and colorectal cancer, and glioma were included for systematic review. Given the availability of studies, a quantitative meta-analysis was performed solely for breast cancer outcomes. A significant inverse association among higher dietary isoflavone intake, higher serum/plasma enterolactone concentrations, and overall mortality and cancer recurrence was found. Among other cancer types, 2 studies reported that higher serum enterolactone and higher intake of lignans were associated with cancer-specific survival for colorectal cancer and glioma, respectively.* ***Conclusions:*** *Dietary phytoestrogens may play a role in survival from breast cancer ; evidence regarding other cancers is too limited to draw any conclusions.*

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INTRODUCTION

Cancer, together with other inflammation-related noncommunicable diseases, has been recognized as a global health threat. The Global Burden of Disease Study[1] reaffirmed this observation, recognizing 24.5 million incident cancer cases and 9.6 million cancer deaths in 2017, worldwide. Several risk factors may account for the burden of noncommunicable diseases, including economic, social, lifestyle, and dietary factors. Among them, dietary factors attract much attention undoubtedly because of their modifiable nature. In fact, the association between diet and cancer has been extensively investigated.[2] Recent outlines of epidemiological evidence have shown a potential causal relationship between specific dietary factors and noncommunicable diseases, including cancer. The most recent comprehensive summary conducted by Global Burden of Disease collaboration reported that in 2017, dietary factors contributed to 11 million deaths globally.[3] Importantly, cardiovascular diseases and cancer were the leading causes of diet-related deaths.[3] Thus, targeting modifiable risk factors, such as dietary factors, could contribute to a decrease in cancer-related mortality and morbidity.

Previous studies on dietary intake and cancer focused on dietary patterns and foods, but also individual nutrients. For instance, a higher adherence to healthy dietary patterns rich in plant-based foods has been associated with a lower risk of several cancers, including colon and breast cancer.[4,5] Notably, higher intake of certain foods has also been inversely associated with cancer risk and mortality, such as fruits and vegetables,[6] coffee and tea,[7–9] nuts,[10] and whole grains.[11] Recent scientific evidence has identified dietary polyphenols as promising compounds that may exert beneficial effects on human health. In fact, numerous meta-analysis have demonstrated that a higher dietary polyphenol intake may be associated with decreased risk of hypertension,[12] diabetes,[13] death,[14] and depression.[15] According to results of a comprehensive meta-analysis of the association between dietary polyphenol and phytoestrogen intakes and different cancer types, higher dietary intake of isoflavones may be inversely associated with risk of lung, stomach, colorectal, and breast cancer.[16] Mechanistic studies underline the protective effect of these bioactive molecules toward cancer, revealing that phytoestrogens exert antioxidant and anti-inflammatory properties, as well as an action through the estrogen receptor (ER), interacting with cancer cell growth and proliferation.[17] Among phytoestrogens and their dietary sources, a summary of the evidence on isoflavones and dietary soy consumption showed that such compounds may contribute to cancer prevention.[18] Nonetheless, a comprehensive summary of the evidence regarding main classes of dietary phytoestrogens (ie, isoflavones and lignans), their biomarkers/metabolites (ie, equol and enterolactone),[19] and cancer survival and recurrence considering all cancer types has been lacking. Thus, the aim for this review was to systematically describe and quantitatively analyze existing studies of the association among dietary intake of phytoestrogen, their blood biomarkers, and overall mortality, cancer-specific survival, and cancer recurrence.

METHODS

The design, analysis, and reporting of this study followed the Meta-Analysis of Observational Studies in Epidemiology guidelines (Table S1 in the Supporting Information online).[20] Moreover, eligibility criteria for the search and meta-analyses were specified using the PICOS approach (ie, determination of the population, intervention/exposure, comparison, outcomes, and study design; (Table 1).

Study selection

A systematic search of PubMed, EMBASE, and Web of Science databases of studies published up to September 2019 was performed using the following search strategy: "((((polyphenols OR polyphenol OR isoflavone OR isoflavones OR daidzein OR genistein OR biochanin A OR formononetin OR glycitein OR lignan OR lignans OR matairesinol OR lariciresinol OR secoisolariciresinol OR pinoresinol OR enterolactone OR enterodiol OR equol OR phytoestrogen OR phytoestrogens)) AND (cancer OR neoplasm OR carcinoma)) AND (survival

Table 1 **PICOS criteria**

	Description
P (population)	Men and women, patients with cancer
I (intervention/exposure)	Dietary phytoestrogens intake, including isoflavones and lignans, as well as individual phytoestrogens. Blood biomarkers of dietary phytoestrogen exposure
C (comparison)	Similar groups characterized by different amount of dietary phytoestrogens intake or different level of blood biomarkers of their intake
O (outcomes)	Reduction in overall mortality, cancer-specific mortality, and cancer recurrence among patients
S (study design)	Systematic review with meta-analysis

OR mortality OR recurrence OR prognosis OR death)) AND (cohort OR prospective OR observational OR population OR case-control OR nested OR follow-up OR followed)." Studies were eligible if they met the following inclusion criteria: (1) observational studies (either prospective or retrospective cohort studies); (2) conducted with patients with cancer; (3) evaluated associations between dietary phytoestrogens and/or their biomarkers and cancer outcomes, including overall mortality, cancer-specific mortality, and recurrence; and (4) assessed and reported hazard ratios (HRs) and their corresponding 95%CIs. As exposure, dietary intake of the following was considered: (1) total isoflavones and their individual components, including daidzein, genistein, glycitein, formononetin, and biochanin A; (2) biomarkers/metabolites of isoflavone intake, including equol; (3) total lignans and their individual components, including matairesinol, lariciresinol, secoisolariciresinol, and pinoresinol; and (4) biomarkers/metabolites of lignan intake, including enterolactone and enterodiol.

Reference lists of eligible studies were also examined for any additional studies not previously identified. If >1 study reported results on the same cohort, only the study including the larger cohort size, the longest follow-up, or the most comprehensive data was included in the meta-analysis. The systematic search and study selection were performed by 2 independent authors.

Data extraction and quality assessment

Data were extracted using a standardized extraction form. The following information was collected: (1) first author name and year of publication; (2) study cohort name and country; (3) study design and median follow-up period; (4) population characteristics; (5) sex and age of participants; (6) cohort size and number of deaths, cancer-related deaths, and cancer recurrence; (7) type of exposure and its main characteristics; (8) distributions of cases and person-years, HRs, and 95%CIs for all categories of exposure; and (9) adjustment covariates. The quality of each eligible study was determined using the Newcastle-Ottawa Quality Assessment Scale,[21] consisting of 3 domains of quality: selection (4 points), comparability (2 points), and outcome (3 points), for a total possible score of 9 points (9 represents the highest quality). Studies scoring 7–9 points, 4–6 points, and 0–3 points were identified as being of high, moderate, and low quality, respectively.

Statistical analysis

Outcomes evaluated in the analyses included overall mortality, cancer-specific mortality, and recurrence. The analyses were performed for dietary phytoestrogen intake as well as for blood biomarkers of phytoestrogens. HRs with 95%CIs for all categories of exposure were extracted for the analysis. Random-effects models were used to estimate pooled results for the highest vs the lowest category of exposure. Only the risk estimates from the most-adjusted models were used in the analysis. Heterogeneity was calculated using the Q test and I^2 statistic. The level of significance for the Q test was $P<0.10$. The I^2 statistic represented the total variation that could be attributed to heterogeneity. I^2 values $\leq$25%, 25%–50%, 50%–75%, and $>75\%$ indicated no, small, moderate, and significant heterogeneity, respectively. A sensitivity analysis by exclusion of 1 study at the time was performed to assess the stability of results and potential sources of heterogeneity. Additional sensitivity analyses were performed to test for potential source of heterogeneity by grouping studies according to menopausal status and ER status. Publication bias was evaluated through a visual investigation of funnel plots for potential asymmetry.

RESULTS

Study identification and selection process

The systematic search yielded a total of 631 studies, of which 402 were excluded on the basis of title and another 170 were excluded after abstract revision, leaving 59 articles for full-text evaluation (Figure 1). After revision of full-text articles, 31 studies were excluded. Finally, 28 articles exploring the association among dietary phytoestrogen intake and/or their blood biomarkers and overall mortality,cancer-specific survival, and cancer recurrence were included in the systematic review.[22–49] Of these, 19 studies examined the association between dietary intake of phytoestrogens and cancer,[22–40] of which 15 focused on breast cancer,[22–36] 1 on colorectal cancer,[37] 1 on prostate cancer,[38] 1 on lung cancer,[39] and 1 on malignant glioma.[40] Nine articles focused on blood biomarkers of dietary phytoestrogen intake and cancer[41–49]; 6 of the 9 studies were on breast cancer,[41–46] 2 on colorectal cancer,[48,49] and 1 on prostate cancer.[47] Data quality was overall high (data not shown). Considering the limited number of studies reporting on the investigated associations, the meta-analysis was performed solely for breast cancer outcomes.

