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

Lead article

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Abstract

Context: Recent studies outlined the potential role of dietary factors in cancer survival patients. **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 cancer patients. **Data Sources:** A systematic search on 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, 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 between higher dietary isoflavone intake, higher serum/plasma enterolactone concentrations and overall mortality and cancer recurrence was found. Among other cancer types, two 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 breast cancer patients survival, while evidence regarding other cancers is too limited to draw any conclusions.

Keywords: isoflavones; lignans; polyphenols; enterolactone; cancer; meta-analysis

Introduction

Cancer, together with other inflammation-related non-communicable diseases, has been recognized as a global health threat. The report of the Global Burden of Disease Study reaffirmed this observation recognizing 24.5 million incident cancer cases and 9.6 million cancer deaths in 2017, worldwide.[1] Several risk factors may account for the burden of non-communicable diseases, including economic and social, lifestyle, and dietary factors. Among them, dietary factors attract a great attention undoubtedly due to 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 non-communicable diseases, including cancer. The most recent comprehensive summary conducted by Global Burden of Disease Study 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 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] Remarkably, latest scientific evidence has pointed out dietary polyphenols as promising compounds that may exert beneficial effects toward 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] mortality,[14] and

depression.[15] Recently, a comprehensive meta-analysis quantitatively analyzing the association between dietary polyphenol and phytoestrogen intakes and different cancer types was published. [16] Interestingly, the results revealed that higher dietary intake of isoflavones may be inversely associated with risk of lung, stomach, colorectal and breast cancer. Mechanistic studies underline the protective effect of these bioactive molecules towards 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, up to now, a comprehensive summary of the evidence regarding main classes of dietary phytoestrogens (i.e., isoflavones and lignans), their biomarkers/metabolites (i.e. equol and enterolactone),[19] and cancer survival and recurrence considering all cancer types has not been conducted. Thus, the aim of the present review was to systematically describe and quantitatively analyze existing studies investigating the association between dietary intake of phytoestrogen as well as 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 (MOOSE) guidelines (Table S1 in the Supporting Information online).[20] Moreover, eligibility criteria for the search and meta-analyses were specified using the PICOS approach: determination of the Population (P), Intervention/Exposure (I), Comparison (C), Outcomes (O), Study design (S) (Table 1).

Study selection

A systematic search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (http://www.embase.com/), and Web of Science (www.webofknowledge.com) 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 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: (i) were observational studies (either prospective or retrospective cohort studies); (ii) were conducted on cancer patients; (iii) evaluated associations between dietary phytoestrogens and/or their biomarkers and cancer outcomes, including overall mortality, cancer-specific mortality, and recurrence; (iv) assessed and reported hazard ratios (HRs) and their corresponding 95% CI. As exposure, dietary intake of the following: i) total isoflavones and their individual components including daidzein, genistein, glycitein, formononetin, and biochanin A; ii) biomarkers/metabolites of isoflavones intake including equol; iii) total lignans and their individual components including matairesinol, lariciresinol, secoisolariciresinol, and pinoresinol; iv) biomarkers/metabolites of lignans intake including enterolactone and enterodiol was considered. Reference lists of eligible studies were also examined for any additional study not previously identified. If more than one 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 was performed by two independent authors.

Data extraction and quality assessment

Data were extracted using a standardized extraction form. The following information was collected: (i) first author name and year of publication; (ii) study cohort name and country; (iii) study design an median follow-up period; (iv) population characteristics; (v) sex and age of participants; (vi) cohort size and number of deaths, cancer-related deaths and cancer recurrence; (vii) type of exposure and its main characteristics; (viii) distributions of cases and person-years, HRs and 95% CIs for all categories of exposure; and (ix) adjustment covariates. The quality of each eligible study was using the Newcastle-Ottawa Quality Assessment Scale,[21] consisting of 3 domains of quality as follows: selection (4 points), comparability (2 points), and outcome (3 points) for a total score of 9 points (9 representing the highest quality). Studies scoring 7-9 points, 4-6 points, and 0–3 points were identified as 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 their blood biomarkers. HRs with 95% CI for all categories of exposure were extracted for the analysis. Random-effects models were used in order to estimate pooled results for the highest versus 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 expressed as $p < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. I^2 values ≤25%, 25–50%, 50–75%, and >75% indicated no, small, moderate, and significant heterogeneity, respectively. A sensitivity analysis by exclusion of one study at the time was performed in order 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 receptor 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, out of which 402 were excluded on the basis of title and 170 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 between dietary phytoestrogen intake and/or their blood biomarkers and overall, cancer-specific survival and cancer recurrence were included in the systematic review.[22-49] In detail, 19 studies examined the association between dietary intake of phytoestrogens and cancer,[22-40] out of which 15 focused on breast cancer,[22-36] one on colorectal cancer,[37] one on prostate cancer,[38] one on lung cancer,[39] and one on malignant glioma.[40] Nine articles focused on blood biomarkers of dietary phytoestrogen intake and cancer,[41-49] out of which 6 were on breast cancer,[41-46] two on colorectal cancer,[48,49] and one 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 between dietary phytoestrogen intake (isoflavones and lignans) and overall mortality, cancer-specific mortality and recurrence in breast cancer patients (Table 2),[22-36] while six examined the association with blood biomarkers of their consumption (Table 3).[41-46] All the studies exploring this association for dietary

phytoestrogens estimated their intake using a Food Frequency Questionnaire (FFQ), which however 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] five on cancer-specific mortality [25,26,32] as well as five on cancer recurrence in breast cancer patients.[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 with I^2:39% and HR: 0.66, 95% CI: 0.55, 0.78 with I^2:0%; respectively).

Only two studies were eligible for the analysis on 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, HR: 0.80, 95% CI: 0.33, 1.93; respectively), possibly due to the limited number of included studies (Figure 3, Table 4 and Figure S2 in the Supporting Information online). Moreover, high heterogeneity among the included studies was observed.

