Meta-Analysis of Soy Intake and Breast Cancer Risk

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Background: High intake of soy foods has been proposed to contribute to the low breast cancer risk in Asian countries. However, results of epidemiologic studies of this association are highly variable, and experimental data suggest that soy constituents can be estrogenic and potentially risk enhancing. Thus, rigorous evaluation of available epidemiologic data is necessary before appropriate recommendations can be made, especially for women at high risk of breast cancer or those who have survived the disease.

Methods: We performed a meta-analysis of 18 epidemiologic studies (12 case–control and six cohort or nested case–control) published from 1978 through 2004 that examined soy exposure and breast cancer risk. Pooled relative risk estimates were based on either the original soy exposure measure defined in each study or on an estimate of daily soy protein intake.

Results: Risk estimates, levels and measures of soy exposure, and control for confounding factors varied considerably across studies. In a pooled analysis, among all women, high soy intake was modestly associated with reduced breast cancer risk (odds ratio [OR] = 0.86, 95% confidence interval [CI] = 0.75 to 0.99); the association was not statistically significant among women in Asian countries (OR = 0.89, 95% CI = 0.71 to 1.12). Among the 10 studies that stratified by menopausal status the inverse association between soy exposure and breast cancer risk was somewhat stronger in premenopausal women (OR = 0.70, 95% CI = 0.58 to 0.85) than in postmenopausal women (OR = 0.77, 95% CI = 0.60 to 0.98); however, eight studies did not provide menopause-specific results, six of which did not support an association. When exposure was analyzed by soy protein intake in grams per day, a statistically significant association with breast cancer risk was seen only among premenopausal women (OR = 0.94, 95% CI = 0.92 to 0.97). Conclusions: Soy intake may be associated with a small reduction in breast cancer risk. However, this result should be interpreted with caution due to potential exposure misclassification, confounding, and lack of a dose response. Given these caveats and results of some experimental studies that suggest adverse effects from soy constituents, recommendations for high-dose isoflavone supplementation to prevent breast cancer or prevent its recurrence are premature.

Breast cancer rates among women in Asian countries have long been noted to be substantially lower than those among women in Western nations (1) but rapidly increase in Asian women following emigration to the United States (2). Because changes in cancer risk following emigration are thought to reflect lifestyle changes, particularly in dietary patterns, these observations have led to a search for protective factors in the Asian diet. Soy-based foods have long been a staple of Asian diets; before 1998 these foods were consumed regularly by only approximately 5% of women in the United States (3,4). However, this figure is...
increasingly being used as food additives and meat substitutes in
that high soy protein intake contributes to low breast cancer inci-

duction of mammary epithelial cell differentiation

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activation of ER-

growth factor receptor tyrosine kinase activity, and inhibition of
reduce breast cancer risk, including the inhibition of epidermal

(8, 9)

(10, 11)

(13–16), enhanced proliferation of human breast
cancer xenografts (17) and normal mammary epithelial cells of
women (13, 18–20) and of rodents (21), and inhibition of the
antiproliferative effects of the antiestrogen tamoxifen in human
breast cancer cells growing in vitro and as xenografts in ovariec-
tomized nude mice (22, 23). However, physiologic doses of ge-
nistein also exhibit potential anticarcinogenesis activities, such
as induction of mammary epithelial cell differentiation (24) and
activation of ER-β, a protein with proapoptotic properties (16).
Daidzein, the other key phytoestrogen in soy, enhances tamoxi-
en efficacy at physiologic levels in a rat model (23). Studies of
breast density, a strong risk factor for breast cancer, have shown
both direct (25) and inverse (26) associations with soy exposure.
In a recent study (27), premenopausal women were randomly as-
signed to 1-year supplementation with isoflavone or placebo and
did not show changes in mammographic density, which suggests
that if soy intake is associated with breast density, it is probably
with long-term or early-life exposure.

Animal studies have generated conflicting data regarding the
ability of genistein or soy to reduce mammary tumorigenesis. In
general, dietary genistein exposure beginning when animals are
exposed to a carcinogen or when the tumors are palpable does
not reduce mammary tumor incidence or multiplicity, regardless
of the level of exposure, but may increase tumor latency (28–32).
Some investigators have reported that genistein reduces growth
of tumors that arise from inoculated human or mouse breast can-
cer cells in premenopausal mouse models (33, 34), and others have
reported that, in ovariecrotomized rat or mouse models of post-
menopause, dietary genistein can promote both carcinogen-induced
estrogen-dependent mammary tumorigenesis and growth of ER-
positive human breast cancer xenografts (35, 36). Furthermore,
prepubertal or pubertal exposure to genistein that is administered
either via injections or feed has consistently been found to reduce
the incidence and/or multiplicity of subsequent carcinogen-
induced, estrogen-dependent mammary tumors (37–39).

Relatively few studies have been reported of soy intake and
risk of breast cancer in women, and the methods and results of
these studies have been variable. Despite the complexity of these
data, high-dose supplements such as soy protein isolates or isofla-
vone capsules are being recommended and directly marketed to
healthy women to prevent breast cancer or to reduce menopausal
symptoms and to breast cancer survivors to prevent recurrence.
Because in vivo and in vitro data show risk-enhancing as well as
risk-reducing effects of genistein and soy, it is important that as-
associations between soy and breast cancer risk be rigorously evalu-
before recommendations can safely be made, especially for
women who already have breast cancer. Therefore, we conducted
a meta-analysis to explore in detail the epidemiologic evidence
relating consumption of soy foods to risk of breast cancer.

METHODS

Literature Review for Meta-Analysis

A search of MEDLINE, EMBASE, and BIOSIS was conducted
using the following terms: genistein, daidzein, soy, tofu, miso,
natto, soybeans, diet, isoflavones, or phytoestrogens, and breast
cancer. Each term also was searched alone without the breast
cancer term. The search was conducted through December 31,
2004. In addition, each reference that was obtained was reviewed
for citations to articles that may have been missed in the search
of the publication databases. An attempt was made to obtain
unpublished data, additional references, and information through
an Internet search of soy, and phytoestrogens or isoflavones.

Classification of Soy Intake

Analyses were based on two related classifications of soy in-
take. First, we used the original measure of soy intake from each
study (regular tofu, fried tofu, soy protein, soy foods, dietary iso-
flavone intake, or urinary isoflavone excretion) and examined
risk associated with the largest difference in exposure between
case patients and control subjects. However, both the measures
used to quantify soy intake and the levels of soy intake varied
considerably across studies. To permit comparison of exposure
across studies using a common measure, we converted soy or
isoflavone exposure in each study to an estimate of grams of soy
protein consumed daily.

