Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies[1–3]

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ABSTRACT

Background: Although several in vitro and animal in vivo studies have suggested that soy or soy isoflavones may exert inhibitory effects on lung carcinogenesis, epidemiologic studies have reported inconclusive results on the association between soy intake and lung cancer.

Objective: The aim of this meta-analysis was to investigate whether an association exists between soy and lung cancer in epidemiologic studies.

Design: We searched PubMed, EMBASE, and the Cochrane Library from their inception to February 2011 for both case-control and cohort studies that assessed soy consumption and lung cancer risk. Study-specific risk estimates were combined by using fixed-effect or random-effect models.

Results: A total of 11 epidemiologic studies that consisted of 8 case-control and 3 prospective cohort studies were included. A significantly inverse association was shown between soy intake and lung cancer with an overall RR of 0.77 (95% CI: 0.65, 0.92). Findings were slightly different when analyses were restricted to 5 high-quality studies (RR: 0.70; 95% CI: 0.45, 0.99). In a subgroup meta-analysis, a statistically significant protective effect of soy consumption was observed in women (RR: 0.79; 95% CI: 0.67, 0.93), never smokers (RR: 0.62; 95% CI: 0.51, 0.76), and Asian populations (RR: 0.86; 95% CI: 0.74, 0.98).

Conclusions: Our findings indicate that the consumption of soy food is associated with lower lung cancer risk. Because of different methods used to assess soy consumption across studies, more well-designed cohort studies or intervention studies that use unified measures of soy intake are needed to fully characterize such an association. *Am J Clin Nutr* 2011;94:1575–83.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths in developed and developing countries. Although cigarette smoking accounts for the vast majority of lung cancer, ~25% of cases worldwide are not attributable to tobacco use (1). Therefore, apart from tobacco control, other primary prevention efforts toward lung cancer should be explored.

Evidence from animal and in vitro studies has suggested that soy may have a protective effect against cancer initiation and cancer prognosis because of its high isoflavone content. Two major forms of soy isoflavones are genistein and daidzein, both of which are primarily present in soy (2). Evidence indicated that soy isoflavones inhibit malignant cell growth through gene modulations related to cell-cycle control, apoptosis, and cell signaling pathways. In addition, genistein has been suggested to act as a potent inhibitor of oxidative stress, angiogenesis, and metastasis (3). Furthermore, epidemiologic studies have shown that soy-isoflavone intake is inversely associated with several hormone-related cancers in human, including breast (4–6), endometrial (7, 8), and ovarian (9–11) cancers, which supports that isoflavones may exert their anticancer effects through an estrogen receptor (ER) signaling pathway (12).

In addition to these hormone-related cancers, an inhibitory effect of genistein against lung carcinogenesis was also shown in several in vitro and animal in vivo studies (13–15). However, epidemiologic studies have yielded conflicting results regarding this topic, and to our knowledge, there has not been any quantitative attempt to summarize the results on the possible soy–lung cancer risk association. Thus, we conducted a quantitative meta-analysis of currently available epidemiologic studies to verify this putative association.

METHODS

Data sources and searches

We searched EMBASE (http://www.embase.com/), MEDLINE (PubMed, http://www.ncbi.nlm.nih.gov/pubmed/), and the Cochrane Library (http://www.thecochranelibrary.com/) from their inception to February 2011 and systematically identified epidemiologic studies that evaluated the effect of soy consumption on the risk of

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lung cancer in human populations. No language restriction was applied. The search strategy included terms for outcome (pulmonary neoplasm and lung cancer) and exposure (soy, soybeans, tofu, miso, natto, soy protein, phytoestrogen, flavonoid, isoflavones, genistein, and daidzein). We also scanned the cited references of retrieved articles to identify any additional relevant studies.

Study selection criteria

A published article was included if it *1*) had a case-control or cohort design, *2*) evaluated the association between soy or soy isoflavones and lung cancer risk, and *3*) reported the OR or RR and its 95% CI. If publications were duplicated or articles from the same study population, the most recent publication was included. Excluded from this analysis were studies that evaluated plasma or urinary isoflavones or dietary isoflavones from other sources rather than soy in association with lung cancer.

