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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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1 **Lead article**

2

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

5

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33 Abstract

34 **Context:** Recent studies outlined the potential role of dietary factors in cancer survival
35 patients. **Objective:** The aim of this study was to summarize the evidence of the relation
36 between dietary intake of phytoestrogens and their blood biomarkers, and overall, cancer-
37 specific mortality and recurrence in cancer patients. **Data Sources:** A systematic search on
38 PubMed, EMBASE, and Web of Science databases of studies published up to September
39 2019 was performed. Databases were searched for prospective and retrospective cohort
40 studies reporting on dietary phytoestrogen intake and/or blood biomarkers and the outcomes
41 investigated. **Data extraction:** Data were extracted from each identified study using a
42 standardized form. **Data analysis:** Twenty-eight articles on breast, lung, prostate, colorectal
43 cancer and glioma were included for systematic review. Given the availability of studies, a
44 quantitative meta-analysis was performed solely for breast cancer outcomes. A significant
45 inverse association between higher dietary isoflavone intake, higher serum/plasma
46 enterolactone concentrations and overall mortality and cancer recurrence was found. Among
47 other cancer types, two studies reported that higher serum enterolactone and higher intake of
48 lignans were associated with cancer-specific survival for colorectal cancer and glioma,
49 respectively. **Conclusions:** Dietary phytoestrogens may play a role in breast cancer patients
50 survival, while evidence regarding other cancers is too limited to draw any conclusions.
51 **Keywords:** isoflavones; lignans; polyphenols; enterolactone; cancer; meta-analysis

52 **Introduction**

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

67

68 Previous studies on dietary intake and cancer focused on dietary patterns and foods, but also
69 individual nutrients. For instance, a higher adherence to healthy dietary patterns, rich in
70 plant-based foods, has been associated with a lower risk of several cancers, including colon
71 and breast cancer.^{4,5} Notably, higher intake of certain foods has also been inversely
72 associated with cancer risk and mortality, such as fruits and vegetables,⁶ coffee and tea,⁷⁻⁹
73 nuts,¹⁰ and whole grains.¹¹ Remarkably, latest scientific evidence has pointed out dietary
74 polyphenols as promising compounds that may exert beneficial effects toward human health.
75 In fact, numerous meta-analysis have demonstrated that a higher dietary polyphenol intake
76 may be associated with decreased risk of hypertension,¹² diabetes,¹³ mortality,¹⁴ and

77 depression.¹⁵ Recently, a comprehensive meta-analysis quantitatively analyzing the
78 association between dietary polyphenol and phytoestrogen intakes and different cancer types
79 was published.¹⁶ Interestingly, the results revealed that higher dietary intake of isoflavones
80 may be inversely associated with risk of lung, stomach, colorectal and breast cancer.
81 Mechanistic studies underline the protective effect of these bioactive molecules towards
82 cancer, revealing that phytoestrogens exert antioxidant and anti-inflammatory properties as
83 well as an action through the estrogen receptor (ER), interacting with cancer cell growth and
84 proliferation.¹⁷ Among phytoestrogens and their dietary sources, a summary of the evidence
85 on isoflavones and dietary soy consumption showed that such compounds may contribute to
86 cancer prevention.¹⁸ Nonetheless, up to now, a comprehensive summary of the evidence
87 regarding main classes of dietary phytoestrogens (i.e., isoflavones and lignans), their
88 biomarkers/metabolites (i.e. equol and enterolactone),¹⁹ and cancer survival and recurrence
89 considering all cancer types has not been conducted. Thus, the aim of the present review was
90 to systematically describe and quantitatively analyze existing studies investigating the
91 association between dietary intake of phytoestrogen as well as their blood biomarkers and
92 overall mortality, cancer-specific survival and cancer recurrence.

93

94 **Methods**

95 The design, analysis, and reporting of this study followed the meta-analysis of Observational
96 Studies in Epidemiology (MOOSE) guidelines (Table S1 in the Supporting Information
97 online).²⁰ Moreover, eligibility criteria for the search and meta-analyses were specified using
98 the PICOS approach: determination of the Population (P), Intervention/Exposure (I),
99 Comparison (C), Outcomes (O), Study design (S) (Table 1).

100

101 *Study selection*

102 A systematic search on PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), EMBASE
103 (<http://www.embase.com/>), and Web of Science (www.webofknowledge.com) databases of
104 studies published up to September 2019 was performed using the following search strategy:
105 “((((polyphenols OR polyphenol OR isoflavone OR isoflavones OR daidzein OR genistein
106 OR biochanin A OR formononetin OR glycitein OR lignan OR lignans OR matairesinol OR
107 lariciresinol OR secoisolariciresinol OR pinoresinol OR enterolactone OR enterodiol OR
108 equol OR phytoestrogen OR phytoestrogens)) AND (cancer OR neoplasm OR carcinoma))
109 AND (survival OR mortality OR recurrence OR prognosis OR death)) AND (cohort OR
110 prospective OR observational OR population OR case-control OR nested OR follow-up OR
111 followed)”. Studies were eligible if they met the following inclusion criteria: (i) were
112 observational studies (either prospective or retrospective cohort studies); (ii) were conducted
113 on cancer patients; (iii) evaluated associations between dietary phytoestrogens and/or their
114 biomarkers and cancer outcomes, including overall mortality, cancer-specific mortality, and
115 recurrence; (iv) assessed and reported hazard ratios (HRs) and their corresponding 95% CI.
116 As exposure, dietary intake of the following: i) total isoflavones and their individual
117 components including daidzein, genistein, glycitein, formononetin, and biochanin A; ii)
118 biomarkers/metabolites of isoflavones intake including equol; iii) total lignans and their
119 individual components including matairesinol, lariciresinol, secoisolariciresinol, and
120 pinoresinol; iv) biomarkers/metabolites of lignans intake including enterolactone and
121 enterodiol was considered. Reference lists of eligible studies were also examined for any
122 additional study not previously identified. If more than one study reported results on the same
123 cohort, only the study including the larger cohort size, the longest follow-up or the most
124 comprehensive data was included in the meta-analysis. The systematic search and study
125 selection was performed by two independent authors.

126

127 *Data extraction and quality assessment*

128 Data were extracted using a standardized extraction form. The following information was
129 collected: (i) first author name and year of publication; (ii) study cohort name and country;
130 (iii) study design and median follow-up period; (iv) population characteristics; (v) sex and age
131 of participants; (vi) cohort size and number of deaths, cancer-related deaths and cancer
132 recurrence; (vii) type of exposure and its main characteristics; (viii) distributions of cases and
133 person-years, HRs and 95% CIs for all categories of exposure; and (ix) adjustment covariates.
134 The quality of each eligible study was using the Newcastle-Ottawa Quality Assessment
135 Scale,²¹ consisting of 3 domains of quality as follows: selection (4 points), comparability (2
136 points), and outcome (3 points) for a total score of 9 points (9 representing the highest
137 quality). Studies scoring 7-9 points, 4-6 points, and 0-3 points were identified as high,
138 moderate, and low quality, respectively.

