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Soy Intake Is Associated With Lower Endometrial Cancer Risk

A Systematic Review and Meta-Analysis of Observational Studies

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Abstract: Epidemiologic studies reporting the effect of soy intake on endometrial cancer risk conveyed conflicting results. We systematically reviewed the literature to investigate whether there was an inverse relation between dietary soy intake and endometrial cancer risk.

PubMed, EMBASE, the Cochrane Library, and 4 main Chinese literature databases were searched from their inception to August 25, 2015 for both case–control studies and cohort studies that assessed the effect of soy intake on endometrial cancer risk. Study-specific most-adjusted odds ratios (ORs) or relative risks (RRs) were combined by using fixed-effects or random-effects model to calculate pooled risk estimates (REs).

A total of 10 epidemiologic studies were included in this meta-analysis, including 8 case–control studies and 2 prospective cohort studies. Dietary soy intake was inversely associated with endometrial cancer risk with an overall RE of 0.81 (95% CI: 0.72, 0.91). In subgroup analyses, a statistically significant protective effect of soy intake was found for unfermented soy food (RE: 0.81, 95% CI: 0.67, 0.97), postmenopausal women (RE: 0.76, 95% CI: 0.61, 0.95), and Asian (RE: 0.79, 95% CI: 0.66, 0.95) and non-Asian population (RE: 0.83, 95% CI: 0.71, 0.96).

Current evidence indicates that soy food intake is associated with lower endometrial cancer risk. Further larger cohort studies are warranted to fully clarify such an association.

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Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, EC = endometrial cancer, ER = estrogen receptor, MOOSE = Meta-Analysis of Observational Studies in Epidemiology, OR = odds ratio, RE = risk estimate, RR = relative risk.

INTRODUCTION

Worldwide, endometrial cancer (EC) is the fifth most common cancer in women, occurring more frequently in developed countries.[1] It has been highly suggested that increased EC risk is associated with prolonged estrogen exposure if not countervailed by progesterone.[2–4] Estrogen exposure includes exogenous estrogen (oral contraceptive medicine or hormone replacement therapy), nulliparity, early menarche and late menopause, etc.[2,5,6] Obesity and low plasma concentration of sex hormone binding globulin are also associated with elevation of EC risk.[7,8]

Phytoestrogens are nonsteroidal plant-derived compounds, structurally similar to endogenous estrogens, and suggested to protect against hormone-dependent cancers.[9,10] The anticancer mechanisms might include inhibition of enzymes that synthesize estrogen, promotion of the production of sex hormone binding globulin, modulation of cell proliferation, apoptosis, and inhibition of angiogenesis and tumor cells.[11–14] Isoflavones, one major class of phytoestrogens, principally including genistein and daidzein, have been vigorously investigated. An almost exclusive dietary source of isoflavones, by far, is soybean which exists in most commonly consumed diet and especially as a staple in Asian-type diet. Evidence from several recent meta-analyses has suggested that soy may have a protective effect against hormone-dependent cancers, such as lung cancer, prostate cancer, ovarian cancer, and breast cancer.[15–20]

In addition to these hormone-related cancers, an inhibitory effect of genistein against endometrial carcinogenesis was also found in experimental studies.[21,22] However, epidemiologic studies reporting the effect of soy intake on EC risk conveyed conflicting results. Furthermore, due to small sample sizes, most studies were not adequately powered to detect the effect of soy intake on EC risk. Thus, in order to provide the latest and more convincing evidence, we systematically reviewed the current available epidemiologic studies to investigate whether soy intake was associated with lower EC risk.

METHODS

This systematic review and meta-analysis was conducted and reported in adherence to MOOSE (Meta-Analysis of Observational Studies in Epidemiology).[23] Since our study was a review of previous published studies, ethical approval or patient consent was not required. Two investigators (GQ-Z and JL-C) independently carried out literature search, eligibility evaluation, data extraction, and quality assessment. Discrepancies between authors were resolved by consensus.