Data extraction and quality assessment

Two of the authors independently evaluated the eligibility of all retrieved studies from the databases and extracted the relevant data from each included study by using a unified data form. The items included in the data form were as follows: study name (together with the first author's name and year of publication), journal name, country and study design, study population, range for follow-up, soy foods or soy products assessed, comparison of soy food intake, study-specific adjusted ORs or RRs with 95% CIs for the highest compared with lowest amount of the soy or soy isoflavones intake, and matched or adjusted variables in the design or data analysis. The 2 lists from the authors were compared, and disagreements were resolved by consensus.

To assess the study quality, a 9-star system on the basis of the Newcastle-Ottawa Scale (16) was used in which a study was judged on 3 broad perspectives as follows: the selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest for case-control or prospective studies, respectively. With consideration that there is a correlation between caloric intake and nutrient consumption, and possibly a direct or indirect causal relation between caloric intake and lung cancer risk, the scoring system was modified by adding an item in which a study with data analysis that used an energy-adjusted residual or nutrient-density model (17) received an additional star. Hence, the full score was 10 stars, and the high-quality study was defined as a study with $\geq$7 awarded stars.

Statistical methods

To compute a summary RR with its 95% CI, we used the study-specific most-adjusted RR or OR (highest compared with lowest amounts of soy intake) and its 95% CI in all analyses. Some studies separated risk estimates according to the different types of soy food and did not report the effect of total soy food or soy product intake. In this situation, the study-specific effect size in overall analysis was recalculated by pooling the risk estimates of such various soy types by using the inverse-variance method (18). We examined heterogeneity in results across studies by using Cochran's Q and I^2 statistics (19).The null hypothesis that the studies are homogeneous was rejected if the P value for heterogeneity was <0.10 or I^2 was $>50\%$. When substantial heterogeneity was detected, the summary estimate on the basis of the random-effects model [by using the method of DerSimonian and Laird (20)] was presented. Otherwise, the pooled estimate that was based on the fixed-effects model [by using the inverse variance method (18)] was presented. Subgroup analyses were carried out by study quality, study design (case-control compared with prospective studies), sex (men compared with women), study population (Asians compared with non-Asians), type of soy food (fermented compared with unfermented), lung cancer histology (adenocarcinoma compared with others), and smoking status (current, ever, and never smokers). We also evaluated the effect of soy-derived isoflavones on lung carcinogenesis in the analyses. To assess the influence of individual studies on the pooled result, we conducted a sensitivity analysis by excluding each study one by one and recalculating the combined estimates on remaining studies.

We used Egger's test (linear regression method) (21) and Begg's test (rank correlation method) (22) to evaluate publication bias. $P < 0.05$ for Egger's or Begg's tests was considered to be representative of a significant statistical publication bias. All data analyses were performed with R 2.12.1 (meta 1.6–1) software (R Development Core Team).

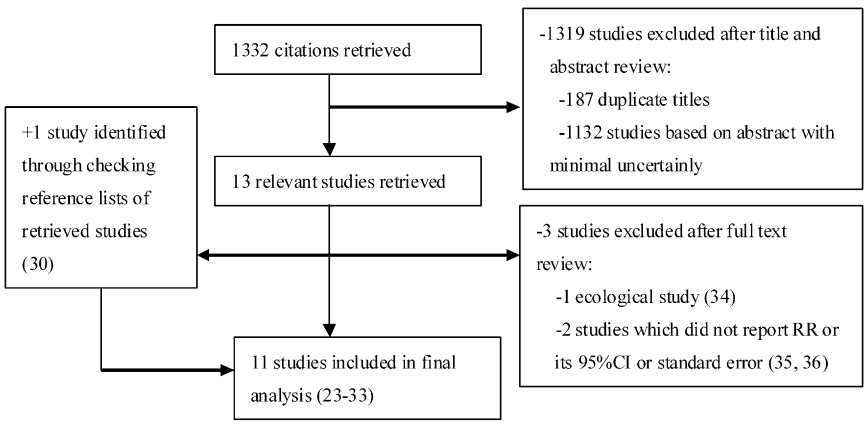

FIGURE 1. References searched and selection of studies in the meta-analysis.

