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Meta-analyses

Dietary isoflavones or isoflavone-rich food intake and breast cancer risk: A meta-analysis of prospective cohort studies

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SUMMARY

Background & aims: Previous studies implied that dietary isoflavone intake may reduce the risk of developing breast cancer, but some have shown ambiguous results. This study aimed to systematically evaluate and summarize available evidence on the effect dietary isoflavone intake has on the risk of developing breast cancer.

Methods: PubMed, Embase, and the Cochrane Library were searched for prospective cohort studies published through April 2017 that evaluated the effect of dietary isoflavone intake on the development of breast cancer.

Results: Sixteen prospective cohort studies, involving 11,169 breast cancer cases and 648,913 participants, were identified and included in our data analysis. The pooled relative risk (RR) of breast cancer was 0.99 for high versus low intake of isoflavones (95% confidence interval [CI], 0.91–1.09; P = 0.876) and 0.99 for moderate versus low intake of isoflavones (95%CI, 0.92–1.05; P = 0.653), with insignificant heterogeneity (P = 0.187 for high versus low, and P = 0.192 for moderate versus low). While a moderate consumption of soy-based foods did not significantly affect breast cancer risk, a high intake of soy-based foods associated with a lower risk of developing breast cancer. Considering specific foods, an increased the risk of developing breast cancer was seen with a moderate intake of formononetin, but no significant associations were found between breast cancer risk and other isoflavone-rich diets.

Conclusions: The present meta-analysis indicates that women with a high dietary intake of soy foods may experience a statistically significant reduction in breast cancer risk. However, moderate formononetin consumption may increase the risk of developing breast cancer.

1. Introduction

Breast cancer is the most commonly diagnosed cancer among women in Western countries and the second highest cause of cancer-related deaths. In 2008, there were approximately 1.38 million new cases diagnosed, and 458,400 deaths were associated with breast cancer [1]. Estrogen has emerged as a major player influencing breast malignancies worldwide [2]. Because previous studies have suggested that isoflavone levels are associated with the level of estrogen, it has been hypothesized that isoflavones may be correlated with breast cancer risk [3,4].

Soy foods containing high levels of isoflavones are traditionally associated with Asian diets more so than Western diets [5,6]. Considering that breast cancer incidence is higher in Western countries than in Asia, researchers have hypothesized that soy foods may decrease the risk of developing breast cancer. The potential role of soy foods in mammary tumorigenesis has already been evaluated through several experiments, each confirming their protective effects against breast cancer [7–9]. Previous meta-analyses suggested that consumption of high levels of isoflavones associated with a reduced risk of breast cancer in Asian populations, but no significant association was found in Western populations [10–12]. However, previous studies analyzing this

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relationship combined prospective cohort studies and retrospective case–control studies. While stratified analyses were conducted to account for different baseline characteristics, variations in the design of the studies may have biased the resulting association between isoflavones and breast cancer risk.

Recently, the relationship between levels of dietary isoflavone intake and risk of developing breast cancer has been studied in numerous prospective cohort studies [13–16], but the reported results were inconsistent with each other. Therefore, we conducted a comprehensive meta-analysis to explore any potential association between levels of dietary isoflavones and breast cancer risk. Furthermore, patients with specific characteristics were evaluated as individual subgroups to determine the relative role of isoflavone consumption on breast cancer risk.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This study was conducted and reported following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [17]. We conducted an electronic search of PubMed, Embase, and Cochrane Library databases from their dates of inception to April 2017 for prospective cohort studies published in English. Using the search terms ("soy" OR "bean" OR "soybean" OR "soyfood" OR "tofu" OR "miso" OR "phytoestrogen" OR "daidzein" OR "genistein" OR "isoflavone") AND ("breast cancer" OR "breast carcinoma" OR "breast neoplasm" OR "breast tumor") AND "prospective" AND "human" AND "English", we inspected medical subject headings for relevant human studies. The reference lists of every relevant original and review article were manually searched to identify additional, eligible studies. If multiple reports were published regarding the same study, only the publication containing the most detailed information regarding exposure and outcome was included.

Two reviewers independently undertook the literature search and study selection using a standardized approach. All inconsistencies were resolved via a third author referring to the original article. Study inclusion criteria were as follow: (1) the study was a prospective cohort study of adult patients (i.e., 18 years or older); (2) the study reported the incidence of breast cancer; (3) the study reported the exposure(s) of interest including isoflavone, soy foods, tofu, miso-soup, genistein, daidzein, biochanin A, formononetin, lignans, kaempferol, quercetin, myricetin, secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, syringaresinol, medioresinol, and coumestrol; and (4) the study reported adjusted risk estimates for the association between dietary isoflavones or isoflavone-rich foods, and breast cancer. Exclusionary criteria were as follow: (1) studies with cross-sectional, case–control, clinical trial, or retrospective cohort design; (2) studies only reporting unadjusted effect estimates or crude data; (3) studies failing to report 95%CIs; (4) studies with the exposure of interest not including dietary isoflavones or isoflavone-rich foods; and (5) studies with the outcome not breast cancer.

2.2. Data collection and quality assessment

Two authors independently read each eligible study and compiled the following information using a standardized electronic data form: first author's surname, publication year, country, sample size, publication date, number of breast cancer cases, exposure evaluation, follow-up duration, and adjusted factors. Each included study's quality was determined using the NOS [18]. This scale is defined by 3 aspects: (1) study group selection (was the exposed cohort representative; selection of non-exposed cohort; was exposure ascertained; demonstration that the outcome of interest was not present at the start of the study); (2) study group comparability on the basis of design or analysis; (3) ascertainment of the outcome of interest (outcome assessment; was follow-up sufficient for desired outcomes to occur; were cohorts adequately followed up). Based on these factors, a rating of 0–9 was allocated to each included study.

