

Research Article

Soy Consumption and Colorectal Cancer Risk in Humans: A Meta-Analysis

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Abstract

The purpose of the present study was to determine the relationship between soy consumption and colorectal cancer risk in humans by conducting a meta-analysis of available epidemiologic studies. We systematically reviewed publications obtained through a Medline literature search and identified four cohort and seven case-control studies on soy and colorectal cancer risk that met the inclusion criteria. We extracted the risk estimate (hazard ratio, relative risk, or odds ratio) of the highest and the lowest reported categories of intake from each study and conducted this analysis using a random-effects model. Our analysis did not find that soy consumption was associated with colorectal cancer risk [combined risk estimate, 0.90; 95% confidence interval (95% CI), 0.79-1.03] nor did the separate analyses on colon cancer (combined risk estimate, 0.88; 95% CI, 0.74-1.06) and rectal cancer (combined risk estimate, 0.88; 95% CI, 0.67-1.14). However, when separately analyzed on the basis of gender, we found that soy was associated with an approximately 21% reduction in colorectal cancer risk in women (combined risk estimate, 0.79; 95% CI, 0.65-0.97; $P = 0.026$), but not in men (combined risk estimate, 1.10; 95% CI, 0.90-1.33). Thus, consumption of soy foods may be associated with a reduction in colorectal cancer risk in women, but not in men. *Cancer Epidemiol Biomarkers Prev*; 19(1); 148–58. ©2010 AACR.

Introduction

The role of diet in the etiology of colorectal cancer, the third leading cause of death by cancer in both men and women in the United States (1), remains an area of active research. The age-standardized incidence rate of colorectal cancer in Asian countries (e.g., China) is lower than that in North America and European countries (2), and the incidence increases substantially in migrants from low-risk to high-risk areas (3, 4). These observations indicate that differences in lifestyle, including dietary practices, between the Eastern and the Western populations may play a role in colorectal cancer etiology.

Soy is a major plant source of dietary protein for humans. An early review of epidemiologic studies (most of which were case-control studies published before 2000) suggested an inverse association between high soy intake

and colon cancer risk in humans (5). In recent years, studies with relatively large study populations specifically designed to assess soy consumption in association with colorectal cancer risk have been conducted, some of which showed a significant inverse association (6, 7). Furthermore, soy diets inhibit chemically induced colon tumorigenesis in animals (8, 9), and isoflavones, a group of bioactive components in soy, may play a role in this inhibitory process (10). There are hardly any clinical studies of the relation between soy and colorectal cancer (11, 12).

The purpose of the present study was to conduct meta-analyses of currently available epidemiologic studies of the association between consumption of soy and colorectal cancer risk to provide a quantitative evaluation in a standardized format that permitted a numerical analysis across studies.

Materials and Methods

We conducted a Medline search, supplemented with a hand-search of article bibliographies and non-indexed medical and professional journals reporting epidemiologic studies that provided quantitative data on soy and colorectal cancer. We used the following terms in combination for the literature search: soy (tofu, soymilk, miso, natto), isoflavones (genistein, daidzein), colorectal cancer (colon, rectum), and epidemiology (cohort, case-control). In addition, we conducted a broader search on diet and colorectal cancer aimed at identifying studies in which the aforementioned terms were not included in abstracts. Furthermore, we contacted investigators for unpublished results that might be useful for the

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analysis. The search was conducted through May 31, 2009. We systematically reviewed and examined whether the identified studies met the following criteria to be included in the analysis: a study (cohort or case-control) must have had soy consumption assessed as a food and/or isoflavone consumption assessed from food intake; it must have provided a risk estimate [hazard ratio, relative risk, or odds ratio (OR)] for colorectal, colon, or rectal cancer incidence as well as its 95% confidence interval (95% CI); and it must have provided information on adjustment for confounding factors. From the results of these studies, we extracted the risk estimate of the highest relative to the lowest intake for the analysis.

The hazard ratio and relative risk were taken to be approximations to OR, and the meta-analysis was done as if all types of ratio were odds ratios. This was justified by the fact that colorectal cancer had a relatively low incidence over the periods of time studied. We calculated the combined risk estimate using a random-effects model in which the effect measures were log OR—weighed by the method of DerSimonian and Laird (13), giving greater weight in the summary measure to studies with smaller standard error of estimate. Furthermore, this model incorporated a test of heterogeneity (Q statistic) into its calculation by which it estimates the magnitude of the heterogeneity and assigns a greater variability to the estimate of overall treatment effect to account for this heterogeneity. We used the methods of Begg and Mazumdar (14) and Egger et al. (15) to detect publication bias. Both methods test for funnel plot asymmetry, the former (14) being based on the rank correlation between the effect estimates and their sampling variances, and the latter (15) 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 and to have the bias corrected. We used the Stata version 9.2 statistical program (StataCorp) for the analysis. All reported P values are from two-sided statistical tests, and differences with $P \leq 0.05$ were considered significant.