TABLE 1
Characteristics of epidemiologic studies of soy food intake and lung cancer risk included in the meta-analysis

First author, year of publication (reference)	Journal	Region and design	Study population [age (y)]	Follow-up (y)	Soy food assessed	Intake comparison	OR/RR(95% CI)	Matched or adjusted variables
Shimazu, 2010 (23)[2]	Am J Clin Nutr	Japan; cohort	M: 481 cases from 36,177 male inhabitants; W: 178 cases from 40,484 female inhabitants (45–74)	11	Soy isoflavones[1]	Amount of soy genistein intake: 48 compared with 9 mg/d	M: 0.89 (0.67, 1.19); W: 0.83 (0.54, 1.29)	Age, study area, smoking, alcohol drinking, menopausal status in women, and total intake of vegetables, fruit, and fish
Ho, 2006 (24)	Prev Med	China; case control (population based)	M: 1403 cases and 3552 control subjects; W: 765 cases and 7416 control subjects (≥60)	—	Soy products[2]	Frequency of soy product consumption: ≥4 times/wk compared with <1 time/mo	M: 0.76 (0.54, 1.05); W: 0.71 (0.46, 1.10)	Age, education, leisure exercise, job type, alcohol drinking, smoking, fruit intake, dairy products, and Chinese tea intake
Schabath, 2005 (25)	JAMA	USA; case control (hospital based)	T[3]: 1674 cases and 1735 matched healthy control subjects (mean: ≥60)	—	Soy isoflavones[4]	Amount of soy isoflavone intake: ≥83.2 compared with ≤8.2 μg/d	T: 0.39 (0.32, 0.48)	Age, sex, ethnicity, smoking status, cigarettes smoked per day, years of smoking, education, income, BMI, and total energy
Seow, 2009 (26)	Cancer Epidemiol Biomarkers Prev	Singapore cohort	W: 298 cases from 35,298 Singapore Chinese women (45–74)	9.6	Soy isoflavones[5]	Amount of soy isoflavone intake: 22 compared with 4 mg · 1000 $kcal^{-1}$ · d^{-1}	W: 0.74 (0.53, 1.04)	Age, year of interview, dialect group, education, BMI, total vegetable intake, total fruit and juice intake, β-cryptoxanthin, total isothiocyanates, duration of smoking, cigarettes per day, and number of years since quitting smoking
Seow, 2002 (27)	Int J Cancer	Singapore; case control (hospital based)	W: 303 cases and 765 control subjects (20–89)	—	Soy Isoflavones[6]	Amount of soy isoflavone intake: <171.6 compared with >69.1 mg/wk	W (smokers): 1.30 (0.64, 2.61); W (never smokers): 0.56 (0.37, 0.85)	Age, place of birth, first-degree relative with history of cancer, duration and intensity of smoking (only for smokers), and fruit intake
Takezaki, 2001 (28)	Br J Cancer	Japan; case control (hospital based)	M: 367 cases and 2964 control subjects; W: 240 cases and 1189 control subjects (40–79)	—	Soy products[7]	Frequency of soy product intake: ≥5 compared with <1 time/wk	M: 1.27 (0.89, 1.82); W: 0.58 (0.36, 0.90)	Age, season and year of visit, occupation, prior lung diseases, smoking status, passive smoking (only for women), and consumption of green vegetables and meat

(Continued)

TABLE 1 (*Continued*)

