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Soy Food Consumption and Risk of Prostate Cancer: A Meta-Analysis of Observational Studies

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Soybean products have been suggested to have a chemo preventive effect against prostate cancer. The aim of this study was to provide a comprehensive meta-analysis on the extent of the possible association between soy-based food consumption and the risk of prostate cancer. Five cohort studies and 8 case-control studies were identified using MEDLINE, EMBASE, CINAHL, Korea Medical Database, KoreaMed, Korean studies Information Service System, Japana Centra Revuo Medicina, China National Knowledge Infrastructure, and a manual search. Summary odds ratios (ORs) comparing high versus low categories of soybean consumptions were calculated on the basis of the random effect model. We analyzed the associations based on the different types of soybean consumptions. The summary ORs (95% CI) for total soy foods were 0.69 (CI = 0.57–0.84) and 0.75 (CI = 0.62–0.89) for nonfermented soy foods. Among individual soy foods, only tofu yielded a significant value of 0.73 (CI = 0.57–0.92). Consumption of soybean milk, miso, or natto did not significantly reduce the risk of prostate cancer. Genistein and daidzein were associated with a lower risk of prostate cancer. This systematic review suggests that soy food consumption could lower the risk of prostate cancer. This conclusion, however, should be interpreted with caution because various biases can affect the results of a meta-analysis.

INTRODUCTION

Prostate cancer was the second most common cancer in men worldwide following lung cancer in 2002. The GLOBOCAN 2002 project presented estimates that in 2002, more than 670,000 men around the world were diagnosed with prostate cancer, and about 220,000 died of the disease (1). Soybean products are promoted as protective against certain types of cancer. Isoflavones such as genistein are believed to have estrogen-like effects in the body.

Indeed, a number of laboratory and animal experiments have found that soy isoflavones may reduce the risk of developing prostate cancer (2–4). Despite these findings, research has yielded mixed results as to whether consuming isoflavones can lower the risk of prostate cancer (5–8). One meta-analysis showed that soy consumption was related to a lower risk of prostate cancer. However, that study had some methodological limitations (9). First, it did not include studies assessing fermented soy food (such as miso and natto in Japan) because the authors thought that fermented food might increase the risk of certain cancers (10). However, to our knowledge, no studies have conclusively demonstrated that consuming fermented soy foods is associated with prostate cancer. Second, the analysis combined measurements from different types of soy foods even though their effects might be of different magnitudes and even though some may have had a positive effect and others a negative one (11).

So far, clinical trials on isoflavones in prostate cancer biomarkers (e.g., prostate-specific antigen) have been conducted (12), but a long-term clinical trial carrying the risk of developing prostate cancer as a primary endpoint would not be feasible. Thus, we conducted a comprehensive systematic review and meta-analysis of observation studies that have described the association between soy food consumption and the risk of prostate cancer. We gleaned our data from the original measurements of soy intake from each individual study to accurately assess the

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effects of different types of soy foods. We also included an assessment of fermented soy foods with a subgroup analysis to reveal any differences in the effects of fermented and nonfermented soy foods (such as soy milk, tofu, and soybeans). Finally, we assessed the contributions of study design and race to prostate cancer risk.

METHODS

Selection Criteria and Search Strategy

To be included, studies had to be cohort studies or case-control studies with an adult population. We included all methods for measuring exposure to soy such as questionnaires, interviews, and serum level or urinary excretion of isoflavones. We did, however, exclude data concerning soy food consumption after cancer diagnosis because dietary soy intake is easily changed. We limited our analyses to studies of clinical cancer outcomes (e.g., diagnosis of prostate cancer). We did not include studies with tumor-related biomarkers or cancer risk factors as outcomes.

We conducted a systematic literature search of MEDLINE (1966 to October 2007), EMBASE (1980 to October 2007), and CINAHL (1982 to October 2007) for studies describing the association between soy food consumption and prostate cancer. Because many traditional foods in Korea, Japan, and China are prepared from soy, we reasoned that numerous studies could have been published in these three languages. Thus, we also searched the Korea Medical Database (KMbase) (http://kmbase.medric.or.kr), KoreaMed (http://www.koreamed.org, Korea Medical database), and KISS (Korean studies Information Service System, http://kiss.kstudy.com/) for studies in Korean; the Japana Centra Revuo Medicina (JAMAS; www.jamas.or.jp) for studies in Japanese; and the China National Knowledge Infrastructure (CNKI) (www.cnki.co.kr) for studies in Chinese. Two search themes, "soy" and "prostate cancer," were combined using the Boolean operator "AND." To make our search as sensitive as possible, we did not limit study designs, and we considered articles published in any language. In addition, we manually searched the reference lists of all identified relevant publications and reviewed selected scientific evidence reports (Agency for Healthcare Research and Quality).