Results

We identified 11 studies on soy consumption and colorectal cancer incidence that met the inclusion criteria (Table 1). Four of these studies were cohort studies (6, 7, 16, 17), and seven were case-control studies (18-24). Furthermore, we identified four studies that assessed soy intake and colorectal cancer mortality (Table 1; refs. 25-28). Food frequency questionnaire was the method of dietary assessment in all of these studies. Because different types of soy foods were evaluated in these studies and some assessed more than one type of soy food, we chose the risk estimate of a measurement in these studies that was the most representative of overall soy consumption or a soy food item that was the most commonly consumed for the analysis. These measurements were prioritized in

descending order of total soy foods or soy products, tofu (bean curd) or miso soup (soy paste soup). We also identified three cohort (6, 7, 17) and three case-control studies (29-31) that assessed isoflavone intake in association with colorectal cancer incidence (Table 2). Seven studies separately presented findings for men and women (7, 17, 19, 22, 25, 26, 28), and one study separately reported results for risk of proximal and distal colon cancer (22). We included data from both men and women and from both proximal and distal colon cancer as independent populations in this analysis. Four studies were excluded from this analysis, one that assessed soy together with other legumes as one food group (32), one that evaluated soy together with vegetables and fruits as a dietary pattern (33), and two that provided no information on confounding factors (34, 35).

Our analysis of the 11 studies that assessed soy and colorectal cancer incidence (6, 7, 16-24) yielded a combined risk estimate of 0.90 (95% CI, 0.79-1.03; $P = 0.134$) and test of heterogeneity $Q = 35.75$ ($P = 0.011$; Fig. 1). The results of our analysis of the four studies on soy and colorectal cancer mortality (25-28) showed a combined risk estimate of 0.98 (95% CI, 0.85-1.14; $P = 0.790$), with $Q = 14.63$ ($P = 0.102$). No publication bias was detected in either analysis by the tests of Begg and Mazumdar (14) and Egger et al. (15), respectively.

Of the 11 studies we analyzed, six separately provided data on women (6, 7, 16, 17, 19, 22) and four on men (7, 17, 19, 22). Our analysis of the six studies on women yielded a combined risk estimate of 0.79 (95% CI, 0.65-0.97; $P = 0.026$) with $Q = 10.92$ ($P = 0.142$; Fig. 2A), and that of the four studies on men yielded a combined risk estimate of 1.10 (95% CI, 0.90-1.33; $P = 0.358$) with $Q = 6.51$ ($P = 0.260$; Fig. 2B). Publication bias was detected in neither analysis.

We further separately analyzed studies that separately provided data on colon cancer and rectal cancer. Seven studies provided data on colon cancer (6, 7, 17, 20, 22-24), and our analysis of these studies yielded a combined risk estimate of 0.88 (95% CI, 0.74-1.06; $P = 0.175$) with $Q = 20.81$ ($P = 0.035$). Five studies provided data on rectal cancer (6, 17, 20, 22, 23), and our analysis of these studies yielded a combined risk estimate of 0.88 (95% CI, 0.67-1.14; $P = 0.329$) with $Q = 12.32$ ($P = 0.055$). No publication bias was detected in either analysis.

Because there were differences in study types (cohort or case-control), study populations (Asians or non-Asians), and types of soy foods assessed (soy foods or products, tofu or miso) among the studies we analyzed, we further conducted stratified analyses to determine the impact of these influences on our analysis. The results of these stratified analyses are in Table 3. Noteworthy, for the category of soy foods/products (6, 7, 17, 23) and of miso (17, 18, 20, 22-24), combined risk estimates were found of 0.79 (95% CI, 0.62-1.00; $P = 0.047$) and 0.89 (95% CI, 0.82-0.97; $P = 0.008$), respectively, whereas the combined risk estimate for tofu (16, 18-22) was not significant (0.97; 95% CI, 0.83-1.13; $P = 0.689$), all without publication bias being detected.