First author, year of publication (reference)	Journal	Region and design	Study population [age (y)]	Follow-up (y)	Soy food assessed	Intake comparison	OR/RR(95% CI)	Matched or adjusted variables
Wakai, 1999 (29)	Lung Cancer	Japan; case control (population based)	T: 333 cases and 666 control subjects (40–89)	—	Soy products[8]	Frequency of soy product intake: almost every day compared with ≤3–4 times/wk	M: 0.82 (0.63, 1.07); W: 1.20 (0.76, 1.91)	Age, sex, residence, education, smoking, and medical history of lung disease
Wu-Williams, 1990 (30)	Br J Cancer	China; case control (population based)	W: 965 cases and 959 control subjects (mean: >55)	—	Soy products[9]	Frequency of soy product intake: >485 compared with <153 times/y	W: 1.00 (0.80, 1.30)	Age, education, personal smoking, and study area
Hu, 1997 (31)	Int J Cancer	China; case control (hospital based)	T: 227 cases and 227 control subjects (mean: 53.2)	—	Soy products[10]	Amount of total soy product intake: >8 compared with <2 kg/y	T: 0.60 (0.40, 1.10)	Age, sex, area of residence, cigarettes smoked per day, duration of smoking, and family income
Cutler, 2008 (32)	Int J Cancer	United States; cohort	W: 849 cases from 34,708 postmenopausal women (55-–69)	18	Soy isoflavones[11]	Amount of soy isoflavone intake: >0.52 compared with ≤0.13 mg/d	W: 0.93 (0.86, 1.00)	Age, energy, education level, race, BMI, multivitamin use, activity level, and smoking pack-years
Matsuo, 2008 (33)	Cancer Sci	Japan; case control (hospital based)	T: 353 cases and 1765 control subjects (18–79)	—	Soy products[12]	Amount of soy consumption: >54.7 compared with <32 g/d	T: 0.56 (0.34, 0.93)	Age, sex, energy intake, and smoking

[1] Results for soy isoflavones reported in terms of those for genistein because of the high correlation between intake estimates for genistein and daidzein; 95.9% of genistein from intakes of 8 food items (miso soup, soy milk, tofu for miso soup, tofu for other dishes, yushidofu, koyadofu, aburaage, and natto).

[2] Unspecified types.

[3] T, total (men and women).

[4] Tofu and unspecified soy sources.

[5] From intakes of 8 food items (tofu, tau pok, tau kwa, yong tau foo, foojook, tofu far, and soy milk).

[6] From intakes of 8 food items (yellow soy beans, soybean milk, sweet soybean curd in syrup, soft soybean cake, firm soybean cake, fried soybean puff, soybean sheets, and sweet soy strips).

[7] Tofu, miso soup, and soybean.

[8] Miso soup and soybean curd.

[9] Bean curd and fermented bean paste.

[10] Soy oil and soybean product.

[11] From intake of 2 food items (tofu and soy milk).

[12] Tofu, miso soup, and natto.

RESULTS

Literature search

Our systematic literature search yielded a total of 11 articles on soy food intake and lung cancer risk in the final analysis (23–33). A flow diagram that shows how we located relevant studies is presented in **Figure 1**. Of the 1332 titles identified from the 3 databases, 1319 articles were excluded after we had reviewed titles and abstracts. After reviewing the full text of the remaining 13 studies (23–29, 34–36), we included 11 studies in the final analysis, of which one study (30) was determined through checking reference lists of retrieved articles. The main reasons for excluding studies in the final review were as follows: one study was an ecological study (34), and 2 studies did not report 95% CIs or SEs of risk estimates (35, 36).

Study characteristics and quality assessment

Descriptive data for the studies included in our analysis were summarized in **Table 1**. The study-design types were as follows: prospective cohort studies [n = 3 (23, 26, 32)], population-based case-control studies [n = 3 (24, 29, 30)], and hospital-based case-control studies [n = 5 (25, 27, 28, 31, 33)]. Studies were conducted in Japan [n = 4 (23, 28, 29, 33)], China [n = 3 (24, 30, 31)], Singapore [n = 2 (26, 27)], and the United States [n = 2 (25, 32)]. Six studies (23–25, 28, 29, 33) presented results by sex. Four studies presented results for women only (26, 27, 30, 32), whereas one article presented results for men and women combined (31). Two studies (28, 29) separated the risk estimates according to the different types of soy food and did not report the effect size of the total soy intake; thus, the study-specific estimates in the overall analysis were recalculated. Most individual studies were matched or adjusted for a wide range of potential confounders, including smoking, passive smoking, energy intake, BMI, physical activity, fruit and vegetables intakes, alcohol drinking, and age. All studies used food-frequency questionnaires to measure soy intakes.