139

140 *Statistical analysis*

141 Outcomes evaluated in the analyses included overall mortality, cancer-specific mortality and
142 recurrence. The analyses were performed for dietary phytoestrogen intake as well as for their
143 blood biomarkers. HRs with 95% CI for all categories of exposure were extracted for the
144 analysis. Random-effects models were used in order to estimate pooled results for the highest
145 versus the lowest category of exposure. Only the risk estimates from the most adjusted
146 models were used in the analysis. Heterogeneity was calculated using the Q test and I^2
147 statistic. The level of significance for the Q test was expressed as $p < 0.10$. The I^2 statistic
148 represented the amount of total variation that could be attributed to heterogeneity. I^2 values
149 $\leq 25\%$, 25-50%, 50-75%, and $>75\%$ indicated no, small, moderate, and significant
150 heterogeneity, respectively. A sensitivity analysis by exclusion of one study at the time was
151 performed in order to assess the stability of results and potential sources of heterogeneity.

152 Additional sensitivity analyses were performed to test for potential source of heterogeneity
153 by grouping studies according to menopausal status and ER receptor status. Publication bias
154 was evaluated through a visual investigation of funnel plots for potential asymmetry.

155

156 **Results**

157 *Study identification and selection process*

158 The systematic search yielded a total of 631 studies, out of which 402 were excluded on the
159 basis of title and 170 after abstract revision, leaving 59 articles for full-text evaluation (Figure
160 1). After revision of full-text articles, 31 studies were excluded. Finally, 28 articles exploring
161 the association between dietary phytoestrogen intake and/or their blood biomarkers and
162 overall, cancer-specific survival and cancer recurrence were included in the systematic
163 review.²²⁻⁴⁹ In detail, 19 studies examined the association between dietary intake of
164 phytoestrogens and cancer,²²⁻⁴⁰ out of which 15 focused on breast cancer,²²⁻³⁶ one on
165 colorectal cancer,³⁷ one on prostate cancer,³⁸ one on lung cancer,³⁹ and one on malignant
166 glioma.⁴⁰ Nine articles focused on blood biomarkers of dietary phytoestrogen intake and
167 cancer,⁴¹⁻⁴⁹ out of which 6 were on breast cancer,⁴¹⁻⁴⁶ two on colorectal cancer,^{48,49} and one
168 on prostate cancer.⁴⁷ Data quality was overall high (data not shown). Considering the limited
169 number of studies reporting on the investigated associations, the meta-analysis was
170 performed solely for breast cancer outcomes.

171

172 *Breast cancer*

173 Fifteen studies explored the association between dietary phytoestrogen intake (isoflavones
174 and lignans) and overall mortality, cancer-specific mortality and recurrence in breast cancer
175 patients (Table 2),²²⁻³⁶ while six examined the association with blood biomarkers of their
176 consumption (Table 3).⁴¹⁻⁴⁶ All the studies exploring this association for dietary

177 phytoestrogens estimated their intake using a Food Frequency Questionnaire (FFQ), which
178 however differed in the number of food items considered (Table 2). Main findings of these
179 studies were quantitatively analyzed using a meta-analytical approach.

180

181 Nine cohorts reported on the association between dietary isoflavone intake and overall
182 mortality,^{22,25,26,29,32,35,36} five on cancer-specific mortality^{25,26,32} as well as five on cancer
183 recurrence in breast cancer patients.^{29,32,34} A significant inverse association was found for
184 overall mortality (HR: 0.84, 95% CI: 0.74, 0.97; Figure 2, Table 4) and breast cancer
185 recurrence (HR: 0.73, 95% CI: 0.64, 0.84; Figure 2, Table 4), with no evidence of publication
186 bias (Figure S1 in the Supporting Information online). However, there was a moderate
187 heterogeneity among the studies investigating the association with overall mortality.
188 Interestingly, after stratification for menopausal status, both associations remained significant
189 for postmenopausal patients (HR: 0.83, 95% CI: 0.68, 1.00 with I²:39% and HR: 0.66, 95%
190 CI: 0.55, 0.78 with I²:0%; respectively).

191

192 Only two studies were eligible for the analysis on the association between dietary lignan
193 intake and overall and breast cancer-specific survival.^{26,31} Nonetheless, analysis did not
194 reveal any significant association (HR: 0.96, 95% CI: 0.49, 1.89, HR: 0.80, 95% CI: 0.33,
195 1.93; respectively), possibly due to the limited number of included studies (Figure 3, Table 4
196 and Figure S2 in the Supporting Information online). Moreover, high heterogeneity among
197 the included studies was observed.

198

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

202 human gut microbiota),¹⁹ and overall mortality,^{42,44,46} as well as cancer-specific
203 mortality,^{42,44,46} while two studies for cancer recurrence in breast cancer patients.^{44,46} The
204 analysis showed a significant inverse association for overall mortality (HR: 0.70, 95% CI:
205 0.49, 0.99; Figure 4, Table 4); however, after stratifying for menopausal status, the
206 association remained significant only for postmenopausal women (HR: 0.66, 95% CI: 0.47,
207 0.92; Table 4), with evidence of moderate heterogeneity. Neither breast cancer-specific
208 mortality (HR: 0.72, 95% CI: 0.51, 1.03; Figure 4, Table 4) nor cancer recurrence (HR: 0.91,
209 95% CI: 0.67, 1.23; Figure 4, Table 4) were associated with serum/plasma enterolactone
210 concentration, except for breast cancer-specific mortality among postmenopausal patients
211 (HR: 0.68, 95% CI: 0.49, 0.96; Table 4). Visual investigation of funnel plots revealed
212 absence of publication bias (Figure S3 in the Supporting Information online).