2.3. Statistical analysis

Statistical analyses were all completed using STATA version 10.0 software (Stata Corp, College Station, TX, USA). The relationship between the consumption of isoflavones or isoflavone-rich foods and the risk of developing breast cancer was examined based on the effect estimates (RR, odds ratio, hazard ratio) and 95%CIs published in the included studies. This included a summary relative risk estimate with 95%CI, which was either directly extracted or indirectly calculated from each study. The fixed-effects model was employed for analyzing data derived from a single study and the inverse variance DerSimonian-Laird random effects model was utilized for inter-study meta-analyses [19,20]. Data heterogeneity was assessed via the I^2 and Q statistics, with p-values <0.10 regarded as statistically significant [21,22]. A sensitivity analysis was performed by excluding each individual study to determine its effect on the overall conclusions [23]. By calculating subgroup RRs and 95%CIs, the relationship between isoflavone or soy food intake and the risk of developing breast cancer was determined by country, menopausal status, the type of exposure evaluation, follow-up duration, adjusted BMI, adjusted smoking, adjusted alcohol, adjusted PA, adjusted total energy intake, adjusted familial breast cancer history, and adjusted HRT [24]. Random-effect models were used to evaluate RR ratios to compare different levels of isoflavone intake versus minimal isoflavone in participants adjusted for specific characteristics [20]. Additionally, we used the Egger's [25] and Begg's tests [26] to examine funnel plot asymmetry. Statistical significance was defined as a p-value <0.05 for all analyses, if not indicated otherwise.

3. Results

3.1. Literature search and study selection

205 studies (PubMed, 63; Embase, 119, Cochrane Library, 23) were identified according to the aforementioned search criteria. After excluding irrelevant and duplicate studies, twenty-one records remained for further screening. An additional five records were removed because they were either unrelated to the topic (n = 1), a meta-analysis (n = 2), or a case-controlled study (n = 2). The resulting sixteen prospective cohort studies were included for analysis [13–19,27–45]. Manually searching the reference lists of these sixteen studies yielded no further eligible studies. Figure 1 depicts a flow diagram of the study selection process, and Table 1 summarizes the characteristics of the included studies.

3.2. Study characteristics

The sixteen studies examined in this meta-analysis include 648,913 participants and 11,169 reported cases of breast cancer. Five of the studies were conducted in the US, four in Japan, two in the UK, one in the Netherlands, one in Sweden, one in France, one in China, and one in Singapore. The sample size ranged from 10,708 to 111,526 participants, while follow-up durations ranged from 2.0 to 14.1 years. Twelve studies reported that patients used food-frequency questionnaires, three employed self-administered questionnaires, and the remaining study used a mail survey

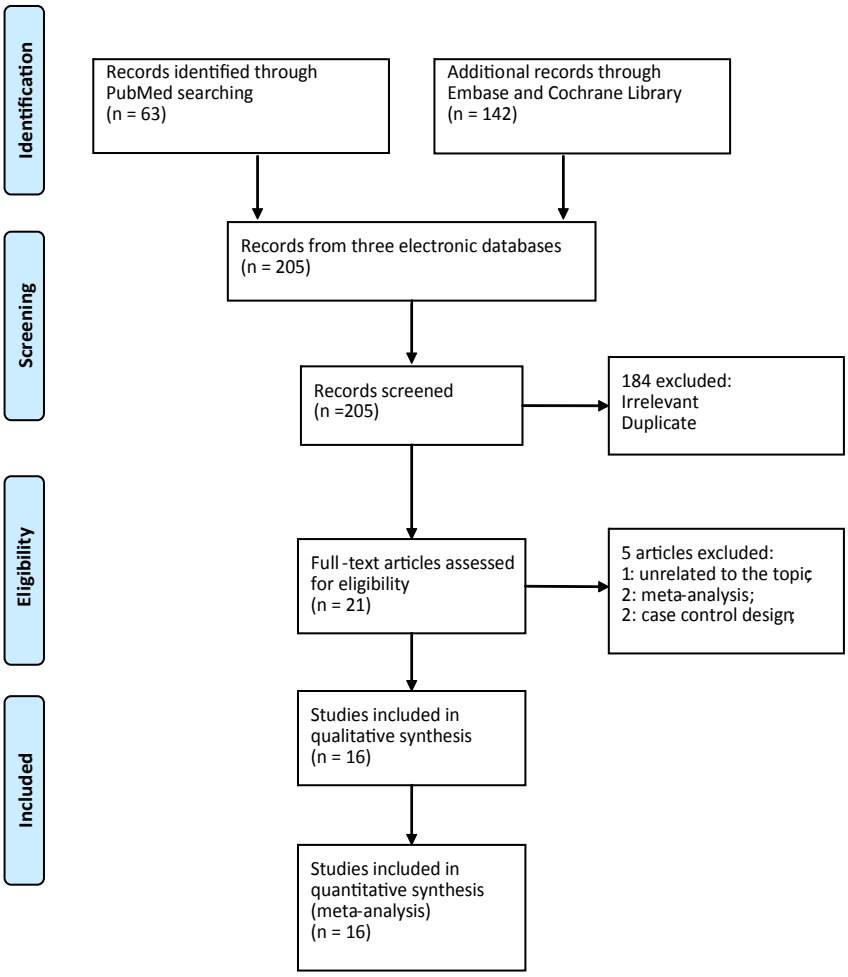


Fig. 1. Flow diagram of the literature search and trials selection process.

questionnaire. These datasets were found to be of moderate to high Newcastle–Ottawa Scale (NOS) quality, with twelve studies scoring 8/9 and the remaining four scoring 7/9 (Table 1).

3.3. Isoflavone intake and breast cancer risk

The included studies examined the effects of high intake (n = 11) and/or moderate intake (n = 10) versus low intake of isoflavones on breast cancer risk. The results indicated that both high and moderate versus low intake of isoflavones had no association with the risk of developing breast cancer (high versus low: relative risk [RR]: 0.99; 95% confidence interval [CI]: 0.91–1.09; P = 0.876; moderate versus low: RR, 0.99; 95%CI, 0.92–1.05; P = 0.653, Fig. 2). The data used in this analysis exhibited an insignificant level of heterogeneity (I^2 = 27.0%; P = 0.187 for high versus low; I^2 = 27.3%; P = 0.192 for moderate versus low), so we performed a sensitivity analysis. Each study was sequentially excluded from the pooled analysis, and the conclusion was unaffected by any specific exclusion (Table 2).

3.4. Soy foods intake and breast cancer risk

Included studies also reported on the effects of high intake (n = 6) and/or moderate intake (n = 4) versus low intake of soy foods on the risk of developing breast cancer. The pooled analysis suggested that a high consumption of soy foods associated with a lower risk of developing breast cancer as compared with a low intake of soy foods (RR: 0.87; 95%CI: 0.76–1.00; P = 0.048; with no evidence of heterogeneity; Fig. 3). However, a moderate intake of soy foods did not significantly affect the risk of developing breast cancer (RR: 0.93; 95%CI: 0.82–1.07; P = 0.323; with insignificant heterogeneity; Fig. 3). While the sensitivity analysis of high versus low intake of soy foods demonstrated some variance in the summary RR, excluding any specific study from the subgroup considering moderate versus low consumption of soy foods had no effect the conclusion (Table 2).