REVIEW METHODS

Two reviewers identified articles eligible for further review by performing an initial screen of identified abstracts or titles. Articles were retained when either of the two reviewers believed that they should be retained. The second screening was based on a full-text review. Any disagreement was resolved by consensus. Information on study design, study characteristics, measurement of soy food consumption and outcomes, adjustment for potential confounders, and estimates of associations were extracted in parallel by two independent investigators. Discrepancies were resolved by discussion and repeated examination of the articles. Both measures used to quantify soy intake, and the levels of soy intake varied considerably among the studies; so we examined the risk associated with the largest differences in exposure. We extracted adjusted relative risks (RRs), hazard ratios, odds ratios (ORs), and 95% confidence intervals (CIs) for the risk of developing prostate cancer in a higher quantity consumer compared to a lower quantity consumer.

We assessed how well the study was done to minimize the risk of bias using the checklist of the Scottish Intercollegiate Guidelines Network (SIGN) (13). The SIGN guidelines include internal validity (selection of subjects, assessment, confounding adjustment, and statistical analysis), overall assessment of the study, and description of the study in relation to 23 key questions structured for cohort studies and 26 for case-control studies. In this study, we considered the studies as poorly qualified if they were not adjusted for potential confounding factors of diet or caloric intake, but the quality of the studies was not a factor of inclusion criteria in our study. To evaluate the robustness of the results, we conducted a sensitivity analysis by excluding the poorly qualified studies.

Statistical Analyses

The ORs were used as the common measure of association across studies by considering the hazard ratios and RRs as ORs. The meta-analysis was performed using STATA version 9.2 (Stata Corp., College Station, TX). Random effect models were used to estimate a summary OR across the studies (14,15). Analyses were separated based on the type of soy food or isoflavone, whether the food was fermented, the race of the study population, and the study design. Sensitivity analyses were performed to assess the effects of study quality. To assess for heterogeneity of ORs across the studies, the Cochrane Q statistic ($P \leq 0.10$ was considered statistically significant) was calculated (16,17). The possibility of publication bias was assessed using the Egger test and visual inspection of a funnel plot (18,19). To estimate whether publication bias could explain the observed associations, we also calculated "fail-safe N" using MetaWin 2.0 (20).

RESULTS

We identified 5 cohort studies and 8 case-control studies that had investigated the association between soy food or isoflavone consumption and the risk for prostate cancer. The cohort studies included 87,844 participants and 1,206 incident cases of prostate cancer, and the case-control studies included 4,018 cases and 4,407 controls (Table 1) (7–10,21–29). Four of the studies were conducted in Japan (8,21,22,24), two in China

TABLE 1
Characteristics of studies included in the meta-analysis

Reference	Study Site/Race	Cases/Controls or Cohort Size	Dietary Assessment	Maximum Follow-Up (yr)
Cohort studies				
Kurahashi, et al. (21)	Japan/Japanese	307/43,509	FFQ (147 items)	9
Allen et al. (22)	Japan/Japanese	196/18,115	FFQ (? items)	33
Nomura et al. (6)	Hawaii/Japanese American	304/5,826	Questionnaire (weekly frequency of intake of tofu and the average serving size)	30
Jacobsen et al. (5)	California/not reported	225/12,395	Questionnaire (frequency of consumption per day)	16
Severson et al. (23)	Hawaii/Japanese	174/7,999	FFQ (20 items)	21
Case-control studies				
Nagata et al. (24)	Japan/Japanese	200/200	semi-quantitative FFQ (? items)	
Jian et al. (25)	China/Chinese	130/274	FFQ (130 items)	
Sonoda et al. (8)	Japan/Japanese	140/140	semiquantitative FFQ (106 items)	
Lee et al. (7)	China/Chinese	133/265	FFQ (? items)	
Kolonel et al. (26)	Canada and United States/multiethnic	1,619/1,618	Dietary history (147 items)	
Strom et al. (27)	United States/American	83/107	FFQ (modified block, ? items)	
Sung et al. (28)	Taiwan/South Mine, Hakka, and Mainland	90/180	Dietary history (147 items; weekly or monthly frequency)	
Villeneuve et al. (29)	Canada/multiethnic	1,623/1,623	FFQ (modified block, 60 items)	