Three studies were eligible for the meta-analysis exploring the association between serum/plasma enterolactone concentration, a biomarker of lignans consumption (enterolactone is a metabolite of lignans which undergo metabolism and modification by

human gut microbiota),[19] and overall mortality,[42,44,46] as well as cancer-specific mortality,[42,44,46] while two studies for cancer recurrence in breast cancer patients.[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) were 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). Visual investigation of funnel plots 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 the 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 as well as lignans and colorectal cancer survival and recurrence was annotated.[37] Accordingly, another population-based study on a sample of 2,051 colorectal cancer patients followed for more than 5 years reported no association between serum genistein (an isoflavone) and overall mortality, cancer-specific mortality and recurrence (Table 3).[48] On the contrary, high plasma pre-diagnostic enterolactone levels were inversely associated with cancer-specific mortality, but solely in females (HR: 0.63, 95% CI: 0.41, 0.99; Table 3).[49]

227 *Prostate cancer*

228 The association between both dietary and serum biomarkers of phytoestrogens and prostate
229 cancer survival was explored in two studies.[38,47] A hospital-based retrospective cohort study
230 conducted on 777 prostate cancer patients followed for 12.7 years recorded 263 deaths,
231 among which 81 were due to prostate cancer. Despite the long follow-up period, the study did
232 not find any significant association for either overall or prostate-cancer specific mortality
233 when comparing the highest *versus* the lowest category of dietary isoflavone intake (Table
234 2).[38] Similarly, no significant results were reported for the association between plasma
235 enterolactone and overall and prostate cancer-specific mortality in a sample of 1,391 prostate
236 cancer patients followed for 6 years (Table 3).[47]

237

238 *Lung cancer*

239 Up to date, one study investigated the possible relationship between pre-diagnostic dietary
240 isoflavones intake and lung cancer survival.[39] The study enrolled 444 lung cancer patients
241 and followed them for 36 months, during which 318 deaths occurred (301 were due to lung
242 cancer). However, after adjusting for potential confounding factors, no significant association
243 between higher isoflavones intake and overall cancer survival was found (HR: 0.97, 95% CI:
244 0.78, 1.20; Table 2).[39]

245

246 *Malignant glioma*

247 One sole prospective cohort study reporting on the association between pre-diagnostic dietary
248 phytoestrogen intake and cancer survival in glioma patients was retrieved in the systematic
249 search.[40] The study, conducted on 748 male and female glioma patients (median age 55.7
250 years), reported 648 deaths over the follow-up period. The exposure of interest included
251 dietary intake of individual isoflavones (formononetin, genistein, daidzein, and biochanin A)

and lignans (coumestrol, matairesinol, and secoisolariciresinol). Authors found that higher dietary intake of secoisolaricinesinol among Grade III glioma patients was associated with a better cancer survival (HR: 0.48, 95% CI: 0.25, 0.92; Table 2).

Discussion

The present study provided a comprehensive review of existing prospective and retrospective studies on the dietary intake of isoflavones and lignans, as well as 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. Performed meta-analyses found that higher dietary isoflavone intake was inversely associated with overall mortality and cancer recurrence among breast cancer patients. 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 analysis stratified for ER receptor status resulted significant, possible due to the limited number of analyzed studies. Among the other cancers investigated, only an association of better survival in colorectal cancer and glioma patients with higher dietary intake of lignans (specifically, serum enterolactone and dietary secoisolaricinesinol, respectively) has been 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, inter-

individual 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] While evidence on 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 scarce results, with most of findings related to phytoestrogens (especially isoflavones) and breast and lung cancer risk.[16] A number of 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 interfering with the initiation, promotion, and progression of cancer.[50,51] However, up to now, no comprehensive evidence has been produced to explore whether such potential benefits would have an impact also in decreasing mortality rate and improve overall survival in cancer patients. 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 breast cancer patients, such as (i) antiproliferative, growth inhibiting and proapoptotic effects mediated by ERβ, caspase-3 activation, direct inhibition of tyrosine kinase and nuclear factor κB (NF-κB) activities[53]; (ii) antiangiogenic activity by inhibiting vascular endothelial growth factor (VEGF) expression through inhibition of transcription factors, such as signal transducer and activator of transcription 3 (STAT3) and hypoxia-

inducible factor (HIF-1), and its receptors Ras/Raf-1/MEK/ERK, PI3K/Akt, and ERK-NF-KB-cMyc-p21[54,55]; (iii) 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-beta signaling[56,57]; (iv) reduction of epigenetic modulation and DNA methylation, which is one 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, with the potentiality of their use as anti-cancer 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] A number of studies also showed therapeutic effects against glioma tumors by inducing critical pro-apoptotic proteins expression and cell apoptosis as well as inhibition of glioma cell migration by modulating mesenchymal properties.[62]

A number of subgroup analyses to test whether some variables should be taken into account as potential effect modifiers was performed. Since the structure of the main isoflavones found in the diet is similar to that of estradiol and that these molecules have been shown to have weak estrogenic activities, it has been hypothesized that some isoflavones may have possible effects on estrogen-target tissues modulated via estrogen receptor-dependent mechanisms.[63,64] However, the analysis failed in finding significant results in strata analysis when examining survival and cancer recurrence by receptor status. In contrast, different associations when

considering pre- and post-menopausal breast cancers were found, underlying a significant decreased risk of the latter. There is evidence that diet may play a crucial role mostly among post- rather than pre-menopausal cancers[4]: these results are not surprising, as several other studies observed a potential preventive role of diet toward post-menopausal breast cancers.[65] The reasons for such findings may rely on the potentially different nature of cancer occurring in younger age, which might be more strongly influenced by genetics, compared to 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 compared to normal weight women, possibly due to the association between BMI and endogenous estrogen concentrations, as in postmenopausal women circulating estrogen concentrations are dependent on the extraglandular production of estrogen in the adipose tissue. On the other hand, an association between BMI and breast cancer risk has not been found among premenopausal women, as 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 the present review and meta-analysis should be considered in light of some limitations. Firstly, a limited number of studies was eligible for the present meta-analysis, so subgroup analysis exploring the possible effect of confounding factors such as other dietary factors (i.e., collinearity with other foods or phytochemicals), family history of cancer, and many others could not be conducted. In addition, the limited number of studies could possibly be the reason why several associations, even though supported by clinical and mechanistic studies, did not result significant. Secondly, most of the observational studies investigating the relation between phytoestrogen intake and cancer rely on the estimation of