Table 1. Epidemiologic studies on soy consumption in association with colorectal cancer risk

| Reference | Design | Description of study | Soy food assessed | Intake comparison* | HR/RR/OR (95% CI) | Confounding factors adjusted |
|---|--------|--|---------------------------|--|---|---|
| Studies that assessed colorectal cancer incidence | | | | | | |
| Yang et al. 2009 (6) | Cohort | 321 incident cases/68,412 cohort size, Chinese, China | Soy foods [†] | ≤12.8 vs >21.0 g/d | Colorectal 0.67 (0.49-0.90) women Colon 0.76 (0.52-1.13) women Rectum 0.55 (0.34-0.90) women | Age, education, household income, physical activity, BMI, menopausal status, family history of colorectal cancer, total caloric intake, and average intakes of fruit, vegetables, red meat, nonsoy calcium, nonsoy fiber, and nonsoy folic acid. |
| Wang et al. 2009 (16) | Cohort | 301 incident cases/38,408 cohort size, female U.S. health professionals, United States | Tofu | <1 time/mo vs ≥1 time/wk | Colorectal 0.54 (0.20-1.46) women | Age, race, total energy intake, randomized treatment assignment, smoking, alcohol use, physical activity, postmenopausal status, hormone replacement therapy use, multivitamin use, BMI, family history of colorectal cancer, ovary cancer or breast cancer, and intake of fruit and vegetables, fiber, folate and saturated fat. |
| Akhter et al. 2008 (17) | Cohort | 886 incident cases/83,063 cohort size, Japanese, Japan | Soy foods [‡] | ≤35.4 vs >169.9 g/d, men ≤35.6 vs >170.3 g/d, women | Colorectal 0.89 (0.68-1.17) men 1.04 (0.76-1.42) women Colon 0.77 (0.55-1.06) men 1.11 (0.77-1.60) women Rectum 1.20 (0.74-1.95) men 0.90 (0.50-1.62) women | Age, public health center area, history of diabetes mellitus, BMI, leisure time physical activity, cigarette smoking, alcohol drinking, and intake of vitamin D, dairy products, meats, vegetable, fruit and fish. Also adjusted for menopausal status and current use of female hormones in women. |
| | | | Miso | Never vs daily | Colorectal 0.88 (0.64-1.10) men 1.03 (0.75-1.43) women | |
| Oba et al. 2007 (7) | Cohort | 213 incident cases/30,221 cohort size, Japanese, Japan | Soy products [§] | ≤49.22 vs >141.09 g/d, men ≤46.29 vs >128.03 g/d, women | Colon 1.24 (0.77-2.00) men 0.56 (0.34-0.92) women | Age, height, alcohol intake, smoking status, BMI, physical exercise, coffee intake, and use of hormone replacement therapy (women only). |

(Continued on the following page)

Table 1. Epidemiologic studies on soy consumption in association with colorectal cancer risk (Cont'd)

| Reference | Design | Description of study | Soy food assessed | Intake comparison* | HR/RR/OR (95% CI) | Confounding factors adjusted |
|------------------------------|--------|---|--|---|--|--|
| Huang et al. 2004 (18) | C-C | 1,352 cases/ 50,706 controls, Japanese, Japan | Bean curd Miso soup | <3 vs ≥3 times/wk <1 time/d vs ≥1 time/d | Colorectal 1.11 (0.92-1.33) Colorectal 0.89 (0.79-1.00) | Age and sex. |
| Le Marchand et al. 1997 (19) | C-C | 1,192 cases/ 1,192 controls, multi-ethnic, United States | Tofu | 0 vs ≥25 g/d | Colorectal 1.0 (0.6-1.6) men 0.9 (0.5-1.5) women | Age, family history of colorectal cancer, alcoholic drink per week, pack-years of cigarette smoking, lifetime recreational activity, Quetelet index 5 y earlier, total calories, egg and calcium intake. |
| Nishi et al. 1997 (20) | C-C | 330 cases/ 660 controls, Japanese, Japan | Tofu Miso soup | <3 vs ≥3 times/wk <3 vs 3 times/d | Colon 0.79 (0.55-1.13) Rectum 1.02 (0.67-1.53) Colon 0.69 (0.42-1.16) Rectum 0.93 (0.54-1.60) | Age, sex and registered residence. |
| Witte et al. 1996 (21) | C-C | 488 cases/ 488 controls, multi-ethnic, United States | Tofu or soybeans | None vs ≥1 serving/wk | Colorectal 0.55 (0.27-1.11) | Race, BMI, physical activity, smoking, calories, saturated fat, dietary fiber, folate, β-carotene and vitamin C. |
| Inoue et al. 1995 (22) | C-C | 432 cases/ 31,782 controls, Japanese, Japan | Bean curd Soybean paste soup | ≤3 vs >3 times/wk ≤3 vs >3 times/wk | Proximal colon 0.9 (0.5-1.6) men 1.3 (0.7-2.4) women Distal colon 1.7 (1.0-2.6) men 0.6 (0.4-1.0) women Rectum 1.2 (0.8-1.7) men 0.9 (0.6-1.5) women Proximal colon 1.2 (0.6-2.2) men 0.8 (0.4-1.4) women Distal colon 0.7 (0.4-1.1) men 0.8 (0.5-1.3) women Rectum 0.8 (0.6-1.2) men 1.1 (0.7-1.8) women | Age. |
| Hoshiyama et al. 1993 (23) | C-C | 181 cases/ 653 controls, Japanese, Japan | Soybean products Miso soup | ≤4 vs ≥8 times/wk <1 cup/d vs ≥2 cups/d | Colon 0.6 (0.3-1.3) Rectum 0.4 (0.2-1.0) Colon 1.9 (0.8-4.4) Rectum 0.8 (0.4-1.6) | Sex and age for colon cancer and selected food items, sex and age for rectal cancer. |