(7,25), one in Taiwan (28), four in the United States (5,6,23,27), one in Canada (29), and one in the United States and Canada (26). The evaluations addressed various soy interventions such as the total consumption of soy food and individual consumption of miso, tofu, soybean milk, natto, isoflavones, and so forth. Among all 13 studies, 10 measured soy consumption using a self-questionnaire, and the remaining 3 used an interview (6,26,28). Seven studies (5,22,23,26–29) did not report exposure differences using a quantitative scale (such as mg/day, g/wk). Instead, these studies used the frequency of consumption without reporting portion sizes and tertiles or quartiles without reporting exact cutoff points (Table 2).

Among the 13 selected studies, 1 cohort study (5) and 3 case-control studies (7,24,26) found an association between soy food consumption and a decreased risk of prostate cancer, with ORs ranging from 0.3 to 0.62 for high compared to low intake. One case-control study (25) found that the intake of fermented soy food increased the risk of prostate cancer (OR = 2.02, 95% CI = 1.08–3.78 for >4 g compared to 0 g/serving /day).

Type of Soy Food and Isoflavone

In the analysis of individual types of soy food, only tofu demonstrated a significant protective effect with no heterogeneity (Table 3). Five studies (6–8,22,23) tested the relationship between tofu and prostate cancer risk, and one case-control study (7) reported a significant relationship between these two factors (OR = 0.58, 95% CI = 0.35–0.96 for >34.5 g compared to 14.3 g/serving/day). The association between tofu consumption and prostate cancer was slightly stronger after we excluded two low-quality studies (22,23) (OR = 0.68; 95% CI = 0.50–0.91; $P = 0.011$; P for heterogeneity = 0.39).

The risk of prostate cancer decreased significantly in association with high consumption of nonfermented soy foods (including tofu, soybean milk, and soybeans), but high consumption of fermented soy foods (including miso and natto) was not associated with the risk of prostate cancer. Four cohort studies (5,6,22,23) and 4 case-control studies (7,8,28,29) tested nonfermented soy food. Among these 8 studies (OR = 0.75, 95% CI = 0.62–0.89; $P = 0.001$; P for heterogeneity = 0.413), one (5) of the cohort studies and one (7) of the case-control

TABLE 2
Effect sizes and 95% confidence intervals (CI) of studies in the meta-analysis[a]