Literature Search and Selection Criteria

PubMed, EMBASE, the Cochrane Library, and 4 main Chinese literature databases, that is, Wan Fang, VIP, SinoMed, and China National Knowledge Infrastructure (CNKI), were searched from their inception to August 25, 2015 by using a

TABLE 1. Search Strategy

Search terms
1. (phytoestrogen OR soy OR soybeans OR legumes OR tofu OR miso OR natto OR soy protein OR isoflavones OR genistein OR daidzein OR formononetin OR glycitein OR biochanin A)
2. (endometrial cancer OR endometrial neoplasm OR uterine cancer)
3. 1 AND 2

combination of Medical Subject Headings or Emtree and related common keywords in all fields. No language restriction was applied. The search strategy is shown in Table 1. The cited references of retrieved articles and previous reviews were also manually checked to identify any additional eligible studies.

Studies meeting the following inclusion criteria were included: observational studies (prospective or retrospective cohort studies and case–control studies); investigated the association between soy or soy isoflavones or soy product intake and EC in adult women; reported adjusted odds ratios (ORs) or relative risks (RRs) and its 95% confidence intervals (CIs). If articles were from the same study population, the largest study was included to avoid duplication of information. Studies were excluded if evaluating: plasma or urinary isoflavones; dietary isoflavones from other sources instead of soy in association with EC.

Data Extraction and Quality Assessment

Relevant data from each included study were documented by using a unified data form. The following information were extracted from each study: study (the first author's name); country, study design, and study period; no. of cases/controls, mean or median age, and ethnicity; soy food assessed; most-adjusted ORs or RRs with 95% CIs for the highest compared with lowest quantile; and matched or adjusted factors in the design or data analysis. Since study-specific data can be obtained from original articles, no authors were contacted.

A 9-star system on the basis of the Newcastle-Ottawa Scale was used to assess the study quality of observational studies.[24] However, because there is a correlation between caloric intake and nutrient consumption, and the possibility that a relation might exist between caloric intake and EC risk cannot be excluded, we modified the Newcastle-Ottawa Scale by adding one item "energy adjusted residual or nutrient-density model in data analyses."[16,25] If studies used the energy adjusted residual or nutrient-density model in their data analyses, an extra star would be assigned. Finally, the total score was 10, and studies with ≥7 stars were defined as high-quality studies.

Statistical Analysis

The study-specific most-adjusted ORs or RRs with its 95% CIs (highest compared with lowest amounts of soy intake) were used to compute a summary risk estimate (RE) with its 95% CI. From the REs, the SE of the estimate (SEE) was directly derived as SEE = [log (95% CI, upper limit) − log (95% CI, lower limit)]/3.92 and was used in the calculation of the pooled estimates. Subgroup analyses were performed according to study design (cohort studies vs. case–control studies), soy-derived isoflavones (genistein vs. daidzein vs. glycitein vs. formononetin vs. biochanin A), soy food (fermented vs. unfermented), menopausal status (premenopausal vs. postmenopausal), and race (Asians vs. non-Asians). Heterogeneity across studies was tested by using the the I^2 statistic, which was a quantitative measure of inconsistency across studies.[26] Studies with an I^2 statistic of ≥50% were considered to have significant heterogeneity. The random effects model was used to calculate pooled REs and its 95% CIs if significant heterogeneity existed. Otherwise, the fixed effects model was applied to calculate the pooled RE.

Funnel plot was carried out to investigate publication bias of all the included studies. A sensitivity analysis was conducted to assess the influence of individual studies on the pooled result, by excluding each study one by one and recalculating the combined RE on the remaining studies. All statistical analyses were performed with RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Study Identification and Selection

Our systematic literature search yielded a total of 10 studies on soy intake and EC risk in the final analysis.[27,28,30–37] One thousand fifty-eight records were identified by searching 7 databases and hand-searching relevant bibliographies. Three hundred five records were excluded for duplicates and an additional 711 records were excluded based on the titles and abstracts. The remaining 42 full-text articles were assessed for eligibility, and 32 were further excluded due to the following reasons: reviews (N = 8); dietary patterns or lifestyle and EC risk (N = 7); specific food (not relevant to phytoestrogen) and EC risk (N = 9); studies which reported OR by different gene polymorphisms (N = 1)[38]; total flavonoid intake and EC risk (N = 1)[39]; studies did not report OR or its 95% CI (N = 1)[40]; and studies based on the same study population (N = 5).[41–45] The selection process is shown in Figure 1.

