

## Meta-analysis of soy food and risk of prostate cancer in men

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There has been considerable interest in recent years in the role of soy in cancer etiology. The purpose of this meta-analysis was to evaluate epidemiologic studies available to date that related soy consumption to the risk of prostate cancer in men. We conducted a thorough Medline search for English-language publications, supplemented with hand-searching of articles' bibliographies and nonindexed medical and professional journals, on epidemiologic studies of soy and prostate cancer. We identified 2 cohort and 6 case-control studies that met the following criteria for meta-analysis: a study must have assessed soy as a food and provided a risk estimate (relative risk or odds ratio) and its 95% confidence interval. Data from the same study population appearing in different journals were only used once with the most recent publication chosen for the analysis. Studies on fermented soy food were not included. We conducted the meta-analysis using a random-effects model. An analysis of these studies yielded an overall risk estimate of 0.70 (95% CI = 0.59–0.83;  $p < 0.001$ ). No publication bias was detected. In summary, results of the analysis showed that consumption of soy food was associated with a lower risk of prostate cancer in men.

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**Key words:** epidemiology; meta-analysis; prostate cancer; soy

Prostate cancer is the second leading cause of cancer-related deaths for American men, exceeded only by lung cancer.<sup>1</sup> It has been suggested that differences in lifestyles, including dietary practice, affect the development of certain chronic diseases, including cancer. Epidemiologic studies suggest that populations consuming plant-based diets have a lower risk of certain cancers than those consuming animal-based diets. In recent years, soy has drawn considerable interest in both the research community and the general public in relation to the risk of cancer in humans. Soy has been a major source of dietary protein in Asians for centuries. Emerging findings from epidemiologic investigation suggest that consumption of soy food is associated with a reduced risk of prostate cancer. These findings have led to clinical and laboratory studies to investigate the efficacy and potential mechanisms of action whereby soy protein and other naturally occurring constituents of soy may lower the risk of prostate cancer.

A challenge commonly encountered when reviewing epidemiologic studies is the variation in magnitude of risk estimates from one study to another, which in turn makes it difficult to draw a general conclusion and establish a relationship. To our knowledge, there has not yet been any quantitative review of epidemiologic studies on soy and prostate cancer. The purpose of this study was to conduct a systematic review of available epidemiologic studies on soy consumption and the risk of prostate cancer and provide a quantitative evaluation in a standardized form permitting a numerical analysis across the studies.

### Material and methods

#### Identification of studies

We conducted a thorough Medline search for articles published in English, supplemented with hand-searching of articles' bibliographies and nonindexed medical and professional journals, on epidemiologic studies of soy and prostate cancer. We reviewed and determined whether the primarily identified studies met the following criteria for inclusion in the meta-analysis. A study must have assessed soy as a food in a form of soy food, soy protein, or soy isoflavones, with the latter 2 derived from the intake of soy

food. The study must have provided a relative risk (RR) or odds ratio (OR) and its 95% confidence interval (95% CI). Twelve studies met the criteria. Data from the same study population appearing in different journals<sup>2–5</sup> were only used once with the most recent publication chosen for meta-analysis.<sup>3,5</sup> Studies assessing fermented soy food were not included,<sup>6,7</sup> because fermented food may be related to the risk of certain cancers.<sup>8</sup> We finalized 8 studies that were qualified for meta-analysis. Two were cohort studies<sup>3,9</sup> and 6 were case-control studies.<sup>5,10–14</sup> Information regarding each of these studies is presented in Table I.

#### Statistical analysis

Because different types of soy food were assessed among the studies and some studies measured more than one type of soy food, we chose the risk estimate of the measurement that was the most representative of soy consumption or an individual item that was the most commonly consumed soy food for meta-analysis. These measurements were prioritized in descending order of total soy food or soy products, soy protein, soy isoflavones, bean curd (tofu) and soymilk. Strom *et al.*<sup>13</sup> assessed daidzein and genistein intake as measurements of soy intake. We chose the risk estimate of genistein for the analysis because genistein is the major isoflavone form in soy. An overall risk estimate was calculated using a random-effects model in which the effect measures are log relative risks or odds ratios weighed by the method of DerSimonian and Laird,<sup>15</sup> in which studies with smaller standard error of estimate are given greater weight in the summary measure. The trim-and-fill method by Duval and Tweedie<sup>16</sup> was performed to detect publication bias due to sampling bias or the systematic omission of difficult-to-find studies (published or unpublished). The statistical program Stata 8.2 (StataCorp, College Station, TX) was used for the analysis. All reported  $p$ -values are from 2-sided statistical tests.

