

Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis¹⁻⁴

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ABSTRACT

Background: Epidemiologic studies have shown that the consumption of soy foods may be associated with a reduction in cancer risk in humans.

Objective: The purpose of this study was to conduct a meta-analysis on the association between soy consumption and prostate cancer risk in men.

Design: We systematically reviewed studies obtained through a thorough Medline literature search and identified 15 epidemiologic publications on soy consumption and 9 on isoflavones in association with prostate cancer risk. We extracted the most adjusted relative risks (RRs) and odds ratios (ORs) of the highest and the lowest reported categories of intake from each study and conducted this analysis using a random-effects model in which studies with smaller SEEs are given greater weight in the summary measure.

Results: Our analysis of studies on soy intake yielded a combined RR/OR of 0.74 (95% CI: 0.63, 0.89; $P = 0.01$). When separately analyzed, studies on nonfermented soy foods yielded a combined RR/OR of 0.70 (95% CI: 0.56, 0.88; $P = 0.01$) and those on fermented soy foods yielded a combined RR/OR of 1.02 (95% CI: 0.73, 1.42; $P = 0.92$). The analysis of studies on isoflavones yielded a combined RR/OR of 0.88 (95% CI: 0.76, 1.02; $P = 0.09$). Further separate analyses showed a combined RR/OR of 0.52 (95% CI: 0.34, 0.81; $P = 0.01$) from studies with Asian populations and 0.99 (95% CI: 0.85, 1.16; $P = 0.91$) from studies with Western populations.

Conclusions: The results of this analysis suggest that consumption of soy foods is associated with a reduction in prostate cancer risk in men. This protection may be associated with the type and quantity of soy foods consumed. *Am J Clin Nutr* 2009;89:1155-63.

INTRODUCTION

The age-standardized incidence rate of prostate cancer is lower in Asian countries than in the United States and European countries (1). However, the incidence rate in Asians living in the United States is substantially higher than that in those living in their homelands (1), and migration studies have shown an increase in prostate cancer incidence in Asian men after emigration to the United States (2). This observation suggests that environmental factors and changes in lifestyles, particularly in dietary practices, affect the etiology of prostate cancer.

Soy has been a major plant source of dietary protein for Asians for centuries, and evidence indicates that soy consumption may

protect against cancer in humans, including prostate cancer (3). We reported in 2005 that soy consumption is associated with a reduction in prostate cancer risk in men, based on the results of a meta-analysis of the limited number of epidemiologic studies available at that time (2 cohort and 6 case-control studies) (4). Since then, more research has been published, and both general public and research communities remain interested in the potential health effects of soy foods. Compared with other plant-based foods, soy contains higher amounts of isoflavones—a group of phenolic compounds that are considered to be bioactive. Because of advances in technology, these compounds have been quantified from various food sources, isoflavone databases have been developed (5), and studies that assessed isoflavone intake in association with prostate cancer are available. Meta-analysis is a statistical analysis of results from independent studies to produce a single estimate of the average treatment effect. Validation of the conclusion from a previous analysis, based on the most recently available studies, is an important aspect of such an analysis. Furthermore, using the accumulation of the available results we were able to assess differences between different types of soy foods and between different study populations in association with the risk of prostate cancer.

The purpose of the present study was to conduct a meta-analysis of now available epidemiologic studies on soy and isoflavone consumption in association with prostate cancer risk in men and to provide a quantitative evaluation in a standardized form permitting a numerical analysis across the studies.

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TABLE 1
Epidemiologic studies on soy consumption in association with prostate cancer risk in men¹