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Table 1. Epidemiologic studies on soy consumption in association with colorectal cancer risk (Cont'd)

| Reference | Design | Description of study | Soy food assessed | Intake comparison* | HR/RR/OR (95% CI) | Confounding factors adjusted |
|---|--------|---|---------------------------|--|---|---|
| Kono et al. 1993 (24) | C-C | 187 cases/1,557 controls, Japanese, Japan | Soy paste soup | <1 vs ≥ 2 bowls/d | Colon 0.87 (0.55-1.37) | Smoking, alcohol use, rank and BMI. |
| Studies that assessed colorectal cancer mortality | | | | | | |
| Iso and Kubota 2007 (25) | Cohort | 648 incident cases/104,742 cohort size, Japanese, Japan | Tofu | <3 vs ≥ 5 times/wk | Colon 1.12 (0.78-1.62) men 0.87 (0.60-1.26) women Rectum 1.21 (0.81-1.83) men 1.00 (0.60-1.68) women | Age and area of study. |
| | | | Miso | 1 bowl/d vs ≥ 2 bowls/d | Colon 0.81 (0.56-1.17) men 0.82 (0.57-1.18) women Rectum 0.81 (0.54-1.23) men 0.93 (0.52-1.66) women | |
| Khan et al. 2004 (26) | Cohort | 3,158 cohort size [¶] , Japanese, Japan | Soybean curd | \leq several times/mo vs \geq several times/wk | Colorectal 1.5 (0.2-11.2) men 0.9 (0.1-6.9) women | Age and smoking status for men; age, health status, health education, health screening and smoking status for women. |
| Hirayama 1990 (27) | Cohort | 265,118 cohort size [¶] , Japanese, Japan | Soybean paste soup | Nondaily vs daily | Colon 1.13 (0.97-1.32) Rectum 1.04 (0.89-1.21) | Age and sex. |
| Ho et al. 2006 (28) | C-C | 870 cases/10,178 controls, Chinese, Hong Kong | Soy products [§] | <1 time/mo vs ≥ 4 times/wk | Colorectal 0.66 (0.40-1.08) men 0.47 (0.28-0.81) women | Age, educational attainment, leisure exercise, job type, alcohol consumption, smoking habits and consumption frequency of fruits, dairy products and Chinese tea. |

NOTE: If not specified, data are from both genders.

Abbreviations: HR, hazard ratio; RR, relative risk; C-C, case-control; BMI, body mass index.

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

[†]Soy foods: soy milk, tofu, fried tofu, dried or pressed tofu, fresh green soy beans, dry soy beans, soy sprouts, and other soy products.

[‡]Tofu, pre-drained tofu, freeze-dried tofu, deep-fried tofu, fermented soybean and soymilk.

[§]Tofu, miso, soybeans, natto, soymilk, okara, dried tofu, fried tofu, deep-fried tofu, and fried tofu with minced vegetables/seaweed.

[¶]Not specified.

[¶]Incident cases not reported.

The results of the analysis of the six studies on isoflavones (6, 7, 17, 29-31) showed a combined risk estimate of 0.76 (95% CI, 0.51-1.13; $P = 0.173$) with $Q = 146.06$ ($P = 0.001$) and $P = 0.711$ and $P = 0.034$ for publication bias by the methods of Begg and Mazumder (14) and Egger et al. (15), respectively. A sensitivity analysis excluding the Ravasco et al. study (31), which caused asymmetry of the funnel plot, yielded a combined risk estimate of 0.84

(95% CI, 0.72-0.98; $P = 0.025$) with $Q = 11.61$ ($P = 0.071$; Fig. 3) and $P = 0.133$ and $P = 0.116$ for publication bias by the Begg and Mazumder (14) and Egger et al. tests (15), respectively. We further carried out stratified analyses on the basis of study sites, because three of these studies were conducted in Asia (6, 7, 17) and the other three in Western countries with non-Asians (29-31). The results of these analyses, presented in Table 3, were suggestive of a

reduced risk in the non-Asian populations, but not in the studies of Asian populations.