3.5. Other flavonoid-rich foods and breast cancer risk

Results regarding other flavonoid-rich food affecting the risk of breast cancer are presented in Table 3. We noted that a high or moderate consumption of tofu (high versus low: RR, 1.32; 95%CI: 0.86–2.03, P = 0.202; moderate versus low: RR, 1.30; 95%CI: 0.81–2.09, P = 0.278), miso-soup (high versus low: RR, 0.67; 95%CI: 0.45–1.00, P = 0.051; moderate versus low: RR, 0.95; 95%CI: 0.72–1.26, P = 0.721), genistein (high versus low: RR, 1.03; 95%CI: 0.92–1.14, P = 0.637; moderate versus low: RR, 1.00; 95%CI: 0.90–1.10, P = 0.935), daidzein (high versus low: RR, 1.02; 95%CI: 0.92–1.13, P = 0.658; moderate versus low: RR, 1.02; 95%CI: 0.93–1.12, P = 0.676), biochanin A (high versus low: RR, 1.06; 95% CI: 0.91–1.23, P = 0.468; moderate versus low: RR, 0.93; 95%CI: 0.81–1.07, P = 0.307), lignans (high versus low: RR, 1.05; 95%CI:

Table 1
Baseline characteristic of studies included.

Study	Publication year	Country	Sample size	Age (year)	BC cases	Exposure evaluation	Categories of dietary isoflavone	Follow-up (year)	Adjusted factors	NOS score
Key [27]	1999	Japan	34759	NA	427	Mail survey questionnaires	Isoflavone-rich foods: higher: ≥5/week; moderate: 2–4/week; Control: ≤1/week	14.1	Attained age, calendar period, city, age at time of bombing and radiation dose	7
Horn-Ross [28]	2002	US	111526	21–103	711	Food-frequency questionnaire	Quintile 4 and 5 were regarded as higher; Quintile 2 and 3 were regarded as moderate; and Quintile 1 was regarded as control	2.0	Age, race, daily caloric intake, family history of BC, age at menarche, nulliparity/age at first full-term pregnancy, PA, and an interaction term for BMI and menopausal status	8
Yamamoto [29]	2003	Japan	21852	40–59	179	Self-administered questionnaire	Higher: 25.3 mg/day (Highest); moderate: 13.0–20.0 mg/day (Second to Third); Control: 6.9 mg/day (lowest)	9.6	Area, age, age at menarche, number of pregnancies, menopausal status, age at first pregnancy, active and passive smoking, alcohol consumption, leisure-time PA, educational level, total EI, and meat, fish, vegetable, and fruit consumption	8
Keinan-Boker [30]	2004	Netherlands	15555	49–70	280	Food-frequency questionnaire	Quartile 4 was regarded as higher; Quartile 2 and 3 were regarded as moderate; and Quartile 1 was regarded as control	5.2	Age at enrollment, age at first full-term delivery, height, weight, parity, PA, use of oral contraceptives or HRT, marital status, academic education, and daily EI.	8
Adebamowo [31]	2005	US	90630	26–46	710	Food-frequency questionnaire	Quintile 4 and 5 were regarded as higher; Quintile 2 and 3 were regarded as moderate; and Quintile 1 was regarded as control	8.0	Age at menarche, parity and age at first birth, family history of BC in mother and/or sister, history of benign breast disease, oral contraceptive use, alcohol consumption, EI, current BMI, height, smoking habit, PA and menopausal status	8
Hedelin [32]	2008	Sweden	45448	30–49	1014	Self-administered questionnaire	Quartile 4 was regarded as higher; Quartile 2 and 3 were regarded as moderate; and Quartile 1 was regarded as control	12.8	Age, BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, cancer in sisters or mothers, and intake of total EI, alcohol, and saturated fat	7
Lee [33]	2009	China	73223	40–70	592	Food-frequency questionnaire	Quintile 4 and 5 were regarded as higher; Quintile 2 and 3 were regarded as moderate; and Quintile 1 was regarded as control	7.4	Age, education, PA, age at first live birth, BMI, season of recruitment, family history of BC, and total EI	8
Butler [13]	2010	Singapore	34028	45–74	629	Food-frequency questionnaire	Quartile 4 was regarded as higher; Quartile 2 and 3 were regarded as moderate; and Quartile 1 was regarded as control	9.9	Age at interview, dialect group, interview year, education, parity, BMI, first-degree relative with diagnosis of BC, and total daily EI	8
Travis [34]	2008	UK	37643	≥20	585	Food-frequency questionnaire	Higher: ≥ 20 mg/day; moderate: 10–20 mg/day; Control: <10 mg/day	7.4	height, BMI group, age at menarche, age at first birth and parity, alcohol consumption, and daily EI, menopausal status and current HRT use	8
Touillaud [35]	2006	French	26868	40–65	402	Food-frequency questionnaire	Higher: 36–112 mg/day; moderate: 22–35 mg/day; Control: 1–22 mg/day	4.2	Years of education, height, BMI, age at menarche, personal history of benign breast disease or lobular carcinoma in situ, family history of BC in first- or second-degree relatives, lifetime use of oral contraceptive, age at first full-term pregnancy and parity, geographic area, alcohol consumption, and dietary energy intake from food.	7
Brasky [14]	2010	US	35016	50–76	880	Food-frequency questionnaire	User vs nonuser	6.0	Age, race, education, BMI, height, fruit consumption, vegetable consumption, alcohol consumption, PA, age at menarche, age at menopause, age at first birth, history of hysterectomy, years of combined HRT, family history of BC, history of benign breast biopsy, mammography, low-dose aspirin use, regular aspirin use, ibuprofen use, naproxen use, and use of multivitamins.	8
Wang [36]	2009	US	38408	≥45	3234	Food-frequency questionnaire	Quintile 4 and 5 were regarded as higher; Quintile 2 and 3 were regarded as moderate; and Quintile 1 was regarded as control	11.5	Age, race, total EI, and randomized treatment assignment, smoking, alcohol use, PA, postmenopausal status, HRT use, multivitamin use, BMI, family history of colorectal cancer, ovary cancer, and BC, and intake of fruit and vegetables, fiber, folate, and saturated fat	8
Ward [15]	2010	UK	10708	40–79	244	Food-frequency questionnaire	Quintile 4 and 5 were regarded as higher; Quintile 2 and 3 were regarded as moderate; and Quintile 1 was regarded as control	9.0	Age, weight, family history of BC, oral contraceptive use, parity, breastfeeding, menopausal HRT use, surgical removal of ovaries, average daily intake of fat and energy, and social class	8
Wada [16]	2013	Japan	15607	≥35	172	Food-frequency questionnaire	Quartile 4 was regarded as higher; Quartile 2 and 3 were regarded as moderate; and Quartile 1 was regarded as control	14.0	Age, BMI, PA, smoking status, alcohol consumption, education years, age at menarche, age at first delivery, menopausal status, parity number, and history of HRT	8
Nishio [37]	2007	Japan	22236	40–79	92	Food-frequency questionnaire	Higher: almost daily; moderate: 3–4/week; Control: <3/week	7.6	Age, study area, family history of BC, age at menarche, age at first birth, use of exogenous female hormone, smoking, consumption of green leafy vegetables, walking time, BMI, and total EI	8
Greenstein [38]	1996	US	35406	NA	1018	Self-administered questionnaire	Consumers vs. nonconsumers	7.0	Major BC risk factors	7