213

214 *Colorectal cancer*

215 Three studies exploring the relation between phytoestrogen and colorectal cancer survival or
216 recurrence met the eligibility criteria and were included in the systematic review.^{37,48,49} A
217 hospital-based study conducted in Spain with a mean follow-up of 8.6 years, recorded 133
218 deaths and 77 cases of colorectal cancer recurrence among 409 patients (Table 2). No
219 significant association between dietary intake of isoflavones as well as lignans and colorectal
220 cancer survival and recurrence was annotated.³⁷ Accordingly, another population-based study
221 on a sample of 2,051 colorectal cancer patients followed for more than 5 years reported no
222 association between serum genistein (an isoflavone) and overall mortality, cancer-specific
223 mortality and recurrence (Table 3).⁴⁸ On the contrary, high plasma pre-diagnostic
224 enterolactone levels were inversely associated with cancer-specific mortality, but solely in
225 females (HR: 0.63, 95% CI: 0.41, 0.99; Table 3).⁴⁹

226

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)

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

255

256 **Discussion**

257 The present study provided a comprehensive review of existing prospective and retrospective
258 studies on the dietary intake of isoflavones and lignans, as well as their blood biomarkers, in
259 the context of cancer survival and recurrence. The systematic review comprised 28 articles
260 reporting on breast, colorectal, prostate, lung and glioma cancer, although most of the
261 investigations focused on breast cancer. Performed meta-analyses found that higher dietary
262 isoflavone intake was inversely associated with overall mortality and cancer recurrence
263 among breast cancer patients. No significant relation between dietary lignan intake and
264 cancer outcomes was found when lignan intake was assessed with conventional self-reported
265 methods, but higher levels of serum/plasma enterolactone were inversely associated with
266 overall cancer survival. Interestingly, when analyses were stratified for menopausal status,
267 the associations remained significant only among postmenopausal patients. Finally, none of
268 the analysis stratified for ER receptor status resulted significant, possible due to the limited
269 number of analyzed studies. Among the other cancers investigated, only an association of
270 better survival in colorectal cancer and glioma patients with higher dietary intake of lignans
271 (specifically, serum enterolactone and dietary secoisolariciresinol, respectively) has been
272 observed.

273 Most of the analyses revealed moderate heterogeneity among the included studies, and
274 several factors could have contributed to these findings, including assessment of
275 phytoestrogen intake, phytoestrogen variability directly related to food quality, inter-

276 individual variation in response to consumption of plant polyphenols and variations in
277 isoflavone and lignan-based foods consumption between Asian and non-Asian individuals.

278

279 Numerous observational studies have investigated the association between polyphenols,
280 including isoflavones and lignans, and human health.¹⁴ While evidence on potential positive
281 effects on health is available, our previous comprehensive overview of the association
282 between total and individual classes of flavonoids and lignans and cancer risk resulted in
283 relatively scarce results, with most of findings related to phytoestrogens (especially
284 isoflavones) and breast and lung cancer risk.¹⁶ A number of mechanisms have been
285 hypothesized to explain the potential benefits of phytoestrogens for preventing cancer,
286 including direct inhibition of oxidative stress and oxidative damage as well as inflammatory-
287 related gene expression, resulting in interfering with the initiation, promotion, and
288 progression of cancer.^{50,51} However, up to now, no comprehensive evidence has been
289 produced to explore whether such potential benefits would have an impact also in decreasing
290 mortality rate and improve overall survival in cancer patients. Laboratory studies suggest that
291 phytoestrogens and their blood metabolites may prevent cancer progression through various
292 pathways, including inhibition of cancer cell proliferation, survival, angiogenesis,
293 inflammation and metastasis.⁵²

294

295 Several properties of phytoestrogens have been suggested to potentially reduce recurrence
296 and mortality in breast cancer patients, such as (i) antiproliferative, growth inhibiting and
297 proapoptotic effects mediated by ER β , caspase-3 activation, direct inhibition of tyrosine
298 kinase and nuclear factor κ B (NF- κ B) activities⁵³; (ii) antiangiogenic activity by inhibiting
299 vascular endothelial growth factor (VEGF) expression through inhibition of transcription
300 factors, such as signal transducer and activator of transcription 3 (STAT3) and hypoxia-

301 inducible factor (HIF-1), and its receptors Ras/Raf-1/MEK/ERK, PI3K/Akt, and ERK-NF-
302 KB-cMyc-p21^{54,55}; (iii) reduction of cancer invasion and the metastatic spread of primary
303 breast tumor through downregulation of matrix metalloproteases expression, which initiate
304 the process of epithelial–mesenchymal transition-related pathways, such as Notch-1 and
305 TGF-beta signaling^{56,57}; (iv) reduction of epigenetic modulation and DNA methylation,
306 which is one of the key mechanisms underlying the maintenance of genome stability and
307 gene expression.⁵⁸ It is interesting that some studies observed a biphasic action of genistein (a
308 soy isoflavone) in certain cell lines, showing a growth stimulation at low concentrations and
309 inhibition at high concentrations, with the potentiality of their use as anti-cancer therapeutic
310 agents.^{59,60} Mechanistic studies have also been published regarding the potential role of
311 phytoestrogens in the prevention of colorectal cancer, for instance by activating or
312 upregulating ER β in the colon and promoting apoptosis in preclinical models and in clinical
313 experience: this activity has been associated with a reduction in colon adenocarcinoma,
314 which may reduce the risk of recurrence in patients at risk.⁶¹ A number of studies also
315 showed therapeutic effects against glioma tumors by inducing critical pro-apoptotic proteins
316 expression and cell apoptosis as well as inhibition of glioma cell migration by
317 modulating mesenchymal properties.⁶²

318

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

326 considering pre- and post-menopausal breast cancers were found, underlying a significant
327 decreased risk of the latter. There is evidence that diet may play a crucial role mostly among
328 post- rather than pre-menopausal cancers⁴: these results are not surprising, as several other
329 studies observed a potential preventive role of diet toward post-menopausal breast cancers.⁶⁵
330 The reasons for such findings may rely on the potentially different nature of cancer occurring
331 in younger age, which might be more strongly influenced by genetics, compared to those
332 occurring in older age, which may depend on lifelong chronic influence of detrimental factors
333 led by unhealthy diets, such as low-grade inflammation and obesity.^{66,67} Interestingly, it has
334 been demonstrated that obese postmenopausal women are at higher risk of breast cancer
335 compared to normal weight women, possibly due to the association between BMI and
336 endogenous estrogen concentrations, as in postmenopausal women circulating estrogen
337 concentrations are dependent on the extraglandular production of estrogen in the adipose
338 tissue. On the other hand, an association between BMI and breast cancer risk has not been
339 found among premenopausal women, as most of the estrogen is produced by the ovaries and
340 its levels are homeostatically regulated by a negative feedback system involving
341 gonadotrophins, therefore estrogen concentration is not directly affected by the levels of
342 adipose tissue.⁶⁸

343 The results of the present review and meta-analysis should be considered in light of some
344 limitations. Firstly, a limited number of studies was eligible for the present meta-analysis, so
345 subgroup analysis exploring the possible effect of confounding factors such as other dietary
346 factors (i.e., collinearity with other foods or phytochemicals), family history of cancer, and
347 many others could not be conducted. In addition, the limited number of studies could
348 possibly be the reason why several associations, even though supported by clinical and
349 mechanistic studies, did not result significant. Secondly, most of the observational studies
350 investigating the relation between phytoestrogen intake and cancer rely on the estimation of

