Original Article

Isoflavone consumption and risk of breast cancer: a dose-response meta-analysis of observational studies

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Epidemiologic studies that examine whether isoflavone consumption protects against breast cancer have yielded inconsistent results. The controversy focuses on the effects of the menopausal status and exposure dose of isoflavone. We aim to conduct a meta-analysis on the association between isoflavone intake and breast cancer risk by comprehensively assessing isoflavone exposure in the targeted populations. We searched PUBMED and EMBASE databases for case-control and cohort studies that assess the association between isoflavone intake and breast cancer risk. We extracted relative risks (RR) and odds ratios (OR) of different reported categories of isoflavone intake from each study. Fixed- or random-effects models were used to summarize dose-response data. Twenty-two studies were selected for the meta-analysis. Overall, the results showed that isoflavone reduced the breast cancer risk (a combined RR/OR of 0.68, 95% CI: 0.52-0.89) in Asian populations rather than Western populations (a combined RR/OR of 0.98, 95% CI: 0.87, 1.11) for the high-dose category. Further analysis showed that the intake of isoflavone in postmenopausal Asian women 0.46 (95% CI: 0.28-0.78) was better than premenopausal 0.63 (95% CI: 0.50-0.80) but similar in postmenopausal Western women 1.00 (95% CI: 0.98-1.02) and premenopausal 0.99 (95% CI: 0.87-1.12). Exposure to high isoflavone may be associated with a reduced breast cancer risk in Asian populations, especially in postmenopausal women. However, no significant difference in the studies of Western populations may be due to the low intake of isoflavone levels.

Key Words: isoflavone, breast cancer, dose-response, meta-analysis, menopause

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females. Based on the GLOBOCAN estimates, 1.38 million new cases of breast cancer were diagnosed globally and 458,400 died of this disease in 2008.[1] Meanwhile, the incidence rates of breast cancer are high in Western countries (greater than 70 per 100,000), and low in Asia (less than 30 per 100,000).[2]

The low incidence rates of breast cancer in Asian countries increased interest in investigating the role that soy might play a part in the cause of breast cancer, as soy food intake is a typical dietary characteristic in these countries.[3] However, a number of epidemiologic studies yielded inconsistent results when exploring the association between soy food or isoflavone intake and breast cancer risk. Trock *et al* [4] performed a meta-analysis of the epidemiologic data that consisted of 18 studies (12 case-control and 6 cohort or nested case-control studies). They found that in a pooled analysis, the association was not statistically significant among women in Asian countries [odds ratio, (OR) = 0.89; 95% confidence interval (CI): 0.71-1.12) for high isoflavone intake. Wu *et al* [5] suggested that isoflavone intake in Asian populations may have protective effects against breast cancer, meanwhile the results showed that isoflavone intake was unrelated to breast cancer risk in Western populations. A recent meta-analysis[6] showed that the protective effect of isoflavone was only seen in studies conducted among Asian populations [risk ratio (RR) = 0.76, 95% CI: 0.65-0.86) but not among Western populations (RR = 0.97, 95% CI: 0.87-1.06) for high isoflavone intake.

The controversy over whether isoflavone has a protective effect against breast cancer focuses on the effects of the menopausal status and isoflavone dose on the association between isoflavone consumption and breast cancer risk. Two large-scale prospective studies performed in Japan[7-8] observed non-significant inverse association between soy food or isoflavone intake and breast cancer risk in both premenopausal and postmenopausal women. Wu *et al* [9] investigated the effects of soy isoflavone intake on breast cancer in a prospective study of 35,303 ethnically Chinese Singaporean women, and

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find that this inverse association was apparent mainly in postmenopausal women (RR = 0.74, 95% CI%: 0.61-0.90), and was not observed in premenopausal women (RR = 1.04, 95% CI: 0.77-1.40). The results of two meta-analyses were inconsistent. Trock *et al* [4] showed that the inverse association was somewhat stronger in premenopausal women (OR = 0.70, 95% CI: 0.58-0.85), while Dong *et al* [6] reported that that the inverse association was not found in premenopausal women (RR = 0.90, 95% CI: 0.64-1.15). In addition, there is no meta-analysis reported on whether menopausal status in Western populations affects the preventive effect of isoflavone intake on breast cancer.

It was hypothesized that isoflavone protect against breast cancer, the dose of isoflavone consumption might influence breast cancer risk.[10-11] The proliferation rate of breast lobular epithelium significantly increased after 14 days of soy supplementation (45mg isoflavone).[12] However, in a two-year randomized, double-blinded, and placebo-controlled trial,[13] 80 or 120 mg/day of isoflavone did not modify breast density in postmenopausal women. One way to resolve these controversies is to conduct comprehensive research on the menopausal status and the exposure dose.