BC: breast cancer; PA: physical activity; BMI: body mass index; HRT: hormone replacement therapy; EI: energy intake.

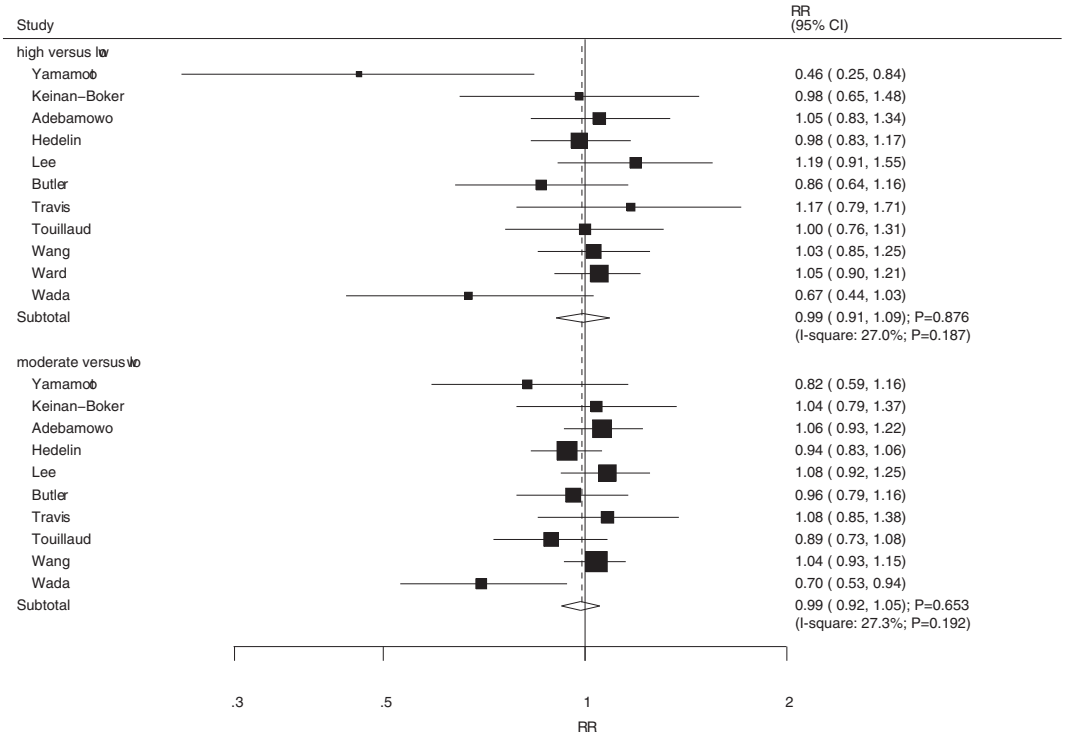


Fig. 2. The relationship between isoflavone intake and the risk of breast cancer.

0.89–1.23, P = 0.574; moderate versus low: RR, 1.04; 95%CI: 0.95–1.15, P = 0.391), kaempferol (high versus low: RR, 1.01; 95%CI: 0.80–1.27, P = 0.933; moderate versus low: RR, 0.95; 95%CI: 0.83–1.08, P = 0.445), quercetin (high versus low: RR, 1.05; 95%CI: 0.83–1.33, P = 0.685; moderate versus low: RR, 1.06; 95%CI: 0.92–1.22, P = 0.418), myricetin (high versus low: RR, 0.99; 95%CI: 0.78–1.26, P = 0.935; moderate versus low: RR, 1.08; 95%CI: 0.94–1.24, P = 0.276), secoisolariciresinol (high versus low: RR, 1.14; 95%CI: 0.98–1.34, P = 0.096; moderate versus low: RR, 1.09; 95%CI: 0.96–1.24, P = 0.201), matairesinol (high versus low: RR, 1.09; 95%CI: 0.94–1.26, P = 0.249; moderate versus low: RR, 0.99; 95%CI: 0.87–1.13, P = 0.880), lariciresinol (high versus low: RR, 1.10; 95%CI: 0.92–1.32, P = 0.301; moderate versus low: RR, 1.06; 95%CI: 0.93–1.20, P = 0.366), pinoresinol (high versus low: RR, 1.03; 95%CI: 0.86–1.24, P = 0.752; moderate versus low: RR, 1.03; 95%CI: 0.90–1.17, P = 0.656), syringaresinol (high versus low: RR, 1.10; 95% CI: 0.92–1.32, P = 0.301; moderate versus low: RR, 1.05; 95%CI: 0.92–1.19, P = 0.453), medioresinol (high versus low: RR, 1.02; 95% CI: 0.85–1.22, P = 0.828; moderate versus low: RR, 1.01; 95%CI: 0.89–1.14, P = 0.874), and coumestrol (high versus low: RR, 0.98; 95%CI: 0.88–1.08, P = 0.672; moderate versus low: RR, 1.04; 95%CI: 0.88–1.24, P = 0.618) were not associated with the risk of developing breast cancer. While a high intake of formononetin was also not associated with the risk of breast cancer (RR: 0.97; 95%CI: 0.85–1.11; P = 0.683), a moderate consumption of formononetin significantly associated with increased risk (RR: 1.16; 95%CI: 1.00–1.34; P = 0.045).