Study-specific quality scores are summarized in **Tables 2** and **3**. The range of quality scores was from 6 to 10; the median score was 6. The median scores of case-control studies and cohort studies were 6 and 8, respectively. High-quality studies (ie, those studies that had $\geq$7 awarded stars) included 2 case-control studies (25, 33) and 3 cohort studies (23, 26, 32).

Overall analyses

As shown in **Figure 2**, our overall analysis of 11 studies showed a 23% reduction in risk of lung cancer with high intake of soy foods (summary RR: 0.77; 95% CI: 0.65, 0.92). Statistically significant heterogeneity was observed in the study results (Q = 84.90, $P < 0.001$, I^2 = 82.3%). There was no indication of a publication bias either from the result of Egger's test (P = 0.315) or Begg's test (P = 0.368).

Subgroup and sensitivity analyses

The effects of soy food intake on lung cancer risk in subgroup meta-analyses are shown in **Table 4**. Compared with the overall analysis, the result was a little different when analyses were restricted to 5 high-quality studies (RR: 0.70; 95% CI: 0.45,

TABLE 2
Methodologic quality of case-control studies included in the meta-analysis[1]

First author, year of publication (reference)	Adequate definition of cases	Representativeness of cases	Selection of control subjects	Definition of control subjects	Control for important factor or additional factor[2]	Exposure assessment	Same method of ascertainment for all subjects	Nonresponse rate[3]	Data analysis that used an energy-adjusted residual or nutrient-density model	Total quality scores
Ho, 2006 (24)	—	☆	☆	☆	☆☆	—	☆	—	—	6
Schabath, 2005 (25)	☆	☆	—	☆	☆☆	—	☆	—	☆	7
Seow, 2002 (27)	☆	—	—	☆	☆☆	—	☆	☆	—	6
Takezaki, 2001 (28)	☆	—	—	☆	☆☆	☆	☆	—	—	6
Wakai, 1999 (29)	☆	☆	☆	☆	☆	—	☆	—	—	6
Wu-Williams, 1990 (30)	☆	☆	☆	☆	☆	—	☆	—	—	6
Hu, 1997 (31)	☆	☆	—	☆	☆☆	—	☆	—	—	6
Matsuo, 2008 (33)	☆	☆	—	☆	☆☆	☆	☆	—	—	7

[1] A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor.
[2] A maximum of 2 stars could be awarded for this item. Studies that controlled for smoking or were conducted in nonsmokers received one star, whereas studies that controlled for other important confounders such as passive smoking and intake of other nutrients received an additional star.
[3] One star was assigned if there was no significant difference in the response rate between control subjects and cases by using the chi-square test ($P > 0.05$).

TABLE 3
Methodologic quality of cohort studies included in the meta-analysis[1]

First author, year of publication (reference)	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor[2]	Outcome assessment	Follow-up long enough for outcomes to occur[3]	Adequacy of follow-up of cohorts[4]	Data analysis that used an energy-adjusted residual or nutrient-density model	Total quality scores
Shimazu, 2010 (23)	☆	☆	☆	☆	☆☆	☆	☆	☆	☆	10
Seow, 2009 (26)	—	☆	☆	☆	☆☆	☆	☆	—	☆	8
Cutler, 2008 (32)	☆	☆	☆	☆	☆☆	☆	☆	—	—	8

[1] A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor.
[2] A maximum of 2 stars could be awarded for this item. Studies that controlled for smoking or were conducted in nonsmokers received one star, whereas studies that controlled for other important confounders such as passive smoking and intake of other nutrients received an additional star.
[3] A cohort study with a follow-up time >8 y was assigned one star.
[4] A cohort study with a follow-up rate >75% was assigned one star.