intake from dietary recalls, which may be affected by bias, including recall bias, phytoestrogen variability directly related to food quality (plant variety, season and environmental factors, food storage and processing) and the reference database used to estimate the polyphenol content. Finally, inter-individual variation in response to consumption of plant phytoestrogens cannot be ruled out. In this context, the use of biomarkers of phytoestrogen intake may help in better assessing real dietary intake,[69] to potentially find stronger associations with cancer and other non-communicable 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 still have to be carried out in this regard by the scientific community.[71]

Conclusions

These results suggest an association between dietary phytoestrogens and breast cancer survival and recurrence, while evidence regarding other cancers is too limited to draw strong conclusions. Today's evidence is not sufficient to provide dietary guidelines regarding these compounds and, therefore, further studies are needed in order to better elucidate the association between phytoestrogens and cancer survival and recurrence. Moreover, the findings of the present 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-ups, exploring the differences among diverse populations and possible collinearity effect of confounding factors. Future studies should also focus on the inter-individual 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, further focus on the gut microbiota composition should be paid as differences in microbial species may condition phytoestrogen metabolite formation

and bioactivity. If confirmed, these findings may be of critical importance to improve health of cancer patients and their chances of recovery over the course of disease.

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581

582 **Table legend**

583 Table 1. PICOS criteria.

584

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

587

588 Table 3. Characteristics of the studies investigating the association between serum/plasma
589 markers of dietary phytoestrogen intake and overall and cancer-specific mortality and
590 recurrence in cancer patients.

591

592 Table 4. Summary hazard ratios (HRs) of overall and overall and cancer-specific mortality
593 and recurrence in breast cancer patients for the highest versus lowest category of dietary
594 intake of isoflavones and lignans and serum/plasma enterolactone concentration.

595

596 **Figure legend**

597 Figure 1. Flow chart of study identification and selection process.

598

599 Figure 2. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality
600 and recurrence in breast cancer patients for the highest versus lowest category of dietary
601 isoflavone intake. “a” indicates dataset associated with postmenopausal women, while “b”
602 indicates dataset associated with premenopausal women.

603

604 Figure 3. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality
605 in breast cancer patients for the highest versus lowest category of dietary lignan intake. “a”

606 indicates dataset associated with postmenopausal women, while “b” indicates dataset
607 associated with premenopausal women.
608
609 Figure 4. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality
610 and recurrence in breast cancer patients for the highest versus lowest category of
611 serum/plasma enterolactone concentration. “a” indicates dataset associated with
612 postmenopausal women, while “b” indicates dataset associated with premenopausal women.
613
614 **Supporting information legend**
615 Table S1. The Meta-analysis of Observational Studies in Epidemiology (MOOSE)
616 guidelines.
617
618 Figure S1. Funnel plot of summary hazard risks (HRs) of overall and cancer-specific
619 mortality and recurrence in breast cancer patients for the highest *versus* lowest category of
620 dietary isoflavone intake.
621
622 Figure S2. Funnel plot of summary hazard risks (HRs) of overall and cancer-specific
623 mortality in breast cancer patients for the highest *versus* lowest category of dietary lignan
624 intake.
625
626 Figure S3. Funnel plot of summary hazard risks (HRs) of overall and cancer-specific
627 mortality and recurrence in breast cancer patients for the highest *versus* lowest category of
628 serum/plasma enterolactone concentration.
629

630 Table 1. PICOS criteria.

PICO	Description
P (Population)	Men and women, cancer patients.
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 cancer patients.
S (Study design)	Systematic review with meta-analysis.

631

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

Author, year	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Sex, age (at cancer diagnosis)	N 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, 5.2y	Breast cancer patients	Premenopausal, postmenopausal	F, 25-64y	1,459 (240/NR/NR)	Dietary isoflavones, postdiagnostic, 76-item FFQ	Overall: T3 vs. T1	0.95 (0.62, 1.45)[#]	-	-	Age at diagnosis, stage of disease, radiotherapy, ER/PR status, total energy intake.
Fink et al. (2007)[26]	LIBCSP, USA	Population-based retrospective cohort, NR	Breast cancer patients	Premenopausal, postmenopausal	F, 25-98y	1,210 (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, USA	Population-based prospective cohort, 6.3y (average)	Breast cancer patients	Premenopausal, postmenopausal	F, 18-79y	1,954 (NR/NR/282)	Dietary daidzein, postdiagnostic, over 100-item FFQ	Overall: Q5 (≥9596.55 ug/d) vs. Q1 (<0.10 ug/d)	-	-	0.96 (0.52, 1.76)	Soy supplement use, BMI 1 year before diagnosis, menopausal status, tobacco pack-years, tumor stage, ER status, age, race and kilocalories.
								Premenopausal: Q5 (≥9596.55 ug/d) vs. Q1 (<0.10 ug/d)	-	-	1.74 (0.63, 4.76)	
								Postmenopausal: Q5 (≥9596.55 ug/d) vs. Q1 (<0.10 ug/d)	-	-	0.70 (0.27, 1.77)	
								ER-/PR-: Q5 (≥9596.55 ug/d) vs. Q1 (<0.10 ug/d)	-	-	1.45 (0.43, 4.95)	
								ER+/PR+: Q5 (≥9596.55 ug/d) vs. Q1 (<0.10 ug/d)	-	-	0.82 (0.40, 1.68)	
							Dietary genistein, postdiagnostic, over 100-item FFQ	Overall: Q5 (≥13025.88 ug/d) vs. Q1 (<0.10 ug/d)	-	-	0.95 (0.52, 1.75)	
								Premenopausal: Q5 (≥13025.88 ug/d) vs. Q1 (<0.10 ug/d)	-	-	1.75 (0.65, 4.76)	