Therefore, we conducted a meta-analysis of observational studies to quantitatively assess the association between isoflavone intake and breast cancer risk in Asian and in Western populations. We also attempted to explore whether menopausal status and the exposure dose would affect breast cancer risk. This analysis will be the latest and presumably larger than previous studies.

METHODS

Search strategy

We conducted a systematic literature search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/home) databases. The search phrase used for both searches was "(soy OR isoflavone OR genistein OR phytoestrogen) AND breast cancer" limited to human studies. Furthermore, we reviewed reference lists of articles and reviews to search for more studies.

Study selection

Studies were included according to the following criteria: 1) the design was observational, i.e., case-control or cohort; 2) the study provided the data for isoflavone consumption; and 3) the study reported relative risk or odds ratio and their corresponding 95% CIs of breast cancer to every isoflavone intake value. The exclusion criteria were as follows: 1) only two categories of isoflavone intake (eg, daily *vs* never) were reported, not allowing adequate classifications; 2) interventions including soy, soy foods, genistein or daidzein cannot be converted to isoflavone intake; 3) the times of isoflavone intake, which can not be an accurate assessment of isoflavone exposure dose; and 4) the endpoint was breast cancer recurrence.

Data extraction

Relevant data included the first author, publication year, country of origin, study design, participant characteristics, relative risk or odds ratio and their corresponding 95% CIs of breast cancer, measure of isoflavone intake and adjustments. To standardize isoflavone intake, we used data from Japan[14] to derive a ratio of 1 mg isoflavone to 301 mg soy protein. We used energy consumption from Japan[15] (2,108 kcal/day) and American[16] (2,370 kcal/day) to estimate the energy consumption of Asian and Western women.

Classification of isoflavone intake

We used the isoflavone consumption per day to estimate the risk of breast cancer. We separated the isoflavone intake in Asian populations and Western populations, because the exposure dose was different. Isoflavone intake was about 25 mg per day in Asian populations,[17] while in Western populations,[18] average daily intake was less than 1mg. For a quantitative study on how isoflavone intake before and after menopausal influence the risk of breast cancer, we created 4 levels of isoflavone consumption in Asian populations: lowest (<5 mg/day), second-lowest (5-15 mg/day), second-highest (15-25 mg/day), and highest (>25 mg/day), while in Western populations: lowest (<100 μg/day), second-lowest (100-500 μg/day), second-highest (500-1000 μg/day), and highest (>1000 μg /day) .

Statistical analysis

We evaluated the heterogeneity among studies by using the Q test (p<0.05). The I^2 statistic was also examined, and we considered an I^2 value >50% to indicate significant heterogeneity between the trials.[19] We used a random-effects model when the test result for heterogeneity was significant. Otherwise, the fixed-effects model was preferred.

For each study, we extracted the OR or RR and 95% CI to measure the relationship between isoflavone intake and breast cancer. We converted OR or RR into their natural logarithms, and the standard error (SE) was calculated from these logarithms and their corresponding 95% CIs. We estimated the pooled OR or RR and 95% CIs of breast cancer for each standardized category of isoflavone consumption by using both fixed- and random-effects models.

We performed a dose-response analysis based on data for categories of isoflavone intake on exposure dose, number of cases and participants, and adjusted logarithm of the RR with its SE.[20-21] We conducted statistical analyses using Stata version 11.0 (StataCorp, College Station, TX, USA). Publication bias was assessed by Egger linear regression test.[22]

RESULTS

The method used to select studies is shown in Figure 1. We identified 22 studies[23-44] that met the inclusion criteria. Characteristics of these studies are presented in Table 1. All the included studies were conducted in Asian and Western women. Of the 22 included studies, 7 had cohort and 15 had case-control designs. Results were presented by menopausal status in 14 of these studies, 9 studies reported results from Asian populations, the other 5 studies reported that from Western populations.