351 intake from dietary recalls, which may be affected by bias, including recall bias,
352 phytoestrogen variability directly related to food quality (plant variety, season and
353 environmental factors, food storage and processing) and the reference database used to
354 estimate the polyphenol content. Finally, inter-individual variation in response to
355 consumption of plant phytoestrogens cannot be ruled out. In this context, the use of
356 biomarkers of phytoestrogen intake may help in better assessing real dietary intake,⁶⁹ to
357 potentially find stronger associations with cancer and other non-communicable diseases. It
358 would be better if the biomarkers used are validated as specific and reflective of the intake of
359 their dietary precursors,⁷⁰ even though much work still have to be carried out in this regard by
360 the scientific community.⁷¹

361

362 **Conclusions**

363 These results suggest an association between dietary phytoestrogens and breast cancer
364 survival and recurrence, while evidence regarding other cancers is too limited to draw strong
365 conclusions. Today's evidence is not sufficient to provide dietary guidelines regarding these
366 compounds and, therefore, further studies are needed in order to better elucidate the
367 association between phytoestrogens and cancer survival and recurrence. Moreover, the
368 findings of the present systematic review and meta-analysis revealed the gap in the literature
369 regarding several cancer types and the need for more advanced studies with significant
370 sample sizes and long follow-ups, exploring the differences among diverse populations and
371 possible collinearity effect of confounding factors. Future studies should also focus on the
372 inter-individual variation in response to consumption of phytoestrogens, and therefore
373 investigate the association not only for their dietary intake but also for the true internal
374 exposure to their metabolites. Last, further focus on the gut microbiota composition should be
375 paid as differences in microbial species may condition phytoestrogen metabolite formation

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

378

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386

387 **References**

- 388 1. Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, et al. Global, Regional,
389 and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With
390 Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A
391 Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 2019.
- 392 2. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer
393 diet. *Nutr J.* 2004;3:19.
- 394 3. Collaborators GBDD. Health effects of dietary risks in 195 countries, 1990-2017: a
395 systematic analysis for the Global Burden of Disease Study 2017. *Lancet.*
396 2019;393(10184):1958-1972.
- 397 4. Grosso G, Bella F, Godos J, et al. Possible role of diet in cancer: systematic review
398 and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk.
399 *Nutr Rev.* 2017;75(6):405-419.
- 400 5. Godos J, Bella F, Sciacca S, Galvano F, Grosso G. Vegetarianism and breast, colorectal
401 and prostate cancer risk: an overview and meta-analysis of cohort studies. *J Hum*
402 *Nutr Diet.* 2017;30(3):349-359.
- 403 6. Angelino D, Godos J, Ghelfi F, et al. Fruit and vegetable consumption and health
404 outcomes: an umbrella review of observational studies. *Int J Food Sci Nutr.*
405 2019;70(6):652-667.
- 406 7. Grosso G, Micek A, Godos J, et al. Coffee consumption and risk of all-cause,
407 cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response
408 meta-analysis. *Eur J Epidemiol.* 2016;31(12):1191-1205.
- 409 8. Tang J, Zheng JS, Fang L, Jin Y, Cai W, Li D. Tea consumption and mortality of all
410 cancers, CVD and all causes: a meta-analysis of eighteen prospective cohort studies.
411 *Br J Nutr.* 2015;114(5):673-683.
- 412 9. Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, Caffeine, and Health
413 Outcomes: An Umbrella Review. *Annu Rev Nutr.* 2017;37:131-156.
- 414 10. Grosso G, Yang J, Marventano S, Micek A, Galvano F, Kales SN. Nut consumption on
415 all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-
416 analysis of epidemiologic studies. *Am J Clin Nutr.* 2015;101(4):783-793.
- 417 11. Zhang B, Zhao Q, Guo W, Bao W, Wang X. Association of whole grain intake with all-
418 cause, cardiovascular, and cancer mortality: a systematic review and dose-response
419 meta-analysis from prospective cohort studies. *Eur J Clin Nutr.* 2018;72(1):57-65.
- 420 12. Godos J, Vitale M, Micek A, et al. Dietary Polyphenol Intake, Blood Pressure, and
421 Hypertension: A Systematic Review and Meta-Analysis of Observational Studies.
422 *Antioxidants (Basel).* 2019;8(6).
- 423 13. Rienks J, Barbaresko J, Oluwagbemigun K, Schmid M, Nothlings U. Polyphenol
424 exposure and risk of type 2 diabetes: dose-response meta-analyses and systematic
425 review of prospective cohort studies. *Am J Clin Nutr.* 2018;108(1):49-61.
- 426 14. Grosso G, Micek A, Godos J, et al. Dietary Flavonoid and Lignan Intake and Mortality
427 in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis.
428 *Am J Epidemiol.* 2017;185(12):1304-1316.
- 429 15. Godos J, Castellano S, Ray S, Grosso G, Galvano F. Dietary Polyphenol Intake and
430 Depression: Results from the Mediterranean Healthy Eating, Lifestyle and Aging
431 (MEAL) Study. *Molecules.* 2018;23(5).