Reference	Design	Description of study	Soy food assessed	Intake comparison ²	RR/OR (95% CI)
Park et al (14) ³	Cohort	4404 incident cases/82,483 cohort size, multiethnic, United States	Soy products ⁴	0 vs ≥ 2.8 g/1000 kcal	0.90 (0.80, 1.01)
Kurahashi et al (13) ⁵	Cohort	307 incident cases/43,509 cohort size, Japanese, Japan	Soy food ⁶	≤ 46.6 g/d vs ≥ 107.4 g/d	0.82 (0.57, 1.19)
Allen et al (12) ⁷	Cohort	196 incident cases/18,115 cohort size, Japanese, Japan	Total soya intake ⁸	2–4 times/wk vs \geq almost daily	0.79 (0.53, 1.18)
Nomura et al (11) ⁹	Cohort	304 incident cases/5826 cohort size, Japanese American, United States	Tofu	0 vs >240 g/wk	0.82 (0.54, 1.23)
Jacobsen et al (9) ¹⁰	Cohort	225 incident cases/12,295 cohort size, Seventh-Day Adventist men, United States	Soy milk	Never vs >1 time/d	0.3 (0.1, 0.9)
Li et al (15) ¹¹	C-C	28 cases/280 controls, Chinese, China	Soybean food ¹²	≤ 2 times/wk vs ≥ 1 time/d	0.29 (0.11, 0.79)
Heald et al (16) ¹³	C-C	433 cases/483 controls, Scottish, Scotland	Soy food ¹⁴	no vs yes	0.52 (0.30, 0.91)
Sonoda et al (20) ¹⁵	C-C	140 cases/140 controls, Japanese, Japan	All soy products ¹⁶	≤ 77 g/d vs ≥ 187.2 g/d	0.53 (0.24, 1.14)
Jian et al (23) ¹⁷	C-C	130 cases/274 controls, Chinese, China	Fermented soy products ¹⁸	0 vs 4 g/d	2.02 (1.08, 3.78)
Lee et al (17) ¹⁹	C-C	133 cases/265 controls, Chinese, China	Soy foods ²⁰	<27.5 g/d vs >111.8 g/d	0.51 (0.28, 0.95)
Kolonel et al (18) ²¹	C-C	1619 cases/1618 controls, multiethnic, United States and Canada	Soy foods ²²	None vs >39.4 g/d	0.62 (0.44, 0.89)
Villeneuve et al (19) ²³	C-C	1623 cases/1623 controls, Multiethnic, Canada	Tofu	None vs some/wk	0.8 (0.6, 1.1)
Sung et al (21)	C-C	90 cases/180 controls, Chinese, Taiwan	Soybean milk	No vs yes	0.95 (0.45, 2.00)
Oishi et al (22)	C-C	100 cases/100 controls, Japanese, Japan	Miso soup	Low vs high intake	0.64 (0.31, 1.34)

¹ RR/OR, combined relative risk/odds ratio; C-C, case-control.

² The highest reported category of intake compared with the lowest category of intake.

³ Confounding factors adjusted for time since cohort entry, ethnicity, family history of prostate cancer, education level, BMI, smoking status, and energy intake.

⁴ Tofu, miso, and vegetarian meat.

⁵ Confounding factors adjusted for age, area, smoking status, drinking frequency, marital status, BMI, and intake of total fatty acids, dairy products, vegetables, and fruit.

⁶ Tofu, natto, and soy milk.

⁷ Confounding factors adjusted for age, calendar period, city of residence, radiation dose, and education level.

⁸ Tofu and miso soup.

⁹ Confounding factors adjusted for age, cigarette smoking, alcohol intake, total calories, arm muscle area, and BMI.

¹⁰ Confounding factors adjusted for age, BMI, age at first marriage, and frequency of consumption of coffee, whole-fat milk, eggs, and citrus fruit.

¹¹ Confounding factors adjusted for education level, BMI, smoking, alcohol consumption, and food frequency.

¹² Tofu and soy milk.

¹³ Confounding factors adjusted for age, total energy intake, family history of prostate and breast cancer, Carstairs Deprivation Index, smoking, and energy intake:basal metabolic rate ratio.

¹⁴ Soya beans, textured vegetable protein, tofu, soya meat substitute, nut roast, nut burgers, and vegetable burgers.

¹⁵ Confounding factors adjusted for cigarette smoking and energy intake.

¹⁶ Tofu, fermented soybeans, soybean paste soup, fried bean curd, soy flour, dried bean curd, soybean milk, soy sauce, and bean sprouts.

¹⁷ Confounding factors adjusted for age, BMI, physical activity, residence, education level, family income, marital status, prostate cancer in first-degree relatives, fresh vegetable and fruit consumption, and tea drinking.

¹⁸ Fermented bean curd and stinking bean curd.

¹⁹ Confounding factors adjusted for total calories and age.

²⁰ Soybean milk, tofu, dried/fried bean curd, fermented beans, dry bean milk cream, and fermented bean milk.

²¹ Confounding factors adjusted for age, education level, ethnicity, geographic area, and calories.

²² Soybeans, tofu, and miso.

²³ Confounding factors adjusted for age, province of residency, race, years since quitting smoking, cigarette pack-years, BMI, rice and pasta, coffee, grains and cereals, alcohol, fruit and fruit juices, tofu, meat, income, and family history of cancer.

METHODS

We conducted a thorough Medline search, supplemented with a hand search of articles' bibliographies and nonindexed medical and professional journals, to locate epidemiologic studies of soy and prostate cancer. We used the following terms in combination for the literature search: soy (tofu, soy milk, miso, and natto), isoflavones (genistein, daidzein), prostate, and epidemiology (cohort, case-control). In addition, we conducted a broader search on diet and prostate cancer aimed at identifying studies in which the aforementioned terms were not included in abstracts. We systematically reviewed and examined whether the primarily identified studies met the criteria to be included in the analysis: a study must have had soy assessed as a food and/or isoflavones assessed from intake of soy foods, a study must have provided a risk estimate [relative risk (RR) or odds ratio (OR)] and its 95% CI, and, for studies with multiple publications from the same study population or studies with the same results published in different journals, we chose the most recent one for the analysis. Excluded from this analysis were intervention studies that measured soy or isoflavones as a dietary supplement and studies that evaluated serum isoflavones in association with prostate cancer.