Study Characteristics

The main characteristics of included studies are described in Table 2. All the included studies were published in English and between 1996 and 2014. Of the included studies, 2 were prospective cohort studies,[36,37] 6 were population-based case–control studies,[27,28,30,31,33,35] and 2 were hospital-based case–control studies.[32,34] Among the 10 studies, 2 were conducted in Japan,[32,37] 1 in China,[35] 1 in Italy,[34] 1 in Australia,[28] and 5 in the United States.[27,30,31,33,36] Several studies presented results by menopausal status, 2 for premenopausal,[27,34] and 3 for postmenopausal.[27,34,36] Most studies were matched or adjusted for a wide range of potential confounders, such as age, age at menarche, parity, energy intake, body mass index, oral contraceptive use, and hormone replacement therapy.

Quality Assessment

Risk-of-bias assessment of the included studies is presented in Tables 3 and 4. Eight studies were rated as a total score of more than 7[27,28,30,31,33,35–37] and the other 2 studies as a score of 5 indicating a high risk of bias.[32,34]

Highest Versus Lowest Category

Our overall analysis of 10 studies showed a 19% reduction in risk of EC with high intake of soy foods (RE: 0.81, 95% CI: 0.72, 0.91), without significant heterogeneity ($I^2 = 20\%$), shown in Figure 2. There was no evidence of significant publication bias by inspection of the funnel plot, shown in Figure 3.
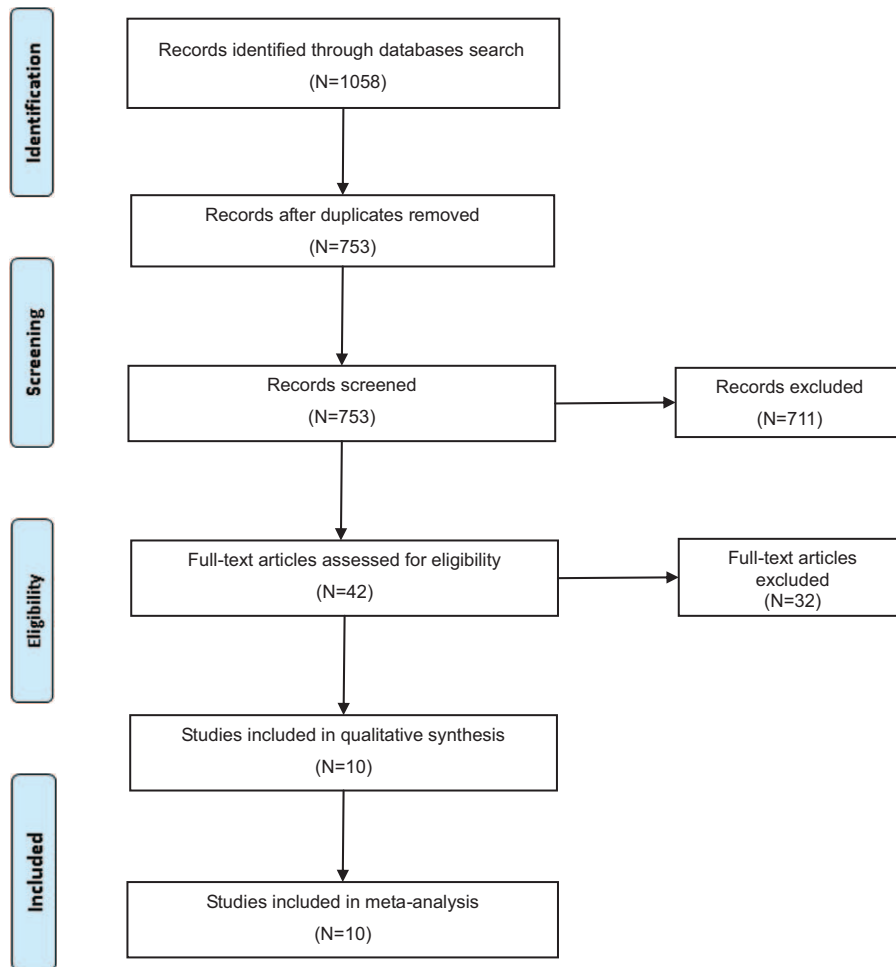
FIGURE 1. Selection process for the studies included in the meta-analysis.