Discussion

In the present study, we analyzed 11 epidemiologic studies (6, 7, 16-24) that assessed the association of soy

consumption with colorectal cancer incidence in humans. In two of these studies soy intake was found to be associated with a significant reduction in colorectal cancer risk in women (6, 7), whereas in the other nine studies no such association was observed in either women or men. Our combined analysis of these 11 studies showed that consumption of soy foods is not associated with the

Table 2. Epidemiologic studies on isoflavone consumption in association with colorectal cancer risk

| Reference | Design | Description of study | Isoflavones assessed | Intake comparison* | HR/RR/OR (95% CI) | Confounding factors adjusted |
|-----------------------------|--------|---|--------------------------|----------------------------|------------------------|---|
| Yang et al. 2009 (6) | Cohort | 321 incident cases/ 68,412 cohort size, Chinese, China | Isoflavones [†] | ≤15.1 vs >48.9 mg/d | 0.76 (0.56-1.01) women | Age, education, household income, physical activity, BMI, menopausal status, family history of colorectal cancer, total caloric intake, and average intakes of fruit, vegetables, red meat, nonsoy calcium, nonsoy fiber and nonsoy folic acid. |
| Akhter et al. 2008 (17) | Cohort | 886 incident cases/ 83,063 cohort size, Japanese, Japan | Genistein [†] | ≤9.1 vs >50.4 mg/d, men | 0.89 (0.67-1.17) men | Age, public health center area, history of diabetes mellitus, BMI, leisure time physical activity, cigarette smoking, alcohol drinking, and intake of vitamin D, dairy products, meats, vegetable, fruit and fish. Also adjusted for menopausal status and current use of female hormones in women. |
| | | | | ≤9.1 vs >49.7 mg/d, women | 1.07 (0.78-1.47) women | |
| Oba et al. 2007 (7) | Cohort | 213 incident cases/ 30,221 cohort size, Japanese, Japan | Isoflavones [†] | 22.45 vs 59.58 mg/d, men | 1.47 (0.90-2.40) men | Age, height, alcohol intake, smoking status, BMI, physical exercise, coffee intake, and the use of hormone replacement therapy (women only). |
| | | | | 21.65 vs 54.59 mg/d, women | 0.73 (0.44-1.18) women | |
| Cotterchio et al. 2006 (29) | C-C | 1,095 cases/ 1,890 controls, Canadian, Canada | Isoflavones [‡] | 0 vs >1.097 mg/d | 0.71 (0.58-0.86) | Age, sex, and total energy intake. |
| Rossi et al. 2006 (30) | C-C | 1,953 cases/ 4,154 controls, Italian, Italy | Isoflavones [‡] | ≤14.4 vs >33.9 µg/d | 0.76 (0.63-0.91) | Age, sex, study center, family history of colorectal cancer, education, alcohol consumption, BMI, occupational physical activity, and energy intake. |
| Ravasco et al. 2005 (31) | C-C | 70 cases/ 70 controls, Portuguese, Portugal | Isoflavones [‡] | ≤5 vs ≥20 mg/d | 0.30 (0.26-0.34) | Age, BMI, colorectal cancer in parents/sibling, smoking status, regular vigorous exercise, and co-morbidities. |

NOTE: If not specified, data are from both genders.

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

[†]Derived from intake of soy foods.

[‡]Derived from food intake (types of foods not specified).

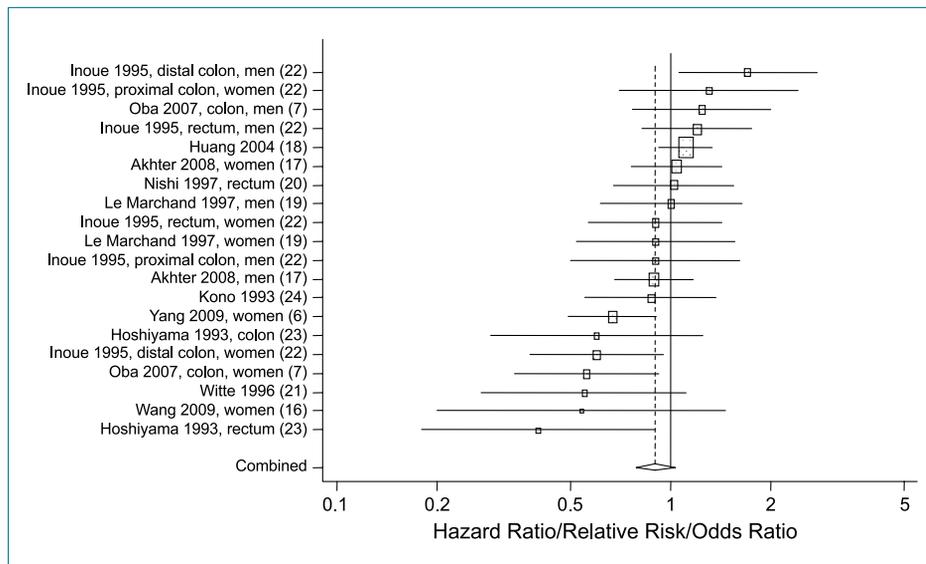


Figure 1. Consumption of soy foods in association with colorectal cancer risk. Each study specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a horizontal line through the box. The vertical dashed line and the lower vertex of the diamond indicate the combined risk estimate of the analysis, and the left and right vertices of the diamond represent its 95% confidence limits. Results of the analysis using the random-effects model (13) yielded a combined risk estimate of 0.90 (95% CI, 0.79-1.03; $P = 0.134$).