We calculated combined RRs and ORs (RR/OR) using the random-effects model in which the effect measures are log RR or

OR weighed by the method of DerSimonian and Laird (6), in which studies with smaller SEEs were given greater weight in the summary measure. We used the methods of Begg and Mazumdar (7) and Egger et al (8) to detect publication bias; both methods test for funnel plot asymmetry, the former (7) being based on the rank correlation between the effect estimates and their sampling variances, and the latter (8) being based on a linear regression of a standard normal deviate on its precision. If a potential bias was detected, we further conducted a sensitivity analysis to assess the robustness of combined effect estimates and the possible influence of the bias. We used the statistical program Stata 9.2 (StataCorp, College Station, TX) for the analysis. All reported *P* values are from 2-sided statistical tests.

RESULTS

We identified 15 publications on soy foods that met the inclusion criteria. Six are cohort studies (9–14), and 9 are case-control studies (15–23). We excluded one study (10) from the analysis because it was an early publication from the same study population that was recently published (11). The 14 studies selected for analysis are presented in chronological order in

TABLE 2
Epidemiologic studies on isoflavone consumption in association with prostate cancer risk in men¹

Reference	Design	Description of study	Isoflavones	Intake comparison ²	RR/OR (95% CI)
Park et al (14) ³	Cohort	4404 incident cases/82,483 cohort size, multiethnic, United States	Total isoflavones	<1.6 vs ≥7.2 mg/1000 kcal	0.93 (0.83, 1.04)
Kurahashi et al (13) ⁴	Cohort	307 incident cases/43,509 cohort size, Japanese, Japan	Genistein	<13.2 vs ≥32.8 mg/d	0.71 (0.48, 1.03)
Nagata et al (24) ⁵	C-C	200 cases/200 controls, Japanese, Japan	Isoflavones ⁶	<30.5 vs ≥89.9 mg/d	0.48 (0.25, 0.93)
Heald et al (16) ⁷	C-C	433 cases/483 controls, Scottish, Scotland	Isoflavones	≤581.1 vs >1982.8 μg/d	1.18 (0.79, 1.75)
Bosetti et al (27) ⁸	C-C	1294 cases/1451 controls, Italian, Italy	Isoflavones ⁹	≤14.7 vs ≥32.2 μg/d	0.98 (0.76, 1.26)
Hedelin et al (26) ¹⁰	C-C	1499 cases/1130 controls, Swedish, Sweden	Isoflavonoids ¹¹	≤1.0 vs ≥2.6 μg/d	0.99 (0.77, 1.28)
Lee et al (17) ¹²	C-C	133 cases/265 controls, Chinese, China	Genistein	<17.9 vs >62.0 mg/d	0.53 (0.29, 0.97)
Strom et al (28) ¹³	C-C	83 cases/107 controls, white, United States	Genistein	19.8 vs 29.7 μg/d ¹⁴	0.71 (0.39, 1.30)

¹ RR/OR, combined relative risk/odds ratio; C-C, case-control.

² The highest reported category of intake compared with the lowest category of intake.

³ Confounding factors adjusted for time since cohort entry, ethnicity, family history of prostate cancer, education level, BMI, smoking status, and energy intake.

⁴ Confounding factors adjusted for age, area, smoking status, drinking frequency, marital status, BMI, and intake of total fatty acids, dairy products, vegetables, and fruit.

⁵ Confounding factors adjusted for cigarette smoking and energy and polyunsaturated fatty acid intakes.

⁶ From intake of 12 soy products (tofu, fermented soybeans, soybean paste soup, bean curd refuse, fried bean curd, fried bean curd with vegetables, soy flour, dried bean curd, soybean milk, soy sauce, green soybeans, and bean sprouts).

⁷ Confounding factors adjusted for age, total energy intake, family history of prostate and breast cancer, Carstairs Deprivation Index, smoking, and energy intake: basal metabolic rate ratio.

⁸ Confounding factors adjusted for age, study center, BMI, family history of prostate cancer, and total calorie intake.

⁹ From intake of vegetables, bean soup, and pulses.

¹⁰ Confounding factors adjusted for age and intakes of antibiotics, zinc, animal fat, total energy, alcohol, vegetable fat, and red meat during the past year.

¹¹ Sum of genistein, daidzein, formononetin, and biochanin A.

¹² Confounding factors adjusted for total calories and age.

¹³ Confounding factors adjusted for age, family history of prostate cancer, alcohol intake, and total calorie intake.

¹⁴ Median intake between cases and controls.