							Dietary glycetin, postdiagnostic, over 100-item FFQ	Postmenopausal: Q5 (≥13025.88 ug/d) vs. Q1 (<0.10 ug/d)	-	-	0.69 (0.27, 1.75)	
								ER-/PR-: Q5 (≥13025.88 ug/d) vs. Q1 (<0.10 ug/d)	-	-	1.34 (0.39, 4.57)	
								ER+/PR+: Q5 (≥13025.88 ug/d) vs. Q1 (<0.10 ug/d)	-	-	0.83 (0.40, 1.69)	
								Overall: Q5 (≥795.40 ug/d) vs. Q1 (<3.62 ug/d)	-	-	0.80 (0.42, 1.50)	
								Premenopausal: Q5 (≥795.40 ug/d) vs. Q1 (<3.62 ug/d)	-	-	1.60 (0.54, 4.72)	
								Postmenopausal: Q5 (≥795.40 ug/d) vs. Q1 (<3.62 ug/d)	-	-	0.51 (0.18, 1.38)	
								ER-/PR-: Q5 (≥795.40 ug/d) vs. Q1 (<3.62 ug/d)	-	-	0.38 (0.08, 1.79)	
								ER+/PR+: Q5 (≥795.40 ug/d) vs. Q1 (<3.62 ug/d)	-	-	0.94 (0.47, 1.89)	
Shu et al. (2009)[33]	SBCSS, China	Population-based prospective cohort, 3.9y	Breast cancer patients	Premenopausal, postmenopausal	F, 20-75y	5,033 (444/534 BC[§])	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)[§]	0.77 (0.60, 0.98)[§]	Age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery received, BMI, menopausal status, ER and progesterone receptor status, tamoxifen use, education level, 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)[§]	0.88 (0.62, 1.25)[§]	
								ER+: Q4 (>62.68 mg/d) vs. Q1 (≤20.00 mg/d)	0.78 (0.53, 1.16)	0.77 (0.54, 1.09)[§]	0.77 (0.54, 1.09)[§]	
De Lorenze et al. (2010)[40]	NR, USA	Population-based prospective cohort, NR	Malignant glioma patients	NA	MF, 55.7y (median)	748 (648/NR/NR)	Coumestrol, prediagnostic, 79-item FFQ	II grade cancer: T3 (>145.5 ug/d) vs. T1 (83.4 ug/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 ug/d) vs. T1 (83.4 ug/d)	1.06 (0.60, 1.87)	-	-	
								IV grade cancer: T3 (>145.5 ug/d) vs. T1 (83.4 ug/d)	1.16 (0.88, 1.54)	-	-	

							Matairesinol, prediagnostic, 79-item FFQ	II grade cancer: T3 (>34.6 ug/d) vs. T1 (<17.6 ug/d)	0.78 (0.36, 1.69)	-	-	
								III grade cancer: T3 (>34.6 ug/d) vs. T1 (<17.6 ug/d)	0.86 (0.48, 1.54)	-	-	
								IV grade cancer: T3 (>34.6 ug/d) vs. T1 (<17.6 ug/d)	1.20 (0.92, 1.57)	-	-	
							Secoisolariciresinol, prediagnostic, 79-item FFQ	II grade cancer: T3 (>146.1 ug/d) vs. T1 (<87.3 ug/d)	1.95 (0.93, 4.10)	-	-	
								III grade cancer: T3 (>146.1 ug/d) vs. T1 (<87.3 ug/d)	0.48 (0.25, 0.92)	-	-	
								IV grade cancer: T3 (>146.1 ug/d) vs. T1 (<87.3 ug/d)	1.32 (1.02, 1.72)	-	-	
							Formononetin, prediagnostic, 79-item FFQ	II grade cancer: T3 (>23.1 ug/d) vs. T1 (<9.3 ug/d)	1.08 (0.46, 2.52)	-	-	
								III grade cancer: T3 (>23.1 ug/d) vs. T1 (<9.3 ug/d)	0.79 (0.43, 1.43)	-	-	
								IV grade cancer: T3 (>23.1 ug/d) vs. T1 (<9.3 ug/d)	1.04 (0.79, 1.37)	-	-	
							Genistein, prediagnostic, 79-item FFQ	II grade cancer: T3 (>291.6 ug/d) vs. T1 (<141.3 ug/d)	1.05 (0.40, 2.74)	-	-	
								III grade cancer: T3 (>291.6 ug/d) vs. T1 (<141.3 ug/d)	1.25 (0.69, 2.27)	-	-	
								IV grade cancer: T3 (>291.6 ug/d) vs. T1 (<141.3 ug/d)	1.35 (1.00, 1.81)	-	-	
							Daidzein, prediagnostic, 79-item FFQ	II grade cancer: T3 (>440.6 ug/d) vs. T1 (269.0 ug/d)	1.70 (0.70, 4.14)	-	-	
								III grade cancer: T3 (>440.6 ug/d) vs. T1 (269.0 ug/d)	1.01 (0.55, 1.85)	-	-	
								IV grade cancer: T3 (>440.6 ug/d) vs. T1 (269.0 ug/d)	1.13 (0.86, 1.49)	-	-	
							Biochanin A, prediagnostic, 79-item FFQ	II grade cancer: T3 (>37.8 ug/d) vs. T1 (15.4 ug/d)	0.60 (0.28, 1.30)	-	-	
								III grade cancer: T3 (>37.8 ug/d) vs. T1 (15.4 ug/d)	0.91 (0.45, 1.88)	-	-	
								IV grade cancer: T3 (>37.8 ug/d) vs. T1 (15.4 ug/d)	1.26 (0.97, 1.64)	-	-	
Kang et al. (2010)[29]	NR, China	Hospital-based prospective cohort, 5.1y	Breast cancer patients	Premenopausal (47.3%), postmenopausal (52.7%)	F, 29-72y	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, estrogen and progesterone receptor 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) vs. Q1 (<15.2 mg/d)	-	-	0.66 (0.49, 0.86)	