Reference	Soy Assessed or Subgroup	Contrast	Adjusted OR (95% CI)	Adjustment
Cohort studies				
Kurahashi et al. (21)	Genistein	<13.2 mg/day vs. ≥ 32.8 mg/day	0.71 (0.48–1.03)	Age, area, smoking status, drinking frequency, marital status, BMI, intake of total fatty acids, dairy, vegetables, and fruits
	Daidzein	<8.5 mg/d vs. ≥ 20.4 mg/day	0.77 (0.52–1.13)	
	Miso soup	<110.0 ml/d vs. ≥ 356.0 ml/day	1.04 (0.72–1.50)	
	Total soy	<46.6 g/d vs. ≥ 107.4 g/day	0.82 (0.57–1.19)	
Allen et al. (22)	Tofu	<2/wk vs. almost daily	0.88 (0.58–1.35)	Age, calendar period, city of residence, radiation dose, and education level
	Miso soup	<2/wk vs. almost daily	0.94 (0.67–1.33)	
	Total soy	Low vs. high	0.79 (0.53–1.18)	
Nomura et al. (6)	Tofu	0 g/wk vs. >240 g/week	0.82 (0.54–1.23)	Age, cigarette smoking, alcohol intake, BMI, total calories and arm muscle area
Jacobsen et al. (5)	Soybean milk	Never vs. >1/day	0.3 (0.1–0.9)	Age, age at first marriage, BMI, frequency of consumption of coffee, whole fat milk, eggs, and citrus fruits
Severson et al. (23)	Tofu	≤ 1/ wk vs. ≥ 5/day	0.35 (0.08–1.43)	Age
	Miso soup	≤ 1/ wk vs. ≥ 5/day	1.24 (0.51–3.04)	
Case-control studies				
Nagata et al. (24)	Isoflavones	<30.5 mg/day vs.≥ 89.9 mg/day	0.48 (0.25–0.93)	Smoking, energy and PUFA intake
	Genistein	<1.1 mg/ay vs. ≥ 2.5 mg/day	0.68 (0.39–1.20)	
	Daidzein	<0.8 mg/day vs.≥ 1.9 mg/day	0.64 (0.36–1.17)	
Jian et al. (25)	Fermented soy	0 g/day vs. >4.0 g/day	2.02 (1.08–3.78)	Age, education, family income, marital status, physical activity, locality of residence, BMI, rostate cancer in first-degree relatives, caloric intake, fresh vegetables, fruits consumption, and tea drinking
Sonoda et al. (8)	Total soy	≤77.0 g/day vs.≥187.2 g/day	0.53 (0.24–1.14)	Cigarettes smoking and energy intake
	Tofu	≤19.7 g/d vs. ≥96.4 g/day	0.47 (0.20–1.08)	
	Natto	≤5.7 g/day vs. ≥40.0 g/day	0.25 (0.05–1.24)	
Lee et al. (7)	Total soy	<27.5 g/day vs. >111.8 g/day	0.51 (0.28–0.95)	Age and total calories
	Tofu	<14.3 g/day vs. >34.5 g/day	0.58 (0.35–0.96)	
	Genistein	<17.9 mg/day vs. >62.0 mg/day	0.53 (0.29–0.97)	
	Daidzein	<10.0 mg/d vs. >36.3 mg/day	0.56 (0.31–1.04)	
Kolonel et al. (26)	Total soy	Lowest vs. highest quintile	0.62 (0.44–0.89)	Age, education, ethnicity, geographic area, and calories
	African American	Lowest vs. 2nd tertile	0.85 (0.60–1.21)	
	White	Lowest vs. highest tertile	0.77 (0.45–1.30)	
	Japanese	Lowest vs. highest tertile	0.73 (0.19–2.80)	
	Chinese	Lowest vs. highest tertile	0.74 (0.37–1.44)	

(*Continued on next page*)

TABLE 2
Effect sizes and 95% confidence intervals (CI) of studies in the meta-analysis[a] (*Continued*)

Reference	Soy Assessed or Subgroup	Contrast	Adjusted OR (95% CI)	Adjustment
Strom et al. (27)	Genistein	Low vs. high	0.71 (0.39–1.30)	Age, family history of prostate cancer, alcohol intake, and total caloric intake
	Daidzein	Low vs. high	0.57 (0.31–1.05)	
	Formononectin	Low vs. high	0.99 (0.54–1.81)	
	Biochanin	Low vs. high	0.92 (0.50–1.70)	
Sung et al. (28)	Soybean milk	Yes vs. no	0.95 (0.45–2.00)	—
Villeneuve et al. (29)	Soybean or tofu	None vs. some	0.8 (0.6–1.1)	Age, province of residence, race, income, family history of cancer, years since quitting smoking, cigarette pack-years, BMI, rice and pasta, coffee, grains, cereals, alcohol, fruit and fruit juices, and meat intake

[a] Abbreviations are as follows: BMI, body mass index; PUFA, polyunsaturated fatty acids; OR, odds ratio.

studies reported an inverse association between nonfermented soy food consumption and the risk for prostate cancer. A sensitivity analysis that excluded three low-quality studies (22,23,28) yielded a slightly stronger result, with a summary OR of 0.69 (95% CI = 0.54–0.89; $P = 0.004$; P for heterogeneity = 0.289).

One study (26) evaluated the consumption of soy food without reporting original intake measurements for individual soy products (such as tofu, soybean milk, natto). Additionally, the results of 4 other studies (7,8,21,22) were based on combined measurements from fermented and nonfermented soy food. Although the overall combination of soy foods was diverse, we regarded this combination as possibly the most accurate description of the way most people consume soy food (i.e., a wide variety), so we combined these measurements as "total soy food." Among the 5 studies that evaluated total soy food consumption, two studies (7,26) concluded that it had a significant protective effect. The summary OR was 0.69 (95% CI = 0.57–0.84; $P < 0.001$), and the P value for heterogeneity was 0.54. Excluding one low-quality study (22) did not change the findings.

When we analyzed individual types of soy isoflavone, genistein (OR = 0.67, 95% CI = 0.52–0.86; $P = 0.002$) and daidzein (OR = 0.66, 95% CI = 0.51–0.86; $P = 0.002$) had significant protective effects for high compared to low intake without heterogeneity.