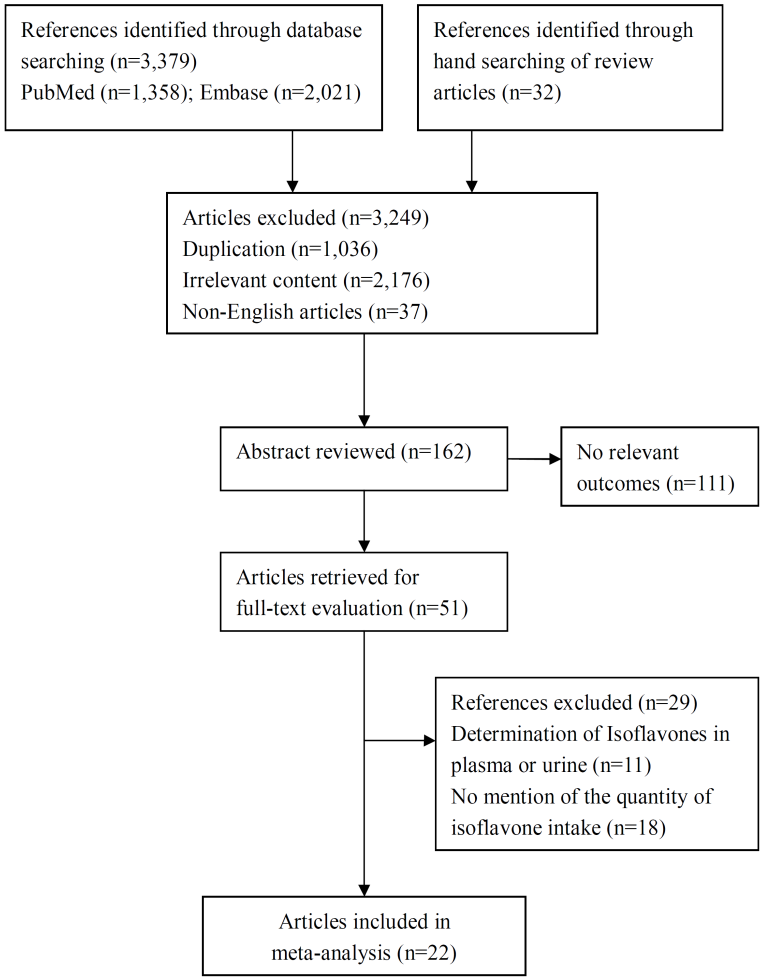

Figure 1. Flowchart showing the number of citations retrieved by individual searches of trials included in the meta-analysis.

Comparisons of the associations between breast cancer risk and isoflavone intake for Asians is shown in Figure 2. The breast cancer risk is 30% lower in Asian women with the highest isoflavone intake (a combined RR/OR of 0.70, 95% CI: 0.57-0.86) than in those with the lowest isoflavone intake. However, significant heterogeneity existed among studies (p for heterogeneity=0.004, I^2 = 60.1%). While in Western populations (shown in Figure 3), the association was not statistically significant (a combined RR/OR of 0.97, 95% CI: 0.89-1.06), no significant heterogeneity for this outcome was found (p for heterogeneity=0.399, I^2 = 4.5%). Further analysis according to study design demonstrated that there is no significant difference between cohort studies and case-control; Asian cohort studies (RR = 0.78, 95% CI: 0.65-0.95) and in case-control (OR = 0.69, 95% CI: 0.52-0.90), Western cohort studies (RR = 1.00, 95% CI: 0.88-1.14) and in case-control (OR = 0.94, 95% CI: 0.83-1.06).

The pooled results of Asian women by meta-analysis were stratified according to different levels of isoflavone consumption (Table 2). The combined RR/OR for breast cancer was 0.68 (95% CI: 0.52-0.89) for the highest level (>25 mg/day), while in Western women (Table 3), the combined RR/OR for breast cancer was 0.98 (95% CI: 0.87-1.11) for the highest level (>1000 μg/day).

We further explored how isoflavone intake before and after menopause influence the risk of breast cancer. In Asian premenopausal women, the combined RR/OR for breast cancer was 0.63 (95% CI: 0.50-0.80) for the highest level (>25 mg/day) (Table 2). In Asian postmenopausal women, the combined RR/OR for breast cancer was 0.46 (95% CI: 0.28-0.78) for the highest level (>25 mg/day) (Table 2). In Western premenopausal women (Table 3), the combined RR/OR for breast cancer was 1.00 (95% CI: 0.98-1.02), p-values for heterogeneity was 0.521. In Western postmenopausal women (Table 3), the combined RR/OR for breast cancer was 0.99 (95% CI: 0.87-1.12), p-values for heterogeneity was 0.926 respectively.

In Asian populations, 9 case-control studies[23-24, 26-28, 30-32,34] were included in the dose-response analysis of isoflavone intake and breast cancer risk. The risk of breast cancer incidence decreased, on average, by 1% for every 10 mg/day increase of soy isoflavones intake (OR = 0.99, 95% CI: 0.96-1.03, p for heterogeneity=0.018).

A statistical analysis of the Egger test was performed in Asian and Western studies. The results showed no publication bias (p >0.05).

DISCUSSION

The present meta-analysis of 12 trials showed that isoflavone intake was associated with a reduced risk of breast cancer in Asian populations. In contrast, isoflavone intake was unrelated to breast cancer risk in 10 studies conducted in Western populations. In addition, compared to the lowest level of isoflavone intake, there was a

Table 1. Characteristics of 22 observational studies on isoflavone consumption and breast cancer risk †