To convert the frequency of tofu intake to an estimate of soy
protein we considered the soy protein composition of tofu, typi-
cal serving size, and the fraction of soy food in the diet contrib-
buted by tofu. Regular tofu (100 g) contains 8.08 or 6.8 g of soy
protein in Western (40) and Asian countries (41), respectively,
and fried tofu contains 17.19 g (40). In Western countries, a
typical tofu serving size is 3.5 ounces (98 g) (40), compared
with 33 g in Japan (42). We did not have data from China for
fried tofu but used the value from the Japan survey (4 g/serving)
because daily soy protein intakes for both countries were simi-
lar. Regular tofu accounts for 42% of soy food intake in Japan
(43), whereas in China, fried tofu accounts for 8.5% of total soy
protein intake (44). Based on a recent evaluation of dietary
isoflavone intake, we assumed that tofu accounted for 20% of
soy protein intake among non-Asian women, with the remainder
coming from additives in baked goods and other foods (45).
Although use of soy foods in Western countries is currently
increasing, subjects in the studies included here were evaluated
in 1994 or earlier, when use of soy foods was less widespread.
Thus, total daily soy protein intake was estimated from tofu
intake as follows: \( SP = FT \times ST \times SPT \times (1/PST) \), in which \( SP = \) total daily soy protein intake (grams per day), \( FT = \) daily frequency of tofu consumption (servings per day), \( ST = \) tofu serving size (grams), \( SPT = \) soy protein composition of tofu (grams per 100 g of tofu), and \( PST = \) proportion of total soy consumption attributed to tofu.

Two studies examined risk associated only with urinary isoflavone levels rather than with intake of soy foods or soy protein (46,47). To convert these urinary isoflavone levels to soy protein intake we used linear regression–derived estimates of mean urinary genistein and daidzein for levels of soy protein intake from Karr et al. (48). Because Karr et al. did not include their regression equations, we derived the following regression equations by re-estimating their predicted mean urinary isoflavone levels on their soy protein intake values (\( Y_g \) and \( Y_d \) are estimated urine genistein and daidzein, respectively, in nmol/day, and \( X \) is actual soy protein intake in grams per day):

\[
Y_g = 119.0 + 272.4X \\
Y_d = 604.4 + 544.3X
\]

Urine isoflavone values from the studies by Ingram et al. (46) and den Tonkelaar et al. (47) were then substituted in these equations to estimate daily soy protein intake. We validated this approach by applying it to two unrelated studies in healthy individuals that provided both urinary isoflavone values and intakes of soy food or soy protein. In a study of healthy Japanese women, we estimated soy protein intake to be 3.67 g/day based on urinary daidzein values, compared with 3.7 g/day derived from the total soy food intake in the study (49). Among healthy Caucasian women we estimated soy protein intake to be 2.4 g/day based on urinary daidzein values, compared with 2.8 g/day estimated from food-frequency data. These validation results suggest that our approach yields consistent estimates of soy protein intake based on urinary isoflavones.

To convert estimated dietary intake of total isoflavones (50–54) to estimates of soy protein intake, we used data from studies of healthy women in the United States (55) and in Japan (56) to derive a ratio of 346 mg of soy protein per mg of isoflavone (United States) or 301 mg of soy protein per mg of isoflavone (Japan). For all studies in which the highest and lowest soy exposure categories included were open-ended, we estimated the midpoint of the lowest and highest quantiles if actual distribution data were not available in the report. We defined the lowest quantile as zero to the low quantile cutpoint reported in the study. For the highest quantile, we defined its range to be the same width as that of the second highest quantile reported in the study. Midpoints of these low and high ranges were used to convert differences in soy food intake to soy protein.

**Statistical Methods**

For each study, we extracted the odds ratio (OR) and 95% confidence interval (CI) for the comparison of the highest versus lowest soy exposure groups. To convert odds ratios based on differences between high and low exposure \((\Delta_i)\) to the log odds ratio per unit change \((\beta_i)\), we used \( \beta_i = \log(OR)/\Delta_i \). If not specifically provided, the standard error \((SE_i)\) for the logarithm of the OR \((\log OR)\) was estimated as \( \log L_i / 3.92\), in which \( L_i \) are the respective upper and lower bounds of the confidence interval for \( L_i \); the \( SE_i \) was squared to estimate the variance of \( L_i \) (57). A test for homogeneity across studies was applied before the ORs were pooled. If homogeneity was not rejected, the method of Woolf (58) was used to obtain a pooled estimate of the OR, obtained as a weighted average of the \( L_i \), with each weight \((w_i)\) equal to the inverse variance of \( L_i \). Variance of the pooled estimate, \( L_P \), obtained as the inverse of the sum of the weights, was used to calculate the confidence interval (58). If homogeneity of OR was rejected, a random-effects model was used to obtain a pooled estimate (59). In this model, we estimated a random-effects variance component \((v)\) that was added to the variance of each individual \( L_i \), and these composite variances were used for the weights. Analyses were conducted for all women combined, women in Asia, and all women stratified by menopausal status. These categories were chosen as potential stratification factors because of a priori hypotheses that they might modify the effects of soy foods on breast cancer risk.

We used odds ratio estimates that were adjusted for multiple potential confounding factors whenever such odds ratios were available. To test the impact of adjustment on the association between soy and breast cancer risk, we compared pooled log odds ratios from studies that did adjust for potential confounding factors \((L_{PA})\) and those from studies that did not \((L_{PC})\); these analyses also incorporated the random-effects variance. The relative impact of adjustment (the “confounding odds ratio”) is provided by the ratio of the pooled odds ratios from adjusted studies to the pooled odds ratios from the unadjusted studies, estimated as \( \exp(L_{PA} - L_{PC}) \) (57). The confounding odds ratio was also used to compare subgroups of studies with different design or study population characteristics, e.g., to compare results based on cohort studies with those based on case–control studies.

If the confounding factor was a continuous variable, we examined whether there was a statistically significant linear trend by performing a weighted linear regression of the study-specific logarithm of the OR \((L_i)\) on the confounding factor \((z_i)\). In this meta-regression approach, the weights \((w_i)\) are the same as those used to derive the pooled odds ratio, i.e., the study-specific inverse variance of the \( L_i \). The regression parameter \((c)\) (change in the log odds ratio per unit change in the confounding variable) can be estimated directly from the data as \( b = c/v \), in which \( c = \sum w_i z_i / \sum w_i - \bar{L}_i \bar{z} \) is the weighted covariance of the \( L_i \) and \( z_i \), \( v = \sum w_i z_i^2 / \sum w_i - \bar{z}^2 \) is the weighted variance of the \( z_i \) and \( L_i \) and \( \bar{z} \) and \( \bar{L} \) are the weighted averages of the \( L_i \) and \( z_i \), respectively (57).

Sensitivity analyses were performed by varying the assumptions used to calculate the exposure levels or by deleting studies based on factors associated with study quality or weight and then evaluating the impact of the changes on the pooled odds ratios. We examined the evidence for publication bias graphically using a funnel plot and quantitatively using a weighted linear regression of the logarithm of the odds ratios on their standard errors, weighted by the inverse variance; two-sided \( P \) values for the regression parameters were determined using Wald statistics (60).