Table 5 reports the pooled REs for soy intake on EC risk in selected subgroups. In the subgroup analyses, by study design, case–control studies showed a preventive effect of soy intake on EC with a RE of 0.83 (95% CI: 0.73, 0.94), similar to the overall analysis. Regarding the type of soy intake, both soy food (RE: 0.79, 95% CI: 0.66, 0.95) and soy-derived isoflavones (RE: 0.84, 95% CI: 0.74, 0.95) had a preventive effect on EC. This beneficial effect remained in unfermented soy food (RE: 0.81, 95% CI: 0.67, 0.97). However, no association was found in any subtypes of isoflavones. When stratified by menopausal status, there was a statistically significant inverse association in postmenopausal women (RE: 0.76, 95% CI: 0.61, 0.95), but not in premenopausal women (RE: 0.72, 95% CI: 0.40, 1.30). This inverse association remained in both Asian population (RE: 0.79, 95% CI: 0.66, 0.95) and non-Asian population (RE: 0.83, 95% CI: 0.71, 0.96).

In sensitivity analyses, further exclusion of any single study did not materially alter the overall combined RE, with a range from a low of 0.77 (95% CI: 0.68, 0.88) to a high of 0.84 (95% CI: 0.74, 0.95) via omission of the study by Neill et al[28] and the study by Ollberding et al,[36] respectively.

DISCUSSION

The present systematic review and meta-analysis identified 10 observational studies investigating soy intake on EC risk. Our analysis showed that soy intake was associated with a 19% reduction in risk of EC when highest reported soy intake was compared with lowest reported soy intake. Moreover, this finding was consistent across sensitivity analyses and most subgroup analyses, and no publication bias was observed.

Comparison With Previous Studies

A meta-analysis by Myung et al[18] was conducted in 2009 on association between soy intake and endocrine-related gynecological cancer. An inverse relation was found between soy intake and EC risk on the basis of only 3 population-based case–control studies. However, the erratum result[27] instead of the corrected data[29] by Horn-Ross et al was analyzed in this meta-analysis, which could probably arouse spurious association between soy intake and risk of EC. Furthermore, we conducted sensitivity analyses according to the data presented in this meta-analysis, and the protective effect of soy was