3.6. Subgroup analyses for isoflavones and soy foods intake

We conducted subgroup analyses to determine possible effects that isoflavones and soy foods had on breast cancer risk within specific populations, while also minimizing the heterogeneity of the data. There were no significant associations found between isoflavone consumption and breast cancer risk based on the predefined factors (Table 4). Furthermore, a high intake of soy foods showed possible protection against breast cancer risk in studies that did not adjust for familial breast cancer history (RR: 0.80; 95% CI: 0.65–0.97; P = 0.025; Table 5). In addition, a moderate soy food intake associated with reduced breast cancer risk if the follow-up duration ≥10.0 years (RR: 0.72; 95%CI: 0.53–0.97; P = 0.030), the study adjusted for smoking status (RR: 0.75; 95%CI: 0.59–0.96; P = 0.024), the study adjusted for alcohol intake (RR: 0.75; 95%CI: 0.59–0.96; P = 0.024), the study did not adjusted for total energy intake (RR: 0.72; 95%CI: 0.53–0.97; P = 0.030), and the study adjusted for hormone replacement therapy (HRT) (RR: 0.72; 95%CI: 0.53–0.97; P = 0.030). However, we noted that adjusting for smoking status (ratio of RR: 0.75; 95%CI: 0.59–0.98; P = 0.033) and alcohol intake (ratio of RR: 0.75; 95%CI: 0.59–0.98; P = 0.033) may bias the relationship between moderate soy food intake and breast cancer risk (Table 2).

3.7. Publication bias

Using funnel plots, we could not rule out the potential for publication bias when considering the relationship between isoflavone intake and the risk of developing breast cancer (Fig. 4). While the Egger and Begg test results showed no evidence of publication bias for moderate intake of isoflavone and breast cancer risk (p-value for Egger: 0.147; p-value for Begg: 0.152), there was potential evidence of publication bias for high intake of isoflavone and breast cancer risk (p-value for Egger: 0.080; p-value for Begg: 0.087). However, adjusting for publication bias by the trim and fill method did not change the conclusions of this study [39].

4. Discussion

Our current study was based on prospective cohort studies and explored all possible correlations between dietary isoflavone intake and the risk of breast cancer. This large quantitative study included

Table 2
Sensitivity analyses for isoflavone, soyfoods intakes and the risk of breast cancer.

Intakes	Comparisons categories	Excluding study	RR and 95%CI	P value	Heterogeneity (%)	P value for heterogeneity
Isoflavone	High versus low	Yamamoto	1.01 (0.94–1.09)	0.699	0.0	0.611
		Keinan-Boker	0.99 (0.90–1.09)	0.853	34.3	0.134
		Adebamowo	0.98 (0.89–1.09)	0.741	33.6	0.139
		Hedelin	0.99 (0.89–1.10)	0.855	33.9	0.137
		Lee	0.98 (0.89–1.07)	0.619	24.9	0.214
		Butler	1.00 (0.91–1.11)	0.936	28.6	0.181
		Travis	0.98 (0.89–1.08)	0.725	31.1	0.160
		Touillaud	0.99 (0.89–1.10)	0.826	34.3	0.133
		Wang	0.98 (0.88–1.09)	0.746	33.9	0.137
		Ward	0.98 (0.88–1.09)	0.670	31.9	0.153
		Wada	1.01 (0.93–1.10)	0.750	11.2	0.339
	Moderate versus low	Yamamoto	0.99 (0.93–1.06)	0.806	28.1	0.195
		Keinan-Boker	0.98 (0.91–1.05)	0.581	34.8	0.139
		Adebamowo	0.97 (0.90–1.05)	0.441	29.4	0.184
		Hedelin	0.99 (0.92–1.07)	0.834	30.1	0.178
		Lee	0.97 (0.91–1.04)	0.429	27.7	0.198
		Butler	0.99 (0.92–1.06)	0.692	34.8	0.140
		Travis	0.98 (0.91–1.05)	0.526	32.8	0.156
		Touillaud	0.99 (0.93–1.07)	0.877	27.9	0.196
		Wang	0.97 (0.90–1.05)	0.450	29.9	0.180
		Wada	1.01 (0.95–1.06)	0.855	0.0	0.594
Soyfoods	High versus low	Yamamoto	0.88 (0.76–1.01)	0.071	0.0	0.556
		Lee	**0.84 (0.71–0.98)**	**0.030**	**0.0**	**0.694**
		Butler	0.89 (0.76–1.05)	0.171	0.0	0.591
		Brasky	**0.84 (0.73–0.98)**	**0.025**	**0.0**	**0.752**
		Wada	0.89 (0.77–1.03)	0.117	0.0	0.691
		Greenstein	0.88 (0.77–1.02)	0.097	0.0	0.614
	Moderate versus low	Yamamoto	0.94 (0.80–1.10)	0.420	51.9	0.125
		Lee	0.87 (0.69–1.11)	0.264	51.6	0.127
		Butler	0.87 (0.70–1.08)	0.217	46.2	0.156
		Wada	0.99 (0.89–1.10)	0.846	0.0	0.730

RR: relative risk; CI: confidence interval.
P<0.05 deem as significant.

648,913 individuals and 11,169 reported cases of breast cancer from 16 prospective cohort studies with a broad demographic range. In our meta-analysis, we failed to detect a significant association between the consumption of isoflavones and the risk of breast cancer. Additional sensitivity and subgroup analyses reiterated this finding, indicating no significant effect of isoflavones on breast cancer risk. While a moderate intake of soy foods was not significantly related to breast cancer risk, a significant correlation was detected between a high intake of soy foods and a reduced risk of breast cancer (RR = 0.87, P = 0.048). Further sensitivity and subgroup analyses, regarding the effect of soy foods, identified multiple associations in different subsets. While moderate formononetin intake may play a harmful role in breast cancer incidence (RR: 1.16, P = 0.045), this study failed to identify a significant relationship between breast