0.99). Significant protective effects of soy intake on lung cancer were observed in women (RR: 0.79; 95% CI: 0.67, 0.93), Asian populations (RR: 0.86; 95% CI: 0.74, 0.98), and never smokers (RR: 0.62; 95% CI: 0.51, 0.76), but the effects were NS in other relevant stratums (*see* Supplemental Figures 1, 2, and 3 under "Supplemental data" in the online issue). The summary RR from studies that evaluated the effect of soy isoflavones intake was 0.63(95% CI: 0.45, 0.90). When stratified by study design, the analysis of cohort studies yielded a RR of 0.92 (95% CI: 0.85, 0.98), whereas the analysis on case-control studies yielded a RR of 0.72 (95% CI: 0.56, 0.92). We showed that the intake of unfermented soy foods (tofu and soy milk) was significantly associated with a decreased risk of lung cancer (RR: 0.83; 95% CI: 0.58, 0.87), but there was no evidence of a preventive effect for fermented soy foods (miso and natto) (RR: 1.06; 95% CI: 0.74, 1.51).

In sensitivity analyses, we recalculated the combined results by excluding one study per iteration. The 11 study-specific RRs ranged from a low of 0.75 (95% CI: 0.62, 0.91) to a high of 0.84 (95% CI: 0.75, 0.94) via omission of the study by Wakai et al (29) and the study by Schabath et al (25), respectively, and were similar without great fluctuation (data not shown).

DISCUSSION

To our knowledge, this is the first meta-analysis to report an association between soy intake and lung cancer risk. Findings from the current study suggested that the consumption of soy food was associated with a 23% reduction in risk of lung cancer for humans when the highest reported intake was compared with the lowest reported intake. This combined estimate was robust across sensitivity analyses and had no observed publication bias.

The inverse association between soy and lung cancer is biologically plausible through the following 2 interactive pathways: estrogen-dependent mechanisms via the ER signaling pathway and/or estrogen-independent mechanisms via the EGFR (epidermal growth factor receptor)–mediated pathway. The role of estrogen in lung carcinogenesis may arise from ERs expressed in normal lung and tumor cell lines and tissues in which the binding of estrogen promotes cell proliferation (37, 38). Because of their close similarity in structure to estrogen, soy isoflavones have a weak affinity for ERs and compete with estradiol at the receptor complex where they act as estrogen agonists or antagonists (3). In addition, 2 in vitro studies (14, 39) suggested that genistein inhibited EGFR kinase activity and enhanced the effect of EGFR-tyrosine kinase inhibitors. A case-control study conducted in Japan showed that soy intake was inversely associated with non–small cell lung carcinoma only in the EGFR-mutated population (33). Moreover, evidence from a clinical study showed that ER-β expression correlated with EGFR mutation, which suggested the functional crosstalk between these 2 pathways (40).

We showed that the magnitude of risk reduction reported in high-quality studies was stronger than that reported in the overall analysis (a 30% compared with 23% risk reduction), which indicated that the association may have been diluted by poor study methodologies. When stratified by study design, the significant protective effect of soy intake against lung cancer was weaker in cohort studies than in case-control studies. These inconsistent findings between 2 different study designs may have been

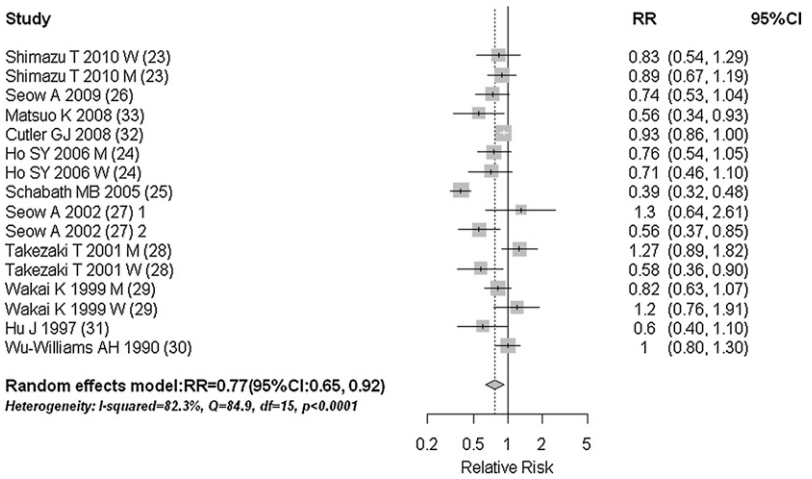

FIGURE 2. Estimates (95% CIs) of soy intake and risk of lung cancer. Squares represent study-specific estimates [size of the square reflects the study-specific statistical weight (ie, inverse of the variance)]; horizontal lines represent 95% CIs; diamonds represent summary estimates with corresponding 95% CIs. Reference 27 provided 2 results, one for smokers [effect size for smokers (1)] and one for never smokers [effect size for never smokers (2)]. M, men; W, women.