- 432 16. Grosso G, Godos J, Lamuela-Raventos R, et al. A comprehensive meta-analysis on
433 dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations.
434 *Mol Nutr Food Res*. 2017;61(4).
- 435 17. Mense SM, Hei TK, Ganju RK, Bhat HK. Phytoestrogens and breast cancer prevention:
436 possible mechanisms of action. *Environ Health Perspect*. 2008;116(4):426-433.
- 437 18. Li N, Wu X, Zhuang W, et al. Soy and Isoflavone Consumption and Multiple Health
438 Outcomes: Umbrella Review of Systematic Reviews and Meta-Analyses of
439 Observational Studies and Randomized Trials in Humans. *Mol Nutr Food Res*.
440 2019:e1900751.
- 441 19. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary
442 (poly)phenolics in human health: structures, bioavailability, and evidence of
443 protective effects against chronic diseases. *Antioxid Redox Signal*. 2013;18(14):1818-
444 1892.
- 445 20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
446 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in
447 Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.
- 448 21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the
449 quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-
450 605.
- 451 22. Boyapati SM, Shu XO, Ruan ZX, et al. Soyfood intake and breast cancer survival: a
452 followup of the Shanghai Breast Cancer Study. *Breast Cancer Res Treat*.
453 2005;92(1):11-17.
- 454 23. Buck K, Zaineddin AK, Vrieling A, et al. Estimated enterolignans, lignan-rich foods,
455 and fibre in relation to survival after postmenopausal breast cancer. *Br J Cancer*.
456 2011;105(8):1151-1157.
- 457 24. Caan BJ, Natarajan L, Parker B, et al. Soy food consumption and breast cancer
458 prognosis. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):854-858.
- 459 25. Conroy SM, Maskarinec G, Park SY, Wilkens LR, Henderson BE, Kolonel LN. The
460 effects of soy consumption before diagnosis on breast cancer survival: the
461 Multiethnic Cohort Study. *Nutr Cancer*. 2013;65(4):527-537.
- 462 26. Fink BN, Steck SE, Wolff MS, et al. Dietary flavonoid intake and breast cancer survival
463 among women on Long Island. *Cancer Epidemiol Biomarkers Prev*. 2007;16(11):2285-
464 2292.
- 465 27. Guha N, Kwan ML, Quesenberry CP, Jr., Weltzien EK, Castillo AL, Caan BJ. Soy
466 isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the
467 Life After Cancer Epidemiology study. *Breast Cancer Res Treat*. 2009;118(2):395-405.
- 468 28. Kang HB, Zhang YF, Yang JD, Lu KL. Study on soy isoflavone consumption and risk of
469 breast cancer and survival. *Asian Pac J Cancer Prev*. 2012;13(3):995-998.
- 470 29. Kang X, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer
471 recurrence and death for patients receiving adjuvant endocrine therapy. *CMAJ*.
472 2010;182(17):1857-1862.
- 473 30. Kyro C, Zamora-Ros R, Scalbert A, et al. Pre-diagnostic polyphenol intake and breast
474 cancer survival: the European Prospective Investigation into Cancer and Nutrition
475 (EPIC) cohort. *Breast Cancer Res Treat*. 2015;154(2):389-401.
- 476 31. McCann SE, Thompson LU, Nie J, et al. Dietary lignan intakes in relation to survival
477 among women with breast cancer: the Western New York Exposures and Breast
478 Cancer (WEB) Study. *Breast Cancer Res Treat*. 2010;122(1):229-235.

- 479 32. Nechuta SJ, Caan BJ, Chen WY, et al. Soy food intake after diagnosis of breast cancer
480 and survival: an in-depth analysis of combined evidence from cohort studies of US
481 and Chinese women. *Am J Clin Nutr.* 2012;96(1):123-132.
- 482 33. Shu XO, Zheng Y, Cai H, et al. Soy food intake and breast cancer survival. *JAMA.*
483 2009;302(22):2437-2443.
- 484 34. Woo HD, Park KS, Ro J, Kim J. Differential influence of dietary soy intake on the risk
485 of breast cancer recurrence related to HER2 status. *Nutr Cancer.* 2012;64(2):198-
486 205.
- 487 35. Zhang FF, Haslam DE, Terry MB, et al. Dietary isoflavone intake and all-cause
488 mortality in breast cancer survivors: The Breast Cancer Family Registry. *Cancer.*
489 2017;123(11):2070-2079.
- 490 36. Zhang YF, Kang HB, Li BL, Zhang RM. Positive effects of soy isoflavone food on
491 survival of breast cancer patients in China. *Asian Pac J Cancer Prev.* 2012;13(2):479-
492 482.
- 493 37. Zamora-Ros R, Guino E, Alonso MH, et al. Dietary flavonoids, lignans and colorectal
494 cancer prognosis. *Sci Rep.* 2015;5:14148.
- 495 38. Taborelli M, Polesel J, Parpinel M, et al. Fruit and vegetables consumption is directly
496 associated to survival after prostate cancer. *Mol Nutr Food Res.* 2017;61(4).
- 497 39. Yang G, Shu XO, Li HL, et al. Prediagnosis soy food consumption and lung cancer
498 survival in women. *J Clin Oncol.* 2013;31(12):1548-1553.
- 499 40. DeLorenze GN, McCoy L, Tsai AL, et al. Daily intake of antioxidants in relation to
500 survival among adult patients diagnosed with malignant glioma. *BMC Cancer.*
501 2010;10:215.
- 502 41. Buck K, Vrieling A, Zaineddin AK, et al. Serum enterolactone and prognosis of
503 postmenopausal breast cancer. *J Clin Oncol.* 2011;29(28):3730-3738.
- 504 42. Guglielmini P, Rubagotti A, Boccardo F. Serum enterolactone levels and mortality
505 outcome in women with early breast cancer: a retrospective cohort study. *Breast*
506 *Cancer Res Treat.* 2012;132(2):661-668.
- 507 43. Jaskulski S, Jung AY, Behrens S, et al. Circulating enterolactone concentrations and
508 prognosis of postmenopausal breast cancer: assessment of mediation by
509 inflammatory markers. *Int J Cancer.* 2018;143(11):2698-2708.
- 510 44. Kyro C, Hansen L, Frederiksen K, et al. Pre-diagnostic plasma enterolactone
511 concentrations and breast cancer prognosis among postmenopausal women - The
512 Danish Diet, Cancer and Health cohort. *Clin Nutr.* 2018;37(6 Pt A):2217-2225.
- 513 45. Olsen A, Christensen J, Knudsen KE, Johnsen NF, Overvad K, Tjønneland A.
514 Prediagnostic plasma enterolactone levels and mortality among women with breast
515 cancer. *Breast Cancer Res Treat.* 2011;128(3):883-889.
- 516 46. Seibold P, Vrieling A, Johnson TS, et al. Enterolactone concentrations and prognosis
517 after postmenopausal breast cancer: assessment of effect modification and meta-
518 analysis. *Int J Cancer.* 2014;135(4):923-933.
- 519 47. Eriksen AK, Kyro C, Norskov N, et al. Prediagnostic enterolactone concentrations and
520 mortality among Danish men diagnosed with prostate cancer. *Eur J Clin Nutr.*
521 2017;71(10):1235-1240.
- 522 48. Jiang R, Poschet G, Owen R, et al. Serum Concentration of Genistein, Luteolin and
523 Colorectal Cancer Prognosis. *Nutrients.* 2019;11(3).