Table 1. Two of these studies are quintile comparisons (11, 18), 4 are quartile comparisons (9, 13, 17, 20), 4 are tertile comparisons (12, 14, 15, 23), and 4 are a comparison between populations with and without soy consumption (16, 19, 21, 22). We extracted the most adjusted risk estimate of the highest reported category of intake relative to the lowest from these studies for comparison. For studies that compared differences between populations with or without soy consumption, we extracted the risk estimate from the soy-consuming population as the highest reported category of intake and that from the non-consuming population as the lowest reported category of intake for comparison. Because different types of soy foods were evaluated in these studies, some of which assessed more than one type of soy food, we chose the risk estimate for the food item that was representative of their soy consumption. These food items were prioritized in descending order of total soy foods or soy products, tofu, soy milk, miso, or natto. We also identified 9 publications [2 cohort studies (13, 14) and 7 case-control studies (16, 17, 24–28)] on isoflavones that met the inclusion criteria (**Table 2**). We excluded one study (25) because it presented results identical to those of a later publication (26). Five of these studies are quartile comparisons (13, 16, 17, 24, 26), and 1 each is a quintile comparison (27), tertile comparison (14), and comparison between populations with low and high intakes (28). Of these studies, 5 assessed isoflavones (14, 16, 24, 26, 27), and 3 evaluated genistein (13, 17, 28). Because genistein is a major soy isoflavone, we analyzed these 8 studies together.

Our analysis of the 14 studies on soy consumption and prostate cancer yielded a combined RR/OR of 0.74 (95% CI: 0.63, 0.89; $P = 0.01$). The results of the analysis are illustrated in **Figure 1**. The test of publication bias gave a P value of 0.16 with the Begg and Mazumdar test (7) and a P value of 0.05 with the test by

Egger et al (8). The study by Park et al (14) weighed 58% of the analysis because of its large sample size. Thus, we conducted a sensitivity analysis to determine its influence on the summary risk estimate. A sensitivity analysis excluding the study by Park et al (14) yielded a combined RR/OR of 0.71 (95% CI: 0.59, 0.87; $P = 0.01$) with $P = 0.20$ and $P = 0.26$ for publication bias by the Begg and Mazumdar (7) and the Egger et al (8) tests, respectively. A further analysis excluding 4 studies that compared differences between populations defined as “with” or “without” soy consumption (16, 19, 21, 22) yielded a combined RR/OR of 0.70 (95% CI: 0.53, 0.93; $P = 0.02$) with no publication bias detected.

One of the interests of the general public is whether differences exist between fermented and nonfermented soy foods in association with cancer, because there is a concern that fermented foods may be associated with cancer risk (23). To answer this question, we separately analyzed studies that provided data on nonfermented soy foods (tofu and soy milk) and those on fermented soy foods, including miso and natto. We identified 8 studies on tofu and soy milk (9, 11, 12, 15, 17, 19–21) (**Table 3**) and 6 on fermented soy foods (10, 12, 13, 20, 22, 23) (**Table 4**). Our analysis of studies on nonfermented soy foods yielded a combined RR/OR of 0.70 (95% CI: 0.56, 0.88; $P = 0.01$; **Figure 2A**), with $P = 0.04$ and $P = 0.03$ for publication bias by the Begg and Mazumdar (7) and Egger et al (8) tests, respectively. Funnel plots from the publication bias tests showed that studies by Jacobsen et al (9) and Li et al (15) contributed to the asymmetry. A sensitivity analysis excluding these 2 studies yielded a combined RR/OR of 0.77 (95% CI: 0.64, 0.93; $P = 0.01$) with $P = 1.0$ and $P = 0.40$ for publication bias by the Begg and Mazumdar (7) and the Egger et al (8) tests, respectively. A further analysis excluding studies that compared