Breast cancer

Fifteen studies explored the association among dietary phytoestrogen intake (isoflavones and lignans) and overall mortality, cancer-specific mortality, and

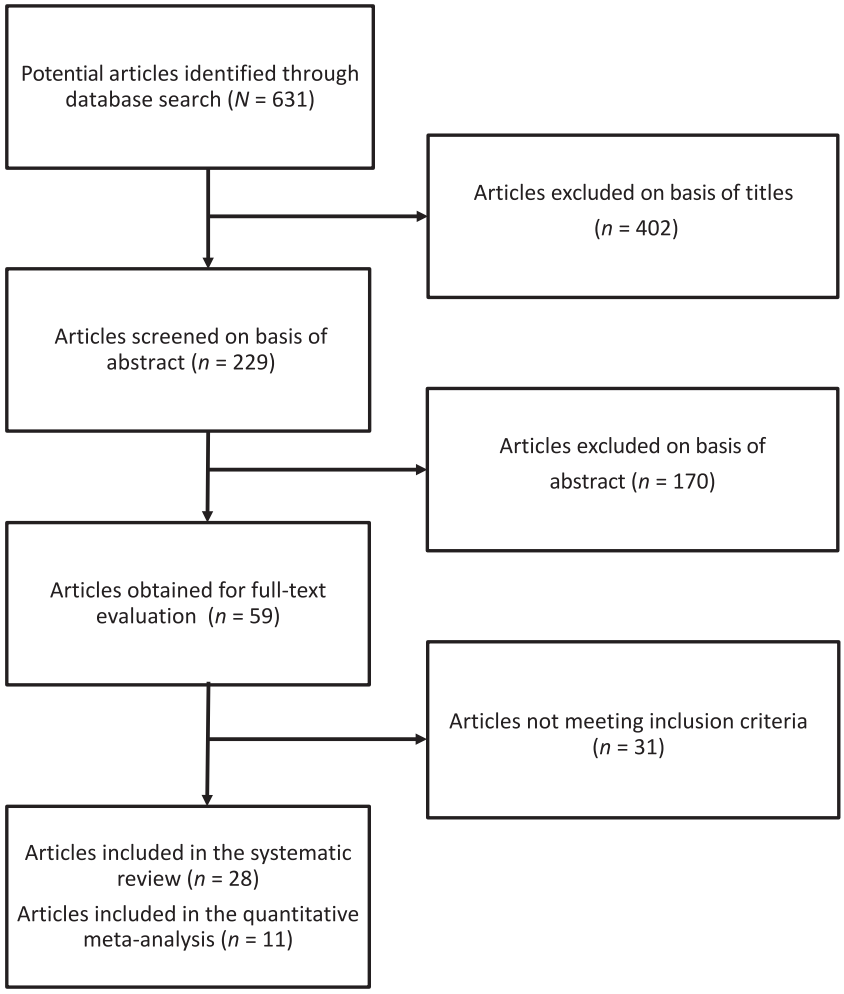

Figure 1 **Flow chart of the study identification and selection process**

recurrence in patients with breast cancer (Table 2),[22–36] and 6 studies examined the association with blood biomarkers of phytoestrogen consumption (Table 3).[41–46] All the studies exploring this association for dietary phytoestrogens estimated phytoestrogen intake using a food frequency questionnaire; however, the questionnaires differed in the number of food items considered (Table 2). Main findings of these studies were quantitatively analyzed using a meta-analytical approach.

Nine cohorts reported on the association between dietary isoflavone intake and overall mortality,[22,25,26,29,32,35,36] 5 reported on cancer-specific mortality.[25,26,32] 5 reported on cancer recurrence in patients with breast cancer.[29,32,34] A significant inverse association was found for overall mortality (HR, 0.84, 95%CI, 0.74–0.97; Figure 2, Table 4) and breast cancer recurrence (HR, 0.73, 95%CI, 0.64–0.84; Figure 2, Table 4), with no evidence of publication bias (Figure S1 in the Supporting Information online). However, there was a moderate heterogeneity among the studies investigating the association with overall mortality. Interestingly, after stratification for menopausal status, both associations remained significant for postmenopausal patients (HR, 0.83, 95%CI, 0.68–1.00, $I^2 = 39\%$; and HR, 0.66, 95%CI, 0.55–0.78, $I^2 = 0\%$, respectively).

Only 2 studies were eligible for the analysis of the association between dietary lignan intake and overall and breast cancer–specific survival.[26,31] Nonetheless, analysis did not reveal any significant association (HR, 0.96, 95%CI, 0.49–1.89; and HR, 0.80, 95%CI, 0.33–1.93, respectively), possibly due to the limited number of included studies (Figure 3, Table 4, Figure S2 in the Supporting Information online). Moreover, there was high heterogeneity among the included studies.

Three studies were eligible for the meta-analysis exploring the association between serum/plasma enterolactone concentration, a biomarker of lignan consumption (enterolactone is a metabolite of lignans that undergo metabolism and modification by human gut microbiota),[19] and overall and cancer-specific mortality.[42,44,46] Two studies were eligible for meta-analysis of cancer recurrence in patients with breast

Table 2 **Characteristics of the studies investigating the association between dietary intake of phytoestrogens and overall and cancer-specific mortality and recurrence in patients**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
Boyapati et al (2005)[22]	Shanghai Breast Cancer Study, China	Population-based prospective cohort, 5.2 y	Patients with BC	Premenopausal, postmenopausal	F, 25–64	1459 (240/NR/ NR)	Dietary isoflavones, postdiagnostic, 76-item FFQ	Overall: T3 vs T1	0.95 (0.62–1.45)[a]	–	–	Age at diagnosis, stage of disease, radiotherapy, ER/PR status, total energy intake
Fink et al (2007)[26]	LIBCSP, United States	Population-based retrospective cohort, NR	Patients with BC	Premenopausal, postmenopausal	F, 25–98	1210 (173/113 BC/NR)	Dietary isoflavones, prediagnostic, 100-item FFQ	Overall: Q5 (>7.48 mg/d) vs Q1 (<0.29 mg/d)	0.52 (0.33–0.82)	0.87 (0.54–1.41)	–	Age at diagnosis, dietary energy intake
								Premenopausal: Q5 (>7.48 mg/d) vs Q1 (<0.29 mg/d)	0.71 (0.34–1.48)	1.03 (0.46–2.28)	–	
								Postmenopausal: Q5 (>7.48 mg/d) vs Q1 (<0.29 mg/d)	0.44 (0.24–0.81)	0.79 (0.43–1.44)	–	
							Dietary lignan, prediagnostic, 100-item FFQ	Overall: Q5 (>9.0 mg/d) vs Q1 (<2.2 mg/d)	1.03 (0.71–1.49)	0.95 (0.60–1.51)	–	
								Premenopausal: Q5 (>9.0 mg/d) vs Q1 (<2.2 mg/d)	1.27 (0.63–2.54)	1.16 (0.52–2.58)	–	
								Postmenopausal: Q5 (>9.0 mg/d) vs Q1 (<2.2 mg/d)	0.98 (0.63–1.54)	0.87 (0.49–1.55)	–	
Guha et al (2009)[27]	LACE, United States	Population-based prospective cohort, 6.3 y (average)	Patients with BC	Premenopausal, postmenopausal	F, 18–79	1954 (NR/NR/ 282)	Dietary daidzein, postdiagnostic, >100-item FFQ	Overall: Q5 (≥9596.55 μg/d) vs Q1 (<0.10 μg/d)	–	–	0.96 (0.52–1.76)	Soy supplement use, BMI 1 y before diagnosis, menopausal status, tobacco pack-years, tumor stage, ER status, age, race, and kilocalories
								Premenopausal: Q5 (≥9596.55 μg/d) vs Q1 (<0.10 μg/d)	–	–	1.74 (0.63–4.76)	
								Postmenopausal: Q5 (≥9596.55 μg/d) vs Q1 (<0.10 μg/d)	–	–	0.70 (0.27–1.77)	
								ER–/PR–: Q5 (≥9596.55 μg/d) vs Q1 (<0.10 μg/d)	–	–	1.45 (0.43–4.95)	
								ER+/PR+: Q5 (≥9596.55 μg/d) vs Q1 (<0.10 μg/d)	–	–	0.82 (0.40–1.68)	
							Dietary genistein,	Overall: Q5 (≥13 025.88 μg/d)	–	–	0.95 (0.52–1.75)	

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Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
							postdiagnostic, >100-item FFQ	vs Q1 (<0.10 μg/d)				
								Premenopausal: Q5 (≥13 025.88 μg/d) vs Q1 (<0.10 μg/d)	–	–	1.75 (0.65–4.76)	
								Postmenopausal: Q5 (≥13 025.88 μg/d) vs Q1 (<0.10 μg/d)	–	–	0.69 (0.27–1.75)	
								ER–/PR–: Q5 (≥13 025.88 μg/d) vs Q1 (<0.10 μg/d)	–	–	1.34 (0.39–4.57)	
								ER+/PR+: Q5 (≥13 025.88 μg/d) vs Q1 (<0.10 μg/d)	–	–	0.83 (0.40–1.69)	
							Dietary glycetin, postdiagnostic, >100-item FFQ	Overall: Q5 (≥795.40 μg/d) vs Q1 (<3.62 μg/d)	–	–	0.80 (0.42–1.50)	
								Premenopausal: Q5 (≥795.40 μg/d) vs Q1 (<3.62 μg/d)	–	–	1.60 (0.54–4.72)	
								Postmenopausal: Q5 (≥795.40 μg/d) vs Q1 (<3.62 μg/d)	–	–	0.51 (0.18–1.38)	
								ER–/PR–: Q5 (≥795.40 μg/d) vs Q1 (<3.62 μg/d)	–	–	0.38 (0.08–1.79)	
								ER+/PR+: Q5 (≥795.40 μg/d) vs Q1 (<3.62 μg/d)	–	–	0.94 (0.47–1.89)	
Shu et al (2009)[33]	SBCSS, China	Population-based prospective cohort, 3.9 y	Patients with BC	Premenopausal, postmenopausal	F, 20–75	5033 (444/534 BC[b])	Dietary isoflavones, postdiagnostic, 77-item FFQ	Overall: Q4 (>62.68 mg/d) vs Q1 (≤20.00 mg/d)	0.79 (0.61–1.03)	0.77 (0.60–0.98)[b]	0.77 (0.60–0.98)[b]	• Age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery received • BMI, menopausal status, ER and PR status, tamoxifen use, education level,