								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, USA	Population-based prospective cohort, 9-125 months	Breast cancer patients	Premenopausal (28.1%), postmenopausal (71.9%)	F, 35-79y	1,122 (160/94 BC/NR)	Dietary lignan, prediagnostic, 121-item FFQ	Premenopausal: Q4 (>257 ug/d) vs. Q1 (<128 ug/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 ug/d) vs. Q1 (<155 ug/d)	0.49 (0.26, 0.91)	0.29 (0.11, 0.76)	-	
Buck et al. (2011)[23]	MARIE, Germany	Population-based prospective cohort, 6.4y	Breast cancer patients	Postmenopausal	F, 50-74y	2,653 (321/235 BC/NR)	Dietary enterolactone, prediagnostic, 176-item FFQ	Overall: Q5 (502.0 ug/d, median) vs. Q1 (146.0 ug/d, median)	0.60 (0.40, 0.89)	0.69 (0.43, 1.10)	-	Tumor size, nodal status, metastasis, grade, ER/PR status, breast cancer detection type, diabetes, menopausal hormone therapy use at diagnosis, study center, and energy intake.
							Dietary enterodiol, prediagnostic, 176-item FFQ	Overall: Q5 (857.5 ug/d, median) vs. Q1 (186.9 ug/d, median)	0.63 (0.42, 0.95)	0.81 (0.51, 1.29)	-	
Caan et al. (2011)[24]	WHEL, USA	Population-based prospective cohort, 7.3y	Breast cancer patients	Premenopausal, postmenopausal	F, 18-70y	3,088 (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)	
								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	Breast cancer patients	Premenopausal (37.3%), postmenopausal (62.7%)	F, 46.7y	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, WHEL)	Population-based prospective cohorts, 7.4y (mean)	Breast cancer patients	Premenopausal, postmenopausal	F, ~54y (mean)	9,514 (1,171/881 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, estrogen receptor/progesterone receptor 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 months	Breast cancer patients	Premenopausal (38.9%), postmenopausal (61.1%)	F, 25-77y	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 months	Breast cancer patients	Premenopausal (52.9%), postmenopausal (47.1%)	F, 45.7y (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 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, USA	Population-based prospective cohort, 6.2y (mean)	Breast cancer patients	Postmenopausal	F, ≥50y	3,842 (804/376 BC/NR)	Dietary isoflavones, prediagnostic, over 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

								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)	-	cohort entry and diagnosis.
								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)[38]	SWHS, China	Population-based prospective cohort, 36 months	Lung cancer patients	NA	F, 66.3y (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 lung cancer in first-degree relatives; intakes of total calories, fruits and non-soy vegetables, time interval between the first food frequency questionnaire survey and lung cancer diagnosis, and use of nonsteroidal anti-inflammatory drugs and vitamin supplements.
Kyro et al. (2015)[30]	EPIC, multicenter	Population-based prospective cohort, 6.3y	Breast cancer patients	Premenopausal (24%), postmenopausal (76%)	F, 59y (median)	11,782 (1,482/753 BC/NR)	Dietary isoflavones, prediagnostic, up to 260-item FFQ	Premenopausal: doubling in 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 receptor status, cancer stage and grading of tumor, stratification for age and country.
								Postmenopausal: doubling in intake	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)	-	
							Dietary lignan, prediagnostic, up to 260-item FFQ	Premenopausal: doubling in intake	1.26 (1.05, 1.51)	1.24 (0.98, 1.58)	-	
								Postmenopausal: doubling in 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, 8.6y (mean)	Colorectal cancer patients	NA	MF, ~67y (median)	409 (133/NR/77)	Dietary isoflavones, NR, over 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 colorectal cancer stage.

							Dietary lignan, NR, over 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, 12.7y	Prostate cancer patients	NA	M, 46-74y	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. 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, smoking status, and pack-years.
Zhang et al. (2017)[35]	BCFR, multicenter	Population-based prospective cohort, 9.4y	Breast cancer patients	Premenopausal (49%), postmenopausal (51%)	F, 51.8y (mean)*	6,235 (1,224/NR/NR)	Dietary isoflavones, prediagnostic and postdiagnostic, 108-item FFQ	Overall: Q4 (≥1.494 mg/d) vs. Q1 (<0.342 mg/d)	0.79 (0.64, 0.97)	-	-	
								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)	-	-	

Abbreviations: ABCPP (After Breast Cancer Pooling Project); BC (breast cancer); BCFR (Breast Cancer Family Registry); BMI (body mass index); DHQ (dietary history questionnaire); EPIC (European Prospective Investigation into Cancer and Nutrition); FFQ (food frequency questionnaire); HR (hazard ratio); LACE (Life After Cancer Epidemiology); LC (lung cancer); LIBCSP (Long Island Breast Cancer Study); MEC (Multiethnic Cohort): NR (not reported); SBCSS (Shanghai Breast Cancer Survival Study); PC (prostate cancer); SWHS (Shanghai Women's Health Study); WEB (Western New York Exposures and Breast Cancer); WHEL (Women's Healthy Eating and Living).