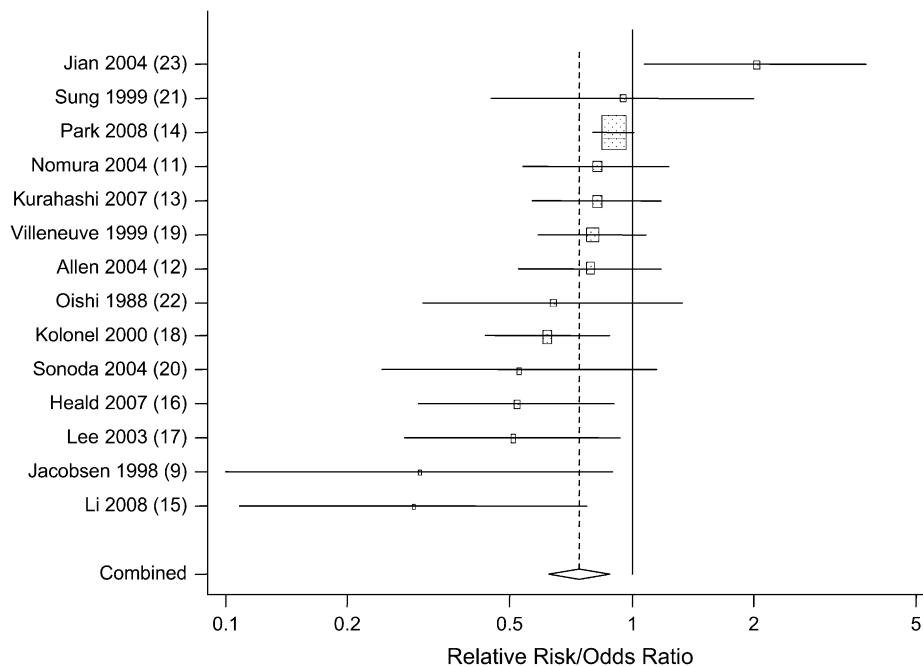


FIGURE 1. Consumption of soy foods in association with prostate cancer risk in men. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a horizontal line through the box. The vertical dashed line and the lower vertex of the diamond indicate the combined relative risk and odds ratio of the analysis, and the left and right vertices of the diamond represent its 95% CI. The results of the analysis using the random-effects model (6) yielded a combined relative risk and odds ratio of 0.74 (95% CI: 0.63, 0.89; $P = 0.01$).

TABLE 3
Epidemiologic studies on consumption of nonfermented soy foods in association with prostate cancer risk in men¹

Reference	Design	Description of study	Soy food assessed	Intake comparison ²	RR/OR (95% CI)
Allen et al (12) ³	Cohort	196 incident cases/18,115 cohort size, Japanese, Japan	Tofu	<2 times/wk vs almost daily	0.88 (0.58, 1.35)
Nomura et al (11) ⁴	Cohort	304 incident cases/5826 cohort size, Japanese American, United States	Tofu	0 vs >240 g/wk	0.82 (0.54, 1.23)
Jacobsen et al (9) ⁵	Cohort	225 incident cases/12,295 cohort size, Seventh-Day Adventist men, United States	Soy milk	Never vs >1 time/d	0.3 (0.1, 0.9)
Li et al (15) ⁶	C-C	28 cases/280 controls, Chinese, China	Tofu and soy milk	≤2 times/wk vs ≥1 time/d	0.29 (0.11, 0.79)
Sonoda et al (20) ⁷	C-C	140 cases/140 controls, Japanese, Japan	Tofu	≤19.7 vs ≥96.4 g/d	0.47 (0.20, 1.08)
Lee et al (17) ⁸	C-C	133 cases/265 controls, Chinese, China	Tofu	<14.3 vs >34.5 g/d	0.58 (0.35, 0.96)
Villeneuve et al (19) ⁹	C-C	1623 cases/1623 controls, multiethnic, Canada	Tofu	None vs some/wk	0.8 (0.6, 1.1)
Sung et al (21)	C-C	90 cases/180 controls, Chinese, Taiwan	Soybean milk	No vs yes	0.95 (0.45, 2.00)

¹ RR/OR, combined relative risk/odds ratio; C-C, case-control.² The highest reported category of intake compared with the lowest category of intake.³ Confounding factors adjusted for age, calendar period, city of residence, radiation dose, and education level.⁴ Confounding factors adjusted for age, cigarette smoking, alcohol intake, total calories, arm muscle area, and BMI.⁵ Confounding factors adjusted for age, BMI, age at first marriage, and frequency of consumption of coffee, whole-fat milk, eggs, and citrus fruit.⁶ Confounding factors adjusted for education level, BMI, smoking, alcohol consumption, and food frequency.⁷ Confounding factors adjusted for cigarette smoking and energy intake.⁸ Confounding factors adjusted for total calories and age.⁹ Confounding factors adjusted for age, province of residency, race, years since quitting smoking, cigarette pack-years, BMI, rice and pasta, coffee, grains and cereals, alcohol, fruit and fruit juices, tofu, meat, income, and family history of cancer.

populations with or without soy consumption (19, 21) yielded a combined RR/OR of 0.74 (95% CI: 0.58, 0.94; $P = 0.02$) with no publication bias detected. Results from the analysis of fermented soy foods showed a combined RR/OR of 1.02 (95% CI: 0.73, 1.42; $P = 0.92$) (Figure 2B) and from that excluding one study that compared populations with or without soy intake (22) yielded a combined RR/OR of 1.10 (95% CI: 0.76, 1.57; $P = 0.62$); no publication bias was detected in either analysis.