Reference	Country	Design and Simple size	Population	OR (95%CI) or RR (95%CI)	Measure of soy intake	Adjustments
Lee *et al.*, 1992 [23]	Singapore	Case-control	Premenopausal Postmenopausal	0.4 (0.2-0.8) 1.8 (0.8-3.6)	SP: 3.4g/day vs. 1.6g/day	menopausal status, age, age at first birth, nulliparity, height, education, family history
Dai *et al.*, 2001 [24]	China	Case-control 1459 cases/1556	All women	0.66 (0.43-1.02)	SP: 91.0 g/week vs. Occasionally	age, education, first degree family history of breast cancer, history of breast fibro adenoma, WHR, age at menarche, physical activity, birth of >1 child, age at first birth, menopausal status, age at menopause, intake of meats, fish, and total energy.
Yamamoto *et al.*, 2003 [25]	Japan	Cohort 179 incident cases/ 21852 cohort size	All women Premenopausal Postmenopausal	0.46 (0.25-0.84) 0.66 (0.25-1.70) 0.32 (0.14-0.71)	IF: 25.3mg/day vs. 6.9mg/day	age, age at menarche, number of pregnancies, menopausal status, age at first pregnancy, active and passive smoking, alcohol consumption, leisure physical activity, education , total energy, and meat, fish, vegetable, and fruit consumption.
Sanderson *et al.*, 2004 [26]	China	Case-control 1459 cases/1556	All women Premenopausal Postmenopausal	1 (0.7-1.5) 1.1 (0.7-1.6) 0.7 (0.4-1.5)	SP: 12.22g/day vs. 6.96g/day	leisure physical activity, parity, and age at first live birth.
Hirose *et al.*, 2005 [27]	Japan	Case-control 167 cases/854	Premenopausal Postmenopausal	0.44 (0.22-0.89) 0.58 (0.3-1.1)	IF: 18.47mg/1000kcal vs. 7.61 mg/1000kcal	age, motives for consultation, smoking, drinking, exercise, energy, family history, age at menarche, parity, age at first full-term pregnancy, BMI.
Kim *et al.*, 2008 [28]	Korea	Case-control 362 cases/362	All women Premenopausal Postmenopausal	0.46 (0.26-0.83) 0.39 (0.22-0.93) 0.22 (0.06-0.88)	SP: 10.55g/day vs. 4.24g/day	drinking, multivitamin use, number of children, breast feeding, quintile of carbohydrate intake, dietary factors
Lee *et al.*, 2009 [29]	China	Cohort 592 incident cases/ 73223 cohort size	All women Premenopausal Postmenopausal	0.81 (0.61-1.07) 0.44 (0.26-0.73) 1.09 (0.78-1.52)	IF: 44.24mg/day vs. 15.93mg.day	age, education, physical activity, age at first live birth, BMI, season of recruitment, family history of breast cancer, and total energy intake.
Zhang *et al.*, 2009 [30]	China	Case-control 756 cases/1009	All women Premenopausal Postmenopausal	0.39 (0.27-0.58) 0.44 (0.28-0.7) 0.31 (0.15-0.64)	IF: 25.40mg/day vs. 7.78mg/day	age, residential area, education, BMI, age at menarche, oral contraceptive use, HRT, breast cancer in first degree relatives, alcohol consumption, tobacco smoking, passive smoking, tea drinking, physical activity, total energy intake.
Iwasaki *et al.*, 2009 [31]	Japan	Case-control 405 cases/472	All women Premenopausal Postmenopausal	0.83 (0.54-1.28) 1.35 (0.72-2.54) 0.62 (0.38-1.01)	IF: 69.1mg/day vs. 22.1mg/day	menopausal status, number of births, family history of breast cancer, smoking status, moderate physical activity, vitamin supplement use.
Zhang *et al.*, 2010 [32]	China	Case-control 438 cases/438	All women	0.54 (0.34-0.84)	IF: 16.89mg/day vs. 3.26mg/day	age at menarche, BMI, history of benign breast disease, family history of breast cancer, physical activity, and passive smoking.
Butler *et al.*, 2010 [33]	Singapore-Chinese	Cohort 629 incident cases/ 34028 cohort size	All women	0.86 (0.64-1.16)	IF: 33.9mg/day vs. 4.6mg/day	education, BMI, first-degree relative with diagnosis of breast cancer, total daily energy intake
Cho *et al.*, 2010 [34]	Korea	Case-control 358 cases/360	All women Premenopausal Postmenopausal	0.81 (0.48-1.38) 1.36 (0.64-2.91) 0.33 (0.15-0.72)	IF: 23.7mg/day vs. 8.5mg/day	age, BMI, family history of breast cancer, current use of dietary supplements, education, occupation, smoking, alcohol intake, physical activity, menopausal status, age at menarche, parity, total energy intake

† OR, odds ratio; RR, relative risk; SP, soy protein intake; IF, isoflavone intake; WHR, waist-to-hip ratio; HRT, hormone replacement therapy.

Table 1. Characteristics of 22 observational studies on isoflavone consumption and breast cancer risk † (cont.)