TABLE 2. Characteristics of Included Observational Studies

Study	Country; Design; Period (Years)	Cases/Controls [Mean or Median Age (y)]; Ethnicity	Soy Food Assessed	Adjusted RR or OR (95% CI)	Matched or Adjusted Factors
Hirose et al[32]	Japan; HCC 1988–1993	145 (55.3)/26751 (45.8) Japanese	Soy products*: ≥3 times/week versus ≤3 times/month	0.76 (0.47, 1.23)	Age, first-visit year
Goodman et al[31]	USA; PCC 1985–1993	332 (58.5)/511 (57.1) Japanese, Caucasian, Native Hawaiian, Filipino, Chinese	Soy products† (g/d): >39.0 versus <8.5	0.51 (0.31, 0.86)	Age, ethnicity, pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, Quetelet index (kg/m²), total calories
Littman et al[33]	USA; PCC 1985–1991	679/944 (45–74)‡ White, Hispanic	Soy products§ (times/week): >1 versus none	0.72 (0.31, 1.70)	Age, county of residence, total energy intake, unopposed estrogen use, smoking, BMI
Horn-Ross et al[27]	USA; PCC 1996–1999	500/470 (35–79)∥ African American, Latina, White	Soy isoflavones¶ (µg/d): ≥2698 versus <1125	1.10 (0.66, 1.70)	Age, race/ethnicity, daily caloric intake, age at menarche, parity, OC use, HRT, BMI
Xu et al[35]	China; PCC 1997–2003	1199/1212 (30–69)# Chinese	Soy isoflavones** (mg/d): >40.3 versus ≤21.3	0.76 (0.61, 0.96)	Age, education, menopausal status, years of menstruation, number of pregnancies, OC use, alcohol consumption, diabetes, BMI, physical activity, caloric intake
Bandera et al[30]	USA; PCC 2001–2005	424 (61.6)/398 (64.3) White, Hispanic, Black, Asian	Soy isoflavones†† (µg/1000 kcal): >666.0 versus <55.3	0.80 (0.50, 1.27)	Age, education, race, age at menarche, menopausal status, age at menopause for postmenopausal women, parity, OC use, HRT, BMI, total calories, physical activity, smoking status, alcohol
Ollberding et al[36]	USA; PCS 1993–1996	489 cases among 46,027 postmenopausal women (61.6) Non-Asian	Soy isoflavones‡‡ (mg/1000 kcal/day): ≥7.82 versus <1.59	0.66 (0.47, 0.91)	Age, race or ethnicity, age at cohort entry, BMI, age at menarche, age at menopause, duration and type of HRT, duration of OC use, parity, smoking status, hypertension, diabetes, total calories
Rossi et al[34]	Italy; HCC 1992–2006	454 (60)/908 (61) Italian	Soy isoflavones§§ (µg/d): >58.2 versus <58.2	0.84 (0.62, 1.14)	Age, study center, year of interview, education, BMI, history of diabetes, age at menarche, menopausal status/age at menopause, parity, OC use, HRT
Neill et al, 2013[28]	Australia; PCC 2005–2007	1288 (61.3)/1435 (60.8) Mostly Caucasian	Soy isoflavones∥∥ (µg/d): >4000 versus <280	1.06 (0.79, 1.43)	Age, state of residence, energy intake, age at menarche, parity, OC use, HRT, BMI, type 2 diabetes, alcohol consumption, smoking status

Study	Country; Design; Period (Years)	Cases/Controls [Mean or Median Age (y)]; Ethnicity	Soy Food Assessed	Adjusted RR or OR (95% CI)	Matched or Adjusted Factors
Budhathoki et al[37]	Japan; PCS 1995–1998	112 cases among 49,121 women (45–74)[¶‖]; Japanese	Soy isoflavones[##] (mg/d): 63.2 versus 17.7	1.06 (0.62, 1.82)	Age, total energy intake, JPHC area, BMI, physical activity, smoking, alcohol consumption, age at menarche, number of deliveries, menopausal status, age at menopause for postmenopausal women, coffee intake, history of diabetes mellitus and cancer

BMI = body mass index; CI = confidence interval; HCC = hospital-based case–control study; HRT = hormone replacement therapy; JPHC = the Japan Public Health Center; OC = oral contraceptive; OR = odds ratio; PCC = population-based case–control study; PCS = prospective cohort study; RR = relative risk.

* Bean curd.
† Tofu and unspecified soy products.
‡ Age range for both cases and age- and county-matched controls.
§ Tofu.
‖ Age range for both cases and age- and ethnicity-matched controls.
¶ Unspecified soy sources.
# Age range for both cases and age- and frequency-matched controls.
** Unspecified soy sources.
†† Soy beans, tofu, soymilk, soy yogurt, frozen soy yogurt, soy ice cream, soy cheese, soy hot dogs/cold cuts, other soy meat substitutes, cooked soybeans or edamame, roasted soy nuts, tempeh, miso soup, alfalfa sprouts, soybeans sprouts, and protein powders made from soy protein isolate.
‡‡ Tofu, miso, and unspecified soy sources.
§§ Soy milk.
‖‖ Soya milk, low-fat soya milk, soya-beans, soya-based meat substitutes, and soya-beans and linseed bread.
¶¶ Age range for all participants.
Miso soup, soymilk, tofu for miso soup, tofu for other dishes, yushidofu (predrained tofu), koyadofu (freeze-dried tofu), aburaage (deep-fried tofu), and natto (fermented soybeans).