risk of colorectal cancer or colon or rectal cancer separately, and the results from our analysis of the four studies on soy and colorectal cancer mortality (25-28) support this finding.

In separate analyses of studies that provided data on the basis of gender, we found that soy consumption was associated with an approximately 21% reduction in colorectal cancer risk in women. This finding may be related to the structural and metabolic similarities of soy isoflavones to mammalian estrogens because of the following observations by others. Epidemiologic (36) and clinical studies (37) have shown a significant reduction in colorectal cancer risk in postmenopausal women who used hormone replacement therapies. In human samples, estrogen receptor gene expression was diminished or absent in colorectal tumors, and introduction of an exogenous estrogen receptor gene in cultured colon carcinoma cells resulted in marked growth suppression (38). Dietary supplementation with isoflavones increased estrogen receptor- β expression but reduced estrogen receptor- α expression in colon of female rats (39), and feeding soy protein to ovariectomized rats in combination with estrone treatment resulted in a greater inhibition of azoxymethane-induced colon tumorigenesis than soy protein alone (40).

We did not find that soy consumption was associated with colorectal cancer risk in men. There is strong evidence from laboratory studies that dietary supplementation with soy protein (8), soy flakes or soy flour (9), fermented miso (41), or soybean curd refuse (42) inhibits experimentally induced colon tumorigenesis in male rats, and soy isoflavones seem to play a role in this inhibition (10). The possible mechanisms include a decrease in colon fatty acid synthesis (43), a reduction in polyamine production (44), an induction of somatostatin (45), and an increase in fecal fat excretion (46). However, human

clinical studies are very limited. Although one small-scale intervention study showed that isoflavone-containing soy protein reduces crypt cell proliferation in colon mucosa biopsies from both male and female subjects with a history of colon polyps or colon cancer (11), another study did not show such a protective effect in men and women (12). Obviously, more clinical trials are warranted to investigate the role of soy intervention in colorectal cancer prevention in both genders.

Our analysis of six studies on isoflavones (6, 7, 17, 29-31) showed that isoflavone consumption was associated with an approximately 16% reduction in colorectal cancer risk. This significant risk reduction was largely attributable to three studies conducted in Western countries (29-31), which was also reflected in the results of the stratified analysis. However, in a recently completed study in the United Kingdom neither serum isoflavones (OR, 1.01; 95% CI, 0.94-1.08) nor urinary isoflavones (OR, 1.03; 95% CI, 0.95-1.11) were associated with colorectal cancer risk (47). Of the six studies we analyzed, Rossi et al. (30) and Cotterchio et al. (29) assessed isoflavone intakes at low $\mu\text{g}/\text{d}$ to low mg/d levels and reported a significant reduction in colorectal cancer risk. In contrast, all three studies conducted in Asian countries (6, 7, 17) reported intakes at levels in the range of several mg/d to $>50 \text{ mg}/\text{d}$, and none of those showed a significant risk reduction. Furthermore, all of the studies conducted in Western countries (29-31) were case-control studies with relatively small study populations, and none of them were designed to study soy. Thus, large-scale investigations specifically designed to study soy are warranted to understand the possible protective role of soy isoflavones in colorectal cancer development in Western populations.

We conducted stratified analyses of the 11 studies on soy and colorectal cancer risk to determine the impact of differences in study types, study populations, and

types of soy foods assessed on our analysis. Results from the analyses of studies by study types (cohort versus case-control) and by study populations (Asians versus non-Asians) were very similar to that from our analysis of the 11 studies. Of the 11 studies analyzed, 4 provided data on soy foods or soy products (6, 7, 17, 23), 6 on tofu (16, 18-22), and 6 on miso (17, 18, 20, 22-24). Results from the stratified analyses showed that soy foods/products and miso intakes were associated with a significant reduction in colorectal cancer risk, whereas tofu consumption was not associated with colorectal cancer risk. Both tofu and miso are the most commonly consumed soy foods in Asian countries, and many epidemiologic studies have used tofu (16, 25) or miso (27) as a marker of soy consumption. Of the four studies that reported intake of soy foods or soy products (6, 7, 17, 23), three included tofu (6, 7, 17) in the category of soy foods or soy pro-

ducts. Thus, caution should be taken in interpreting these results.