(continued)

Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
												income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity
								ER-: Q4 (>62.68 mg/d) vs Q1 (≤20.00 mg/d)	0.85 (0.58–1.24)	0.88 (0.62–1.25)[b]	0.88 (0.62–1.25)[b]	
								ER+: Q4 (>62.68 mg/d) vs Q1 (≤20.00 mg/d)	0.78 (0.53–1.16)	0.77 (0.54–1.09)[b]	0.77 (0.54–1.09[b]	
DeLorenze et al (2010)[40]	NR, United States	Population-based prospective cohort, NR	Patients with malignant glioma	NA	MF, 55.7 (median)	748 (648/NR/NR)	Coumestrol, prediagnostic, 79-item FFQ	II grade cancer: T3 (>145.5 μg/d) vs T1 (83.4 μg/d)	0.77 (0.33–1.75)	–	–	Reporting status, age at diagnosis, treatment, education, marital status, total calories, smoking, age at first alcoholic drink
								III grade cancer: T3 (>145.5 μg/d) vs T1 (83.4 μg/d)	1.06 (0.60–1.87)	–	–	
								IV grade cancer: T3 (>145.5 μg/d) vs T1 (83.4 μg/d)	1.16 (0.88–1.54)	–	–	
							Matairesinol, prediagnostic, 79-item FFQ	II grade cancer: T3 (>34.6 μg/d) vs T1 (<17.6 μg/d)	0.78 (0.36–1.69)	–	–	
								III grade cancer: T3 (>34.6 μg/d) vs T1 (<17.6 μg/d)	0.86 (0.48–1.54)	–	–	
								IV grade cancer: T3 (>34.6 μg/d) vs T1 (<17.6 μg/d)	1.20 (0.92–1.57)	–	–	
							Secoisolariciresinol, prediagnostic, 79-item FFQ	II grade cancer: T3 (>146.1 μg/d) vs T1 (<87.3 μg/d)	1.95 (0.93–4.10)	–	–	
								III grade cancer: T3 (>146.1 μg/d) vs T1 (<87.3 μg/d)	0.48 (0.25–0.92)	–	–	
									1.32 (1.02–1.72)	–	–	

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Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
								IV grade cancer: T3 (>146.1 μg/d) vs T1 (<87.3 μg/d)				
							Formononetin, prediagnostic, 79-item FFQ	II grade cancer: T3 (>23.1 μg/d) vs T1 (<9.3 μg/d)	1.08 (0.46–2.52)	–	–	
								III grade cancer: T3 (>23.1 μg/d) vs T1 (<9.3 μg/d)	0.79 (0.43–1.43)	–	–	
								IV grade cancer: T3 (>23.1 μg/d) vs T1 (<9.3 μg/d)	1.04 (0.79–1.37)	–	–	
							Genistein, prediagnostic, 79-item FFQ	II grade cancer: T3 (>291.6 μg/d) vs T1 (<141.3 μg/d)	1.05 (0.40–2.74)	–	–	
								III grade cancer: T3 (>291.6 μg/d) vs T1 (<141.3 μg/d)	1.25 (0.69–2.27)	–	–	
								IV grade cancer: T3 (>291.6 μg/d) vs T1 (<141.3 μg/d)	1.35 (1.00–1.81)	–	–	
							Daidzein, prediagnostic, 79-item FFQ	II grade cancer: T3 (>440.6 μg/d) vs T1 (269.0 μg/d)	1.70 (0.70–4.14)	–	–	
								III grade cancer: T3 (>440.6 μg/d) vs T1 (269.0 μg/d)	1.01 (0.55–1.85)	–	–	
								IV grade cancer: T3 (>440.6 μg/d) vs T1 (269.0 μg/d)	1.13 (0.86–1.49)	–	–	
							Biochanin A, prediagnostic, 79-item FFQ	II grade cancer: T3 (>37.8 μg/d) vs T1 (15.4 μg/d)	0.60 (0.28–1.30)	–	–	
								III grade cancer: T3 (>37.8 μg/d) vs T1 (15.4 μg/d)	0.91 (0.45–1.88)	–	–	
								IV grade cancer: T3 (>37.8 μg/d) vs T1 (15.4 μg/d)	1.26 (0.97–1.64)	–	–	
Kang et al (2010)[29]	NR, China	Hospital-based prospective cohort, 5.1 y	Patients with BC	Premenopausal (47.3%), postmenopausal (52.7%)	F, 29–72	524 (154/132 BC/ 185)	Dietary isoflavones, postdiagnostic, FFQ	Premenopausal: Q4 (>42.3 mg/d) vs Q1 (<15.2 mg/d)	1.05 (0.78–1.71)	–	0.88 (0.61–1.23)	Age at diagnosis, TNM stage, ER/ PR status, chemotherapy and radiotherapy
								Postmenopausal: Q4 (>42.3 mg/d) vs Q1 (<15.2 mg/d)	0.88 (0.56–1.24)	–	0.67 (0.54–0.85)	
								ER+/PR+ among postmenopausal: Q4 (>42.3 mg/d)	–	–	0.66 (0.49–0.86)	

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Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
								vs Q1 (<15.2 mg/d)				
								ER+/PR– among postmenopausal: Q4 (>42.3 mg/d) vs Q1 (<15.2 mg/d)	–	–	1.12 (0.81–1.66)	
								ER–/PR+ among postmenopausal: Q4 (>42.3 mg/d) vs Q1 (<15.2 mg/d)	–	–	1.05 (0.74–1.61)	
McCann et al (2010)[31]	WEB, United States	Population-based prospective cohort, 9–125 mo	Patients with BC	Premenopausal (28.1%), postmenopausal (71.9%)	F, 35–79	1122 (160/94 BC/ NR)	Dietary lignan, prediagnostic, 121-item FFQ	Premenopausal: Q4 (>257 μg/d) vs Q1 (<128 μg/d)	2.14 (0.82–5.56)	1.84 (0.65–5.27)	–	Age, race, total energy, stage at diagnosis, BMI, and education
								Postmenopausal: Q4 (>318 μg/d) vs Q1 (<155 μg/d)	0.49 (0.26–0.91)	0.29 (0.11–0.76)	–	
Buck et al. (2011)[23]	MARIE, Germany	Population-based prospective cohort, 6.4 y	Patients with BC	Postmenopausal	F, 50–74y	2653 (321/235 BC/NR)	Dietary enterolactone, prediagnostic, 176-item FFQ	Overall: Q5 (502.0 μg/d, median) vs Q1 (146.0 μg/d, median)	0.60 (0.40–0.89)	0.69 (0.43–1.10)	–	Tumor size, nodal status, metastasis, grade, ER/PR status, BC detection type, diabetes, menopausal hormone therapy use at diagnosis, study center, and energy intake
							Dietary enterodiol, prediagnostic, 176-item FFQ	Overall: Q5 (857.5 μg/d, median) vs Q1 (186.9 μg/d, median)	0.63 (0.42–0.95)	0.81 (0.51–1.29)	–	
Caan et al (2011)[24]	WHEL, United States	Population-based prospective cohort, 7.3 y	Patients with BC	Premenopausal, postmenopausal	F, 18–70	3088 (271/NR/ 448)	Dietary isoflavones, postdiagnostic, 153-item FFQ	Overall: Q4 (>16.33 mg/d) vs Q1 (<0.7 mg/d)	0.46 (0.20–1.05)	–	0.78 (0.46–1.31)	Stage, grade, ER/PR status, menopausal status, chemotherapy treatment, radiation, age, education, race, soy supplements intervention group, presence of hot flash symptoms, and their interaction, tamoxifen
								ER+/PR+: Q4 (>16.33 mg/d) vs Q1 (<0.7 mg/d)	0.31 (0.10–0.98)	–	0.84 (0.47–1.51)	

(continued)

Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
								ER–/PR–: Q4 (>16.33 mg/d) vs Q1 (<0.7 mg/d)	0.86 (0.25–2.90)	–	0.62 (0.19–2.03)	
Kang et al. (2012)[28]	NR, China	Hospital-based prospective cohort, NR	Patients with BC	Premenopausal (37.3%), postmenopausal (62.7%)	F, 46.7	288 (125/NR/NR)	Dietary isoflavones, prediagnostic, 95-item FFQ	Overall: >35.30 mg/d vs <8.45 mg/d	0.25 (0.09–0.54)	–	–	Age, education level, alcohol use, smoking status, menopausal status, ER/PR status, tamoxifen use, oral contraceptive use, and TNM stage
Nechuta et al (2012)[32]	ABCPP (pooled analysis of SBCSS, LACE, and WHEL)	Population-based prospective cohorts, 7.4 y (mean)	Patients with BC	Premenopausal, postmenopausal	F, ~54 (mean)	9514 (1171/881 BC/1348)	Dietary isoflavones, postdiagnostic, FFQ (SBCSS, LACE, WHEL)	Overall: ≥10.0 mg/d vs <4.0 mg/d	0.87 (0.70–1.10)	0.83 (0.64–1.07)	0.75 (0.61–0.92)	Age at diagnosis, ER/PR status, TNM stage, chemotherapy, radiotherapy, hormonal therapy, smoking, BMI, exercise, cruciferous vegetable intake, parity, menopausal status, study, race/ethnicity, and education
								Premenopausal: ≥10.0 mg/d vs <4.0 mg/d	1.11 (0.77–1.60)	0.97 (0.66–1.43)	0.93 (0.69–1.26)	
								Postmenopausal: ≥10.0 mg/d vs <4.0 mg/d	0.84 (0.61–1.14)	0.78 (0.54–1.14)	0.64 (0.48–0.87)	
								ER+: ≥1.00 mg/d vs <4.0 mg/d	0.91 (0.69–1.20)	0.93 (0.67–1.28)	0.81 (0.63–1.04)	
								ER–: ≥1.00 mg/d vs <4.0 mg/d	0.81 (0.54–1.23)	0.67 (0.43–1.05)	0.64 (0.44–0.94)	
Woo et al (2012)[34]	NR, Korea	Hospital-based prospective cohort, 32.6 mo	Patients with BC	Premenopausal (38.9%), postmenopausal (61.1%)	F, 25–77	339 (NR/NR/25)	Dietary isoflavones, prediagnostic, FFQ	Overall: T3 (≥15.2 mg/d) vs T1 (<7.4 mg/d)	–	–	0.56 (0.20–1.53)	Total energy intake, cancer stage, age at baseline, menopausal status, alcohol intake, herceptin use, and tamoxifen use
Zhang et al (2012)[36]	NR, China	Hospital-based prospective cohort, 52.1 mo	Patients with BC	Premenopausal (52.9%), postmenopausal (47.1%)	F, 45.7 (mean)	616 (79/NR/NR)	Dietary isoflavones, NR, FFQ	Overall: Q4 (>28.83 mg/d) vs Q1 (<7.56 mg/d)	0.62 (0.42–0.90)	–	–	Age, education level, smoking, drinking, family history of cancer, menopause status, tamoxifen

(continued)

Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
												use, TNM stage, ER status, chemotherapy and radiotherapy
								ER–: Q4 (>28.83 mg/d) vs Q1 (<7.56 mg/d)	0.78 (0.47–0.98)	–	–	
								ER+: Q4 (>28.83 mg/d) vs Q1 (<7.56 mg/d)	0.59 (0.40–0.93)	–	–	
Conroy et al (2013)[25]	MEC, United States	Population-based prospective cohort, 6.2 y (mean)	Patients with BC	Postmenopausal	F, ≥50	3842 (804/376 BC/NR)	Dietary isoflavones, prediagnostic, >180-item FFQ	Overall: T3 (≥10.4 mg/d) vs T1 (<4.3 mg/d)	0.98 (0.79–1.21)	1.01 (0.74–1.39)	–	BMI, age at diagnosis, ethnicity, energy intake, stage, hormone receptor status, treatment, cardiovascular comorbidity, history of diabetes, smoking status, years between cohort entry and diagnosis
								ER+/PR+: T3 (≥5.5 mg/1000 kcal) vs T1 (<2.5 mg/1000 kcal)	1.03 (0.75–1.42)	1.01 (0.59–1.73)	–	
								ER–/PR–: T3 (≥5.5 mg/1000 kcal) vs T1 (<2.5 mg/1000 kcal)	1.08 (0.69–1.70)	0.96 (0.54–1.72)	–	
Yang et al (2013)[39]	SWHS, China	Population-based prospective cohort, 36 mo	Patients with LC	NA	F, 66.3 (mean)	444 (318/301 LC/ NR)	Dietary isoflavones, prediagnostic, 77-item FFQ	Overall: 90th percentile (53.5 mg/d) vs 10th percentile (10.2 mg/d)	0.97 (0.78–1.20)	–	–	Age at diagnosis; education; cigarette smoking; BMI; menopausal status; history of LC in first-degree relatives; intakes of total calories, fruits, and nonsoy vegetables; time interval between the first FFQ survey and lung cancer diagnosis; and use of nonsteroidal anti-inflammatory drugs and vitamin supplements

(continued)

Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
Kyro et al (2015)[30]	EPIC, multicenter	Population-based prospective cohort, 6.3 y	Patients with BC	Premenopausal (24%), postmenopausal (76%)	F, 59 (median)	11 782 (1482/753 BC/NR)	Dietary isoflavones, prediagnostic, ≤260-item FFQ	Premenopausal: doubling of intake	1.00 (0.98–1.03)	1.00 (0.97–1.02)	–	Lifestyle factors including alcohol, BMI, HRT use, schooling, smoking status, physical activity index; intake of other polyphenol classes; ER status; cancer stage and grading of tumor; stratification for age and country
								Postmenopausal: doubling of intake	1.00 (0.99–1.01)	1.00 (0.98–1.01)	–	
							Dietary lignan, prediagnostic, ≤260-item FFQ	Premenopausal: doubling of intake	1.26 (1.05–1.51)	1.24 (0.98–1.58)	–	
								Postmenopausal: doubling of intake	0.94 (0.86–1.04)	0.83 (0.72–0.96)	–	
Zamora-Ros et al (2015)[37]	NR, Spain	Hospital-based prospective cohort, 8.6 y (mean)	Patients with CRC	NA	MF, ∼67 (median)	409 (133/NR/77)	Dietary isoflavones, NR, >600-item DHQ	Overall: T3 (>0.3 mg/d) vs T1 (<0.2 mg/d)	0.97 (0.62–1.53)	–	0.60 (0.33–1.09)	Sex, age, total energy, and CRC stage
							Dietary lignan, NR, >600-item DHQ	Overall: T3 (>0.9 mg/d) vs T1 (<0.6 mg/d)	0.83 (0.50–1.37)	–	0.68 (0.36–1.26)	
Taborelli et al (2017)[38]	NR, Italy	Hospital-based retrospective cohort, 12.7 y	Patients with PC	NA	M, 46–74	777 (263/81 PC/NR)	Dietary isoflavones, prediagnostic, 78-item FFQ	Overall: Q4 vs Q1	0.76 (0.54–1.08)	1.21 (0.61–2.37)	–	Area of residence at diagnosis, calendar period, age at diagnosis, years of education, Gleason score, BMI, smoking habits, and total energy intake
Zhang et al (2017)[35]	BCFR, multicenter	Population-based prospective cohort, 9.4 y	Patients with BC	Premenopausal (49%), postmenopausal (51%)	F, 51.8 (mean)[c]	6235 (1224/NR/NR)	Dietary isoflavones, pre- and postdiagnostic, 108-item FFQ	Overall: Q4 (≥1.494 mg/d) vs Q1 (<0.342 mg/d)	0.79 (0.64–0.97)	–	–	Age, study site, and total caloric intake, race/ethnicity, education, total fiber intake, Health Eating Index-2010, treatment type, recreational physical activity, BMI, alcohol use,

(continued)

Table 2 **Continued**

Reference	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Patient sex and age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure and method of assessment	Dietary phytoestrogen categories	Overall mortality HR (95%CI)	Cancer-specific mortality HR (95%CI)	Cancer recurrence HR (95%CI)	Adjustment covariates
												smoking status and pack-years
								Premenopausal: Q4 (≥1.494 mg/d) vs Q1 (<0.342 mg/d)	0.93 (0.68–1.27)	–	–	
								Postmenopausal: Q4 (≥1.494 mg/d) vs Q1 (<0.342 mg/d)	0.78 (0.59–1.05)	–	–	
								ER+/PR+, ER+/PR–, ER–/PR+: Q4 (≥1.494 mg/d) vs Q1 (<0.342 mg/d)	0.90 (0.69–1.19)	–	–	
								ER–/PR–: Q4 (≥1.494 mg/d) vs Q1 (<0.342 mg/d)	0.49 (0.29–0.83)	–	–	

a Among those with no recent dietary change.

b Includes recurrence and breast cancer–specific mortality.

c Age at enrollment.