Subgroup Analysis

In the 5 studies that evaluated the association between total soy food consumption and prostate cancer, 4 studies enrolled Asian populations, and one study (26) included both Asian and Western subjects. Exclusion of the Western population did not change the findings (OR = 0.73, 95% CI = 0.58–0.90; $P = 0.004$), although there was no significant relationship between total soy food consumption and prostate cancer in the Western population (OR = 0.83, 95% CI = 0.62–1.11; $P = 0.198$). We could not isolate Western population data for nonfermented soy food and tofu because the majority of the studies were conducted in Asian and multiethnic populations.

The analyses that included only cohort studies did not yield significant results, although these analyses did reveal that the risk of prostate cancer tended to decrease with consumption of tofu, nonfermented soy food, and total soy food. In contrast, the analyses that included only case-control studies yielded more significant protective effects for tofu, nonfermented soy food, and total soy food (Table 4).

Assessment of Publication Bias

The Begg funnel plots were symmetric, and the Egger tests provided no evidence of publication bias for tofu ($t = -2.62$, $P = 0.079$) and for total soy food ($t = -1.26$, $P = 0.295$). However, for nonfermented soy food analysis, a visual inspection of the Begg funnel plot (Fig. 1) and the Egger test provided evidence for publication bias ($t = -2.49$, $P = 0.047$). We calculated the number of studies with null results that would be required to eliminate the significance we observed for these associations. These fail-safe numbers were 11.9 for tofu, 23.2 for total soy food, and 32.3 for the nonfermented soy food.

TABLE 3
Summary odds ratios (ORs) for the association between soy consumption and prostate cancer[a]

	No. of Studies	Summary OR (95% CI)	*P* Value	*P* Value for Heterogeneity
Type of soy food				
Tofu	5	0.73 (0.57–0.92)	0.009	0.428
Soybean milk	2	0.57 (0.19–1.76)	0.332	0.089
Natto	1	0.25 (0.05–1.25)	0.091	—
Miso	3	1.00 (0.79–1.27)	0.991	0.820
Total soy food	5	0.69 (0.57–0.84)	<0.001	0.544
Fermented soy food				
Yes	5	1.10 (0.76–1.57)	0.620	0.100
No	8	0.75 (0.62–0.89)	0.001	0.413
Type of soy isoflavone				
Genistein	4	0.67 (0.52–0.86)	0.002	0.873
Daidzein	4	0.66 (0.51–0.86)	0.002	0.772
Biochanin	1	0.92 (0.50–1.69)	0.789	—
Formonectin	1	0.99 (0.54–1.82)	0.974	—

[a] Abbreviation is as follows: CI, confidence interval.

TABLE 4
Subgroup analysis of soy consumption and prostate cancer according to study design[a]

	No. of Studies	Summary OR (95% CI)	*P* Value	*P* Value for Heterogeneity
Tofu				
All study	5	0.73 (0.57–0.92)	0.009	0.428
Cohort study	3	0.82 (0.62–1.10)	0.182	0.499
Case-control study	2	0.55 (0.36–0.85)	0.007	0.678
Nonfermented soy food				
All study	8	0.75 (0.62–0.89)	0.001	0.413
Cohort study	4	0.72 (0.49–1.06)	0.094	0.221
Case-control study	4	0.73 (0.58–0.92)	0.008	0.443
Total soy food				
All study	5	0.69 (0.57–0.84)	<0.001	0.544
Cohort study	2	0.81 (0.62–1.06)	0.116	0.892
Case-control study	3	0.58 (0.44–0.77)	<0.001	0.831

[a] Abbreviations are as follows: OR, odds ratio; CI, confidence interval.

DISCUSSION

The current meta-analysis suggests an inverse association between soy food consumption and risk of prostate cancer. Subjects who consumed higher amounts of total and nonfermented soy food had a lower risk for prostate cancer compared to those who consumed relatively less. Analyses regarding individual types of soy food suggested that these effects were due to the consumption of tofu. Furthermore, the associations persisted and remained statistically significant in sensitivity analyses performed to assess the potential effect of study quality. Additionally, we observed similar inverse associations between genistein or daidzein intake and the risk of prostate cancer. It might be due to the strong correlation with each other and/or the same food sources that contain both ingredients (27,30,31). Given this consistency, we concluded that these relationships could be real, but further studies are needed to clarify the associations.