The present study provides a quantitative analysis of available epidemiologic studies on soy consumption and colorectal cancer risk in humans. We conducted stratified analyses, examined publication bias and had it corrected if detected, and used the random-effects model (13), which estimates the magnitude of the heterogeneity and assigns a greater variability to the combined risk estimate to account for the heterogeneity if detected. Like all meta-analyses, however, our analysis may have limitations. First, most of the studies, particularly the early case-control studies, were not designed solely to evaluate the association between soy consumption and colorectal cancer risk, and there were wide variations in dietary assessments among the studies. For example, of the 11 studies, only five reported the use

Figure 2. Consumption of soy foods in association with colorectal cancer risk in (A) women, with combined risk estimate of 0.79 (95% CI, 0.65-0.97; $P = 0.026$) and (B) men, with combined risk estimate: of 1.10 (95% CI, 0.90-1.33; $P = 0.358$). Both analyses were conducted using the random-effects model (13).

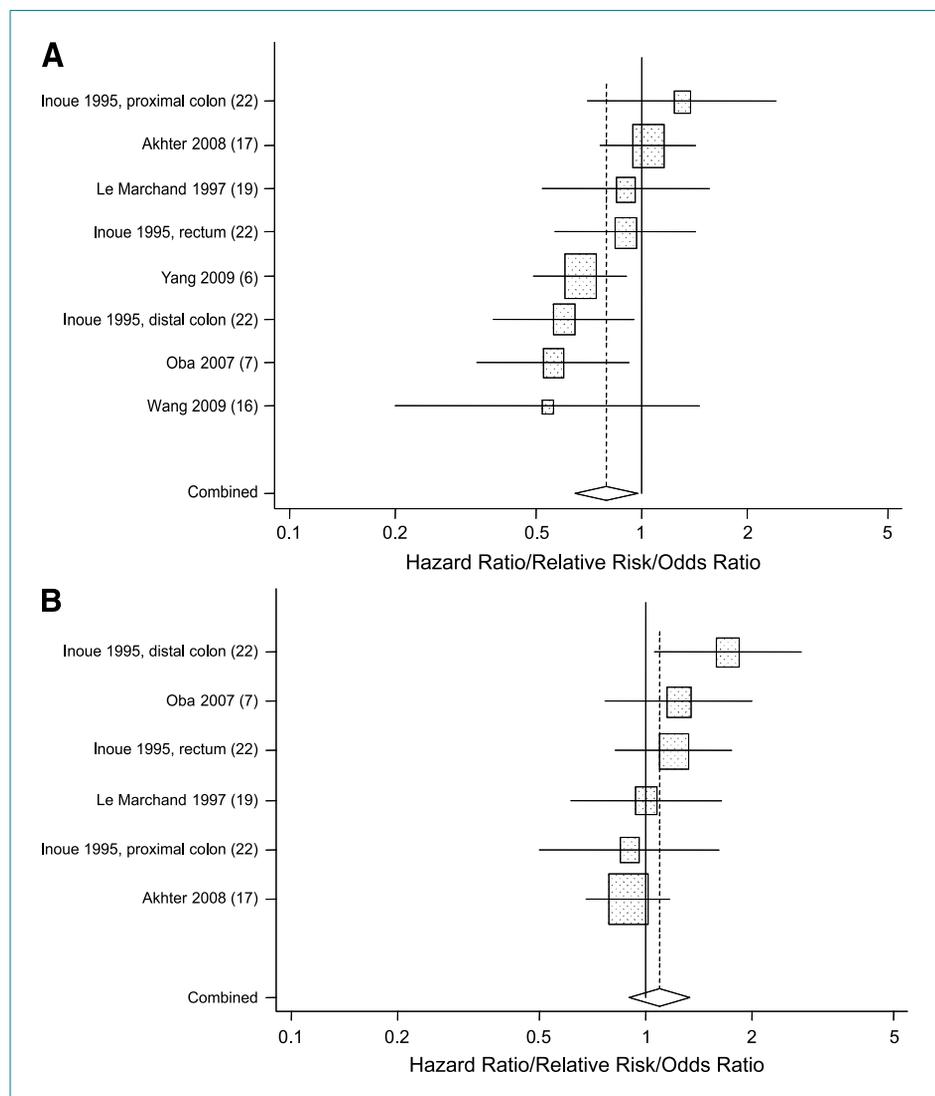


Table 3. Results of stratified analysis on the basis of study types, study populations and types of soy foods assessed