**RESULTS**

Twenty-three articles published from 1978 through December 31, 2004, were identified for review (3,46,47,50–54,61–75). One study (68) was excluded because it was based on soy intake in the husbands of breast cancer patients; one study was excluded (75)
Table 1. Studies of soy and breast cancer risk used in meta-analysis

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Design</th>
<th>Population*</th>
<th>OR (95% CI) or RR (95% CI)†</th>
<th>Measure of soy intake (exposure differences)</th>
<th>Adjustment factors, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 1992 (61)</td>
<td>Hospital-based case–control</td>
<td>Premenopausal (109/207) Postmenopausal (91/213)</td>
<td>0.4 (0.2 to 0.8) 1.8 (0.8 to 3.6)</td>
<td>Soy protein ≥3.5 vs. &lt;1.6 g/day</td>
<td>Premenopausal: age, age at first birth. Postmenopausal: age, nulliparity, height, education, family history.</td>
</tr>
<tr>
<td>Hirose et al., 1995 (63)</td>
<td>Hospital-based case–control</td>
<td>Premenopausal (606/2275) Postmenopausal (443/6186)</td>
<td>0.78 (0.60 to 1.0) 0.96 (0.70 to 1.31)</td>
<td>Bean curd ≥3 times/wk vs. ≤3 times/mo</td>
<td>Age and year of first visit to clinic. Adjustment for other breast cancer risk factors and dietary factors was done only for high vs. not high intake, with minimal impact: ratio of adjusted to crude OR was 0.96 and 1.08 for premenopausal and postmenopausal, respectively.</td>
</tr>
<tr>
<td>Yuan et al., 1995 (62)</td>
<td>Population-based case–control</td>
<td>Shanghai (534/534) Tianjin (300/300)</td>
<td>0.9 (0.6 to 1.3) 1.4 (0.7 to 3.0)</td>
<td>Soy protein (95th vs. 5th percentile)</td>
<td>Age, age of menarche, parity, duration of lactation, age at first use of oral contraceptives, benign breast disease, family history, energy, education and (only in Shanghai) cycle length, weight.</td>
</tr>
<tr>
<td>Wu et al., 1996 (65)</td>
<td>Population-based case–control</td>
<td>All women (596/958) Premenopausal (421/656) Postmenopausal age ≤55 (170/295)</td>
<td>0.66 (0.50 to 0.88) 0.64 (0.46 to 0.90) 0.73 (0.43 to 1.24)</td>
<td>Tofu ≥55 times/y vs. ≤12 times/y</td>
<td>Not adjusted (CIs not provided for adjusted values). Minimal effects of adjustment: ratios of adjusted to crude OR were 1.02, 1.05, and 0.96 for all women, premenopausal and postmenopausal, respectively. Age, age at menarche, parity, alcohol, total fat intake. Matched on age, area of residence.</td>
</tr>
<tr>
<td>Greenstein et al., 1996 (3)</td>
<td>Cohort</td>
<td>Postmenopausal (1018/34388)</td>
<td>0.76 (0.50 to 1.18)</td>
<td>Soy or tofu (consumers vs. nonconsumers)</td>
<td>“Major breast cancer risk factors” (not specified). Only 3% of cohort consumed any soy foods.</td>
</tr>
<tr>
<td>Ingram et al., 1997 (46)</td>
<td>Population-based case–control</td>
<td>All women (144/144)</td>
<td>0.47 (0.17 to 1.33)</td>
<td>Urinary daidzein (&gt;1300 nmol/day)</td>
<td>Age at menarche, alcohol, total fat intake. Matched on age, area of residence.</td>
</tr>
<tr>
<td>Witte et al., 1997 (64)</td>
<td>Case–control (unaffected sisters of patients)</td>
<td>Premenopausal (140/222)</td>
<td>0.5 (0.2 to 1.1)</td>
<td>Tofu or soybean (1 time/week vs. none)</td>
<td>Age, age at menarche, parity, alcohol, oral contraceptives, BMI, energy. Prevalent and incident cases with bilateral breast cancer. Only 5% of subjects consumed any soy foods.</td>
</tr>
<tr>
<td>Chie et al., 1997 (66)</td>
<td>Hospital-based case–control</td>
<td>All women (175/571)</td>
<td>2.0 (0.9 to 4.3)</td>
<td>Tofu (fried) (1 time/week vs. none)</td>
<td>Education, BMI, age at menarche, age at first full-term pregnancy, age at menopause, parity, lactation, family history, caloric intake. Age matched.</td>
</tr>
<tr>
<td>Key et al., 1999 (70)</td>
<td>Cohort</td>
<td>All women (427/489/989) Premenopausal (not stated) Postmenopausal</td>
<td>1.07 (0.78 to 1.47) 1.16 (0.56 to 2.38) 1.05 (0.73 to 1.49)</td>
<td>Tofu ≥5 times/week vs. ≤1 time/week</td>
<td>Age, calendar period, city, and age at time of atom bombs, estimated radiation dose.</td>
</tr>
<tr>
<td>Dai et al., 2001 (71)</td>
<td>Population-based case–control</td>
<td>All women (1459/1556) Premenopausal (952/990) Postmenopausal (501/562)</td>
<td>0.66 (0.46 to 1.02) 0.53 (0.39 to 0.72) 0.49 (0.33 to 0.74)</td>
<td>Soy protein (4th vs. 1st quartile) Soy protein (5th vs. 1st quintile) Soy protein (5th vs. 1st quintile)</td>
<td>Age, family history, breast fibroadenoma, waist-to-hip ratio, age at menarche, age at first birth, age at menopause, menopausal status, physical activity, parity, intake of meats and fish, and total energy.</td>
</tr>
<tr>
<td>Shu et al., 2001 (72)</td>
<td>Population-based case–control</td>
<td>All women (1272/1610) Premenopausal (398/471) Postmenopausal (826/1077)</td>
<td>1.00 (0.79 to 1.30) 1.20 (0.75 to 2.00) 0.96 (0.71 to 1.30)</td>
<td>Total isoflavones (4th vs. 1st quartile)</td>
<td>Age, ethnicity, age at menarche, parity, lactation, benign breast disease, family history, education, composite of menopausal status, BMI and hormone replacement, caloric intake.</td>
</tr>
<tr>
<td>Horn-Ross et al., 2001 (50)</td>
<td>Population-based case–control</td>
<td>All women (1753/571) Premenopausal (541/989) Postmenopausal (1212/989)</td>
<td>0.95 (0.80 to 1.13) 1.06 (0.87 to 1.27) 1.17 (1.00 to 1.37)</td>
<td>Soy protein (5th vs. 1st quartile) Soy protein (95th vs. 1st quartile) Soy protein (100th vs. 1st quintile)</td>
<td>Age, ethnicity, age at menarche, parity, lactation, benign breast disease, family history, education, composite of menopausal status, BMI and hormone replacement, caloric intake.</td>
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</table>
Table 1 (continued).