[§] includes recurrence and breast cancer-specific mortality

*age at enrolment

[#]among those with no recent dietary change

634

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

Author, year	Cohort name, country	Study design, median follow-up	Population	Menopausal status	Sex, age (at cancer diagnosis)	N 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, 6.1y	Breast cancer patients	Postmenopausal	F, 50-74y	1,140 (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, breast cancer detection type, diabetes, HRT use at diagnosis, BMI, and physical activity.
								Overall: per 10 nmol/L increment	0.94 (0.88, 1.00)	-	-	
								ER-positive: Q4 (≥42.3 nmol/L) vs. Q1 (≤7.8 nmol/L)	0.91 (0.45, 1.84)	-	-	
								ER-positive: per 10 nmol/L increment	0.96 (0.89, 1.04)	-	-	
								ER-negative: Q4 (≥42.3 nmol/L) vs. Q1 (≤7.8 nmol/L)	0.27 (0.08, 0.87)	-	-	
								ER-negative: 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, 10y	Breast cancer patients	Postmenopausal	F, 60y (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 hormone replacement therapy.
								Overall: per 20 nmol/L increment	0.82 (0.70, 0.96)	0.88 (0.75, 1.03)	-	
								ER-positive: >20.5 nmol/L vs. ≤20.5 nmol/L	0.43 (0.26, 0.69)	0.59 (0.32, 1.09)	-	
								ER-negative: >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, 5-10y*	Breast cancer patients	Premenopausal (29.3%), postmenopausal (70.7%)	F, 58.5y (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, 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, 5.4y	Breast cancer patients	Postmenopausal	F, 50-74y	2,182 (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 draw 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-positive: Q4 (>45.1 nmol/L) vs. Q1 (≤8.5 nmol/L)	0.76 (0.46, 1.24)	-	-	
								ER-positive: per 10 nmol/L increment	0.95 (0.91, 1.00)	-	-	
								ER-negative: Q4 (>45.1 nmol/L) vs. Q1 (≤8.5 nmol/L)	0.37 (0.16, 0.89)	-	-	
								ER-negative: 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, 6y	Prostate cancer patients	NA	M, 51-64y (at baseline)	1,391 (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 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, 5.3y	Breast cancer patients	Postmenopausal	F, 50-74y	1,743 (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 draw, BMI and HRT use at diagnosis.
Kyro et al. (2018)[49]	Diet, Cancer and Health, Denmark	Population-based prospective cohort, ~7y	Colorectal cancer patients	NA	MF, 66y (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)	-	
Kyro et al. (2018)[44]	Diet, Cancer and Health, Denmark	Population-based prospective cohort, 9y	Breast cancer patients	Postmenopausal	F, 64y (median)	1,457 (404/250 BC/267)	Plasma enterolactone, prediagnostic	Overall: Q4 (≥36.9 nmol/L) vs. Q1 (≤9.5 nmol/L)	0.85 (0.65, 1.13)	0.89 (0.62, 1.27)	1.05 (0.72, 1.51)	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, 5.2y	Colorectal cancer patients	NA	MF, 68.2y (mean)	2,051 (475/254 CRC/400)	Serum genistein, postdiagnostic	Genistein: Q4 (≥14.13 ng/uL) vs. Q1 (<10.08 ng/uL)	1.00 (0.77, 1.30)	0.83 (0.58, 1.19)	0.98 (0.72, 1.34)	Age, gender, stage, cancer site, BMI, education, physical activity, screening detected tumor, chemotherapy, diabetes, CVD, constipation, interval between chemotherapy and blood drawn, interval between surgery and blood drawn.
								Genistein: log transformed	1.03 (0.90, 1.19)	0.96 (0.80, 1.15)	1.05 (0.89, 1.25)	

Abbreviations: BC (breast cancer); CRC (colorectal cancer); DACHS (Darmkrebs: Chancen der Verhütung durch Screening); F (female); HR (hazard ratio); M (male); NA (not applicable); NR (not reported); PC (prostate cancer); y (years).
*restricted to 5-10 years (median follow-up of entire study: 23 years).

638 Table 4. Summary hazard ratios (HRs) of overall mortality, cancer-specific mortality, and
639 cancer recurrence in breast cancer patients for the highest versus lowest category of dietary
640 intake of isoflavones and lignans and serum/plasma enterolactone concentration.

	No. of datasets (cohorts)	HR (95% CI)	I^2	$P_{heterogeneity}$
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

NA: not applicable.