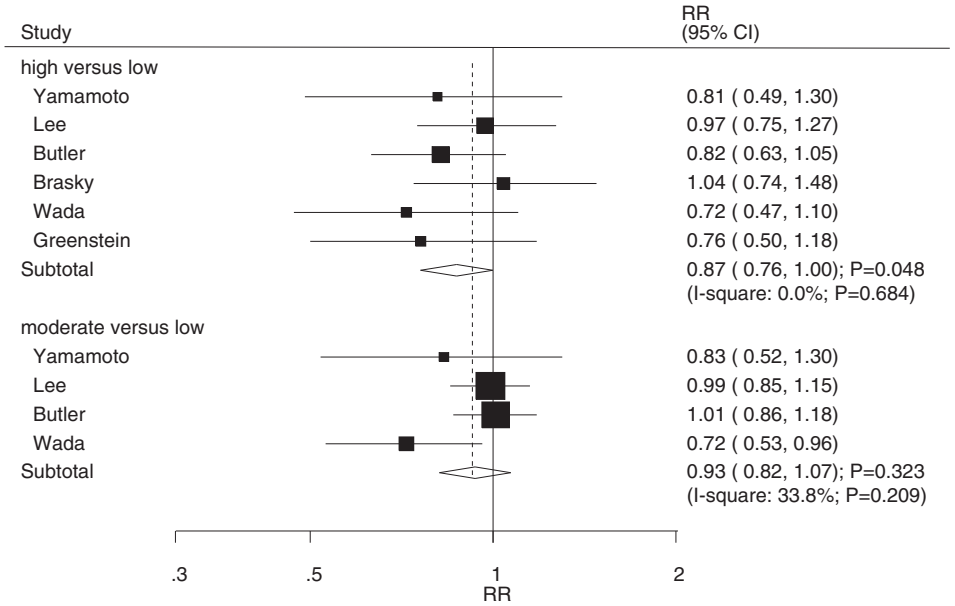


Fig. 3. The relationship between soyfoods intake and the risk of breast cancer.

Table 3
The summary RRs of other flavonoid-rich foods intakes and the risk of breast cancer.

Types	Number of studies	High versus low	P value	Number of studies	Moderate versus low	P value
Tofu	2	1.32 (0.86–2.03)	0.202	1	1.30 (0.81–2.09)	0.278
Miso-soup	2	0.67 (0.45–1.00)	0.051	2	0.95 (0.72–1.26)	0.721
Genistein	3	1.03 (0.92–1.14)	0.637	2	1.00 (0.90–1.10)	0.935
Daidzein	3	1.02 (0.92–1.13)	0.658	2	1.02 (0.93–1.12)	0.676
Biochanin A	2	1.06 (0.91–1.23)	0.468	1	0.93 (0.81–1.07)	0.307
Formononetin	2	0.97 (0.85–1.11)	0.683	1	1.16 (1.00–1.34)	0.045
Lignans	4	1.05 (0.89–1.23)	0.574	3	1.04 (0.95–1.15)	0.391
Kaempferol	1	1.01 (0.80–1.27)	0.933	1	0.95 (0.83–1.08)	0.445
Quercetin	1	1.05 (0.83–1.33)	0.685	1	1.06 (0.92–1.22)	0.418
Myricetin	1	0.99 (0.78–1.26)	0.935	1	1.08 (0.94–1.24)	0.276
Secoisolariciresinol	2	1.14 (0.98–1.34)	0.096	1	1.09 (0.96–1.24)	0.201
Matairesinol	2	1.09 (0.94–1.26)	0.249	1	0.99 (0.87–1.13)	0.880
Lariciresinol	1	1.10 (0.92–1.32)	0.301	1	1.06 (0.93–1.20)	0.366
Pinoresinol	1	1.03 (0.86–1.24)	0.752	1	1.03 (0.90–1.17)	0.656
Syringaresinol	1	1.10 (0.92–1.32)	0.301	1	1.05 (0.92–1.19)	0.453
Medioresinol	1	1.02 (0.85–1.22)	0.828	1	1.01 (0.89–1.14)	0.874
Coumestrol	3	0.98 (0.88–1.08)	0.672	2	1.04 (0.88–1.24)	0.618

cancer risk and tofu, miso-soup, genistein, daidzein, biochanin A, lignans, kaempferol, quercetin, myricetin, secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, syringaresinol, medioresinol, and coumestrol.

The mechanism underlying the preventive role of soy foods against breast cancer remains unclear. One possible reason may be that isoflavones are structurally-similar to estradiol and may play a similar role as estrogen [40,41]. Furthermore, isoflavones may inhibit aromatase synthesis by binding to the estrogen receptor, which might competitively block the binding of more potent natural estrogens [41–43]. Previous studies have already demonstrated estrogen exposure might contributed to the risk of breast cancer, which may explain the previously hypothesized relationship between isoflavones and the risk of breast cancer [44,45].

We are aware of several, previously published systematic reviews or meta-analyses that are relevant to this work. Qin et al. systematically reviewed evidence before April 2006 regarding the association between soy foods and breast cancer risk. They

Table 4
Subgroup analysis for isoflavone intakes and the risk of breast cancer.

Factor	Subgroup	Number of included studies	High versus low	P value	Number of included studies	Moderate versus low	P value
Country	Asia	4	0.80 (0.56–1.14)	0.218	4	0.91 (0.76–1.09)	0.308
	Europe or US	7	1.03 (0.95–1.12)	0.510	6	1.00 (0.95–1.07)	0.876
	Asia vs Europe or US	–	0.78 (0.54–1.12)	0.175	–	0.91 (0.75–1.10)	0.330
Menopausal status	Premenopausal	7	1.06 (0.93–1.20)	0.379	6	0.99 (0.90–1.10)	0.911
	Postmenopausal	6	0.83 (0.63–1.11)	0.212	5	0.85 (0.66–1.08)	0.181
	Premenopausal vs Postmenopausal	–	1.28 (0.94–1.74)	0.123	–	1.16 (0.89–1.52)	0.261
Type of exposure evaluation	FFQ	9	1.02 (0.94–1.11)	0.589	8	1.00 (0.93–1.08)	0.971
	Other	2	0.71 (0.34–1.48)	0.363	2	0.93 (0.82–1.04)	0.186
	FFQ vs other	–	1.44 (0.69–3.01)	0.337	–	1.08 (0.93–1.24)	0.311
Follow-up duration	≥10.0 years	3	0.95 (0.80–1.13)	0.555	3	0.93 (0.79–1.09)	0.347
	<10.0 years	8	1.01 (0.90–1.14)	0.867	7	1.01 (0.94–1.09)	0.734
	≥10.0 vs < 10.0 years	–	0.94 (0.76–1.16)	0.566	–	0.92 (0.77–1.10)	0.361
Adjusted BMI	Yes	9	1.00 (0.92–1.09)	0.943	9	0.99 (0.93–1.06)	0.806
	No	2	0.73 (0.33–1.64)	0.449	2	0.82 (0.58–1.15)	0.250
	Yes vs no	–	1.37 (0.61–3.07)	0.444	–	1.21 (0.85–1.71)	0.289
Adjusted smoking	Yes	4	0.84 (0.64–1.12)	0.243	4	0.94 (0.81–1.10)	0.467
	No	7	1.02 (0.94–1.12)	0.581	6	0.98 (0.92–1.06)	0.654
	Yes vs no	–	0.82 (0.61–1.10)	0.194	–	0.96 (0.81–1.14)	0.628
Adjusted alcohol	Yes	7	0.96 (0.83–1.10)	0.538	7	0.96 (0.88–1.05)	0.393
	No	4	1.04 (0.93–1.16)	0.523	3	1.03 (0.93–1.15)	0.563
	Yes vs no	–	0.92 (0.77–1.10)	0.381	–	0.93 (0.81–1.07)	0.318
Adjusted PA	Yes	6	0.94 (0.77–1.14)	0.533	6	1.00 (0.90–1.10)	0.931
	No	5	1.01 (0.92–1.11)	0.869	4	0.95 (0.87–1.04)	0.243
	Yes vs no	–	0.93 (0.75–1.16)	0.517	–	1.05 (0.92–1.20)	0.454
Adjusted total EI	Yes	9	1.01 (0.91–1.11)	0.874	8	0.99 (0.93–1.06)	0.830
	No	2	0.87 (0.57–1.31)	0.500	2	0.87 (0.59–1.28)	0.491
	Yes vs no	–	1.16 (0.76–1.78)	0.494	–	1.14 (0.77–1.69)	0.519
Adjusted family history of BC	Yes	6	1.04 (0.96–1.13)	0.369	5	1.01 (0.95–1.08)	0.776
	No	5	0.83 (0.64–1.08)	0.162	5	0.92 (0.80–1.07)	0.300
	Yes vs no	–	1.25 (0.95–1.65)	0.107	–	1.10 (0.94–1.29)	0.250
Adjusted HRT use	Yes	8	1.01 (0.93–1.10)	0.764	7	0.98 (0.90–1.06)	0.607
	No	3	0.84 (0.55–1.29)	0.427	3	1.00 (0.88–1.14)	0.964
	Yes vs no	–	1.20 (0.78–1.86)	0.406	–	0.98 (0.84–1.14)	0.796