Reference	Country	Design and Simple size	Population	OR (95%CI) or RR (95%CI)	Measure of soy intake	Adjustments
Horn-Ross *et al.*, 2001 [35]	USA	Case-control 1326 cases/1657	All women Premenopausal Postmenopausal	1.00 (0.79-1.30) 1.00 (0.98-1.02) 0.96 (0.71-1.30)	IF: 2,775ug/day vs. 1,048 ug/day	race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, BMI, HRT; and daily caloric intake.
Wu *et al.*, 2002 [36]	Asian-Americans	Case-control 501 cases/594	All women	0.61 (0.39-0.97)	IF: 12.68 mg/1000 kcal vs. 1.79 mg/ 1000 kcal	Intake of leafy greens, smoking history, alcohol intake, physical activity and family history of breast cancer
Silva *et al.*, 2004 [37]	South Asian women in England	Case-control 240 cases/477	All women	0.58 (0.33-1.00)	IF: 470ug/day vs. 125ug/day	Age at menarche, age at first birth, , parity, breast feeding, family history of breast cancer, menopausal status, time since menopause and years of formal education
Keinan-boker *et al.*, 2004 [38]	Dutch	Cohort 280 incident cases/ 15555 cohort size	All women	0.98 (0.65, 1.48)	IF: 0.54mg/day vs. 0.26mg/day	age at enrollment, age at first full-term delivery, height, weight, parity, physical activity score, use of oral contraceptives or hormone replacement therapy, marital status, academic education, and daily energy intake
Linseisen *et al.*, 2004 [39]	German	Case-control 278 cases/666	All women	0.85 (0.54-1.33)	IF: 441.1ug/day vs. 176.5ug/day	first-degree family history of breast cancer, number of births, duration of breast-feeding, energy intake, BMI, alcohol consumption and education.
Touillaud *et al.*, 2006 [40]	France	Cohort 402 incident cases/ 26868 cohort size	All women	1.00 (0.76-1.31)	IF: 112 ug/day vs. 22 ug/day	education, height, BMI, age at menarche personal history of benign breast disease, family history of breast cancer, lifetime use of oral contraceptive, age at first full-term pregnancy (FFTP) , parity, geographic area, alcohol consumption and dietary energy intake
Fink *et al.*, 2007 [41]	USA	Case-control 1434 cases/1440	All women Premenopausal Postmenopausal	0.95 (0.74-1.22) 1.14 (0.76-1.72) 1.02 (0.76-1.38)	IF: 0.62 mg/day vs. 0.17mg.day	age and energy intake
Cotterchio *et al.* 2008 [42]	Canada	Case-control 3063 cases/3430	All women Premenopausal Postmenopausal	1.06 (0.87, 1.30) 0.96 (0.69, 1.33) 1.09 (0.83, 1.41)	IF: 1,237ug/day vs. 82ug/day	age, family history breast cancer, history of benign breast disease, dietary fiber intake, age at first live birth.
Travis *et al.*, 2008 [43]	England	Cohort 585 incident cases/ 37643 cohort size	All women Premenopausal Postmenopausal	1.17 (0.79-1.71) 1.31 (0.95-1.81) 0.95 (0.66-1.38)	IF: 20mg/day vs. 10mg/day	BMI, age at menarche age at first birth and parity, age at first birth, alcohol consumption, daily energy intake, where appropriate, menopausal status and HRT
Hedelin *et al.*, 2008 [44]	Sweden	Cohort 1014 incident cases/ 45448 cohort size	All women Premenopausal Postmenopausal	0.98 (0.83-1.17) 1.04 (0.81-1.34) 0.93 (0.73-1.18)	IF: 945.6ug/day vs. 6.69ug/day	age, BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, cancer in sisters or mothers, and intake of total energy intake, alcohol, and saturated fat.

† OR, odds ratio; RR, relative risk; SP, soy protein intake; IF, isoflavone intake; WHR, waist-to-hip ratio; HRT, hormone replacement therapy.