attributed to greater recall and selection biases in case-control studies because of their retrospective nature. In case-control studies, cases that developed lung cancer were more likely to change their dietary behavior as well as soy consumption for their ill health. Because information of soy food intake was collected after cancer diagnosis, the earlier long-term dietary habit may have been strongly influenced by the recent diet, and a spurious association would have been observed. Likewise, the use of hospital-based control subjects in 5 of 8 case-control studies (25, 27, 28, 31, 33) might have led to selection bias because some control subjects were suffering from conditions that would have made them more inclined to changes in dietary patterns. However, this selection bias was minimized in the remaining 3 population-based case-control studies (24, 29, 30).

The significant inverse associations between soy and lung cancer appeared to be confined to women, never smokers, and

TABLE 4
Summary risk estimates of the association between soy food consumption and lung cancer risk

			Heterogeneity test			
	No. of studies	RR (95% CI)	Q	P	I^2 (%)	References
All studies	11	0.77 (0.65, 0.92)	84.90	<0.001	82.3	23–33
High-quality studies	5	0.70 (0.45, 0.99)	65.08	<0.001	92.3	23, 25, 26, 32, 33
Soy-derived isoflavones	5	0.63 (0.45, 0.90)	26.52	<0.001	81.8	23, 25–27, 32
Study design						
Cohort	3	0.92 (0.85, 0.98)	1.93	0.587	0	23, 26, 32
Case control	8	0.72 (0.56, 0.92)	54.82	<0.001	79.9	24, 25, 27–31, 33
Population based	3	0.87 (0.77, 1.02)	4.76	0.313	15.9	24, 29, 30
Hospital based	5	0.67 (0.45, 0.98)	37.97	<0.001	84.2	25, 27, 28, 31, 33
Sex						
M	6	0.67 (0.42, 1.07)	56.70	<0.001	91.2	23–25, 28, 29, 33
F	10	0.79 (0.67, 0.93)	25.80	0.004	61.3	23–26, 27,[1] 28–30, 32, 33
Histologic type of lung cancer						
Adenocarcinoma	3	0.70 (0.52, 0.93)	2.12	0.346	5.7	26, 28, 29
Others	3	0.65 (0.45, 0.93)	2.54	0.280	21.4	26, 28, 29
Soy type						
Fermented soy food	5	1.06 (0.74, 1.51)	13.05	0.022	61.7	26, 28, 29, 31, 33[2]
Unfermented soy food	4	0.83 (0.58, 0.87)	2.57	0.767	0	26, 28, 29, 33
Smoking status						
Current smokers	3	0.80 (0.39, 1.61)	15.00	<0.001	86.6	23, 25, 27
Ever smokers	6	0.77 (0.55, 1.07)	22.50	0.001	72.8	23, 25, 26, 29,[3] 32, 33
Never smokers	6	0.62 (0.51, 0.76)	4.04	0.775	0	23,[3] 25–27, 29,[3] 32
Study population						
Asians	9	0.86 (0.74, 0.98)	13.60	0.137	33.8	23,[3] 24, 26–31, 33
Non-Asians	2	0.61 (0.26, 1.42)	62.01	<0.001	98.4	25, 32

[1] Study provided 2 results (one for smokers and one for never smokers).
[2] Study provided 2 results (one for miso soup and one for natto).
[3] Study provided 2 results (one for men and one for women).

East Asian populations in the subgroup analyses. Because never-smoking status, East Asian ethnicity, and female sex are associated with EGFR gene mutation (41–43) and a high correlation between ER expression and EGFR gene mutation (40, 44) in lung cancer, it is likely that there is functional crosstalk between the EGFR-mediated and ERs signaling pathways in lung carcinogenesis, which could explain these current discrepancies. However, because of the limited number of studies included, the discrepancies would have been accidental and the play of chance could not be ruled out.