TABLE 3. Risk-of-Bias Assessment of Case–Control Studies*

Study	Adequate Definition of Cases	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability	Exposure Assessment	Same Method of Ascertainment for All Subjects	Nonresponse Rate	Energy-Adjusted Residual or Nutrient-Density Model	Total Score
Neill et al[28]	☆	☆	☆	☆	☆☆	—	☆	—	☆	8
Horn-Ross et al[27]	☆	☆	☆	☆	☆☆	—	☆	—	☆	8
Bandera et al[30]	☆	☆	☆	☆	☆☆	—	☆	—	☆	8
Goodman et al[31]	☆	☆	☆	☆	☆☆	—	☆	—	☆	8
Hirose et al[32]	☆	☆	—	☆	☆	—	☆	—	—	5
Littman et al[33]	☆	☆	☆	☆	☆☆	—	☆	☆	—	7
Rossi et al[34]	☆	☆	—	—	☆☆	—	☆	—	—	5
Xu et al[35]	☆	☆	☆	☆	☆☆	—	☆	—	—	7

* Risk of bias was assessed with use of the Newcastle-Ottawa Scale. A higher overall score corresponds to a lower risk of bias; a score of <7 (out of 10) indicates a high risk of bias.

TABLE 4. Risk-of-Bias Assessment of Prospective Cohort Studies*

Study	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Outcome of Interest Not Present at Start of Study	Comparability	Assessment of Outcome	Length of Follow-Up	Adequacy of Follow-Up	Energy-Adjusted Residual or Nutrient-Density Model	Total Score
Ollberding et al[36]	☆	☆	☆	☆	☆☆	☆	☆	—	☆	9
Budhathoki et al[37]	☆	☆	☆	☆	☆☆	☆	☆	☆	☆	10

* Risk of bias was assessed with use of the Newcastle-Ottawa Scale. A higher overall score corresponds to a lower risk of bias; a score of <7 (out of 10) indicates a high risk of bias.
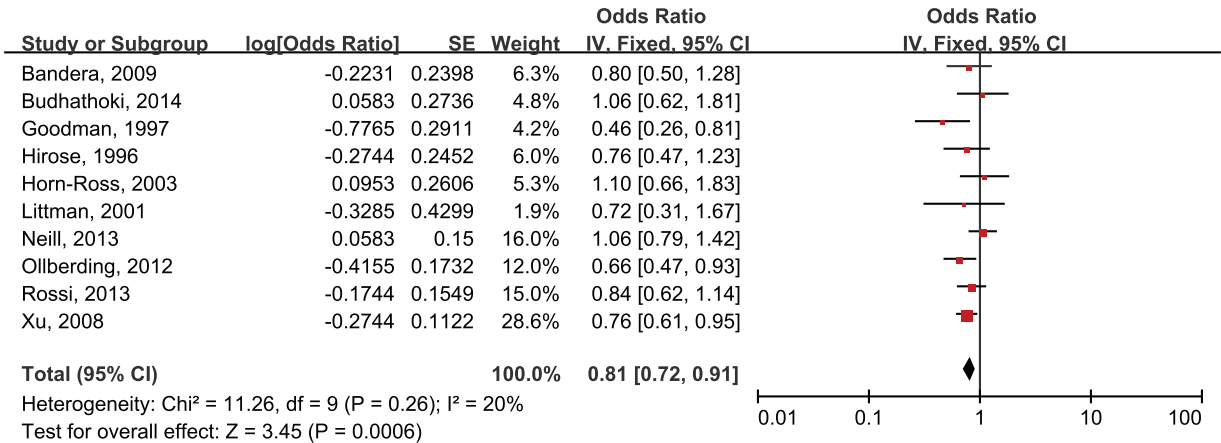
FIGURE 2. Risk estimates (95% CIs) of soy intake and risk of endometrial cancer.

unstable from an overall RE of 0.78 (95% CI: 0.62, 0.97), to 0.86 (95% CI: 0.67, 1.11) when omitting Goodman et al, or to 0.74 (95% CI: 0.52, 1.06) when omitting Xu et al. In contrast with the previous meta-analysis, the present one strongly suggested that soy intake was inversely associated with lower EC risk. Moreover, subgroup analyses and sensitivity analyses did not materially alter the pooled result and no publication bias was observed, which added robustness to our main findings.