Abbreviations: ABCPP, After Breast Cancer Pooling Project; BC, breast cancer; BCFR, Breast Cancer Family Registry; BMI, body mass index; CRC, colorectal cancer; DHQ, dietary history questionnaire; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HR, hazard ratio; HRT, hormone replacement therapy; LACE, Life After Cancer Epidemiology; LC, lung cancer; LIBCSP, Long Island Breast Cancer Study; MARIE, Mammary Carcinoma Risk Factor Investigation; MEC, Multiethnic Cohort: NA, not applicable; NR, not reported; SBCSS, Shanghai Breast Cancer Survival Study; PC, prostate cancer; PR, progesterone receptor; SWHS, Shanghai Women's Health Study; WEB, Western New York Exposures and Breast Cancer; WHEL, Women's Healthy Eating and Living; Q, quintile; T, tertile.

cancer.[44,46] The analysis showed a significant inverse association for overall mortality (HR, 0.70, 95%CI, 0.49–0.99; Figure 4, Table 4); however, after stratifying for menopausal status, the association remained significant only for postmenopausal women (HR, 0.66, 95%CI, 0.47–0.92; Table 4), with evidence of moderate heterogeneity. Neither breast cancer–specific mortality (HR, 0.72, 95%CI, 0.51–1.03; Figure 4, Table 4) nor cancer recurrence (HR, 0.91, 95%CI, 0.67–1.23; Figure 4, Table 4) was associated with serum/plasma enterolatone concentration, except for breast cancer–specific mortality among postmenopausal patients (HR, 0.68, 95%CI, 0.49–0.96; Table 4). Funnel plots of the data revealed absence of publication bias (Figure S3 in the Supporting Information online).

Colorectal cancer

Three studies exploring the relation between phytoestrogen and colorectal cancer survival or recurrence met the eligibility criteria and were included in this systematic review.[37,48,49] A hospital-based study conducted in Spain with a mean follow-up of 8.6 years recorded 133 deaths and 77 cases of colorectal cancer recurrence among 409 patients (Table 2). No significant association between dietary intake of isoflavones or lignans and colorectal cancer survival and recurrence was noted.[37] Accordingly, another population-based study of a sample of 2051 patients with colorectal cancer who were followed for >5 years reported no association between serum genistein (an isoflavone) level and overall mortality, cancer-specific mortality, and recurrence (Table 3).[48] However, in a third study, high plasma enterolactone levels prediagnosis were inversely associated with cancer-specific mortality, but only in women (HR, 0.63, 95%CI, 0.41–0.99; Table 3).[49]

Prostate cancer

The association between dietary and serum biomarkers of phytoestrogens and prostate cancer survival was explored in 2 studies.[38,47] A hospital-based, retrospective, cohort study conducted using data from 777 patients with prostate cancer who were followed for 12.7 years recorded 263 deaths, among which 81 were due to prostate cancer. Despite the long follow-up period, no significant association was found for either overall or prostate cancer–specific mortality when comparing the highest vs the lowest category of dietary isoflavone intake (Table 2).[38] Similarly, no significant results were reported for the association between plasma enterolactone and overall and prostate cancer–specific mortality in a sample of 1391 patients with prostate cancer who were followed for 6 years (Table 3).[47]

Lung cancer

To date, to our knowledge, 1 study has investigated the possible relationship between prediagnosis dietary isoflavone intake and lung cancer survival.[39] The study enrolled 444 patients with lung cancer and followed them for 36 months, during which 318 deaths occurred (301 were due to lung cancer). However, after adjusting for potential confounding factors, no significant association between greater intake of isoflavones and overall cancer survival was found (HR, 0.97, 95%CI, 0.78–1.20; Table 2).[39]

Malignant glioma

One prospective cohort study reporting on the association between prediagnosis dietary phytoestrogen intake and cancer survival in patients with glioma was retrieved in the systematic search.[40] The study, conducted with 748 male and female patients with glioma (median age, 55.7 years), reported 648 deaths over the follow-up period. The exposure of interest included dietary intake of individual isoflavones (namely, formononetin, genistein, daidzein, and biochanin A) and lignans (namely, coumestrol, matairesinol, and secoisolariciresinol). Higher dietary intake of secoisolaricinesinol among patients with grade III glioma was associated with better cancer survival rate (HR, 0.48, 95%CI, 0.25–0.92; Table 2).

DISCUSSION

This study provides a comprehensive review of existing prospective and retrospective studies on the dietary intake of isoflavones and lignans, as well as of their blood biomarkers, in the context of cancer survival and recurrence. The systematic review comprised 28 articles reporting on breast, colorectal, prostate, lung, and glioma cancer, although most of the investigations focused on breast cancer. Meta-analyses showed higher dietary isoflavone intake was inversely associated with overall mortality and cancer recurrence among patients with breast cancer. No significant relation between dietary lignan intake and cancer outcomes was found when lignan intake was assessed with conventional self-reported methods, but higher levels of serum/plasma enterolactone were inversely associated with overall cancer survival. Interestingly, when analyses were stratified for menopausal status, the associations remained significant only among postmenopausal patients. Finally, none of the analyses stratified for ER status resulted is statistically significant findings, possibly because of the limited number of analyzed studies. Among the other cancers investigated, only an association of improved

Table 3 **Characteristics of the studies investigating the association among serum/plasma markers of dietary phytoestrogen intake and overall and cancer-specific mortality and recurrence in patients**

Reference	Cohort name, country	Study design, median follow-up (y)	Population	Menopausal status	Patient sex, age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure	Biomarkers of phytoestrogen intake categories	All-cause mortality RR (95%CI)	Cancer-specific mortality RR (95%CI)	Cancer recurrence RR (95%CI)	Adjustment covariates
Buck et al (2011)[41]	MARIE, Germany	Population-based prospective cohort, 6.1	Patients with BC	Postmenopausal	F, 50–74	1140 (162/124 BC/NR)	Serum enterolactone, postdiagnostic	Overall: Q4 (≥42.3 nmol/L) vs Q1 (≤7.8 nmol/L)	0.58 (0.34–0.99)	–	–	Tumor size, nodal status, metastases, grade, ER/PR status, BC detection type, diabetes, HRT use at diagnosis, BMI, and physical activity
								Overall: per 10 nmol/L increment	0.94 (0.88–1.00)	–	–	
								ER+: Q4 (≥42.3 nmol/L) vs Q1 (≤7.8 nmol/L)	0.91 (0.45–1.84)	–	–	
								ER+: per 10 nmol/L increment	0.96 (0.89–1.04)	–	–	
								ER–: Q4 (≥42.3 nmol/L) vs Q1 (≤7.8 nmol/L)	0.27 (0.08–0.87)	–	–	
								ER–: per 10 nmol/L increment	0.91 (0.81–1.02)	–	–	
Olsen et al (2011)[45]	Diet, Cancer and Health, Denmark	Population-based prospective cohort, 10	Patients with breast cancer	Postmenopausal	F, 60 (median)	424 (111/80 BC/ NR)	Plasma enterolactone, prediagnostic	Overall: >20.5 nmol/L vs ≤20.5 nmol/L	0.47 (0.32–0.68)	0.56 (0.36–0.87)	–	Tumor grade at diagnosis, baseline levels of alcohol intake, and use of HRT
								Overall: per 20 nmol/L increment	0.82 (0.70–0.96)	0.88 (0.75–1.03)	–	
								ER+: >20.5 nmol/L vs ≤20.5 nmol/L	0.43 (0.26–0.69)	0.59 (0.32–1.09)	–	
								ER–: >20.5 nmol/L vs ≤20.5 nmol/L	0.56 (0.27–1.13)	0.52 (0.25–1.09)	–	
Guglielmini et al (2012)[42]	NR, Italy	Hospital-based retrospective cohort, 5-10[a]	Patients with BC	Premenopausal (29.3%), postmenopausal (70.7%)	F, 58.5 (median)	300 (180/112 BC/ NR)	Serum enterolactone, postdiagnostic	Premenopausal: ≥10 nmol/L vs <10 nmol/L	1.85 (0.49–6.93)	1.77 (0.46–6.86)	–	Menopausal status, tumor size, nodal status,

(continued)

Table 3 **Continued**

Reference	Cohort name, country	Study design, median follow-up (y)	Population	Menopausal status	Patient sex, age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure	Biomarkers of phytoestrogen intake categories	All-cause mortality RR (95%CI)	Cancer-specific mortality RR (95%CI)	Cancer recurrence RR (95%CI)	Adjustment covariates
												adjuvant chemotherapy and adjuvant tamoxifen
								Postmenopausal: ≥10 nmol/L vs <10 nmol/L	0.48 (0.28–0.82)	0.52 (0.29–0.94)	–	
Seibold et al (2014)[46]	MARIE, Germany	Population-based prospective cohort, 5.4	Patients with BC	Postmenopausal	F, 50–74	2182 (269/194 BC/188)	Serum/plasma enterolactone, postdiagnostic	Overall: Q4 (>45.1 nmol/L) vs Q1 (≤8.5 nmol/L)	0.59 (0.40–0.87)	0.59 (0.37–0.94)	0.77 (0.51–1.16)	Tumor size, nodal status, metastases status, histological grading, ER/PR status, BMI, radiotherapy, smoking, physical activity, MHT use, time between blood collection and enterolactone measurement
								Overall: per 10 nmol/L increment	0.94 (0.90–0.98)	0.94 (0.89–0.99)	0.99 (0.95–1.02)	
								ER+: Q4 (>45.1 nmol/L) vs Q1 (≤8.5 nmol/L)	0.76 (0.46–1.24)	–	–	
								ER+: per 10 nmol/L increment	0.95 (0.91–1.00)	–	–	
								ER–: Q4 (>45.1 nmol/L) vs Q1 (≤8.5 nmol/L)	0.37 (0.16–0.89)	–	–	
								ER–: per 10 nmol/L increment	0.92 (0.83–1.02)	–	–	
Eriksen et al (2017)[47]	Diet, Cancer and Health, Denmark	Population-based prospective cohort, 6	Patients with PC	NA	M, 51–64 (at baseline)	1391 (460/301 PC/NR)	Plasma enterolactone, prediagnostic	Overall: Q4 (>35 nmol/L) vs Q1 (<10 nmol/L)	0.83 (0.64–1.09)	0.95 (0.68–1.32)	–	BMI, smoking status, physical activity, antibiotics use and