| | Combined risk estimate (95% CI) | P | Test of heterogeneity Q | P | Publication bias | References |
|----------------------------------|------------------------------------|-------|----------------------------|-------|------------------|---------------------------|
| All studies (n = 11) | 0.90 (0.79-1.03) | 0.134 | 35.75 | 0.011 | Not detected | (6, 7, 16-24) |
| Study types | | | | | | |
| Cohort (n = 4) | 0.83 (0.66-1.05) | 0.116 | 9.96 | 0.076 | Not detected | (6, 7, 16, 17) |
| Case-control (n = 7) | 0.95 (0.82-1.09) | 0.438 | 20.79 | 0.107 | Not detected | (18-24) |
| Study populations | | | | | | |
| Asians (n = 8) | 0.91 (0.79-1.05) | 0.191 | 33.16 | 0.070 | Not detected | (6, 7, 17, 18, 20, 22-24) |
| Non-Asians (n = 3) | 0.81 (0.60-1.11) | 0.189 | 2.64 | 0.450 | Not detected | (16, 19, 21) |
| Soy types | | | | | | |
| Soy foods/products (n = 4) | 0.79 (0.62-1.00) | 0.047 | 13.16 | 0.041 | Not detected | (6, 7, 17, 23) |
| Tofu (n = 6) | 0.97 (0.83-1.13) | 0.689 | 18.69 | 0.096 | Not detected | (16, 18-22) |
| Miso (n = 6) | 0.89 (0.82-0.97) | 0.008 | 8.042 | 0.841 | Not detected | (17, 18, 20, 22-24) |
| Study sites (isoflavone studies) | | | | | | |
| Asian (n = 3) | 0.93 (0.76-1.15) | 0.493 | 6.89 | 0.142 | Not detected | (6, 7, 17) |
| Western (n = 3) | 0.54 (0.29-1.04) | 0.064 | 86.14 | 0.001 | Not detected | (29-31) |

of a validated questionnaire (6, 7, 16, 17, 19) whereas the other studies did not provide such information. Most of the studies assessed frequency of intake, but only a few evaluated intake quantity, and the measurement units varied across the studies. Second, the studies varied in the number of potential confounding factors for which they had adjusted. Some cohort studies published in recent years provided detailed information of adjustment for confounders (6, 16, 17), whereas some early case-control studies adjusted for fewer such factors (18, 22). Third, the use of food frequency questionnaires in case-control studies, in which recall bias is an

inherent problem, may have affected the result of the analysis.

In summary, our analysis of currently available epidemiologic studies suggests that consumption of soy foods is associated with a reduction in colorectal cancer risk in women, but not in men. Considering that colorectal cancer is the third leading cause of death by cancer in both men and women in the United States (1), further investigations with strong dietary assessment tools and appropriate adjustment for confounding factors are warranted to evaluate the potentially protective role of dietary soy and isoflavones in colorectal cancer etiology.

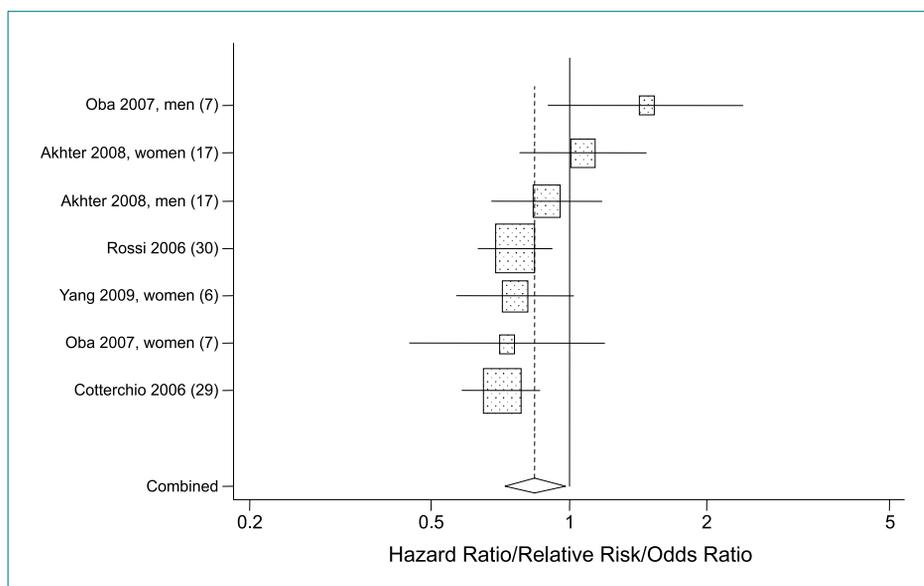


Figure 3. Isoflavone consumption in association with colorectal cancer risk. The combined risk estimate was 0.84 (95% CI, 0.72-0.98; $P = 0.025$) by the random-effects model (13).

Disclosure of Potential Conflicts of Interest

None of the authors had any conflicts of interest to report.

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