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Design</th>
<th>Population*</th>
<th>OR (95% CI) or RR (95% CI)†</th>
<th>Measure of soy intake (exposure differences)</th>
<th>Adjustment factors, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>den Tonkelaar et al., 2001 (47)</td>
<td>Nested case–control</td>
<td>Postmenopausal (88/268)</td>
<td>0.83 (0.46 to 1.51)</td>
<td>Urinary genistein (3rd vs. 1st tertile)</td>
<td>Crude OR. Adjustment for age, height, weight, parity, age at menopause, benign breast disease, family history, estrogen replacement, smoking did not change OR (&lt;10% change).</td>
</tr>
<tr>
<td>Wu et al., 2002 (51)‡</td>
<td>Population-based case–control</td>
<td>All women (501/594)</td>
<td>0.61 (0.39 to 0.97)</td>
<td>4th vs. 1st quartile: Adult isoflavone intake</td>
<td>Birthplace, education, age at menarche, parity, current BMI, menopausal status, use of replacement hormones, energy, dark green leafy vegetables, smoking, alcohol, physical activity, family history. Matched on age, ethnicity.</td>
</tr>
<tr>
<td></td>
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<td>Premenopausal (208/289)</td>
<td>0.65 (0.38 to 1.10)</td>
<td>Adult isoflavone intake</td>
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<td></td>
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<td>Postmenopausal (283/304)</td>
<td>0.60 (0.30 to 1.19)</td>
<td>Adult isoflavone intake</td>
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<td>0.64 (0.29 to 1.42)</td>
<td>Adult isoflavone intake</td>
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<td>0.39 (0.21 to 0.70)</td>
<td>Adult isoflavone intake</td>
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<td>0.41 (0.21 to 0.81)</td>
<td>Adult isoflavone intake</td>
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<tr>
<td>Horn-Ross et al., 2002 (53)</td>
<td>Cohort</td>
<td>All women (711/222249)</td>
<td>1.0 (0.7 to 1.3)</td>
<td>Genistein intake (5th vs. 1st quintile)</td>
<td>Age, race, caloric intake, family history, age at menarche, age at first birth, parity, physical activity, interaction between menopausal status and BMI.</td>
</tr>
<tr>
<td>Yamamoto et al., 2003 (52)</td>
<td>Cohort</td>
<td>All women (179/209354)</td>
<td>0.46 (0.25 to 0.84)</td>
<td>Isoflavone intake (4th vs. 1st quartile)</td>
<td>Age, age at menarche, age at first pregnancy, parity, menopausal status, smoking, alcohol, physical activity, education, energy, consumption of meat, fish, vegetables, and fruit.</td>
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<tr>
<td></td>
<td></td>
<td>Premenopausal (89/93628)</td>
<td>0.66 (0.25 to 1.70)</td>
<td>Isoflavone intake (4th vs. 1st quartile)</td>
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<td></td>
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<td>Postmenopausal (87/111637)</td>
<td>0.32 (0.14 to 0.71)</td>
<td>Isoflavone intake (4th vs. 1st quartile)</td>
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<tr>
<td>Lineisen et al., 2004 (54)</td>
<td>Population-based case–control</td>
<td>Premenopausal (278/666)</td>
<td>0.85 (0.54 to 1.33)</td>
<td>Isoflavone intake (4th vs. 1st quartile)</td>
<td>Family history, parity, lactation, energy, BMI, alcohol, education. Matched on age, study region.</td>
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<td></td>
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<td>0.47 (0.29 to 0.74)</td>
<td>Genistein intake (4th vs. 1st quartile)</td>
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<td>0.62 (0.40 to 0.95)</td>
<td>Daidzein intake (4th vs. 1st quartile)</td>
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<tr>
<td>Grace et al., 2004 (73)</td>
<td>Nested case–control</td>
<td>All women (111/217)</td>
<td>1.16 (0.97 to 1.39)</td>
<td>Urinary genistein (twofold increase)</td>
<td>BMI, menopausal status, parity, hormone replacement therapy, smoking, family history, saturated fat intake. Matched on age, recruitment date.</td>
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<td>1.12 (0.96 to 1.31)</td>
<td>Urinary daidzein (twofold increase)</td>
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<td>1.17 (0.94 to 1.45)</td>
<td>Dietary genistein (twofold increase)</td>
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<td></td>
<td>1.18 (0.93 to 1.48)</td>
<td>Dietary daidzein (twofold increase)</td>
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</table>

*Parentheses represent (No. of case patients/No. of control subjects) for case–control studies or (No. of case patients/No. of person-years) for cohort studies, except for Greenstein et al. (3), in which parentheses represent (No. of case patients/No. of women at baseline). BMI = body mass index, kg/m².
†OR = odds ratio; RR = relative risk; CI = confidence interval.
‡For premenopausal and postmenopausal populations, 95% CIs for adult isoavone intake were provided by Dr. Wu (personal communication), whereas those for adolescent tofu intake were estimated.

because it only had 18 case patients and 20 control subjects. A third study (67) was excluded because it did not test for an association between soy consumption and risk of breast cancer. Two studies (3, 66) that were reported only as published abstracts were included in the analyses because of the relatively small number of studies available. Four manuscripts reported on the same study. Two of these used smaller subsets of the main case–control study and were not included in the analysis (69, 74) and two reported on the entire study (71, 72). Of the latter two, one report was based on usual adult dietary intake of soy protein that was derived from a food frequency questionnaire with a comprehensive list of soy foods and provided estimates of risk for all women combined (71). The second report was based on soy protein intake during adolescence derived from an abbreviated questionnaire that included tofu, soymilk, and a category for “other” soy foods and provided estimates of premenopausal and postmenopausal breast cancer risk (72). We included the data from Dai et al. (71) in the pooled estimates of risk for all women because of the more comprehensive dietary assessment. The data from Shu et al. (72) were included in pooled estimates of premenopausal and postmenopausal risk. The report by Yuan et al. (62) describes two case–control analyses, one performed in Shanghai and the other in Tianjin, China. Each analysis used different case patients and control subjects, and they were thus treated as two separate studies in our meta-analysis. Thus, a total of 18 individual studies (described in 17 manuscripts) were included in the meta-analysis.

Of the 18 studies, 12 were case–control studies and six were cohort studies or case–control studies nested in a prospective cohort (Table 1; Supplementary Table 1, available at http://jnci.cancerspectrum.oxfordjournals.org/jnci/content/vol98/issue7). Six studies used frequency of tofu (or soybean curd) consumption as the measure of soy intake (50, 52–54), one used soy intake from 18 individual studies (described in 17 manuscripts) were included in the meta-analysis. Six studies used frequency of tofu (or soybean curd) consumption as the measure of soy intake (50, 52–54).
isoflavones (73), and one used both tofu intake during adolescence and isoflavone intake during adulthood (51).