(continued)

Table 3 **Continued**

Reference	Cohort name, country	Study design, median follow-up (y)	Population	Menopausal status	Patient sex, age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure	Biomarkers of phytoestrogen intake categories	All-cause mortality RR (95%CI)	Cancer-specific mortality RR (95%CI)	Cancer recurrence RR (95%CI)	Adjustment covariates
												defined daily doses
								Overall per 20 nmol/L increment	0.95 (0.90–1.02)	0.98 (0.92–1.05)	–	
Jaskulski et al (2018)[43]	MARIE, Germany	Population-based prospective cohort, 5.3	Patients with BC	Postmenopausal	F, 50–74	1743 (180/121 BC/NR)	Serum/plasma enterolactone, postdiagnostic	Overall: doubling in concentration	0.93 (0.87–0.99)	0.91 (0.84–0.99)	–	Age at diagnosis, center, tumor size, nodal status, grade, ER/PR status, detection type, time between OP and blood collection, BMI, and HRT use at diagnosis.
Kyro et al (2019)[49]	Diet, Cancer and Health, Denmark	Population-based prospective cohort, ∼7	Patients with CRC	NA	MF, 66 (median)	953 (535/385 CRC/NR)	Plasma enterolactone, prediagnostic	Female: Q4 (≥38.6 nmol/L) vs Q1 (≤9.9 nmol/L)	0.70 (0.47–1.07)	0.63 (0.41–0.99)	–	Age, smoking status, schooling, quantification of cigarette smoking, waist circumference, alcohol intake, intake of processed meat and frequency of bowel movements
								Female: doubling in concentration	0.92 (0.84–1.00)	0.88 (0.80–0.97)	–	
								Male: Q4 (≥37.2 nmol/L) vs Q1 (≤8.9 nmol/L)	1.27 (0.91–1.78)	1.52 (1.00–2.31)	–	
								Male: doubling in concentration	1.07 (0.99–1.15)	1.10 (1.01–1.21)	–	
			Patients with BC	Postmenopausal	F, 64 (median)				0.85 (0.65–1.13)	0.89 (0.62–1.27)	1.05 (0.72–1.51)	

(continued)

Table 3 **Continued**

Reference	Cohort name, country	Study design, median follow-up (y)	Population	Menopausal status	Patient sex, age at cancer diagnosis (years)	Total population (overall deaths/ cancer-specific deaths/ recurrence)	Exposure	Biomarkers of phytoestrogen intake categories	All-cause mortality RR (95%CI)	Cancer-specific mortality RR (95%CI)	Cancer recurrence RR (95%CI)	Adjustment covariates
Kyro et al (2018)[44]	Diet, Cancer and Health, Denmark	Population-based prospective cohort, 9				1457 (404/250 BC/267)	Plasma enterolactone, prediagnostic	Overall: Q4 (≥36.9 nmol/L) vs Q1 (≤9.5 nmol/L)				Smoking status at baseline, smoking intensity, schooling, BMI at baseline, physical activity measure at baseline, and hormone use at baseline
								Overall: doubling in concentration	0.95 (0.89–1.01)	0.93 (0.86–1.00)	0.96 (0.89–1.04)	
Jiang et al (2019)[48]	DACHS, Germany	Population-based prospective cohort, 5.2	Patients with CRC	NA	MF, 68.2 (mean)	2051 (475/254 CRC/400)	Serum genistein, postdiagnostic	Genistein: Q4 (≥14.13 ng/μL) vs Q1 (<10.08 ng/μL)	1.00 (0.77–1.30)	0.83 (0.58–1.19)	0.98 (0.72–1.34)	Age, sex, stage, cancer site, BMI, education, physical activity, screening-detected tumor, chemotherapy, diabetes, CVD, constipation, interval between chemotherapy and blood collection interval between surgery and blood collection
								Genistein: log transformed	1.03 (0.90–1.19)	0.96 (0.80–1.15)	1.05 (0.89–1.25)	

a Restricted to 5–10 years (median follow-up of entire study, 23 years).

Abbreviations: BC, breast cancer; BMI, body mass index; CRC, colorectal cancer; CVD, cardiovascular disease; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; ER, estrogen receptor; F, female; HR, hazard ratio; HRT, hormone replacement therapy; M, male; MARIE, Mammary Carcinoma Risk Factor Investigation; MHT, menopausal hormone therapy; NA, not applicable; NR, not reported; OP, operation; PC, prostate cancer; PR, progesterone receptor; Q, quintile; T, tertile.

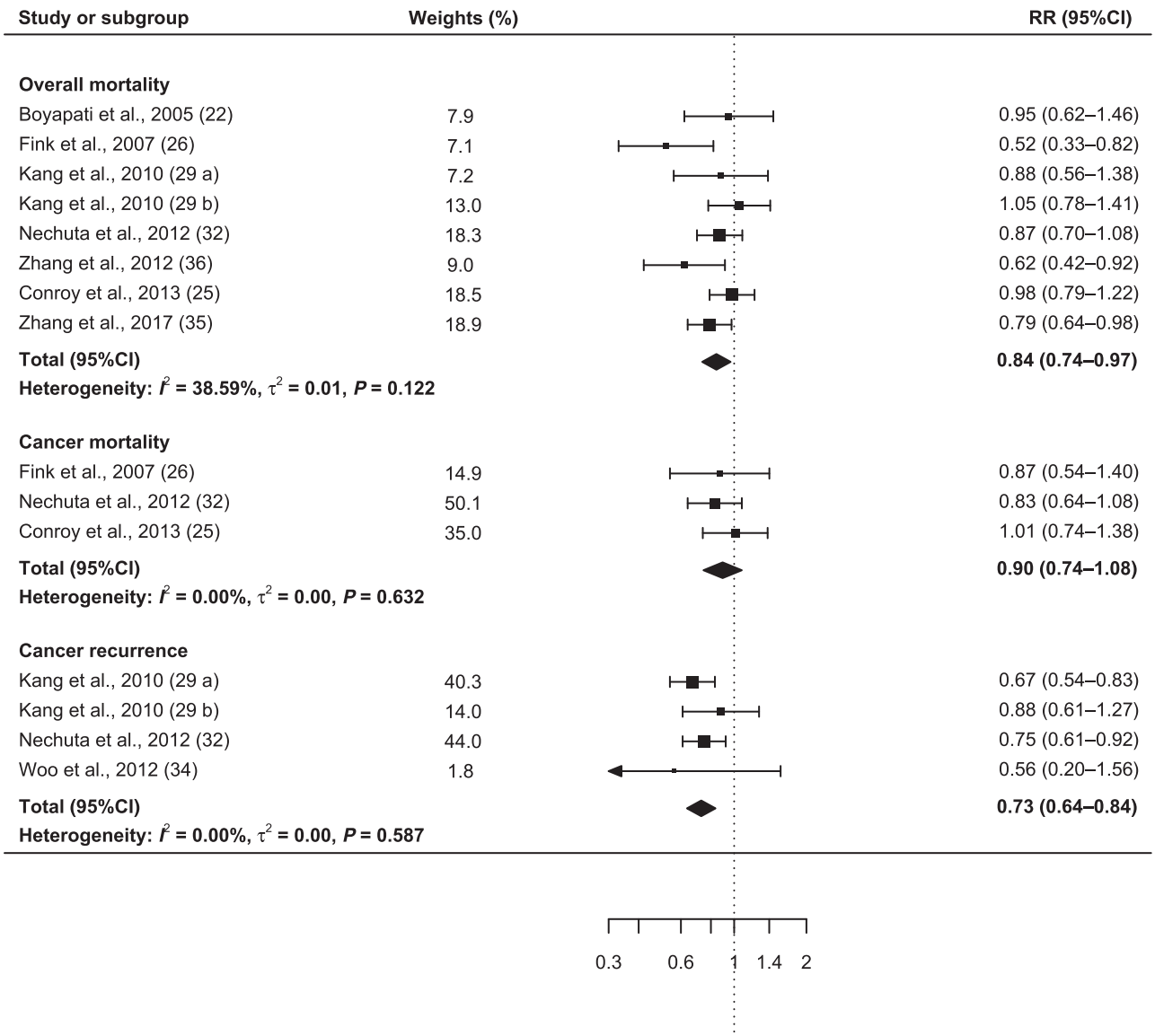

Figure 2 **Forest plot of summary hazard ratios of overall and cancer-specific mortality of and recurrence in patients with breast cancer for the highest vs lowest category of dietary isoflavone intake. [a]The data set is associated with postmenopausal women. [b]The data set is associated with premenopausal women. *Abbreviation:* IV, inverse variance**

survival rates among patients with colorectal cancer and those with glioma who had greater dietary intake of lignans (specifically, serum enterolactone and dietary secoisolaricinesinol, respectively) was observed.

Most of the analyses revealed moderate heterogeneity among the included studies, and several factors could have contributed to these findings, including assessment of phytoestrogen intake, phytoestrogen variability directly related to food quality, interindividual variation in response to consumption of plant polyphenols, and variations in isoflavone- and lignan-based foods consumption between Asian and non-Asian individuals.