- 524 49. Kyro C, Frederiksen K, Holm M, et al. Prediagnosis plasma concentrations of
525 enterolactone and survival after colorectal cancer: the Danish Diet, Cancer and
526 Health cohort. *Br J Nutr.* 2019;122(5):552-563.
- 527 50. Pons DG, Vilanova-Llompарт J, Gaya-Bover A, et al. The phytoestrogen genistein
528 affects inflammatory-related genes expression depending on the ERalpha/ERbeta
529 ratio in breast cancer cells. *Int J Food Sci Nutr.* 2019;70(8):941-949.
- 530 51. Danciu C, Avram S, Pavel IZ, et al. Main Isoflavones Found in Dietary Sources as
531 Natural Anti-inflammatory Agents. *Curr Drug Targets.* 2018;19(7):841-853.
- 532 52. Mali AV, Padhye SB, Anant S, Hegde MV, Kadam SS. Anticancer and antimetastatic
533 potential of enterolactone: Clinical, preclinical and mechanistic perspectives. *Eur J
534 Pharmacol.* 2019;852:107-124.
- 535 53. Lecomte S, Demay F, Ferriere F, Pakdel F. Phytochemicals Targeting Estrogen
536 Receptors: Beneficial Rather Than Adverse Effects? *Int J Mol Sci.* 2017;18(7).
- 537 54. Basu P, Maier C. Phytoestrogens and breast cancer: In vitro anticancer activities of
538 isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives. *Biomed
539 Pharmacother.* 2018;107:1648-1666.
- 540 55. Liu HX, Wang Y, Lu Q, et al. Bidirectional regulation of angiogenesis by
541 phytoestrogens through estrogen receptor-mediated signaling networks. *Chin J Nat
542 Med.* 2016;14(4):241-254.
- 543 56. Uifalean A, Schneider S, Ionescu C, Lalk M, Iuga CA. Soy Isoflavones and Breast
544 Cancer Cell Lines: Molecular Mechanisms and Future Perspectives. *Molecules.*
545 2015;21(1):E13.
- 546 57. Lee GA, Hwang KA, Choi KC. Roles of Dietary Phytoestrogens on the Regulation of
547 Epithelial-Mesenchymal Transition in Diverse Cancer Metastasis. *Toxins (Basel).*
548 2016;8(6).
- 549 58. Hsieh CJ, Hsu YL, Huang YF, Tsai EM. Molecular Mechanisms of Anticancer Effects of
550 Phytoestrogens in Breast Cancer. *Curr Protein Pept Sci.* 2018;19(3):323-332.
- 551 59. Ziaei S, Halaby R. Dietary Isoflavones and Breast Cancer Risk. *Medicines (Basel).*
552 2017;4(2).
- 553 60. Douglas CC, Johnson SA, Arjmandi BH. Soy and its isoflavones: the truth behind the
554 science in breast cancer. *Anticancer Agents Med Chem.* 2013;13(8):1178-1187.
- 555 61. Williams C, DiLeo A, Niv Y, Gustafsson JA. Estrogen receptor beta as target for
556 colorectal cancer prevention. *Cancer Lett.* 2016;372(1):48-56.
- 557 62. Jiang D, Rasul A, Batool R, et al. Potential Anticancer Properties and Mechanisms of
558 Action of Formononetin. *Biomed Res Int.* 2019;2019:5854315.
- 559 63. Sirotkin AV, Harrath AH. Phytoestrogens and their effects. *Eur J Pharmacol.*
560 2014;741:230-236.
- 561 64. Krizova L, Dadakova K, Kasparovska J, Kasparovsky T. Isoflavones. *Molecules.*
562 2019;24(6).
- 563 65. Chato M, Li Y, Ma Z, Coote J, Du J, Chen X. Involvement of Corticotropin-Releasing
564 Factor and Receptors in Immune Cells in Irritable Bowel Syndrome. *Front Endocrinol
565 (Lausanne).* 2018;9:21.
- 566 66. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and
567 cancer: an update and emerging new evidence. *Lancet Oncol.* 2017;18(8):e457-e471.
- 568 67. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity
569 and adverse breast cancer risk and outcome: Mechanistic insights and strategies for
570 intervention. *CA Cancer J Clin.* 2017;67(5):378-397.

- 571 68. Travis RC, Key TJ. Oestrogen exposure and breast cancer risk. *Breast Cancer Res.*
572 2003;5(5):239-247.
- 573 69. Garcia-Aloy M, Rabassa M, Casa-Agustench P, Hidalgo-Liberona N, Llorach R,
574 Andreas-Lacueva C. Novel strategies for improving dietary exposure assessment:
575 Multiple-data fusion is a more accurate measure than the traditional single-
576 biomarker approach. *Trends Food Sci Technol.* 2017;69:220-229.
- 577 70. Brennan L. Moving toward Objective Biomarkers of Dietary Intake. *J Nutr.*
578 2018;148(6):821-822.
- 579 71. Dragsted LO, Gao Q, Scalbert A, et al. Validation of biomarkers of food intake-critical
580 assessment of candidate biomarkers. *Genes Nutr.* 2018;13:14.
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)		

								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)	
							Dietary glycerin, postdiagnostic, over 100-item FFQ	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 ^s)	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)	-	-	

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	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)	-	-	Age at diagnosis, TNM stage, estrogen and progesterone receptor status, chemotherapy and radiotherapy.
									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)	-	-									
	Premenopausal: Q4 (>42.3 mg/d) vs. Q1 (<15.2 mg/d)	1.05 (0.78, 1.71)	-	0.88 (0.61, 1.23)									
	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)									

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	ER+/PR- among postmenopausal: Q4 (>42.3 mg/d) vs. Q1 (<15.2 mg/d)	-	-	1.12 (0.81, 1.66)	Age, race, total energy, stage at diagnosis, BMI, and education.	
								ER-/PR+ among postmenopausal: Q4 (>42.3 mg/d) vs. Q1 (<15.2 mg/d)	-	-	1.05 (0.74, 1.61)		
								Premenopausal: Q4 (>257 ug/d) vs. Q1 (<128 ug/d)	2.14 (0.82, 5.56)	1.84 (0.65, 5.27)	-		
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 enterodiols, 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
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.	

Author (Year)	Study Design	Population	Age (mean)	Sample Size	Intervention	Comparison	Effect Size (95% CI)	Effect Size (95% CI)	Effect Size (95% CI)	Notes	
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)
								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)
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)	-	-
								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)	-

								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. 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.	
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)	-		
								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

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Table 3. Characteristics of the studies investigating the association between serum/plasma markers of dietary phytoestrogen intake and overall 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

								Overall: per 10 nmol/L increment	0.94 (0.90, 0.98)	0.94 (0.89, 0.99)	0.99 (0.95, 1.02)	status, BMI, radiotherapy, smoking, physical activity, MHT use, time between blood draw and enterolactone measurement.
								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. Age, smoking status, schooling, quantification of cigarette smoking, waist circumference, alcohol intake, intake of processed meat and frequency of bowel movements.
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)	-	
								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

								Overall: doubling in concentration	0.95 (0.89, 1.01)	0.93 (0.86, 1.00)	0.96 (0.89, 1.04)	measure at baseline, and hormone use at baseline.
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				
<i>Overall mortality</i>	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
<i>Cancer-specific mortality</i>	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
<i>Cancer recurrence</i>	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				
<i>Overall mortality</i>	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
<i>Cancer-specific mortality</i>	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
<i>Cancer recurrence</i>	0 (0)	NA	NA	NA
Premenopausal	0 (0)	NA	NA	NA
Postmenopausal	0 (0)	NA	NA	NA
Serum/plasma enterolactone				
<i>Overall mortality</i>	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
<i>Cancer-specific mortality</i>	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
<i>Cancer recurrence</i>	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.