For many of the studies, no statistically significant association between soy intake and risk of breast cancer was observed (Fig. 1; Supplementary Table 1, available at http://jnci.cancerspectrum.oxfordjournals.org/jnci/content/vol98/issue7). Two of the studies (61,63) gave results stratified by menopausal status but did not give the combined results, so the stratified results are shown (Fig. 1; Supplementary Table 1, available at http://jnci.cancerspectrum.oxfordjournals.org/jnci/content/vol98/issue7). Among subgroups that were of prior interest, the studies of premenopausal women appeared to exhibit a more consistent inverse association between soy intake and breast cancer risk than the Asian studies (Fig. 2). When the data from all studies were pooled (Table 2; Supplementary Table 1, available at http://jnci.cancerspectrum.oxfordjournals.org/jnci/content/vol98/issue7), there was substantial heterogeneity, and this heterogeneity remained within strata of Asian studies and studies of postmenopausal women, but not among studies of premenopausal women. Overall, the association between soy intake and risk of breast cancer was small but statistically significant (OR = 0.86, 95% CI = 0.75 to 0.99). Inverse associations between soy intake and breast cancer risk were somewhat stronger among premenopausal women (OR = 0.70, 95% CI = 0.58 to 0.85) than among postmenopausal women (OR = 0.77, 95% CI = 0.60 to 0.98). However, pooled menopause-specific results may be spuriously low—these results omit eight studies that did not provide results stratified by menopausal status, and six of the eight studies did not show an inverse association (3,46,47,53,62,64,66,73). The relationship between soy intake and breast cancer risk was similar among women in Western countries but not statistically significant [including two studies of Asian Americans (51,65)] with OR = 0.84 (95% CI = 0.70 to 1.00) and was slightly weaker among women in Asian countries (OR = 0.89, 95% CI = 0.71 to 1.12); these two odds ratios did not differ (P = .70). However, if the two studies conducted among Asian Americans are included with the studies of women in Asian countries, the odds ratio was similar to that of all women combined but not statistically significant (OR = 0.83, 95% CI = 0.68 to 1.02). Exclusion of the two studies that were reported as abstracts only (3,66) did not change the above results (data not shown).

Most studies adjusted their analyses for some breast cancer risk factors, but the effect of adjustment was relatively minor. In the 11 studies in which both crude and adjusted estimates could be compared (46,50–52,54,61,63,65,70,71,73), the odds ratios were reduced by adjustment as frequently as they were increased. To evaluate the potential impact on heterogeneity of adjustment for confounding factors or of comparing studies
Table 2. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk associated with high versus low soy intake, as defined in each original study, by study population

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of studies (case patients)</th>
<th>Heterogeneity of ORs</th>
<th>OR (95% CI)</th>
<th>Model used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Χ² (df)*</td>
<td>P†</td>
<td></td>
</tr>
<tr>
<td>All women</td>
<td>18 (9182)</td>
<td>41.06 (19)</td>
<td>.002</td>
<td>0.86 (0.75 to 0.99)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (4323)</td>
<td>23.72 (9)</td>
<td>.005</td>
<td>0.89 (0.71 to 1.12)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>10 (3351)†</td>
<td>14.41 (9)</td>
<td>.108</td>
<td>0.70 (0.58 to 0.85)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>10 (3784)‡</td>
<td>26.72 (9)</td>
<td>.002</td>
<td>0.77 (0.60 to 0.98)</td>
</tr>
</tbody>
</table>

*Degrees of freedom (df) does not equal N−1 because studies that provided separate values for premenopausal and postmenopausal women contributed 2 df, and the report by Yuan et al. (62) of two geographically distinct case-control studies also contributed 2 df.
†P values (two-sided) were based on the chi-square test of heterogeneity (58).
‡The study by Key et al. (70) did not provide numbers of cases by menopausal status but did give numbers by age group. For this table, the Key et al. study contributed 150 case patients aged ≤54 years ("premenopausal") and 277 aged ≥55 years ("postmenopausal").

stratified on the basis of a study design or population subgroup, we compared the pooled odds ratios from studies that adjusted for or exhibited a particular factor with that of studies that did not adjust for or did not exhibit the factor. The ratio of these two pooled odds ratios can be considered as a "confounding odds ratio," OR_C (and 95% confidence interval). If OR_C >1, it indicates that studies that adjusted for a confounding factor (or represented a particular stratum) exhibited larger odds ratios than studies that did not adjust; i.e., the inverse association is diminished by adjustment. Conversely, if OR_C <1, adjustment (or the particular factor) is associated with smaller odds ratios than those that did not adjust; i.e., the inverse association is strengthened by adjustment.

When the pooled odds ratios from studies that adjusted for a confounding factor were compared with those of studies that did not (or when studies across two different strata were compared), body mass index (BMI) was the only factor that resulted in a statistically significant difference (BMI-adjusted studies, OR = 0.99 versus unadjusted studies OR = 0.74, yielding a confounding odds ratio OR_C = 1.34, 95% CI = 1.04 to 1.72; P = .022, Table 3; Supplementary Table 1, available at http://jnci.oxfordjournals.org/content/vol98/issue7). In other words, studies that adjusted for BMI had 34% larger odds ratios (suggesting a weaker inverse association), on average, than studies that did not adjust. Cohort or nested case-control studies also exhibited somewhat larger pooled odds ratios (OR_C = 0.93) than retrospective case-control studies (OR = 0.83), resulting in OR_C = 1.12, but this difference was not statistically significant.

Finally, we explored possible associations between publication year and either the odds ratio or study weight. Weighted meta-regression revealed no association between year of publication and the log odds ratio (b = .016, P = .14) or the study weight (b = 2.51, P = .14) (unweighted analysis). There was also no association between the year enrollment began and the odds ratio or the study weight (data not shown).

There was great variability among the studies in the definitions of high and low exposure (Table 1; Supplementary Table 1, available at http://jncicancerspectrum.oxfordjournals.org/content/vol98/issue7). For example, in some studies (64-66) high exposure was defined as consumption of tofu one or more times per week, whereas in two studies (62) the difference in intake between the high and low exposure categories was 18 g of soy protein.

Table 3. Comparison of association of soy intake and breast cancer risk among studies that adjusted versus those that did not adjust for a confounding factor (or comparison subgroup of studies with different values for a design factor)

<table>
<thead>
<tr>
<th>Comparison groups (no. of studies)</th>
<th>Unadjusted or denominator stratum</th>
<th>Comparison OR_C (95% CI)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort or nested case-control studies (6)</td>
<td>Retrospective case-control studies (12)</td>
<td>1.12 (0.84 to 1.49)</td>
<td>.434</td>
</tr>
<tr>
<td>Population-based case-control studies (8)</td>
<td>Hospital or sister control case-control studies (4)¶</td>
<td>0.89 (0.59 to 1.35)</td>
<td>.584</td>
</tr>
<tr>
<td>Asian studies (8)</td>
<td>Western studies (10)§</td>
<td>1.06 (0.79 to 1.42)</td>
<td>.699</td>
</tr>
<tr>
<td>Postmenopausal (10)</td>
<td>Premenopausal (10)¶</td>
<td>1.09 (0.80 to 1.40)</td>
<td>.345</td>
</tr>
<tr>
<td>Soy protein/isoflavones¶ (12)</td>
<td>Tofu (6)</td>
<td>1.00 (0.76 to 1.33)</td>
<td>.978</td>
</tr>
<tr>
<td>Soy protein/tofu (10)</td>
<td>Isoflavones (8)</td>
<td>1.00 (0.75 to 1.32)</td>
<td>.974</td>
</tr>
<tr>
<td>BMI adjusted (9)</td>
<td>BMI not adjusted (9)</td>
<td>1.34 (1.04 to 1.72)</td>
<td>.022</td>
</tr>
<tr>
<td>Energy adjusted (10)</td>
<td>Energy not adjusted (8)</td>
<td>0.98 (0.73 to 1.31)</td>
<td>.887</td>
</tr>
<tr>
<td>Other dietary factors adjusted (6)</td>
<td>Other dietary factors not adjusted (12)</td>
<td>0.85 (0.63 to 1.16)</td>
<td>.304</td>
</tr>
</tbody>
</table>