As a result of subgroup analysis by race from 5 studies evaluating the association between total soy consumption and prostate cancer, the effect of total soy in 4 Asian studies was the same as the effect of total soy in all of 5 studies. However, we could not make a conclusion of the race difference on the effect of soy intake on the risk of developing prostate cancer because only one study of a Western population was investigated. Natto, soybean milk, and miso were only investigated in a few studies, so

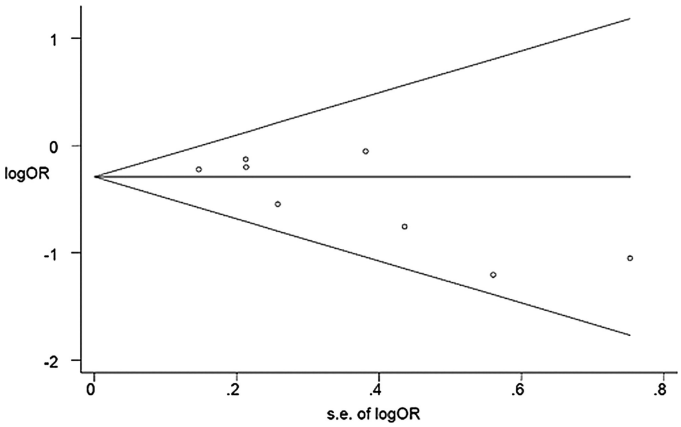

FIG. 1. Begg's funnel plot with pseudo 95% confidence limits for nonfermented soy food. OR, odds ratio.

we could not conclude whether consuming them has no effect or if the effect of these foods is masked by the small number of studies.

Notably, we observed evidence of a publication bias that might have led to asymmetry in the funnel plots. In these situations, the combined effect of the meta-analysis would overestimate the treatment's effect. Therefore, we investigated the statistical stability of the meta-analysis results by calculating fail-safe numbers. For the current analyses, these numbers were relatively small according to a commonly used criterion that requires a fail-safe number to be $5n + 10$, where n is the original number of studies in the analysis (20).

Research design seemed to play an important role in generating the heterogeneity across the studies. Whereas the protective effect was observed among case-control studies, cohort studies tended to show null results. The possible explanations for this situation are recall bias in case of case-control studies and publication bias in both designs (32). The recall bias would arise if prostate cancer patients recalled their dietary history differently compared with controls. The publication of "positive" studies may have overestimated the association in case-control studies. However, considering the tendency of inverse associations and the small number of selected studies, an authentic relationship may exist, although we cannot verify such a relationship in this review.

Difficulty in this study is that people may consume different types of soy food (fermented and nonfermented soy) that may or may not mediate different levels of protection. This possibility makes it difficult to estimate the exact effect of individual soy foods. As shown in this study, the magnitude and direction of the effects of individual soy food were quite different. To estimate the effect of one type of soy food, the primary study should have adjusted the effect of consumption of another type of soy food.

Confounding effect is also a critical threat to the validity of results from observational studies. People who choose to eat soy may also make other lifestyle decisions that lower the risk of cancer (e.g., lower fat intake, higher vegetable and fruit intake, more frequent exercise). Theoretically, these positive lifestyle confounders could overestimate the benefit effect of soy intake. Among the 13 selected studies, 3 did not consider any other lifestyle confounders, but we regarded these studies as being of poor quality, and we excluded them in the sensitivity analysis. However, the exclusion of the studies did not change the statistical significance.

Our results may be influenced by inconsistent measurement tools for evaluating dietary intake, sensitivity of the questionnaire or interview to assess relevant food items for soy intake, and/or the soy content of food. Another limitation of dietary assessment is that the nutrient values of the same food may be different due to the variability in laboratory techniques, food sources, growing methods, preparation apparatus, process, and so forth. In addition, lack of data concerning food composition (33), as well as lack of information about the soy portion sizes that the subjects consumed (5), complicated the dietary analyses. Only 5 studies addressed the validity of their questionnaires. Also, the reports included in this study lacked standardization of categorization and analysis of soy consumption. Although the OR or RR of the high or highest consumption versus low or lowest consumption was used for combining effect size, it was not uniform across the studies. Misclassification of soy intake may have occurred due to measurement errors (7). However, such misclassification is often assumed to be nondifferential, leading to an underestimation of any true associations of dietary components and risk rather than an overestimation (34).