### Results

Table I summarizes studies that met the criteria for meta-analysis. Cohort and case-control studies are separately presented in descending chronologic order. Five studies were completed in North America (United States and Canada) mainly with Caucasians,<sup>13</sup> Western European descendants,<sup>12</sup> multiethnic populations,<sup>11</sup> Seventh-Day Adventists,<sup>9</sup> and Japanese Americans.<sup>3</sup> Three were completed in Asian countries with Japanese<sup>10</sup> and Chinese.<sup>5,14</sup> The risk estimate (RR or OR) from these studies ranges from 0.3 to 0.95, and there is no study with a risk estimate  $\geq 1.0$ . The results are statistically significant in 3 studies.<sup>5,9,11</sup> Results of the meta-analysis yielded an overall risk estimate of 0.70 (95% CI = 0.59–0.83;  $p < 0.001$ ). No publication bias was detected. It suggests that the potential sampling bias is not large enough in our analysis to influence the conclusion drawn. Results of the meta-analysis are illustrated in Figure 1.

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TABLE 1 – DESCRIPTION OF EPIDEMIOLOGIC STUDIES ON SOY CONSUMPTION AND PROSTATE CANCER IN MEN

Reference	Design	Description of subjects, race and study site	Soy food assessed	Intake comparison	RR/OR (95% CI) <sup>1</sup>
Nomura <i>et al.</i> <sup>3</sup> (2004) <sup>3</sup>	Cohort	304 incident cases/5,826 cohorts, Japanese American men, United States	Tofu	0 vs. > 240 g/day	0.82 (0.54–1.23)
Jacobsen <i>et al.</i> <sup>9</sup> (1998) <sup>4</sup>	Cohort	225 incident cases/12,295 cohorts, Seventh-Day Adventist men, United States	Soy milk	Never vs. > 1 time/day	0.30 (0.10–0.90)
Sonoda <i>et al.</i> <sup>10</sup> (2004) <sup>5</sup>	C-C <sup>2</sup>	140 cases/140 controls, Japanese, Japan	Soy products	≤ 77 g/day vs. ≥ 187.2 g/day	0.53 (0.24–1.14)
Lee <i>et al.</i> <sup>5</sup> (2003) <sup>6</sup>	C-C	133 cases/265 controls, Chinese, China	Soy foods	< 27.5 g/day vs. > 111.8 g/day	0.51 (0.28–0.95)
Kolonel <i>et al.</i> <sup>11</sup> (2000) <sup>7</sup>	C-C	1,619 cases/1,618 controls, multiethnic population, <sup>10</sup> United States and Canada	Soyfoods	0 vs. 39.4 g/day	0.62 (0.44–0.89)
Villeneuve <i>et al.</i> <sup>12</sup> (1999) <sup>8</sup>	C-C	1,623 cases/1,623 controls, multiethnic population, <sup>11</sup> Canada	Tofu or soybean Genistein <sup>12</sup>	None vs. some No data	0.80 (0.60–1.10) 0.71 (0.39–1.30)
Strom <i>et al.</i> <sup>13</sup> (1999) <sup>9</sup>	C-C	83 cases/107 controls, Caucasian, United States	Soybean milk	No vs. yes	0.95 (0.45–2.00)
Sung <i>et al.</i> <sup>14</sup> (1999)	C-C	90 cases/180 controls, Chinese, Taiwan			

<sup>1</sup>RR/OR (95% CI): relative risk or odds ratio (95% confidence interval).<sup>2</sup>C-C: case-control. Confounding factors adjusted.<sup>3</sup>Age, cigarette smoking, alcohol intake, total calories, arm muscle area and body mass index.<sup>4</sup>Age, body mass index, frequency of consumption of coffee, whole fat milk, eggs and citrus fruits, age at first marriage.<sup>5</sup>Cigarette smoking and energy intake.<sup>6</sup>Age and total calories.<sup>7</sup>Age, education, ethnicity, geographic area and calories.<sup>8</sup>Age, province of residency, race, years since quitting smoking, cigarette pack-years, body mass index, rice and pasta, coffee, grains and cereals, alcohol, fruit and fruit juices, meat, income and family history of cancer.<sup>9</sup>Age, family history of prostate cancer, alcohol intake and total calorie intake.<sup>10</sup>African American, white, Chinese and Japanese.<sup>11</sup>Western European and Asian descents, aboriginal, black, Indian and others.<sup>12</sup>Estimated from intake of soy-containing foods.