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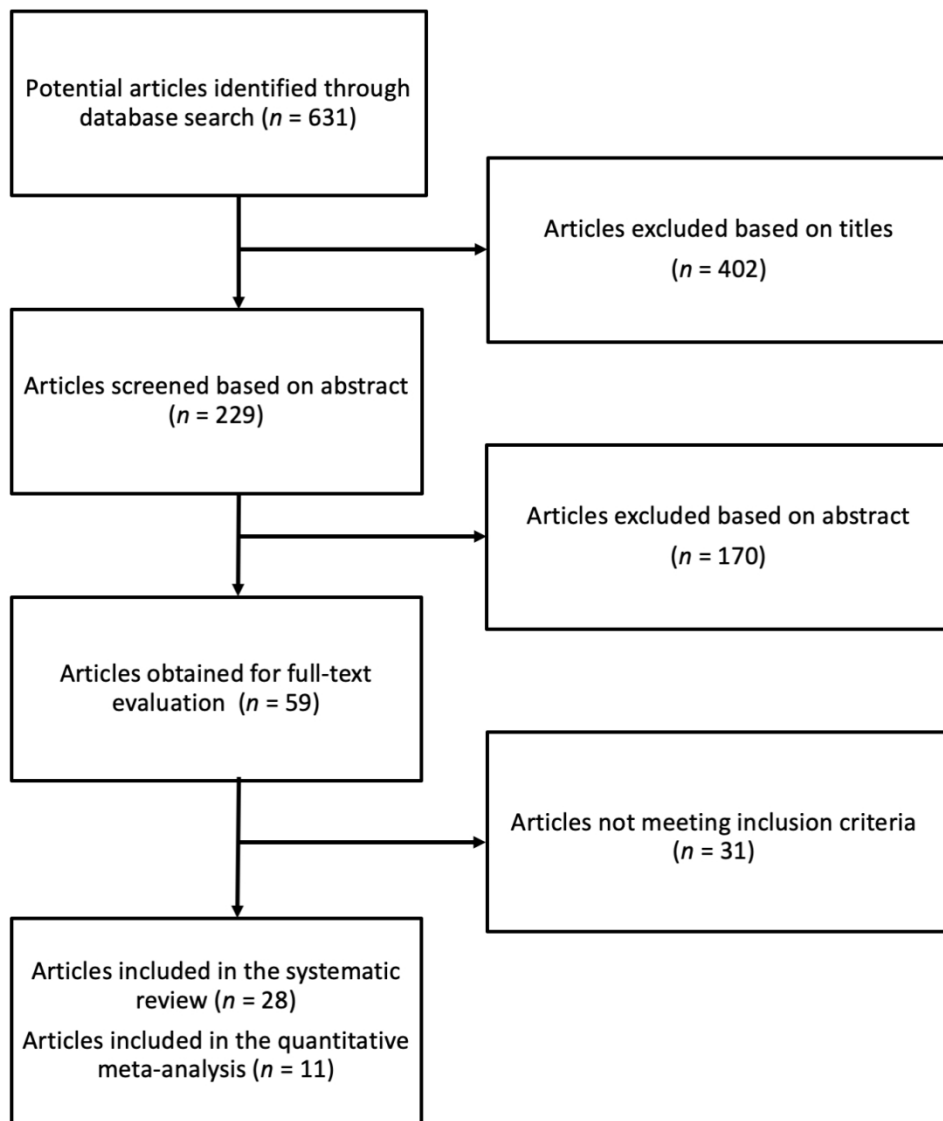


Figure 1. Flow chart of study identification and selection process.

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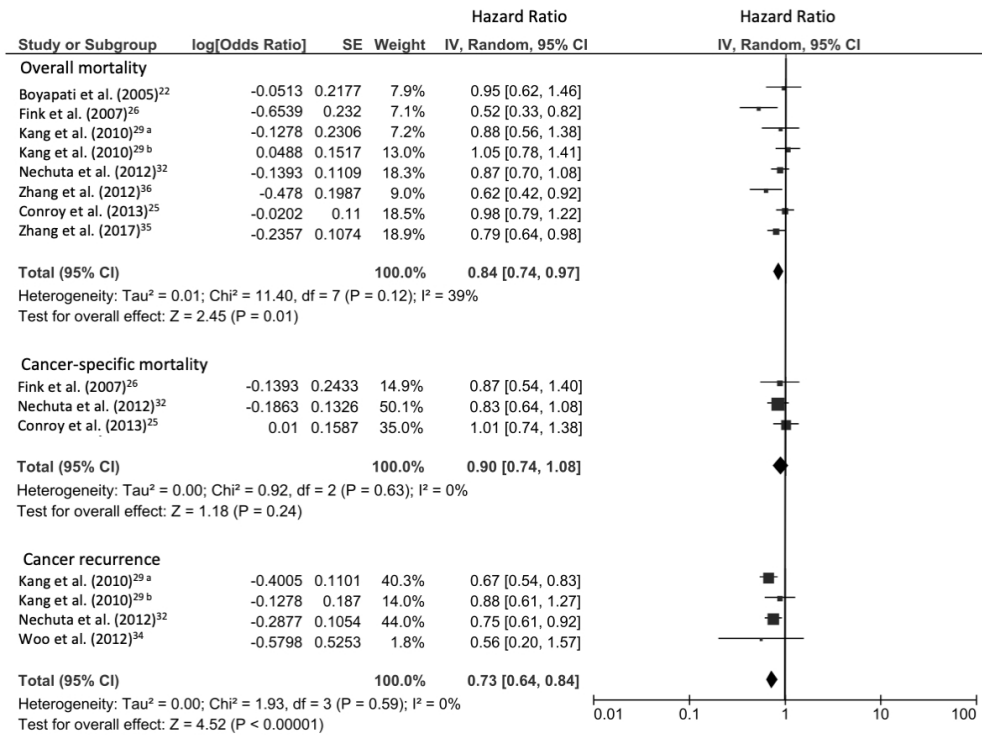


Figure 2. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality and recurrence in breast cancer patients for the highest versus lowest category of dietary isoflavone intake. "a" indicates dataset associated with postmenopausal women, while "b" indicates dataset associated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