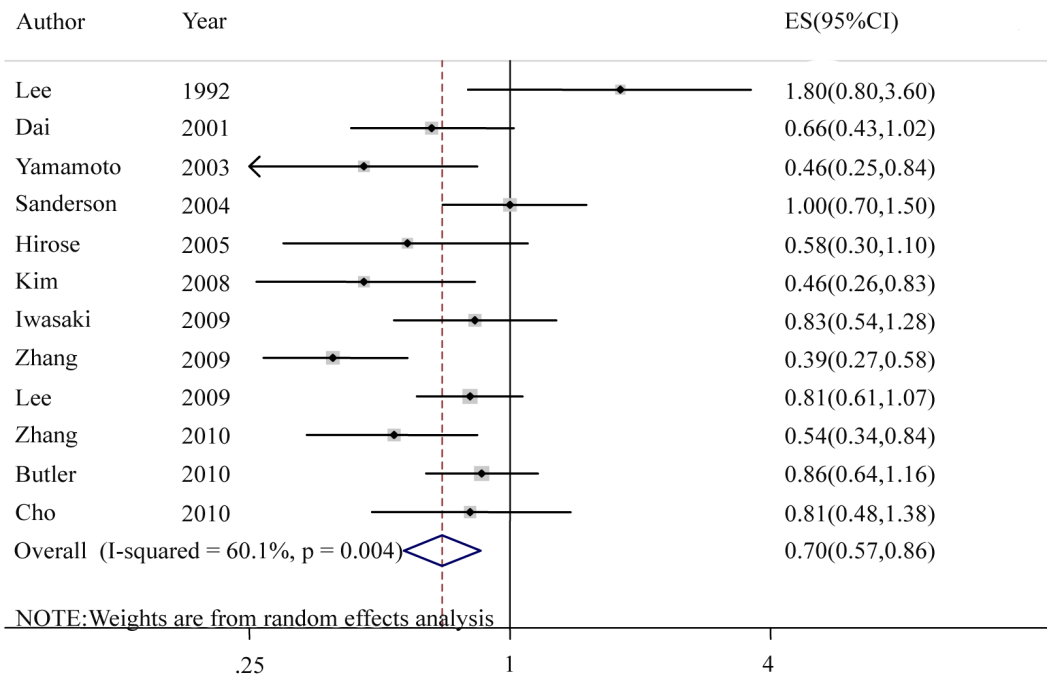

Figure 2. Forest plot of the highest compared with the lowest categories of intake of isoflavone and breast cancer risk in Asian women. The results of the analysis using the random-effects model yielded a combined relative risk and odds ratio.

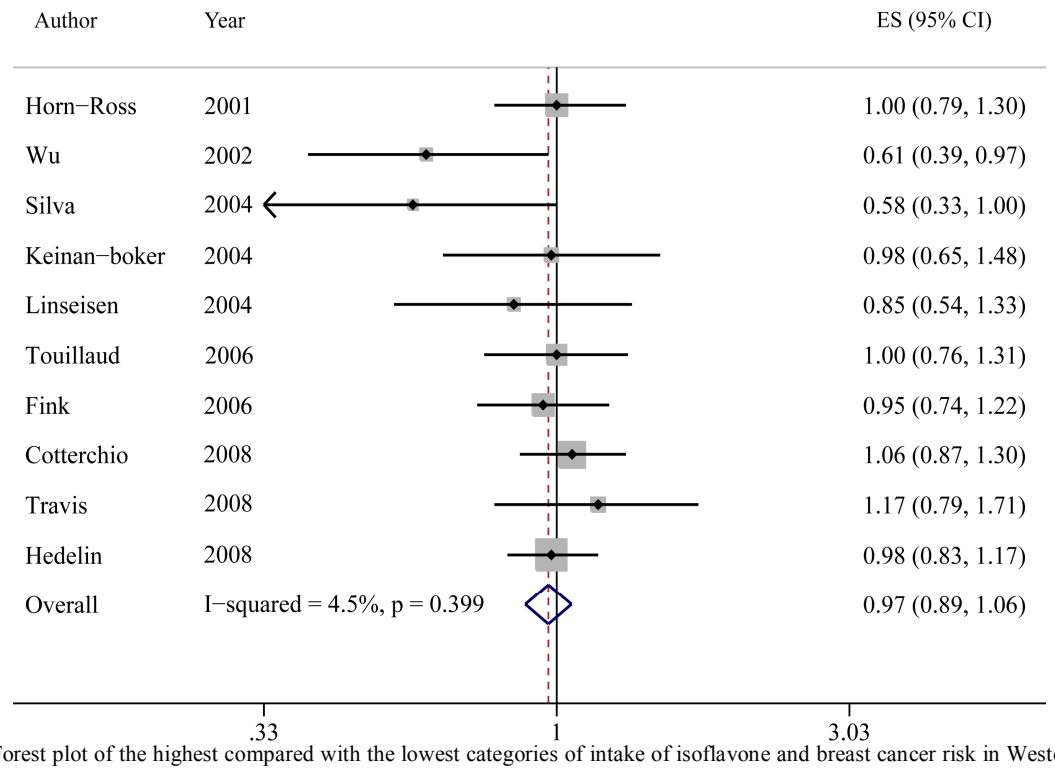

Figure 3. Forest plot of the highest compared with the lowest categories of intake of isoflavone and breast cancer risk in Western women. The results of the analysis using the fixed-effects model yielded a combined relative risk and odds ratio.

statistically significant reduction in the risk of breast cancer in Asian women with high-dose soy isoflavone intake (>25mg/day), and the inverse association of isoflavone consumption with breast cancer incidence was stronger in postmenopausal women than in premenopausal women. However, regardless of isoflavone exposure dose and menopausal status, there were no statistically differences in the studies of Western populations.