The plausible biological mechanisms through which soy products may protect against EC include estrogen-dependent mechanisms via the estrogen receptor (ER) signaling pathway and estrogen-independent mechanisms. Prolonged estrogen exposure has been indicated to be associated with higher risk of EC.[2–4] Estrogen acts via the ER, which consists of 2 subtypes in endometrium, ER alpha and ER beta. It is thought that ER alpha mediates the proliferative effect of estrogens and functions as a tumor promoter,[46] while ER beta is proved to act as an ER alpha antagonist and function as a tumor suppressor.[47–50] Isoflavones, which are structurally similar to estrogen, show weak estrogenic activity and could compete with estrogen at the ER complex.[51] It has been shown that genistein, one major type of isoflavones, has a higher affinity for ER beta than for ER alpha.[18,52] Estrogen-independent mechanisms include inhibition of 17beta-hydroxysteroid dehydrogenase, antioxidative effects, induction of apoptosis, inhibition of angiogenesis and

cancer cell growth, and promotion of the production of sex hormone binding globulin.[14,53–60]

The association between soy intake and EC in cohort studies becomes null based on only 2 studies. However, the study by Ollberding et al,[36] 1 of the 2 included studies, was conducted in postmenopausal women. When stratified by menopausal status, we observed a protective role in postmenopausal women, but not in premenopausal women, which suggested that menopausal status maybe an important modifier of the effect of isoflavones on EC. One probable reason is that soy isoflavones may be effective only at low sex hormone concentrations as shown in postmenopausal women. Another explanation is that the mechanism by which isoflavones act might involve the ovarian synthesis of sex hormone or the alteration of other menstrual cycle characteristics.[61,62] Of note, the lack of effect in premenopausal women could also be due to the small sample sizes included in this subgroup analysis. Nevertheless, further studies that assess the effects of soy intake on EC risk separately in pre- and postmenopausal women are still warranted.

Our findings indicated that unfermented soy foods was inversely associated with EC risk, whereas a null association was found between fermented soy foods and EC risk based on only one cohort study by Budhathoki et al.[37] The result was consistent with the meta-analysis by Yang et al,[16] which suggested that unfermented soy foods was inversely associated with lung cancer risk, not fermented soy foods. Another meta-analysis[63] studied the effects of fermented and unfermented soy foods separately on gastric cancer risk, which also showed that a high intake of unfermented soy foods was associated with lower gastric cancer risk, whereas fermented soy foods was associated with an increased risk of gastric cancer. Only few experimental studies found that fermented soy foods intake could exert an inhibitory effect on breast, stomach, and colon tumorgenesis.[64–67] To our knowledge, no experimental or observational studies explored the probable effects of fermented and unfermented soy foods separately on EC. Since soy foods exist in most commonly consumed diet worldwide, and especially as a staple in Asian-type diet, our study lays stress on the need for further studies to clarify the difference between fermented and unfermented soy foods in the etiology and prevention of EC.

Notably, the exact mechanisms by which soy products may protect against endocrine-related cancers have not been fully elucidated. Isoflavones were shown to inhibit growth of breast
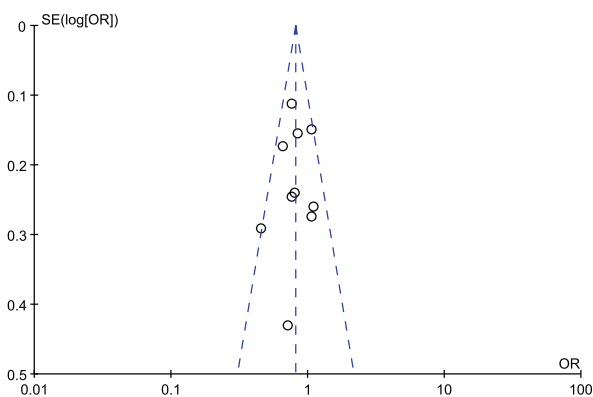

FIGURE 3. Funnel plot of risk estimates of all studies included in the meta-analysis.