The analysis of the 8 studies on isoflavones yielded a combined RR/OR of 0.88 (95% CI: 0.76, 1.02; $P = 0.09$) with no publication bias detected by either method (7, 8). The results of this analysis are illustrated in Figure 3. A further analysis excluding the study (28) that compared populations with the low and the high intakes of isoflavones yielded a combined RR/OR of 0.85 (95% CI: 0.68, 1.06; $P = 0.15$) with no publication bias detected. We further analyzed studies conducted in Asian countries (13,

TABLE 4
Epidemiologic studies on consumption of fermented soy foods in association with prostate cancer risk in men¹

Reference	Design	Description of study	Soy food assessed	Intake comparison ²	RR/OR (95% CI)
Kurahashi et al (13) ³	Cohort	307 incident cases/43,509 cohort size, Japanese, Japan	Miso soup	≤110 mL/d vs ≥356 mL/d	1.04 (0.72, 1.50)
Allen et al (12) ⁴	Cohort	196 incident cases/18,115 cohort size, Japanese, Japan	Miso soup	<2 times/wk vs almost daily	0.94 (0.67, 1.33)
Severson et al (10) ⁵	Cohort	174 incident cases/7999 cohort size, Japanese American, United States	Miso soup	≤1 time/wk vs ≥5 times/wk	1.24 (0.51, 3.04)
Sonoda et al (20) ⁶	C-C	140 cases/140 controls, Japanese, Japan	Natto	≤5.7 g/d vs ≥40 g/d	0.25 (0.05, 1.24)
Jian et al (23) ⁷	C-C	130 cases/274 controls, Chinese, China	Fermented and stinking bean curd	0 vs 4 g/d	2.02 (1.08, 3.78)
Oishi et al (22)	C-C	100 cases/100 controls, Japanese, Japan	Miso soup	Low vs high intake	0.64 (0.31, 1.34)

¹ RR/OR, combined relative risk/odds ratio; C-C, case-control.² The highest reported category of intake compared with the lowest category of intake.³ Confounding factors adjusted for age, area, smoking status, drinking frequency, marital status, BMI, and intake of total fatty acids, dairy products, vegetables, and fruit.⁴ Confounding factors adjusted for age, calendar period, city of residence, radiation dose, and education level.⁵ Confounding factors adjusted for age.⁶ Confounding factors adjusted for cigarette smoking and energy intake.⁷ Confounding factors adjusted for age, BMI, physical activity, residence, education level, family income, marital status, prostate cancer in first-degree relatives, fresh vegetable and fruit consumption, and tea drinking.