In our analysis, the isoflavone exposure doses were quite different between Asian and Western countries. The difference may be due to the Western diet, in which isoflavone was mainly contained in bread, vegetables and other non-legumes. Those kinds of food had low and varied isoflavone content. In contrast, Asian people took in isoflavone through soy foods, such as tofu, in which the isoflavone content is similar.[17-18]

We studied only the isoflavone content by oral intake to simplify the conversion relationship. Studies on isoflavone levels in blood or urine samples are scarce and have been performed mainly in Western populations. Iwasaki *et al* [8] found a statistically significant inverse association between plasma genistein and risk of

Table 2. Pooled risk and 95% CI of breast cancer risk according to isoflavone consumption in Asian women †

group	5-15 mg/day			15-25 mg/day			>25 mg/day		
	No. of studies	*p* for hetero-geneity‡	Pooled estimate (95% CI)	No. of studies	*p* for hetero-geneity	Pooled estimate (95% CI)	No. of studies	*p* for hetero-geneity	Pooled estimate (95% CI)
Premenopausal§	3	0.419	0.67 (0.49-0.92)	6	0.083	0.74 (0.59-0.92)	6	0.089	0.63 (0.50-0.80)
Postmenopausal	3	0.796	0.52 (0.35- 0.77)	6	0.049	0.63 (0.42-0.93)	6	0.004	0.46 (0.28-0.78)
All women¶	5	0.043	0.75 (0.57- 0.98)	8	0.597	0.78 (0.68-0.89)	8	0.002	0.68 (0.52-0.89)

† Pooled risk, Pooled estimate of combined relative risk/odds ratio.
‡ If *p* for heterogeneity<0.05, we use random-effect model. Otherwise, fixed-effect model is used.
§ Yamamoto *et al*.[25], Hirose *et al*.[27], Kim *et al*.[28], Lee *et al*.[29], Zhang *et al*.[30], Cho *et al*.[34] are included in the analysis.
¶ Dai *et al*.[24], Yamamoto *et al*.[25], Hirose *et al*.[27], Kim *et al*.[28], Lee *et al*.[29], Zhang *et al*.[30], Butler *et al*.[33], Cho *et al*.[34] are included in the analysis.

Table 3. Pooled risk and 95% CI of breast cancer risk according to isoflavone consumption in Western women †

	No. of studies	*p* for heterogeneity‡	Pooled estimate (95% CI)
Premenopausal§	5	0.521	1.00 (0.98, 1.02)
Postmenopausal	5	0.926	0.99 (0.87, 1.12)
All women			
100-500 μg/day¶	5	0.384	1.08 (0.93, 1.25)
500-1000 μg/day	5	0.437	0.95 (0.81, 1.10)
>1000 μg/day††	4	0.114	0.98 (0.87, 1.11)

† Pooled risk, Pooled estimate of combined relative risk/odds ratio.
‡ If *p* for heterogeneity<0.05, we use random-effect model. Otherwise, fixed-effect model is used.
§ Horn-Ross *et al*.[35], Fink *et al*.[41], Cotterchio *et al*.[42], Travis *et al*.[43], Hedelin *et al*.[44] are included in the analysis.
¶ Linseisen *et al*.[39], Silva *et al*.[37], Keinan-boker *et al*.[38], Fink *et al*.[41], Cotterchio *et al*.[42] are included in the analysis.
†† Horn-Ross *et al*.[35], Fink *et al*.[41], Cotterchio *et al*.[42], Hedelin *et al*.[44] are included in the analysis.

breast cancer, but no association between plasma daidzein and breast cancer risk. Trock *et al* [4] determined levels of soy protein intake by using linear regression-derived estimates of mean urinary genistein and daidzein. Nevertheless, we excluded studies on blood and urine isoflavone, because, in addition to isoflavone intake, other components in diet and subject age are associated with blood and urinary isoflavone concentrations.

Furthermore, isoflavone exposure dose plays a key role in studying the possible effect of isoflavone on breast cancer. Wu *et al* [5] showed an approximately 16% risk reduction per 10mg of isoflavone intake per day in Asian women. However, another study [6] showed that the risk of breast cancer incidence decreased by 4% for every 10 mg/day increase of isoflavone intake in Asians. In our study, the results showed no significant dose-response relationship in Asian women, suggesting that the dose of isoflavone intake may need to reach a certain amount in order to reduce the risk of breast cancer.

The results showed that in Asian women, risk was lowest in the highest category (>25 mg/day), and that risk in the low-dose category (5-15 mg/day) was similar to the medium-dose category (15-25 mg/day). This result was also supported by the dose-response relationship analysis, [6] which showed no significant association between isoflavone intake and the risk of breast cancer. Thus, it can not be simply concluded that a higher isoflavone intake leads to a lower breast cancer risk. In Western women, both the low-dose category (100-500 μg/day) and the high-dose category (>1000 μg/day) did not significantly reduce the risk of breast cancer. Different results from Western populations and Asian populations suggested that isoflavone exposure dose may be an influential factor in the study of isoflavone and the risk of breast cancer.