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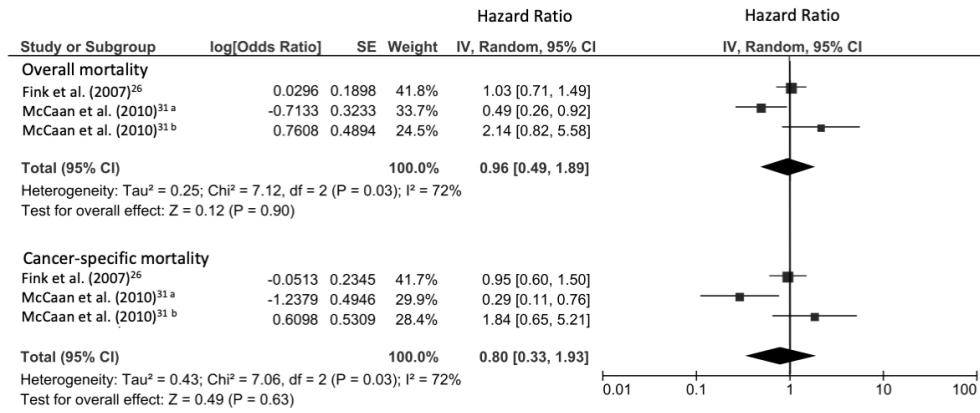


Figure 3. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality in breast cancer patients for the highest versus lowest category of dietary lignan intake. "a" indicates dataset associated with postmenopausal women, while "b" indicates dataset associated with premenopausal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

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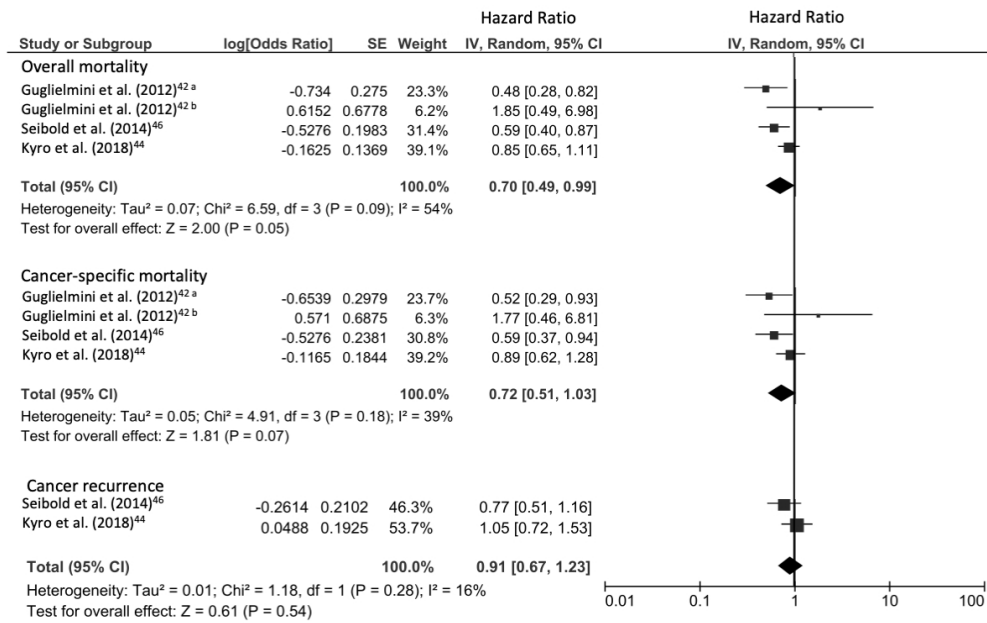


Figure 4. Forest plot of summary hazard risks (HRs) of overall and cancer-specific mortality and recurrence in breast cancer patients for the highest versus lowest category of serum/plasma enterolactone concentration. "a" indicates dataset associated with postmenopausal women, while "b" indicates dataset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

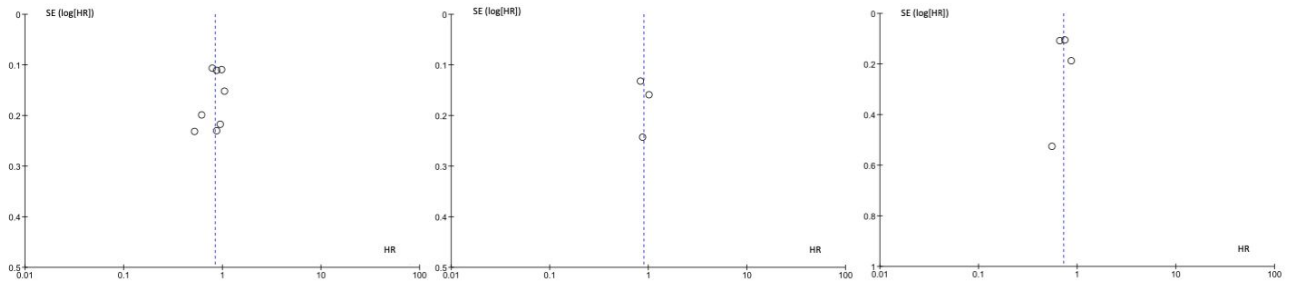


Figure S2. Funnel plot of summary hazard risks (HRs) of overall and cancer specific mortality in breast cancer patients for the highest versus lowest category of dietary lignan intake.

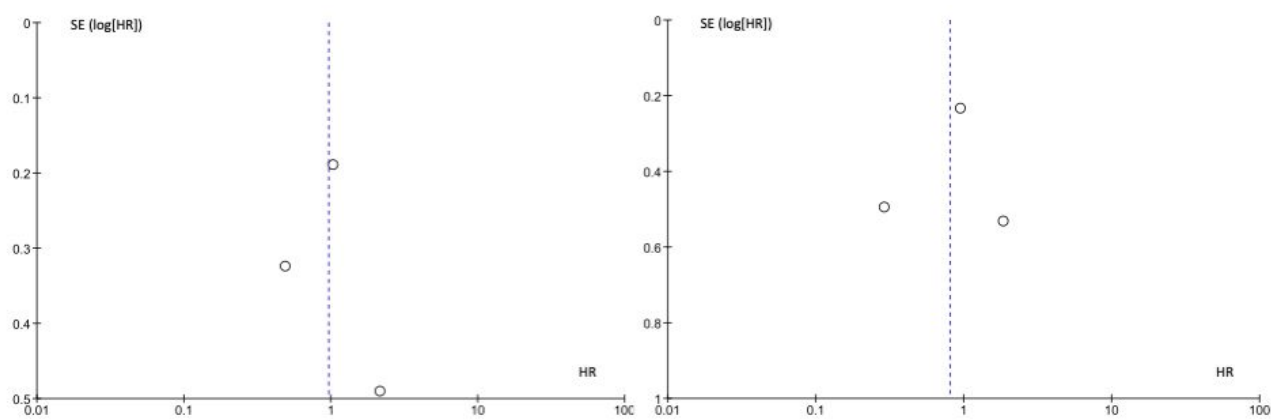


Figure S3. Funnel plot of summary hazard risks (HRs) of overall and cancer specific mortality and recurrence in breast cancer patients for the highest versus lowest category of serum/plasma enterolactone concentration.