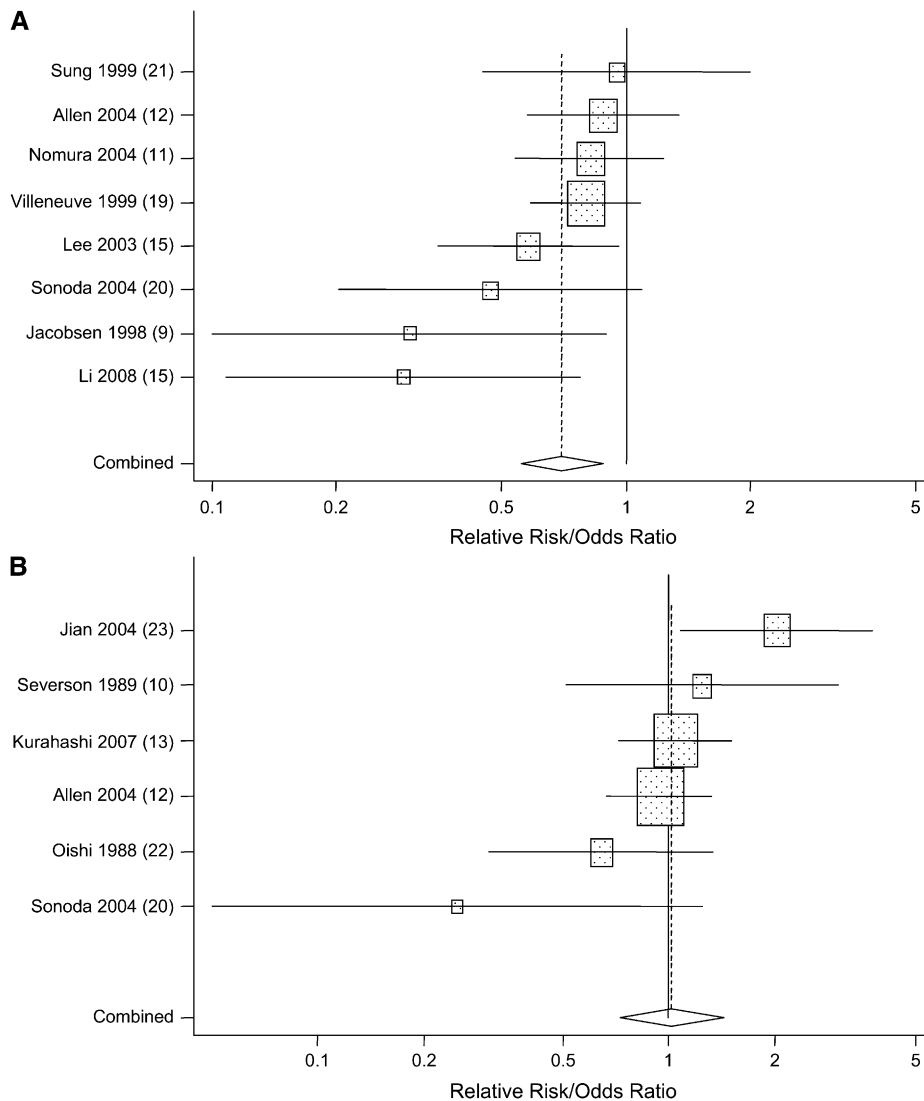


FIGURE 2. Consumption of nonfermented (A) and fermented (B) soy foods in association with prostate cancer risk in men. The combined relative risk and odds ratio of the analysis for nonfermented soy foods was 0.70 (95% CI: 0.56, 0.88; $P = 0.01$). The combined relative risk and odds ratio of the analysis for fermented soy foods was 1.02 (95% CI: 0.73, 1.42; $P = 0.92$). Both analyses used the random-effects model (6).

17, 24) and studies conducted in European countries (16, 26, 27) and in the United States in whites (28). Our analysis of studies in Asian populations yielded a combined RR/OR of 0.52 (95% CI: 0.34, 0.81; $P = 0.01$) and that in Western populations yielded a combined RR/OR of 0.99 (95% CI: 0.85, 1.16; $P = 0.91$); no publication bias was detected in either analysis.

DISCUSSION

The results of the present analysis of 14 studies showed that consumption of soy foods was associated with a reduction in prostate cancer risk of $\approx 26\%$ in men when the highest reported intake was compared with the lowest reported intake. We found similar results in the sensitivity analysis, in which the study (14) that weighed the most heavily in the analysis and the studies (16, 19, 21, 22) that only compared populations with or without soy consumption were not included, which indicated that these studies did not drastically influence the summary risk estimate. The results of the present analysis are consistent with our pre-

vious meta-analysis of 8 studies (4) and strengthen its conclusion that soy consumption may be associated with a reduction in prostate cancer risk in men.

From the separate analysis of nonfermented soy foods and fermented soy foods, we found that consumption of tofu and soy milk was associated with a reduction in prostate cancer risk of $\approx 30\%$ when the highest reported category of intake was compared with the lowest reported category of intake, whereas intake of fermented soy foods was not associated with the risk. To our knowledge, no study has compared the effects of fermented soy foods with those of nonfermented soy foods on tumorigenesis in laboratory animals. Dietary supplementation with miso inhibits mammary (29), stomach (30), and colon carcinogenesis (31), but no such study has been conducted in a prostate model. Our results suggest that there are differences between these 2 types of soy foods. Because tofu, soy milk, miso, and natto are all commonly consumed soy foods, well-designed studies are warranted to better understand the roles and the differences between fermented and nonfermented soy foods in prostate cancer etiology and prevention.



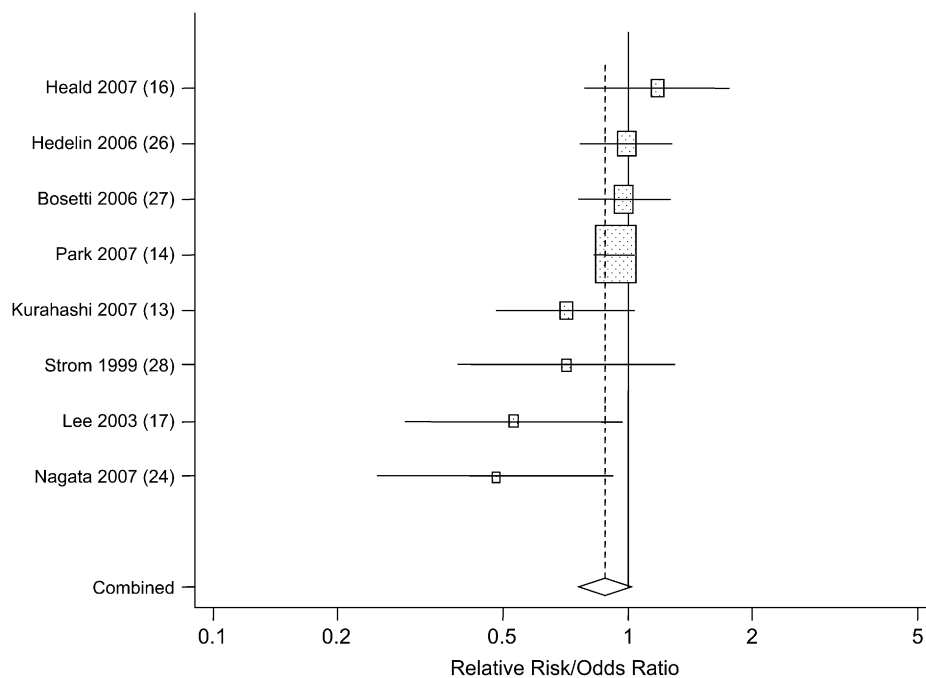


FIGURE 3. Isoflavone consumption in association with prostate cancer risk in men. The results of the analysis using the random-effects model (6) yielded a combined relative risk and odds ratio of 0.88 (95% CI: 0.76, 1.02; $P = 0.09$).