*For a binary confounding factor, the confounding odds ratio (OR_C) is the ratio of the pooled odds ratio for studies that did adjust for the specific confounding factor versus the pooled odds ratio for studies that did not adjust. For two separate subgroups of studies such as different study design or population groups, OR_C is the ratio of the pooled odds ratio for studies comprising one subgroup (numerator) versus the pooled odds ratio for the studies comprising the other subgroup (denominator).
†P values (two-sided) were calculated using the z-statistic (57).
‡This comparison includes only the 12 case-control studies.
§Considers two studies of Asian Americans by Wu et al. (51,65) as Western studies.
¶Some studies included estimates of the effect in both premenopausal and postmenopausal women, so the total estimates for both groups exceed the number of studies.
||Some studies include exposure measured by dietary isoflavone intake, dietary genistein intake, or urinary isoflavone excretion.
Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk per gram of soy protein intake daily for individual studies

<table>
<thead>
<tr>
<th>Author, year*</th>
<th>No. of case patients</th>
<th>Original measure of soy intake</th>
<th>High vs. low exposure difference</th>
<th>OR (95% CI) per 1 g soy protein/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 1992</td>
<td>200</td>
<td>Soy protein, g/day</td>
<td>0.8, 4.5</td>
<td>1.00, 5.00</td>
</tr>
<tr>
<td>Hirose et al., 1995</td>
<td>1049</td>
<td>Tofu, per week</td>
<td>0.5, 5</td>
<td>0.38, 3.82</td>
</tr>
<tr>
<td>Yuan et al., 1995 (Shanghai)</td>
<td>534</td>
<td>Soy protein, g/day</td>
<td>1.0, 19.0</td>
<td>1.00, 19.00</td>
</tr>
<tr>
<td>Yuan et al., 1995 (Tianjin)</td>
<td>300</td>
<td>soy protein, g/day</td>
<td>1.0, 19.0</td>
<td>1.00, 19.00</td>
</tr>
<tr>
<td>Wu et al., 1996</td>
<td>596</td>
<td>Tofu, per week</td>
<td>6, 104</td>
<td>0.04, 0.68</td>
</tr>
<tr>
<td>Greenstein et al., 1996</td>
<td>1018</td>
<td>Soy or tofu</td>
<td>None, any</td>
<td>0.00, 0.57</td>
</tr>
<tr>
<td>Ingram et al., 1997</td>
<td>144</td>
<td>Urinary daidzein, nmol/day</td>
<td>300, 1500</td>
<td>0.165, 0.736</td>
</tr>
<tr>
<td>Witte et al., 1997 (premeno)</td>
<td>140</td>
<td>Tofu/soybean, per week</td>
<td>None, 1</td>
<td>0.00, 1.13</td>
</tr>
<tr>
<td>Chie et al., 1997</td>
<td>175</td>
<td>Tofu (fried), per week</td>
<td>None, 1</td>
<td>0.00, 1.15</td>
</tr>
<tr>
<td>Key et al., 1999</td>
<td>427</td>
<td>Tofu, per week</td>
<td>0.5, 6</td>
<td>0.38, 4.58</td>
</tr>
<tr>
<td>Dai et al., 2001</td>
<td>1459</td>
<td>Soy protein, g/wk</td>
<td>9.3, 157.3</td>
<td>2.08, 7.62</td>
</tr>
<tr>
<td>Horn-Ross et al., 2001</td>
<td>1727</td>
<td>Dietary isoflavones, µg/day</td>
<td>524, 3339</td>
<td>0.03, 0.165</td>
</tr>
<tr>
<td>den Tonkelaar et al., 2001</td>
<td>88</td>
<td>Urinary genistein, µmol/mol creatinine</td>
<td>48.4, 196.6</td>
<td>1.1, 5.8</td>
</tr>
<tr>
<td>Wu et al., 2002</td>
<td>501</td>
<td>Tofu in adolescence</td>
<td>0.5/month, 6/week</td>
<td>0.04, 0.68</td>
</tr>
<tr>
<td>Horn-Ross et al., 2002</td>
<td>711</td>
<td>Dietary genistein, µg/day</td>
<td>321, 2496</td>
<td>0.11, 0.89</td>
</tr>
<tr>
<td>Yamamoto et al., 2003</td>
<td>179</td>
<td>Dietary isoflavones, mg/day</td>
<td>6.9, 25.3</td>
<td>2.08, 7.62</td>
</tr>
<tr>
<td>Linseisen et al., 2004</td>
<td>278</td>
<td>Dietary isoflavones, mg/day</td>
<td>0.087, 0.478</td>
<td>0.03, 0.165</td>
</tr>
<tr>
<td>Grace et al., 2004</td>
<td>111</td>
<td>Dietary isoflavones, mg/day</td>
<td>0.149, 0.736</td>
<td>0.05, 0.25</td>
</tr>
</tbody>
</table>

*Postmeno = postmenopausal; premeno = premenopausal.
†If the original published soy intake measure included open-ended categories for lowest and/or highest intake, the difference was estimated using the midpoints of these categories. If the actual midpoints were not provided, they were estimated as follows. For the lowest category the midpoint was taken as halfway between zero and the lowest category midpoint. For the highest category, the midpoint was taken as the category endpoint plus half the width of the second highest category.
‡Total dietary isoflavones derived from sum of dietary genistein plus daidzein, taking midpoints of 25th and 75th percentiles.

Table 5. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk per gram of soy protein intake daily by study population

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of studies (case patients)</th>
<th>Test heterogeneity of ORs</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>18 (9182)</td>
<td>42.20 (19)</td>
<td>0.97 (0.94 to 1.00)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (4323)</td>
<td>23.48 (9)</td>
<td>0.98 (0.95 to 1.01)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>10 (3351)†</td>
<td>13.80 (9)</td>
<td>0.94 (0.92 to 0.96)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>10 (3784)‡</td>
<td>18.16 (9)</td>
<td>0.95 (0.89 to 1.00)</td>
</tr>
<tr>
<td>Soy protein as original measure</td>
<td>3 (2493)</td>
<td>12.08 (4)</td>
<td>0.99 (0.98 to 1.00)</td>
</tr>
</tbody>
</table>

*df = degrees of freedom. df does not equal N - 1 because studies that provided separate values for premenopausal and postmenopausal women contributed 2 df, and the report by Yuan et al. (62) of two geographically distinct case-control studies also contributed 2 df.
†P values (two-sided) were based on the chi-square test of heterogeneity (58).
‡The study by Key et al. (70) did not provide numbers of cases by menopausal status but did give numbers by age group. For this table, the Key et al. study contributed 150 case patients aged ≤ 54 years (“premenopausal”) and 277 aged ≥ 55 years (“postmenopausal”).
of soy protein/day and provide only weak evidence of a dose-response (again considering that eight studies did not provide menopause-specific data and could not be included in the above estimates).