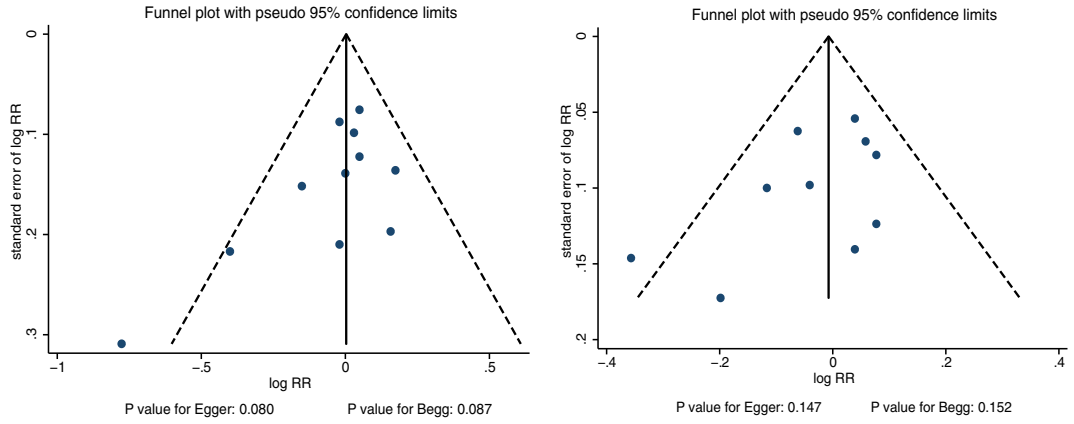
BC: breast cancer; PA: physical activity; BMI: body mass index; FFQ: Food-frequency questionnaire; HRT: hormone replacement therapy; EI: energy intake.

Table 5
Subgroup analysis for soyfoods intakes and the risk of breast cancer.

Factor	Subgroup	Number of included studies	High versus low	P value	Number of included studies	Moderate versus low	P value
Country	Asia	4	0.86 (0.73–1.00)	0.054	4	0.93 (0.82–1.07)	0.323
	Europe or US	2	0.91 (0.67–1.24)	0.556	0	–	–
	Asia vs Europe or US	–	0.95 (0.67–1.34)	0.749	–	–	–
Menopausal status	Premenopausal	3	0.85 (0.54–1.36)	0.502	3	0.90 (0.74–1.08)	0.245
	Postmenopausal	5	0.90 (0.73–1.11)	0.323	3	0.88 (0.66–1.15)	0.345
	Premenopausal vs Postmenopausal	–	0.94 (0.57–1.57)	0.825	–	1.02 (0.73–1.43)	0.896
Type of exposure evaluation	FFQ	4	0.89 (0.77–1.04)	0.140	3	0.94 (0.80–1.10)	0.420
	Other	2	0.78 (0.57–1.08)	0.134	1	0.83 (0.52–1.31)	0.425
	FFQ vs other	–	1.14 (0.80–1.62)	0.464	–	1.13 (0.69–1.85)	0.618
Follow-up duration	≥10.0 years	1	0.72 (0.47–1.10)	0.130	1	0.72 (0.53–0.97)	0.030
	<10.0 years	5	0.89 (0.77–1.03)	0.117	3	0.99 (0.89–1.10)	0.846
	≥10.0 vs < 10.0 years	–	0.81 (0.52–1.27)	0.366	–	0.73 (0.53–1.00)	0.051
Adjusted BMI	Yes	4	0.89 (0.77–1.04)	0.140	3	0.94 (0.80–1.10)	0.420
	No	1	0.81 (0.50–1.32)	0.397	1	0.83 (0.52–1.31)	0.425
	Yes vs no	–	1.10 (0.66–1.83)	0.716	–	1.13 (0.69–1.85)	0.618
Adjusted smoking	Yes	2	0.76 (0.55–1.04)	0.090	2	0.75 (0.59–0.96)	0.024
	No	3	0.92 (0.78–1.08)	0.316	2	1.00 (0.90–1.11)	0.993
	Yes vs no	–	0.83 (0.58–1.18)	0.295	–	0.75 (0.59–0.98)	0.033
Adjusted alcohol	Yes	3	0.88 (0.69–1.11)	0.273	2	0.75 (0.59–0.96)	0.024
	No	2	0.89 (0.74–1.07)	0.211	2	1.00 (0.90–1.11)	0.993
	Yes vs no	–	0.99 (0.73–1.34)	0.941	–	0.75 (0.59–0.98)	0.033
Adjusted PA	Yes	4	0.92 (0.77–1.09)	0.333	3	0.87 (0.70–1.08)	0.217
	No	1	0.82 (0.64–1.06)	0.128	1	1.01 (0.86–1.18)	0.902
	Yes vs no	–	1.12 (0.83–1.52)	0.462	–	0.86 (0.66–1.13)	0.276
Adjusted total EI	Yes	3	0.88 (0.74–1.04)	0.142	3	0.99 (0.89–1.10)	0.846
	No	2	0.88 (0.62–1.26)	0.500	1	0.72 (0.53–0.97)	0.030
	Yes vs no	–	1.00 (0.67–1.48)	1.000	–	1.38 (1.00–1.89)	0.051
Adjusted family history of BC	Yes	2	1.00 (0.81–1.23)	0.963	1	0.99 (0.85–1.15)	0.896
	No	3	0.80 (0.65–0.97)	0.025	3	0.87 (0.69–1.11)	0.264
	Yes vs no	–	1.25 (0.94–1.67)	0.131	–	1.14 (0.86–1.51)	0.369
Adjusted HRT use	Yes	2	0.88 (0.62–1.26)	0.500	1	0.72 (0.53–0.97)	0.030
	No	3	0.88 (0.74–1.04)	0.142	3	0.99 (0.89–1.10)	0.846
	Yes vs no	–	1.00 (0.67–1.48)	1.000	–	0.73 (0.53–1.00)	0.051