Numerous observational studies have investigated the association between polyphenols, including isoflavones and lignans, and human health.[14] Although evidence of potential positive effects on health is available, our previous comprehensive overview of the association between total and individual classes of flavonoids and lignans and cancer risk resulted in relatively few results, with most of findings related to phytoestrogens (especially isoflavones) and breast and lung cancer risk.[16] Several mechanisms have been hypothesized to explain the potential benefits of phytoestrogens for preventing cancer, including direct inhibition of oxidative stress and oxidative damage as well as inflammatory-related gene expression, resulting in interference in the initiation, promotion, and progression of cancer.[50,51] However, to our knowledge, no comprehensive evidence has been produced to explore whether such potential benefits would have an impact also in

Table 4 **Summary hazard ratios of overall mortality, cancer-specific mortality, and cancer recurrence in patients with breast cancer for the highest vs lowest category of dietary intake of isoflavones and lignans and serum/plasma enterolactone concentration**

Dietary compound	No. of data sets (no. of cohorts)	HR (95%CI)	I^2 (%)	*P* for heterogeneity
Dietary isoflavones				
Overall mortality	8 (9)	0.84 (0.74–0.97)	39	0.12
Premenopausal	4 (6)	1.00 (0.83–1.20)	0	0.69
Postmenopausal	5 (7)	0.83 (0.68–1.00)	39	0.16
ER+	4 (6)	0.86 (0.71–1.05)	41	0.17
ER–	4 (6)	0.78 (0.57–1.05)	41	0.17
Cancer-specific mortality	3 (5)	0.90 (0.74–1.08)	0	0.63
Premenopausal	2 (4)	0.98 (0.69–1.39)	0	0.90
Postmenopausal	3 (5)	0.89 (0.71–1.11)	0	0.53
ER+	2 (4)	0.95 (0.72–1.26)	0	0.80
ER–	2 (4)	0.77 (0.54–1.09)	0	0.33
Cancer recurrence	4 (5)	0.73 (0.64–0.84)	0	0.59
Premenopausal	2 (4)	0.91 (0.72–1.15)	0	0.82
Postmenopausal	2 (4)	0.66 (0.55–0.78)	0	0.80
ER+	3 (4)	0.84 (0.63, 1.11)	64	0.06
ER–	2 (4)	0.82 (0.51, 1.34)	72	0.06
Dietary lignans				
Overall mortality	3 (2)	0.96 (0.49, 1.89)	72	0.03
Premenopausal	2 (2)	1.52 (0.86, 2.68)	0	0.39
Postmenopausal	2 (2)	0.72 (0.37, 1.41)	68	0.08
Cancer-specific mortality	3 (2)	0.80 (0.33, 1.93)	72	0.03
Premenopausal	2 (2)	1.38 (0.73, 2.60)	0	0.49
Postmenopausal	2 (2)	0.54 (0.19, 1.57)	73	0.06
Cancer recurrence	0 (0)	NA	NA	NA
Premenopausal	0 (0)	NA	NA	NA
Postmenopausal	0 (0)	NA	NA	NA
Serum/plasma enterolactone				
Overall mortality	4 (3)	0.70 (0.49, 0.99)	54	0.09
Premenopausal	1 (1)	1.85 (0.49, 6.93)	NA	NA
Postmenopausal	3 (3)	0.66 (0.47, 0.92)	57	0.10
Cancer-specific mortality	4 (3)	0.72 (0.51, 1.03)	39	0.18
Premenopausal	1 (1)	1.77 (0.46, 6.86)	NA	NA
Postmenopausal	3 (3)	0.68 (0.49, 0.96)	37	0.20
Cancer recurrence	2 (2)	0.91 (0.67, 1.23)	16	0.28
Premenopausal	0 (0)	NA	NA	NA
Postmenopausal	2 (2)	0.91 (0.67, 1.23)	16	0.28

Abbreviations: ER, estrogen receptor; HR, hazard ratio; NA, not applicable.

decreasing mortality rate and improve overall survival in patients with cancer. Laboratory studies suggest that phytoestrogens and their blood metabolites may prevent cancer progression through various pathways, including inhibition of cancer cell proliferation, survival, angiogenesis, inflammation, and metastasis.[52]

Several properties of phytoestrogens have been suggested to potentially reduce recurrence and mortality in patients with breast cancer, such as (1) antiproliferative, growth-inhibiting and proapoptotic effects mediated by ERβ, caspase-3 activation, direct inhibition of tyrosine kinase and nuclear factor κB activities[53]; (2) antiangiogenic activity by inhibiting vascular endothelial growth factor expression through inhibition of transcription factors, such as signal transducer and activator of transcription 3 and hypoxia-inducible factor, and its receptors Ras/Raf-1/MEK/ERK, PI3K/Akt, and ERK-NF-KB-cMyc-p21[54,55]; (3) reduction of cancer invasion and the metastatic spread of primary breast tumor through downregulation of matrix metalloproteases expression, which initiate the process of epithelial–mesenchymal transition-related pathways, such as Notch-1 and TGF-β signaling[56,57]; and (4) reduction of epigenetic modulation and DNA methylation, which is 1 of the key mechanisms underlying the maintenance of genome stability and gene expression.[58] It is interesting that some studies observed a biphasic action of genistein (a soy isoflavone) in certain cell lines, showing a growth stimulation at low concentrations and inhibition at high concentrations, and thus their potential use as anticancer therapeutic agents.[59,60] Mechanistic studies have also been published regarding the potential role of phytoestrogens in the prevention of colorectal cancer, for instance by activating or upregulating ERβ in the colon and promoting apoptosis in preclinical models and in clinical experience. This activity has been associated with a reduction in colon adenocarcinoma, which may reduce the risk of recurrence in patients at risk.[61] Several

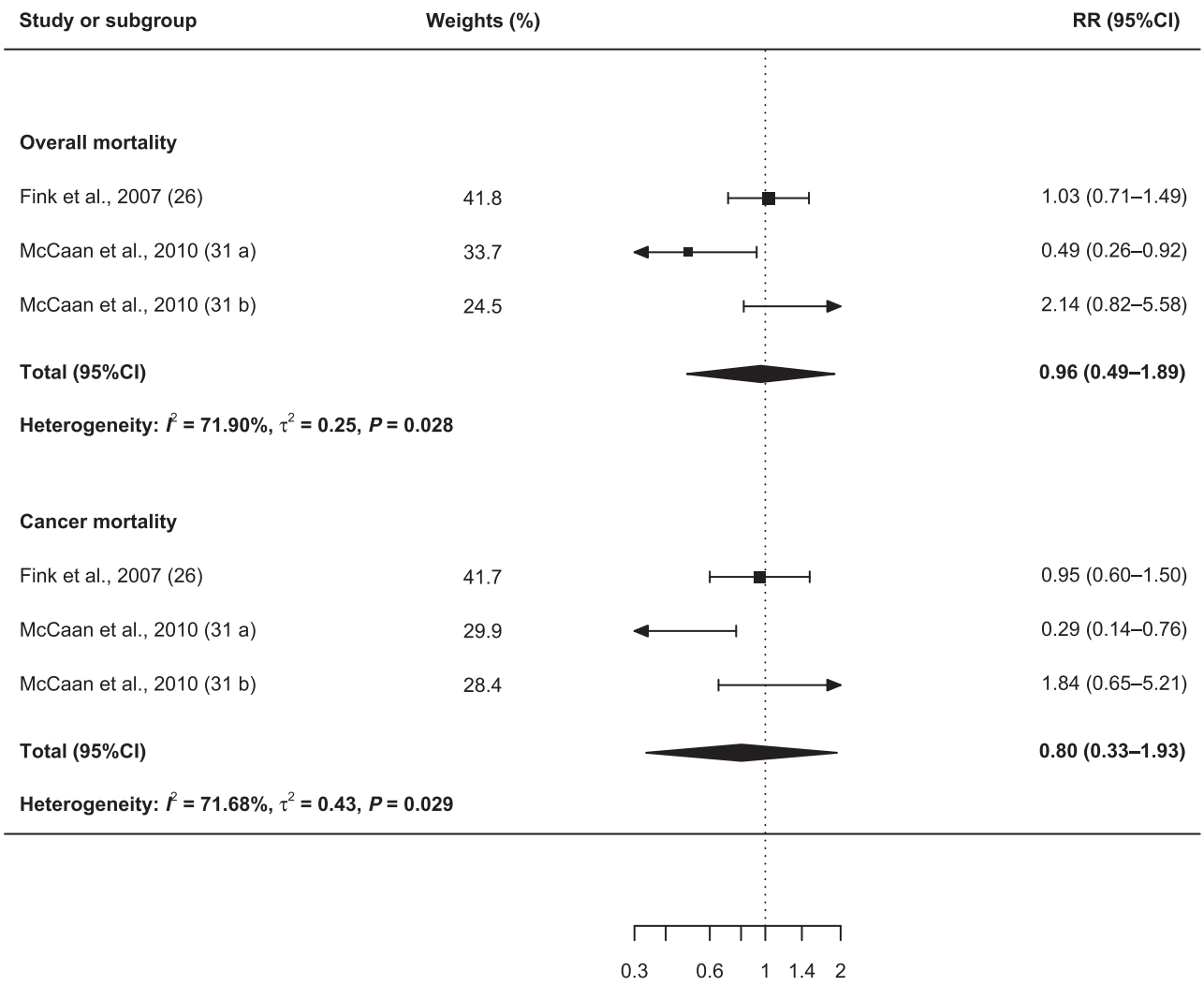

Figure 3 **Forest plot of summary hazard ratios of overall and cancer-specific mortality in patients with breast cancer for the highest vs lowest category of dietary lignan intake. [a]The data set is associated with postmenopausal women. [b]The data set is associated with premenopausal women. *Abbreviation:* IV, inverse variance**

studies also showed therapeutic effects against glioma tumors by inducing critical pro-apoptotic protein expression and cell apoptosis as well as inhibition of glioma cell migration by modulating mesenchymal properties.[62]