TABLE 5. Subgroup Analyses for Dietary Soy Intake on Endometrial Cancer Risk

	No. of Studies	RE	95% CI	*P*-Value	I^2 (%)	Refs.
All studies	10	0.81	0.72, 0.91	0.26	20	27,28,30–37
High-quality studies	8	0.81	0.71, 0.93	0.13	37	27,28,30,31,33,35–37
Study design						
Cohort	2	0.80	0.51, 1.26	0.14	53	36,37
Case control	8	0.83	0.73, 0.94	0.27	21	27,28,30–35
Population based	6	0.83	0.71, 0.96	0.12	42	27,28,30,31,33,35
Hospital based	2	0.82	0.63, 1.06	0.73	0	32,34
Soy-derived isoflavones	7	0.84	0.74, 0.95	0.32	14	27,28,30,34–37
Genistein	4	0.90	0.74, 1.08	0.12	49	27,28,30,36
Daidzein	4	0.85	0.65, 1.10	0.10	52	27,28,30,36
Glycitein	3	0.84	0.68, 1.03	0.64	0	28,30,36
Formononetin	3	1.03	0.82, 1.28	0.85	0	27,28,30
Biochanin A	2	1.16	0.91, 1.47	0.49	0	27,28
Soy food	6	0.79	0.66, 0.95	0.39	5	31–34,36,37
Fermented soy food	1	0.89	0.50, 1.60	n. a	n. a	37
Unfermented soy food	6	0.81	0.67, 0.97	0.59	0	31–34,36,37
Menopausal status						
Premenopausal	2	0.72	0.40, 1.30	0.59	0	27,34
Postmenopausal	3	0.76	0.61, 0.95	0.53	0	27,34,36
Study population						
Asians	3	0.79	0.66, 0.95	0.52	0	32,35,37
Non-Asians	7	0.83	0.71, 0.96	0.13	39	27,28,30,31,33,34,36

CI = confidence interval; RE = risk estimate.

cancer cells at high concentration, but stimulate the growth at low concentration.[18,68,69] Soy isoflavones at particularly high consumption resulting in relatively high incidence of endometrial hyperplasia has also been found in a randomized, double-blinded, placebo-controlled trial.[70] Hence, the protective effects of soy isoflavones on EC should be viewed with caution, since the possibility of biphasic effects of soy isoflavones still cannot be excluded.

Several potential limitations should be taken into consideration when interpreting the results. First, among the 10 included studies, only 2 were cohort studies, whereas the other 8 were case–control studies. Case–control studies were highly subject to recall bias and selection bias. Hence, additional well-designed cohort studies are needed to confirm our findings. Second, the adjusted confounding variables were highly variable across the included studies. However, the study-specific most-adjusted ORs or RRs were used to pool the REs, so we could minimize the effects of confounding factors as much as possible, such as age, age at menarche, body mass index, oral contraceptive use, hormone replacement therapy, energy intake, and parity. Third, the sufficient amount of soy intake for the prevention of EC cannot be defined in our study, because the included studies used different quantile ranges to categorize their data which resulted in different increments of quantitative exposure were used for pooling. In addition, some food composition databases were incomplete because of not containing the whole range of soy foods consumed by the study population, which could probably lead to underestimate soy foods consumed. Also, the analytical methods in these databases used to determine the soy food values varied across included studies. Hence, the optimal amount of soy food remains to be explored in future studies.

In conclusion, the present systematic review and meta-analysis suggested that soy intake was associated with lower EC risk. Because of methodological shortcomings of included studies, various soy sources, and different methods used to assess soy consumption across studies, these findings from our study should be interpreted cautiously and confirmed in future research.

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