BC: breast cancer; PA: physical activity; BMI: body mass index; FFQ: Food-frequency questionnaire; HRT: hormone replacement therapy; EI: energy intake.

demonstrated that the consumption of soy foods may be associated with a decreased risk of breast cancer due to isoflavones [10]. Xie et al. summarized and analyzed isoflavone intake and the risk of breast cancer progression in women, finding that a high intake of isoflavones significantly reduced the risk of breast cancer in Asian women, but no similar effect was found in Western populations. The reason for this may have been that Western populations generally consume less isoflavones [11]. However, due to the small number of prospective cohort studies in this analysis, the results might be imprecise. Chen et al. performed a meta-analysis of 35 studies to evaluate the relationship between soy isoflavone intake and breast cancer risk in premenopausal and postmenopausal women separately. They found that soy isoflavone intake could lower the risk of breast cancer for both pre- and post-menopausal women in Asian populations, but no significant association was found in Western populations [12]. However, the traditional case control studies were employed in this analysis may have biased the relationship between soy isoflavone intake and breast cancer.



A. High versus low isoflavone intake

B. Moderate versus low isoflavone intake

Fig. 4. Funnel plot for high or moderate isoflavone intake and breast cancer.

Further, although subgroup analysis based on study design, country, publication year were conducted, while numerous factors were not illustrated, including the type of exposure evaluation, follow-up duration, adjusted body mass index (BMI), adjusted smoking, adjusted alcohol, adjusted physical activity (PA), adjusted total energy intake, adjusted family history of breast cancer, and adjusted HRT. In addition, whether these associations differ according to the characteristics of participants remains controversial. In comparison, this meta-analysis focused on prospective cohort studies to avoid the potential for uncontrolled biases, including only the most comprehensive, relevant studies in the analysis. Additionally, this study evaluated relationships between specific patient or study characteristics and the risk of breast cancer by using subgroup analyses.

This study did not find a significant association between a high or moderate intake of isoflavones and the risk of breast cancer. While a moderate consumption of soy foods was also not significantly associated with breast cancer risk, this study suggests that a high intake of soy foods may lower the risk of breast cancer. Most of the included studies support these findings, however Yamamoto et al. suggested that frequent intake of miso soup and isoflavones was associated with a reduced risk of breast cancer [29]. In addition, Wada et al. indicated that a moderate intake of soy and isoflavones had a protective effect on postmenopausal breast cancer [16]. These discrepancies may be due to study-specific definitions of high, moderate, and low intake of isoflavones or soy foods. Furthermore, because the conflicting studies derived their results from a smaller number of cohorts than the present meta-analysis, there may be increased variance in the results. Therefore, this study used relative results to provide a synthetic and comprehensive review. While multiple subgroup analyses of this work indicated that high or moderate intake of soy foods might affect the risk of breast cancer, these conclusions may be unreliable since smaller cohorts were available for such subsets. Finally, the summary RR indicated higher formononetin intake has no significant effect on breast cancer, while moderate formononetin intake was associated with an increased risk of breast cancer. This relationship should be verify in future large scale prospective studies due to only 1 study reported the association of formononetin intake with the risk of breast cancer [28].

Three strengths of our study should be highlighted. First, only prospective cohort studies were included, which could eliminate selection and recall bias. Second, the large sample size allowed us to quantitatively assess the association of isoflavone intake with the risk of breast cancer, and hence the findings of this study were more robust than those of any individual study. Third, the relationship between isoflavone intake and the risk of breast cancer in specific subpopulations was assessed, comparing these relationships with the corresponding subsets.

Several limitations should also be acknowledged regarding this meta-analysis. Different methods were employed by individual studies to assess the exposure to isoflavones, including mail survey questionnaires, self-administered questionnaires, and different types of food-frequency questionnaires. This may have biased the association between isoflavone intake and breast cancer. We could not obtain information on the percentage or indication for HRT in most cohorts. Further, subgroup analysis according to mean age was not conducted due to smaller number of studies were included in each subset. In addition, the adjusted factors, which may play an important role in the progression of breast cancer, differ between the included studies. Additionally, the range of dietary isoflavone intake and the cut-off values for the categories differed between studies, which might biases the association of dietary isoflavone with the risk of breast cancer. Finally, the criteria of dietary isoflavone intake level are different between Asia and Western countries, which might biases the relationship between dietary isoflavone intake and breast cancer.

5. Conclusion

Based on this systematic review and meta-analysis, a high intake of soy foods exhibits a beneficial role in reducing the risk of breast cancer. Further studies are warranted to explain the mechanism(s) involved in the association between isoflavones and breast cancer. More prospective cohort studies are also needed to determine the causality of this relationship.

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Author contributions

Ting-Ting Zhao, Zhi-Feng Miao, Feng Jin and Ji-Guang Li designed the research; Ting-Ting Zhao, Ying-Ying Xu and Hui-Ting Dong wrote the article; Qun Liu, Guo-Lian Zhu and Hao Xu analyzed and interpreted data; Ting-Ting Zhao, Feng Jin and Zhi-Feng Miao revised the article critically; Zhi-Feng Miao had primary responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest

The authors have declared no conflicts of interest.

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