We could not extract any information about the interactions between soy and other nutrients from the reviewed reports. Further studies including potential effect modifiers such as dietary patterns and lifestyle are needed to refine the role of soy intake in prostate cancer risk.

Researchers believe that the isoflavones in soy may play a role in reducing the risk of cancer. Isoflavones are sometimes called "plant estrogens" or "phytoestrogens" because they act like weak forms of estrogen and block cells from using other forms of estrogen. Short-term intervention studies have shown that serum sex hormone-binding globulin concentrations are elevated in men who consume tofu (35,36). In addition, intake of phytoestrogens may reduce cell proliferation and angiogenesis and increase apoptosis (37–39).

Yan and Spitznagel (9) examined the relationship between soy intake and prostate cancer risk in a meta-analysis of epidemiologic studies. The meta-analysis included two cohort studies (5,6) and 6 case-control studies (7,8,26–29). They concluded that the consumption of soy foods correlated with an approximately 30% reduction in prostate cancer risk (9). Although our study revealed a similar finding, we made a more comprehensive methodological effort: We included a more complete literature search, conducted subgroup analyses by individual soy food or isoflavone type, and performed sensitivity analyses.

In summary, the results of this meta-analysis suggest a protective role of soy food consumption against prostate cancer. It is possible that the weak estrogen-like effect of isoflavones might help prevent prostate cancer, but these results should be evaluated in future studies for definitive conclusions to be made. The results herein highlight the need for future research to establish whether this association is causal and to clarify the underlying mechanisms.