Our analysis on soy-derived isoflavones showed that soy isoflavones were associated with an ~27% of risk reduction in lung cancer. This finding was supported by results from study of plasma isoflavones (45). Nonetheless, results from our separate analysis according to study populations showed a significant protective effect of soy isoflavones in Asians but not in Westerners (data not shown). Such a difference could be attributed to the much-lower average intake of soy isoflavones in Westerners than that in Asians. By comparison, Culter et al (32) reported an interquintile intake range of 0.07–1.83 mg soy isoflavones/ d of in 34,708 postmenopausal women in Iowa, and Schabath et al (25) reported a median intake of <0.6 mg soy isoflavones/d in elderly adults in Huston. A study in Japan (23) estimated isoflavone intakes to be 9–48 mg genistein/d and ~6–30 mg daidzein/d in 36,177 men and 40,484 women, and a study in Singapore (26) reported an interquartile intake range of 4–22 mg isoflavones/d (after adjustment for total energy) in 35,298 women. Apparently, there is a great difference in soy isoflavones intakes between these 2 populations. Another explanation for the difference is that the protective impact of soy isoflavones observed in Asians may have resulted from a lifelong or early exposure to soy.

Our findings suggested that the intake of unfermented soy foods (tofu and soy milk) was inversely associated with lung cancer risk, whereas such a protective effect disappeared with intakes of fermented soy foods (miso and natto), which suggested that the protection could be associated with different types of soy food. To our knowledge, no published data has compared the effects of these 2 types of soy foods on carcinogenesis in animal experiments. Although dietary supplementation with miso showed an inhibitory effect on breast (46), stomach (47), and colon (48) tumorgenesis, there is currently no published study available in a lung model to our knowledge. Because tofu, miso, soy milk, and natto are the most commonly consumed soy foods worldwide, our analysis underscores the need for future studies to clarify the difference between fermented and unfermented soy foods in the etiology and prevention of lung cancer.

There were several limitations in our meta-analysis. First, because of the inability to fully adjust for various confounders, the protective effect of soy intake on lung cancer could be attributed to other healthy habits related to soy consumption, such as more exercise, high fruit and vegetables consumption, and reduced alcohol use. However, most included studies have adjusted for a wide range of potential confounders. For example, all studies adjusted for smoking, 5 studies adjusted for fruit and vegetables intakes (23, 24, 26–28), 2 studies adjusted for alcohol drinking (23, 24), and 3 studies adjusted for physical activity or total energy intake (25, 32, 33). Second, because of the use of food-frequency questionnaires in each component studies, our findings were likely to be influenced by the misclassification of soy consumption. In cohort studies, this misclassification could be nondifferential and would bias results toward the null, whereas the influence of a misclassification on the results in case-control studies is difficult to predict. Third, because of different methods used to assess and report soy intake across studies, we failed to evaluate a dose-response relation between soy food intake and lung cancer. In our analysis, all studies, except 2 studies (28, 30), provided dose-response data, of which 6 studies (24, 25, 27, 29, 32, 33) observed a significant trend (ie, an increasing benefit with increasing amounts of soy can be from increases in the frequency and amount of soy consumption), but this significant trend was not shown in 3 other studies (23, 26, 31). Finally, substantial heterogeneity was shown across the component studies. This heterogeneity was not surprising because of variations in methods of soy assessment, study design, study population, amounts of soy consumption compared, and adjustments across studies.

In conclusion, our analysis indicates that soy intake is associated with lower lung cancer risk. Because of the limited number of studies, the findings from our study need to be confirmed in future research in well-designed cohort or intervention studies. In addition, the underlying mechanisms and active compounds in soy that may be responsible for the relation remain to be further elucidated.

The authors' responsibilities were as follows—W-SY: study design, literature search, systematic review and data collection, statistical analysis, interpretation of results, and preparation of the manuscript; H-LZ: literature search, systematic review and data collection, and statistical analysis; Y-BX: principal investigator, study design, statistical analysis, and interpretation of results; and all authors: contribution to critical review of the manuscript. None of the authors had a conflict of interest.

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