641

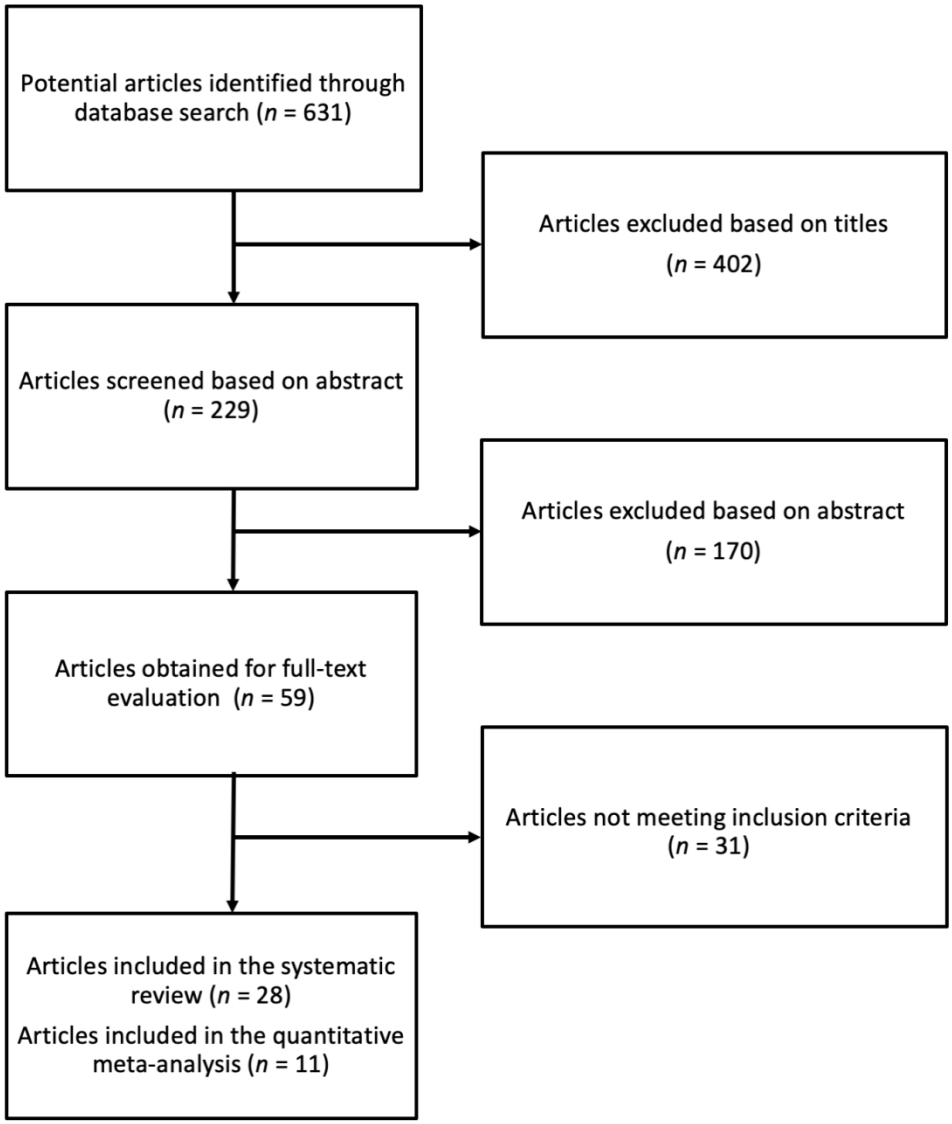

Figure 1. Flow chart of study identification and selection process.

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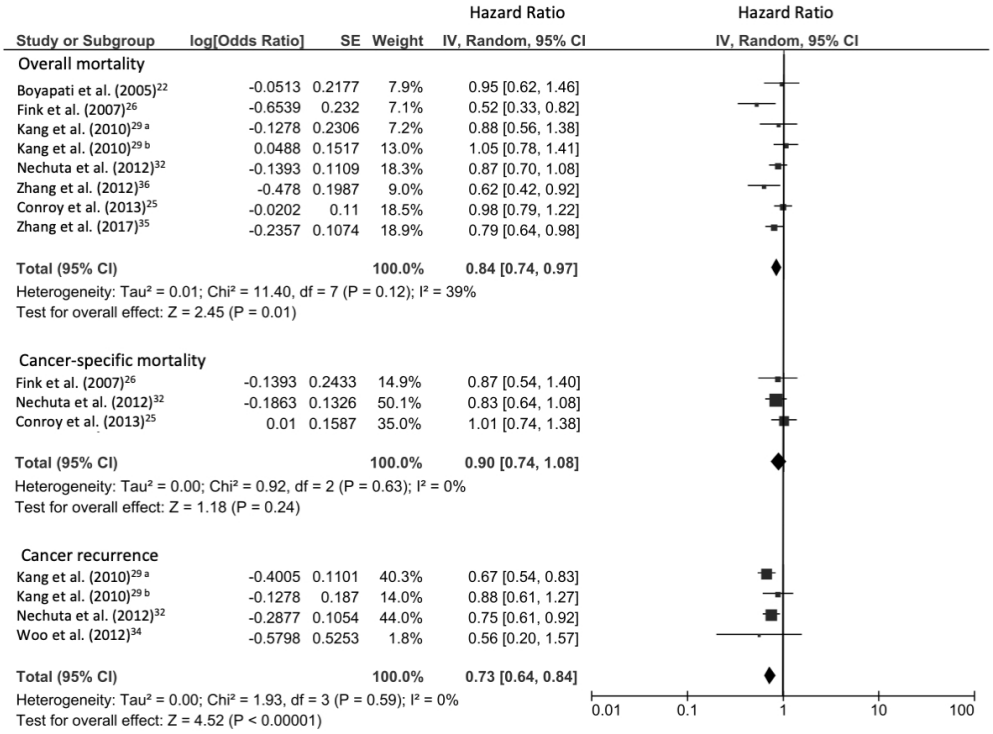

Figure 2. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality and recurrence in breast cancer patients for the highest versus lowest category of dietary isoflavone intake. "a" indicates dataset associated with postmenopausal women, while "b" indicates dataset associated with premenopausal women.

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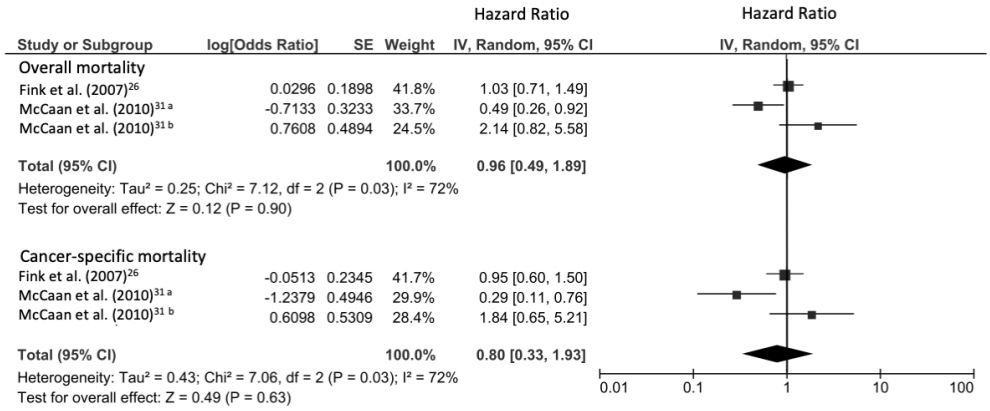

Figure 3. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality in breast cancer patients for the highest versus lowest category of dietary lignan intake. "a" indicates dataset associated with postmenopausal women, while "b" indicates dataset associated with premenopausal women.