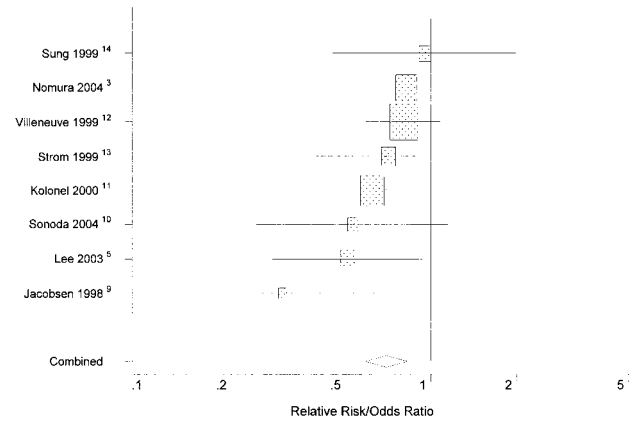


FIGURE 1 – Soy consumption in relation to prostate cancer risk in men. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a horizontal line through the box. The vertical dashed line and the lower vertex of the diamond indicate the overall risk estimate of the analysis, and left and right vertices of the diamond represent its 95% CI. The overall risk estimate of the analysis was 0.70 (95% CI = 0.59–0.83;  $p < 0.001$ ).

## Discussion

We examined the relationship between soy intake and prostate cancer risk in men using epidemiologic studies that met the inclusion criteria for meta-analysis. Results of the analysis showed that consumption of soy food was related to an approximately 30% reduction in prostate cancer risk.

All studies involved in this meta-analysis were published in recent years. These studies were primarily designed to investigate the role of soy food in relation to prostate cancer risk or they assessed soy as a major food item of a dietary assessment in the investigation. The strength of these studies is that detailed information is provided in study design, including selection criteria for cases and controls and methods of data collection. Two of these studies are cohort studies with a  $\geq 15$ -year follow-up period.<sup>3,9</sup> In-person interviews were conducted in 4 studies during data collection.<sup>3,5,10,11</sup> Confounding factors were adjusted in most of these studies. Limitations to these studies include relatively small study populations ( $< 100$  cases)<sup>13,14</sup> and no adjustment for confounding factors in one case-control study.<sup>14</sup>

Results of our analysis are consistent with findings from a cross-national analysis of prostate cancer mortality in relation to nutritional and socioeconomic factors using data from 59 countries from United Nations sources.<sup>17</sup> In 42 countries from which the appropriate data are available, soy consumption is correlated with a significantly lower mortality rate from prostate cancer (regression coefficient =  $-0.62$ ;  $p = 0.0001$ ). The protection from soy is at least 4 times greater than that from any other dietary factor when data are analyzed on an effect size per kilocalorie basis.

Soy contains a relatively higher amount of isoflavones compared with other plant food sources. For this reason, investigators in recent years have used serum or urinary isoflavones as a marker of soy intake in human studies.<sup>18</sup> Ozasa *et al.*<sup>19</sup> conducted a case-control study nested in a cohort study and found that Japanese men with a higher serum level of isoflavones have a lower odds ratio of prostate cancer compared with those with a lower level of isoflavones. These results suggest that prostate cancer risk is inversely related to soy intake and are consistent with the findings from our meta-analysis.

Prostate-specific antigen (PSA) has been clinically used as a marker of prostate health. To our knowledge, there has not been any epidemiologic report on soy consumption in relation to changes in PSA concentrations in men. However, short-term studies are available. Dalais *et al.*<sup>20</sup> reported that soy intervention in

patients scheduled to undergo radical prostatectomy significantly decreases serum PSA level compared with the controls. Spentzos *et al.*<sup>21</sup> assessed soy intervention in patients who had already had primary therapy for prostate adenocarcinoma. A PSA reduction by 50% was the primary endpoint. No patient has a PSA reduction by 50%; however, there is a trend toward a longer PSA doubling time during the soy intervention. Kumar *et al.*<sup>22</sup> conducted an investigation with “watchful-waiting” patients. Soy protein intervention results in a serum PSA reduction in a greater number of subjects compared with the placebo, but the mean changes between the groups are not statistically significant. Studies with healthy older men show no significant difference in PSA reduction between soy proteins containing different levels of isoflavones.<sup>23,24</sup> Long-term interventions with larger study populations and a defined health status are warranted.

The exact mechanisms by which soy consumption is associated with a lower risk of prostate cancer remain to be elucidated. Sex

hormones have long been suspected to play a role in the development of prostate cancer. Short-term intervention studies show that serum sex hormone-binding globulin concentrations increase in men consuming tofu.<sup>25,26</sup> Nagata *et al.*<sup>27</sup> reported that serum total and free testosterone concentrations are inversely correlated with soy intake in Japanese men. Other studies show that there are no changes in serum sex hormones in men consuming soy food.<sup>28,29</sup> Laboratory investigations have revealed that dietary supplementation with isolated soy protein inhibits experimentally induced development and growth of prostate tumor in animals.<sup>30–32</sup> The likely mechanisms related to the inhibition may include a reduction in cell proliferation and angiogenesis and an increase in apoptosis.<sup>30–32</sup>

In summary, the results of our meta-analysis of available epidemiologic studies demonstrated that consumption of soy food was related to a lower risk of prostate cancer in men.

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