Because several assumptions were necessary to transform the original definitions of high versus low exposure to estimates of risk increase per gram of soy protein per day, we performed a sensitivity analysis. This analysis examined the likelihood that the assumptions used to derive the estimate of soy protein exposure in any one study had an unduly large influence on the pooled result. We changed the estimated difference between high and low soy protein intake in one study at a time to either double the difference or decrease it by 50%, then pooled the odds ratios using the revised estimate. The pooled odds ratios were changed only minimally; the largest change was a 4.3% decrease in the odds ratio (to 0.90) for premenopausal women when the exposure difference was halved in the study by Hirose et al. (63) (data not shown). We also calculated pooled odds ratios after excluding the study with the largest weight, excluding the two studies with the largest and smallest odds ratio, and excluding the six studies with fewer than 200 case patients. None of the pooled odds ratios changed by greater than 0.01, with the exception of studies in premenopausal women, of which the change was 0.02 (i.e., from 0.94 to 0.92) when the study with the largest weight was excluded. No confidence intervals changed in a way that would affect interpretation (data not shown).

We also performed sensitivity analyses for the pooled odds ratios based on the original soy intake measure using the same exclusions and also excluding all studies with exposure based exclusively on tofu. The largest change was for premenopausal women when the study with the largest weight was omitted, which changed the pooled odds ratio from 0.70 to 0.66. Again, confidence intervals did not change in a meaningful way (data not shown). Thus, the pooled results appear robust to potential influential observations, regardless of whether the original or estimated soy protein exposure measure was used.

Finally, we evaluated the likelihood of publication bias using a funnel plot of the log (odds ratio) versus its standard error (Fig. 3). To investigate any differences between large and small studies we arbitrarily designated studies with fewer than 200 case patients as small and those with at least 200 case patients as large (Fig. 3). The funnel plot does not suggest publication bias, because there are similar numbers of small studies (or those with large standard error) with OR<1.0 compared with OR>1.0. Publication bias would have been suggested if the preponderance of small studies was biased toward OR<1.0 (60). However, interpreting this plot visually is subjective, so we also used a regression approach to determine whether there was a correlation between the effect size [log (odds ratio)] and its standard error. This approach produced a statistically nonsignificant (regression) coefficient (b = −.56, P = .524), confirming the lack of bias.

**Discussion**

The meta-analysis included results from 12 case-control and six cohort or nested case-control studies. Among all studies, there was a small reduction in risk of breast cancer with high soy intake versus low intake (OR = 0.86, 95% CI = 0.75 to 0.99). The magnitude of the relationship was similar, but not statistically significant, when only women in Western countries or only Asian women were considered. Associations were somewhat stronger within menopause-specific strata, but these analyses omitted eight studies that did not provide stratified results, six of which did not support an overall association. Considered as a body of evidence, these studies support a small reduction in breast cancer risk associated with intake of soy foods, although interpretation of these results is tempered by lack of a dose response and inconsistencies in the data.

This meta-analysis evaluated the strength of current evidence for the role of a high soy diet in reducing breast cancer risk. Like all meta-analyses, it has potential limitations resulting from the availability, quality, and heterogeneity of the published data. For example, most studies were not originally designed to test the soy/breast cancer hypothesis, methods for measuring soy intake and expressing exposure differences differed across studies, substantial variation exists in the percentage of the population that regularly consumes soy and in the amount they consume, and the extent to which confounding factors were controlled differed among studies. These limitations can complicate interpretation of the summary statistics.

We cannot exclude the possibility that the observed risk estimates were attenuated owing to nondifferential measurement error in the individual studies; there are many potential sources of such error. Few studies were originally designed to test the effect of soy as a risk factor, used a validated instrument, or included portion sizes. Six studies based exposure estimates only on intake of tofu. Tofu contributes the largest amount of soy to most Asian diets, so relative ranking of subjects with respect to high and low intake should be possible with even crude intake measures (76). However, in Western diets the majority of isoflavone intake for most people comes from nonsoy foods, such as soy additives in baked goods, tuna, or coffee (45), and it is unlikely that levels of intake from such foods would coincide with recorded levels from soy foods such as tofu.

Because soy additives in the diet are difficult to quantify with most food frequency instruments and tofu intake is unlikely to correspond with total soy intake in most Western diets, the potential for misclassification may be larger in studies of Western women than Asian women. Use of a single spot urine sample to measure isoflavone levels could be another source of misclassification. These levels may be highly variable owing to time of day and timing with respect to meals. Absorption of isoflavones can differ by ethnicity or other factors, leading to variations in
excreted levels despite similar levels of soy protein intake (50). Although these sources of misclassification are likely to be non-differential, differential measurement error is also possible if soy intake is associated with other diet or behaviors associated with breast cancer.

Differential measurement error could arise from recall bias, or if differential participation rates induced selection bias. Because most of these studies were not originally designed to test the soy/breast cancer hypothesis and because the potential preventive effects of soy were not widely known during the period when most of these studies were conducted, selective reporting of soy intake seems unlikely. However, recall bias could still arise if soy intake were associated with other breast cancer–related behaviors. Cohort and nested case–control studies exhibited somewhat weaker associations than retrospective case–control studies, consistent with such a possibility. The potential for selection bias must also be considered, particularly in the Western studies, among which soy foods were consumed by 5% or fewer of subjects. For example, control subjects who agree to participate may be more health conscious than the general population of women without breast cancer.

Because the studies we analyzed used different definitions of high and low intake, they varied greatly in the actual exposure effect that they measured. High intake for most Western studies corresponded with low intake in most studies of Asians. To improve comparability of these different exposure levels, we attempted to derive risk estimates based on a common exposure measure using estimated daily soy protein intake (grams). We found that the resulting risk estimates appeared robust to variation in the assumptions used to derive exposure. Although it is likely that conversion from the original exposure measures to estimated soy protein intake in grams per day entails some error, it illustrates the large variation across studies in exposure differences. Analyses based on these estimates of soy protein intake showed similar odds ratios across subgroups, ranging from 0.94 to 0.98 per g of daily soy protein intake (Table 5; Supplementary Table 2, available at http://jncancerspectrum.oxfordjournals.org/jnci/content/vol98/issue7). There was little evidence of a dose response.

To provide some perspective, consumption of one 3.5-ounce (98 g) serving of tofu per week, the most common cutpoint for high exposure among the studies that measured tofu consumption, would provide 7.92 g of soy protein/week—the equivalent of 1.13 g of soy protein/day from tofu (40). Thus, the pooled odds ratios shown in Table 5 (based on 1.0 g of soy protein/day) are very near to those that would be expected for one serving of tofu per week.

The apparent reduction in breast cancer risk associated with greater soy intake was similar or even slightly stronger in Western populations than in Asian populations, despite much lower soy intake. This could reflect a greater degree of uncontrolled confounding in the Western studies. Because of the very low percentage of women who consumed soy foods in the Western studies, it is possible that soy intake is a surrogate for other risk-lowering behaviors. The four Western studies with the strongest association based on the estimated soy protein measure included a low proportion of subjects who regular consumed soy foods—3% (3), 5% (64), and 25% (65)—and the foods had a low proportion (4%-8%) of total isoflavone contributed by soy foods (54). The subjects in these studies probably differ in other factors associated with a more health-conscious lifestyle or, for the Asian-American women, with a more traditional lifestyle. Such factors may be difficult to separate from the measurements of soy intake.