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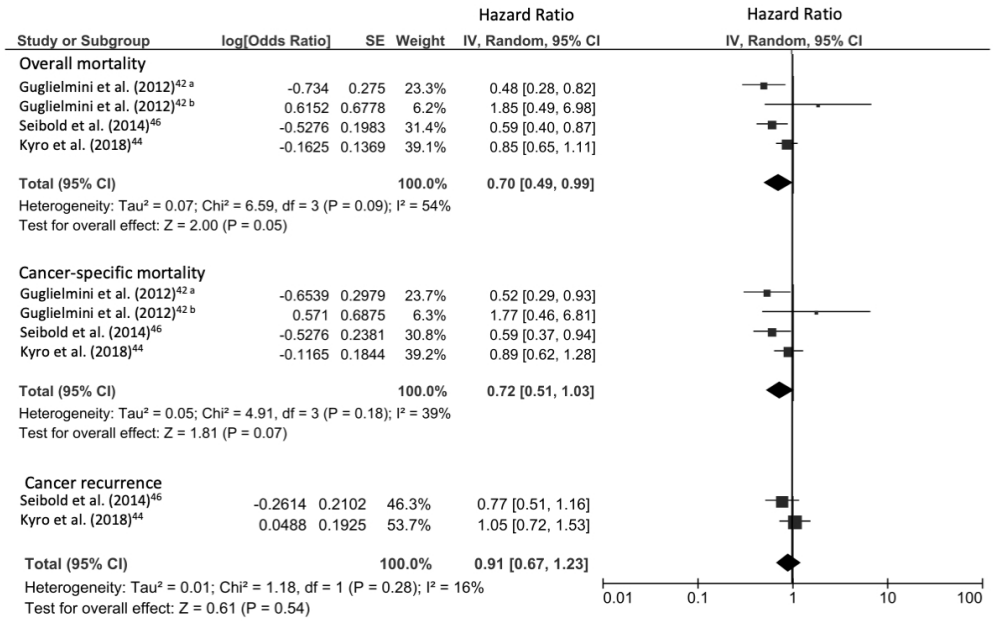

Figure 4. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality and recurrence in breast cancer patients for the highest versus lowest category of serum/plasma enterolactone concentration. "a" indicates dataset associated with postmenopausal women, while "b" indicates dataset associated with premenopausal women.

420x260mm (72 x 72 DPI)

Table S1. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Table 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, 8

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	7, 8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7, 8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table1, Table2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-12, Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supp. Info.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9, 10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15, 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

Figure S1. Funnel plot of summary hazard risks (HRs) of overall and cancer specific mortality and recurrence in breast cancer patients for the highest versus lowest category of dietary isoflavone intake.

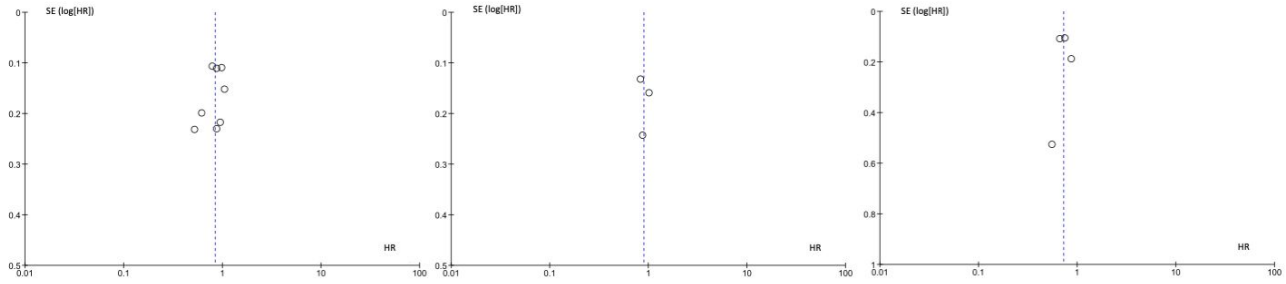

Figure S2. Funnel plot of summary hazard risks (HRs) of overall and cancer specific mortality in breast cancer patients for the highest versus lowest category of dietary lignan intake.

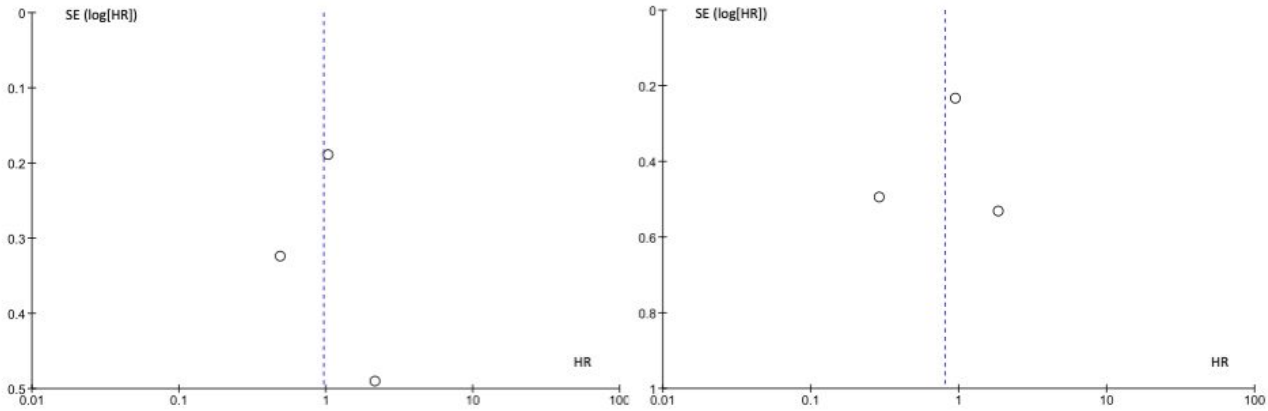

Figure S3. Funnel plot of summary hazard risks (HRs) of overall and cancer specific mortality and recurrence in breast cancer patients for the highest versus lowest category of serum/plasma enterolactone concentration.