Subgroup analyses were performed to test whether some variables should be taken into account as potential effect modifiers. Because the structure of the main isoflavones found in the diet is similar to that of estradiol and because these molecules have weak estrogenic activities, it has been hypothesized that some isoflavones may have possible effects on estrogen target tissues modulated via ER-dependent mechanisms.[63,64] However, strate analysis did not reveal significant results when examining survival and cancer recurrence by receptor status. In contrast, different associations were found when considering pre- and postmenopausal breast cancers, underlying a significant decreased risk for the latter. There is evidence that diet may play a crucial role mostly among post- rather than premenopausal cancers[4]; these results are not surprising, because several other studies observed a potential preventive role of diet relative to postmenopausal breast cancers.[65] The reasons for such findings may rely on the potentially different nature of cancer occurring at younger ages, which may be more strongly influenced by genetics, compared with those occurring in older age, which may depend on lifelong chronic influence of detrimental factors led by unhealthy diets, such as low-grade inflammation and obesity.[66,67] Interestingly, it has been demonstrated that obese postmenopausal women are at higher risk of breast cancer than are normal-weight women, possibly due to the association between body mass index and endogenous estrogen concentrations (circulating estrogen concentrations in postmenopausal women depend on the extraglandular production of

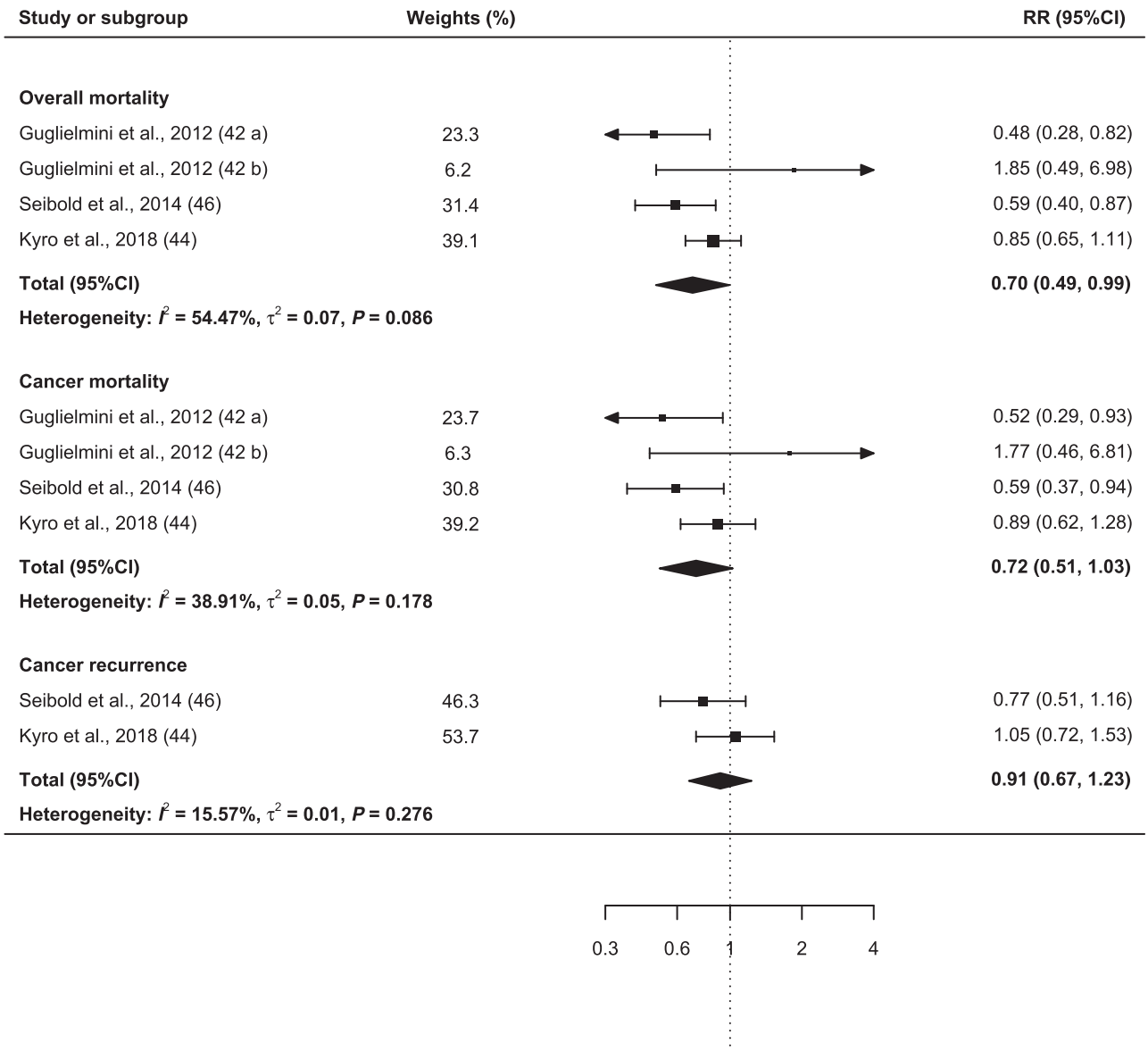

Figure 4 **Forest plot of summary hazard ratios of overall and cancer-specific mortality and recurrence in patients with breast cancer for the highest vs lowest category of serum/plasma enterolactone concentration. [a]The data set is associated with postmenopausal women. [b]The data set is associated with premenopausal women. *Abbreviation:* IV, inverse variance**

estrogen in the adipose tissue). On the other hand, an association between body mass index and breast cancer risk has not been found among premenopausal women, because most of the estrogen is produced by the ovaries and its levels are homeostatically regulated by a negative feedback system involving gonadotrophins; therefore, estrogen concentration is not directly affected by the levels of adipose tissue.[68]

The results of this review and meta-analysis should be considered in light of some limitations. First, a was a limited number of studies eligible for this meta-analysis, so subgroup analysis exploring the possible effect of confounding factors such as other dietary factors (eg, collinearity with other foods or phytochemicals) and family history of cancer, among others, could not be conducted. In addition, the limited number of studies could possibly be the reason why several associations were not significant, even though supported by clinical and mechanistic studies. Second, most of the observational studies investigating the relation between phytoestrogen intake and cancer relied on the estimation of intake from dietary recalls, which may be affected by bias, including recall bias, phytoestrogen variability directly related to food quality (eg, plant variety, season and environmental factors, food storage and processing) and the reference database used to estimate the polyphenol content. Finally, interindividual variation in response to consumption of plant phytoestrogens cannot be ruled

out. In this context, the use of biomarkers of phytoestrogen intake may help better assess real dietary intake[69] to potentially find stronger associations with cancer and other noncommunicable diseases. It would be better if the biomarkers used are validated as specific and reflective of the intake of their dietary precursors,[70] even though much work in this regard still is needed.[71]

CONCLUSIONS

The results reported here suggest an association between dietary phytoestrogens and breast cancer survival and recurrence; evidence regarding other cancers is too limited to draw strong conclusions. There is not sufficient evidence to provide dietary guidelines regarding these compounds; therefore, additional studies are needed to better elucidate the association between phytoestrogens and cancer survival and recurrence. Moreover, the findings of this systematic review and meta-analysis revealed the gap in the literature regarding several cancer types and the need for more advanced studies with significant sample sizes and long follow-up periods that explore the differences among diverse populations and a possible collinearity effect of confounding factors. Future studies should also focus on the interindividual variation in response to consumption of phytoestrogens and, therefore, investigate the association not only for their dietary intake but also for the true internal exposure to their metabolites. Last, more focus should be placed on the gut microbiota composition because differences in microbial species may condition phytoestrogen metabolite formation and bioactivity. If confirmed, these findings may be of critical importance to improve the health of patients with cancer and their chances of recovery over the course of disease.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Meta-Analysis of Observational Studies in Epidemiology guidelines**

Figure S1 **Funnel plot of summary hazard ratios (HRs) of overall and cancer-specific mortality of and recurrence in patients with breast cancer for the highest vs lowest category of dietary isoflavone intake**

Figure S2 **Funnel plot of summary hazard ratios (HRs) of overall and cancer-specific mortality of patients with breast cancer for the highest vs lowest category of dietary lignan intake**

Figure S3 **Funnel plot of summary hazard ratios (HRs) of overall and cancer-specific mortality of and recurrence in patients with breast cancer for the highest vs lowest category of serum/plasma enterolactone concentration**

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