Isoflavone are estrogen-like compounds that are much less potent than estradiol and are ER-A-selective ligands. They can change metabolism of endogenous estrogens, potentially exerting indirect effects on estrogenic pathways.[45] There has been some evidence that suggest that the menopausal status of women may modulate the effects of isoflavone. A large prospective cohort study showed protective effect of isoflavone intake against premenopausal breast cancer, but no significant association was found between isoflavone intake and postmenopausal breast cancer.[29] However, other studies obtained inconsistent results.[30,34] In our study, the protective effect of isoflavone consumption in Asian postmenopausal women is significantly stronger than that in premenopausal women, but in Western women, no significant differences were found between premenopausal and postmenopausal women. The Westerners results may suggest that low-dose isoflavone intake could not reduce the risk of breast cancer.

The protective effect of isoflavone on breast cancer risk in Asian women is also attributed to long-term or early exposure to isoflavone. Some studies suggest that early isoflavone exposure can protect against breast cancer, and that isoflavone intake since childhood or adolescence may influence the risk of breast cancer incidence.[29, 36,46]

The present analysis provides a quantitative evaluation of available epidemiologic studies on the association between isoflavone intake and breast cancer risk. Similar to all meta-analyses, this meta-analysis has limitations. The first limitation is that significant heterogeneity is detected among the trials. Our analysis indicates that differences in the amount of isoflavone intake and timing of isoflavone exposure largely contribute to the substantial heterogeneity. Besides, two different types of studies (case-control and cohort studies) may lead to heterogeneity. More cohort studies are needed to verify the conclusion. The second limitation is that isoflavone consumption is assessed only in a small number of studies. We fail to determine the effect of isoflavone on breast cancer when its intake is more than 30mg in Asians because of lack of reports on higher doses of isoflavone intake.

In addition, the apparent protective effect of isoflavone on breast cancer risk can be explained by other healthy lifestyles, such as high vegetable and fruit intake, more physical activities, and low alcohol consumption.[33,47-49] Meanwhile, the present study suggest that consumption of soy foods or isoflavone is more likely to be beneficial if initiated before puberty or during adolescence,[50-51] which suggest that longer-term follow-up results need to be studied. The case-control study, with a relatively short time, and even cohort studies have a follow-up time of rarely over ten years. In our analysis, the longest follow-up time was 7.4 years.[29]

In conclusion, the present meta-analysis indicates that isoflavone intake reduces the risk of breast cancer incidence in Asian women when the intake of isoflavone was high. This reduction is most significant in postmenopausal women, although significant heterogeneity is detected. However, regardless of isoflavone exposure dose and menopausal status there were no significant differences in the studies of Western populations, which suggested that isoflavone exposure dose may be an important effect modifier in these associations. More high-quality rigorous studies, especially long-term follow-up studies on the association between isoflavone intake and breast cancer, should be performed to confirm our results and explore the exact mechanisms of action of isoflavone in breast cancer.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Original Article

Isoflavone consumption and risk of breast cancer: a dose-response meta-analysis of observational studies

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大豆异黄酮摄入量与乳腺癌发生风险的关系：观察性研究剂量反应的整合分析

关于大豆异黄酮的摄入能否预防乳腺癌发生风险的流行病学研究结论不一致，而争议主要集中在大豆异黄酮的摄入时间不同和暴露剂量差异对乳腺癌的发生风险是否有影响。研究目标是通过整合分析，探讨大豆异黄酮摄入量与目标人群乳腺癌发生风险的关系。通过检索 PubMed 和 EMBASE 数据库中的病例对照研究和队列研究，评估大豆异黄酮摄入量与乳腺癌发生风险的关联。从每一项研究中，提取大豆异黄酮摄入量和对应的相对危险度（RR）或者比值比(OR)，利用固定或随机效应模型来评估剂量反应数据。结果符合入选标准的研究有 22 项。经整合分析后得出，高剂量的大豆异黄酮摄入在亚洲人群（合并 RR/OR: 0.68, 95％CI: 0.52-0.89）的效果要好于西方人群（RR/OR: 0.98, 95％CI: 0.87-1.11）。进一步的分析表明，亚洲女性绝经后（RR/OR: 0.46, 95％CI: 0.28-0.78）摄入异黄酮预防乳腺癌的效果好于绝经前摄入（RR/OR: 0.63, 95%CI: 0.50-0.80)，而西方女性中绝经后（RR/OR: 1.00, 95%CI: 0.98-1.02）摄入异黄酮预防乳腺癌的效果与绝经前摄入（RR/OR: 0.99, 95%CI: 0.87-1.12)无显著差别。因此，高剂量的异黄酮摄入在亚洲人群中可能降低乳腺癌的发生风险，尤其是在绝经后女性中。然而在西方人群的研究中没有发现显著的差异，可能是由于西方人群异黄酮的摄入量较低。

关键字：异黄酮、乳腺癌、剂量反应、整合分析、绝经期