Our analysis of studies on isoflavone consumption showed that isoflavones were marginally, but not significantly ($P = 0.09$), associated with a reduction in prostate cancer risk. However, the results of our separate analysis based on study populations showed a significant risk reduction from studies in the Asian populations, but not from those in the Western populations. These results are consistent with and are supported by findings from studies of serum isoflavones. For example, results from 2 nested case-control studies in Japan showed that plasma (32) and serum genistein and daidzein (33) are associated with a reduction in prostate cancer risk in Japanese men when the highest reported subgroup of plasma or serum isoflavones was compared with the lowest, and a significant reduction was observed with serum equol (33)—a metabolite of daidzein. However, results from 2 case-control studies in the United Kingdom with Western populations showed that serum isoflavones are not associated with prostate cancer risk (16, 34). Interestingly, the estimated isoflavone intakes from the studies we analyzed in Asian populations are all reported in mg/d, which is consistent with the reported intakes in Asians (35), whereas, those from studies in Western populations are all reported in $\mu\text{g}/\text{d}$. Clearly, there is a difference in isoflavone intake from diet between these 2 populations. Whereas the available literature on isoflavones and cancer remains limited, results from the studies we analyzed provide evidence of the difference in isoflavone intakes between the Asian and the Western populations and the effect of this difference on the risk of prostate cancer. Furthermore, of the studies we analyzed, 4 provide results on both soy and isoflavones (13, 14, 16, 17). Results from 3 of these studies are internally compatible concerning the association of soy and isoflavone intakes with prostate cancer risk (13, 14, 17), but one study conducted in Scotland is not (16). It should be noted that soy is not the only plant food that provides isoflavones. In fact, isoflavones in many Western diets come from various food

sources in addition to soy (36). Thus, some caution should be used in interpreting isoflavone intake in relation to soy consumption.

The inverse associations between soy consumption and prostate cancer risk from the epidemiologic studies are supported by animal studies showing that dietary soy protein (37, 38) and soy phytochemical extracts (39) inhibit experimentally induced prostate tumorigenesis. However, a study also shows that soy protein increases prostate tumor growth in an androgen-independent model (40). Genistein, a major soy isoflavone, inhibits prostate tumor development in animals (41, 42) and proliferation of prostate cancer cells in culture (43, 44). The proposed anticancer mechanisms of isoflavones may be associated with an inhibition in 5- α reductase activity (45) and an increase in vitamin D concentrations in prostate tissue (46). Intervention studies in human subjects are limited and the results are inconsistent. Soy protein does not affect prostate-specific antigen concentrations in healthy subjects (47, 48). Some studies have shown that soy protein reduces prostate specific antigen concentrations (49) and isoflavones (50) increase prostate specific antigen doubling time in prostate cancer patients, whereas others have shown no such effects (51, 52). Current ongoing clinical trials (53) of soy protein in prostate cancer patients, on their completion, may help us further understand the role of soy in prostate cancer prevention.

The present analysis provided a quantitative evaluation of available epidemiologic studies on soy intake and prostate cancer risk in men. Like all meta-analyses, it has limitations. The first is the potential publication bias. We detected publication bias from the analyses that included the study with a large sample size (14) or studies (9, 15) that contributed to the asymmetry of the funnel plot of the tests (7, 8). We corrected the bias accordingly using the sensitivity analysis with these studies excluded so an approximate symmetry could be formed with the funnel plot.

Results from the sensitivity analysis were very similar to those of the original meta-analysis, and there was no change in the level of statistical significance. This suggests that observed potential bias did not affect the summary measures to a large extent. However, it should be kept in mind that the present analysis used published studies, which may be more likely to report statistically significant results. The second limitation is the heterogeneity of the available data. For example, most studies, particularly those published in early years, were not specifically designed to study soy, and the way the soy intake was quantified and the extent to which confounding factors were controlled differed across studies. Whereas the present analysis used the random-effects model (6), which considers the statistical heterogeneity in its calculation of summary measures, this limitation may complicate the interpretation of the results.

In summary, the results of the present analysis of the up-to-date available epidemiologic studies suggest that consumption of soy foods is associated with a reduction in prostate cancer risk in men. Our results from analyses of nonfermented soy foods and isoflavones support this food-disease relation and suggest that this protection is related to the type and quantity of soy foods consumed. With an ever-increasing awareness and interest in diet and cancer prevention, well-designed investigations on soy and prostate cancer are warranted.

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