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REFERENCES

1. IARC: *GLOBOCAN 2002, Cancer Incidence, Mortality and Prevalence Worldwide (2002 estimates)*. Retrieved from www-dep.iarc.fr. Accessed January 22, 2009.
2. Naik HR, Lehr JE, and Pienta KJ: An in vitro and in vivo study of antitumor effects of genistein on hormone refractory prostate cancer. *Anticancer Res* **14,** 2617–2620, 1994.
3. Zhang JX, Hallmans G, Landström M, et al.: Soy and rye diets inhibit the development of Dunning R3327 prostatic adenocarcinoma in rats. *Cancer Lett* **114**. 313–314, 1997.
4. Schleicher R, Zheng M, Zhang M, and Lamartiniere CA: Genistein inhibition of prostate cancer cell growth and metastasis in vivo. *Am J Clin Nutr* **68,** 1526S(Abstract), 1998.
5. Jacobsen BK, Knutsen SF, and Fraser GE: Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). *Cancer Causes Control* **9,** 553–557, 1998.
6. Nomura AM, Hankin JH, Lee J, and Stemmermann GN: Cohort study of tofu intake and prostate cancer: no apparent association. *Cancer Epidemiol Biomarkers Prev* **13,** 2277–2279, 2004.
7. Lee MM, Gomez SL, Chang JS, Wey M, Wang RT, and Hsing AW: Soy and Isoflavone consumption in relation to prostate cancer risk in China. *Cancer Epidemiol Biomarkers Prev* **12,** 665–668, 2003.
8. Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, et al.: A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. *Cancer Sci* **95,** 238–242, 2004.
9. Yan L and Spitznagel EL: Meta-analysis of soy food and risk of prostate cancer in men. *Int J Cancer* **117,** 667–669, 2005.
10. Wu AH, Yang D, and Pike MC: A meta-analysis of soyfoods and risk of stomach cancer: the problem of potential confounders. *Cancer Epidemiol Biomarkers Prev* **9,** 1051–1058, 2000.
11. Qin LQ, Xu JY, Wang PY, and Hoshi K: Soyfood intake in the prevention of breast cancer risk in women: a meta-analysis of observational epidemiological studies. *J Nutr Sci Vitaminol* **52,** 428–436, 2006.
12. Messina M, Kucuk O, and Lampe JW: An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels. *J AOAC Int* **89,** 1121–1134, 2006.
13. *Critical appraisal: Notes and checklists for systematic reviews and meta-analysis*. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network (SIGN). Retrieved October 2, 2007 from http://www.sign.ac.uk/methodology/checklists.html
14. Egger M, Smith GD, and Altman DG: *Systematic Reviews in Health Care: Meta-Analysis in Context,* 2nd ed. London: BMJ, 2007.
15. DerSimonian R and Laird N: Meta-analysis in clinical trials. *Control Clin Trials* **7,** 177–188, 1986.
16. Higgins JP, Thompson SG, Deeks JJ, and Altman DG: Measuring inconsistency in meta-analyses. *BMJ* **327,** 560–557, 2003.
17. Higgins JP and Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* **21,** 1539–1558, 2002.
18. Begg CB and Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50,** 1088–1101, 1994.
19. Egger M, Davey Smith G, Schneider M, and Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315,** 629–634, 1997.
20. Rosenthal R: The "file drawer" problem and tolerance for null results. *Psychol Bull* **86,** 638–641, 1979.
21. Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, and Tsugane S: Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. *Cancer Epidemiol Biomarkers Prev* **16,** 538–545, 2007.
22. Allen NE, Sauvaget C, Roddam AW, Appleby P, Nagano J, et al.: Prospective study of diet and prostate cancer in Japanese men. *Cancer Causes Control* **15,** 911–920, 2004.
23. Severson RK, Nomura AM, Grove JS, and Stemmermann GN: Prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* **49,** 1857–1860, 1989.
24. Nagata Y, Sonoda T, Mori M, Miyanaga N, Okumura K, et al.: Dietary isoflavones may protect against prostate cancer in Japanese men. *J Nutr* **137,** 1974–1979, 2007.
25. Jian L, Zhang DH, Lee AH, and Binns CW: Do preserved foods increase prostate cancer risk. *Br J Cancer* **90,** 1792–1795, 2004.
26. Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, et al.: Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers Prev* **9,** 795–804, 2000.
27. Strom SS, Yamamura Y, Duphorne CM, Spitz MR, Babaian RJ, Pillow PC, and Hursting SD: Phytoestrogen intake and prostate cancer: a case-control study using a new database. *Nutr Cancer* **33,** 20–25, 1999.
28. Sung JFC, Lin RS, Pu Y, Chen YC, Chang HC, and Lai MK: Risk factors for prostate carcinoma in Taiwan: a case-control study in a Chinese population. *Cancer* **86,** 484–491, 1999.
29. Villeneuve PJ, Johnson KC, Kreiger N, and Mao Y: Risk factors for prostate cancer: results from the Canadian national enhanced cancer surveillance system. *Cancer Causes Control* **10,** 355–367, 1999.
30. Pillow PC, Duphorne CM, Chang S, et al.: Development of a database for assessing dietary phytoestrogen intake. *Nutr Cancer* **33,** 3–19, 1999.
31. Margaret RR, John HC, Michael SM, et al.: A newly constructed and validated isoflavone database for the assessment of total genistein and daidzein intake. *Br J Nutr* **95,** 204–213, 2006.
32. Malina N, Virtanen M, Pietinen P, Virtamo J, Albanes D, Hartman AM, and Heinonen OP: A comparison of prospective and retrospective assessments of diet in a study of colorectal cancer. *Nutr Cancer* **32,** 146–153, 1998.
33. Peeters PH, Keinan-Boker L, van der Schouw YT, and Grobbee DE: Phytoestrogens and breast cancer risk: review of the epidemiological evidence. *Breast Cancer Res Treat* **77,** 171–183, 2003.
34. Wu AH, Ziegler RG, Horn-Ross PL, Nomura AM, West DW, et al.: Tofu and risk of breast cancer in Asian-Americans. *Cancer Epidemiol Biomarkers Prev* **5,** 901–906, 1996.
35. Habito RC, Montalto J, Leslie E, and Ball MJ: Effects of replacing meat with soybean in the diet on sex hormone concentrations in healthy adult males. *Br J Nutr* **84,** 557–563, 2000.
36. Habito RC and Ball MJ: Postprandial changes in sex hormones after meals of different composition. *Metabolism* **50,** 505–511, 2001.

37. Bylund A, Zhang JX, Bergh A, Damber JE, Widmark A, et al.: Rye bran and soy protein delay growth and increase apoptosis of human LNCaP prostate adenocarcinoma in nude mice. *Prostate* **42,** 304–314, 2000.
38. Zhou JR, Gugger ET, Tanaka T, Guo Y, Blackburn GL, and Clinton SK: Soybean phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. *J Nutr* **129,** 1628–1635, 1999.
39. Zhou JR, Yu L, Zhong Y, Nassr RL, Franke AA, Gaston SM, and Blackburn GL: Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. *Prostate* **53,** 143–153, 2002.