When we analyzed the impact on the odds ratio of potential confounders, BMI was the only statistically significant contributor to heterogeneity; studies that adjusted for BMI exhibited weaker associations than those that did not adjust. However, few studies adjusted for other potentially important confounders such as alcohol consumption, breast-feeding, or physical activity. These are likely to be inversely (alcohol) or directly (breast-feeding, physical activity) associated with soy intake, a traditional Asian lifestyle, or a more health-conscious Western lifestyle. Thus, we cannot exclude uncontrolled confounding as a source of error in the observed associations.

If the association between greater soy intake and lower breast cancer risk is real, what could explain the apparent lack of association between intake levels and size of the risk reduction in Western and Asian studies? Breast cancer risk for the average woman is much higher in Western women (133 per 100,000) (77) than in Asian women (39 per 100,000) (78), undoubtedly reflecting a higher burden of risk factors such as late age at first full-term pregnancy, early menarche, obesity/lack of physical activity, alcohol consumption, and adverse nutritional factors. Therefore, there may be fewer potentially harmful pathways for soy to impact breast cancer risk among Asian women, and much larger differences in exposure may be needed to detect a level of risk reduction similar to that associated with smaller differences among Western women. This is analogous to the relative benefits of giving chemotherapy to patients with a high versus low risk of recurrence (79). Alternatively, the risk reduction due to soy may reach a plateau at a relatively low level (76). Such an explanation would be consistent with the lack of dose response observed in this meta-analysis and the similar or possibly even smaller risk reduction among women in Asian countries than in Western countries.

For either of the above explanations to be true, soy would need to exhibit strong anticancer effects at these Western intake levels that correspond with low intake levels in Asian countries. It is difficult to evaluate the likelihood of such a low-dose effect. Plasma isoflavone levels in Western women are much less than 1 μmol/L (12). This level has not been adequately explored in experimental studies, which have used levels orders of magnitude higher. Thus, for the results in Western women to represent a true association between soy intake and breast cancer risk, they would involve anticarcinogenic effects that have not yet been demonstrated.

A possible explanation for similar reductions in breast cancer risk associated with different soy intake levels in Western and Asian women relates to the timing of exposure. Studies conducted by our group (38) and others (80) show that prepubertal exposure to genistein reduces carcinogen-induced breast cancer in rats (81). Asian women are likely to have been exposed to soy during early life. This observation is consistent with associations between childhood soy exposure and reduced breast cancer risk in studies by Wu et al. (51) and Shu et al. (72) and an association between soy intake and reduced breast cancer risk among Asian-Americans observed only in the subgroup not born in the United States (63). If early life is the critical period for soy exposure, then studies based on adult exposure may not capture the association with breast cancer risk and could underestimate the association in Asian women. Conversely, because most Western women would not have experienced early-life soy food exposures, their exposures in adulthood may be relatively more important in affecting risk. However, this would still require...
anticarcinogenic effects at fairly low exposure levels during adulthood.

If low levels of soy exposure in adulthood can reduce breast cancer risk, what biologic changes could be responsible? Soy supplementation has no clear association with serum estrogen levels in premenopausal (82) or postmenopausal (83,84) women, so systemic hormonal effects are unlikely to contribute to reduced risk of breast cancer. There is also no evidence either that genistein would block ER-α activation or prevent ovarian estrogen from activating the estrogen receptor. Several other mechanisms have been proposed to explain soy’s beneficial health effects (85). In experimental systems, genistein exhibits a wide range of biologic changes that could potentially reduce breast cancer risk, although many of these changes occur only at pharmacologic concentrations (10,11). One mechanism attributed to genistein at physiologic concentrations is its ability to act as an antioxidant. However, in human studies antioxidant effects have been mixed, with some studies finding no effect at physiologic doses (86,87) and others observing effects for some but not other biomarkers of antioxidant effect (88,89); the latter study used an isoflavone supplement with isoflavone levels fourfold higher than those in a typical Japanese diet (90).

Like estrogens (91), genistein may induce cell differentiation (24). In the rodent mammary gland, genistein induces morphologic differentiation, reducing the number of targets for malignant transformation (81). Epithelial differentiation is a hallmark outcome of pregnancy that has been proposed to explain why pregnancy reduces breast cancer risk (91). However, in older women, whose breasts are more likely to have acquired malignant cells than those of younger women, estrogens or genistein may promote the growth of malignant cells; increased breast epithelial differentiation may not be sufficient to counteract these effects.

There are also data suggesting that soy or isoflavones could increase breast cancer risk. Exposure to physiologic concentrations of genistein in vitro activates ER-α and induces normal and malignant cell proliferation in vitro and in vivo (13–16,18,35,36). These findings suggest an estrogenic effect and a theoretical potential for increased breast cancer risk, although the estrogenic effects of soy appear to be minimal, even in postmenopausal women (83,84). Data from human tumor xenograft models suggest that genistein may reduce the antineoplastic effects of tamoxifen (22,23), although daidzein was found to enhance the effect of tamoxifen (23). However, recurrence after excision of the primary tumor was reduced by addition of soy protein to the diets of rats before administration of carcinogen (92). The effect may depend on the form of soy or isoflavone. A recent study in the ovariectomized xenograft model showed that the degree of processing of soy influences the biologic activity of the resulting soy products (93). Soy flour did not stimulate tumor growth, whereas tumors in animals receiving progressively more refined soy products showed growth enhancement, despite equivalent concentrations of genistein intake in all groups. This result suggests that highly processed soy supplements such as soy protein isolate, isoflavone-rich soy extracts, or isoflavone capsules exhibit activity that is not present in foods made from soybeans or soy flour, such as those consumed in Asian diets. Little or no research has been done in women with long-term consumption of such highly processed soy supplements.

This meta-analysis of the epidemiologic literature reveals a small inverse association between soy intake and breast cancer risk in both Western and Asian women. Limitations of the available data do not permit exclusion of artificial explanations for the apparent effect, such as misclassification, uncontrolled confounding, or selection bias. The similar magnitude of the apparent risk reduction in Western and Asian populations, despite large differences in exposure levels, suggests either artifact, differential levels of confounding and misclassification, or true differences in effect based on timing of exposure.

Because of the many gaps in knowledge and inconsistencies revealed by this analysis and review of relevant studies, we cannot recommend widespread use of high-dose isoflavone supplements by women at high risk for breast cancer or by breast cancer survivors. However, there are no data to suggest that consumption of soy foods in amounts consistent with an Asian diet is detrimental to breast health, and such a diet is likely to confer benefits to other aspects of health. Now that soy food consumption is increasing in Western societies, epidemiologic studies should evaluate exposure at different periods of life, and focus on better quantitation of soy foods and soy additives to food, combined with use of repeated urine isoflavone measurements with consistent timing and efforts to include an adequate range of exposures. Furthermore, experimental studies based on physiologic dose levels are needed to clarify estrogenic and nonestrogenic isoflavone activities in the breast.

REFERENCES


NOTES

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