
Li-Qiang QIN1,2*, Jia-Ying XU1, Pei-Yu WANG3 and Kazuhiko HOSHI2

1 School of Radiology and Public Health, Soochow University, Suzhou, 215123, China
2 Department of Obstetrics and Gynecology, School of Medicine, University of Yamanashi, Yamanashi 409–3898, Japan
3 Department of Social Medicine and Health Education, School of Public Health, Peking University, Beijing, 100083, China

(Received May 1, 2006)

Summary Many studies have suggested that the intake of soy products may protect against the occurrence of breast cancer because of the considerable amount of isoflavones they contain. To review the results of the observational studies, we performed this meta-analysis of the relevant literature. We searched Medline for reports that examined the association between soyfood consumption (or isoflavone intake) and breast cancer risk from January 1966 to April 2006. The random-effects model was used to estimate the pooled relative risk (RR). Twenty-one independent studies (14 case-control studies and 7 cohort studies) were included in the final analysis. The pooled RR of breast cancer for soyfood intake was 0.75 with a 95% CI of 0.59–0.95. As the main types of soyfood in Japan and China, tofu and miso showed clear protective effects. Isoflavone intake resulted in a 20% decrease in risk (RR = 0.81, 95% CI 0.67–0.99). The pooled RR varied little according to study stratification. When the studies published in Japanese and Chinese were added, the inverse associations between soyfood, tofu and breast cancer risk became slightly stronger. The weak association of miso was possibly due to the high concentration of salt in miso soup. In the present analysis, we did not find strong evidence for publication bias in the combination of the studies. This meta-analysis supported the hypotheses that soyfood intake may be associated with a decreased risk of breast cancer due to the isoflavones. Further epidemiological studies need to be conducted with more comprehensive information about the soyfood, and more accurate assessment of the isoflavones.

Key Words breast cancer, soyfood, isoflavone, meta-analysis

Breast cancer is the most common cancer among women in Western countries and is second only to lung cancer as a cause of cancer death (1, 2). Despite a marked increase in recent years, the incidence rates for breast cancer in most Asian countries have been much lower than those in Western countries (2, 3). For example, the breast cancer incidence in China is about 6 times lower than that in the United States (3). Data from studies of migrant populations support the hypothesis that dietary changes may alter the risk of disease (4). Among the dietary items, soyfood, which is widely consumed in Asian countries, has drawn considerable interest in both the research community and the general public. Since 1995, the sales of soy-based products in the USA have increased 20% per year, with a large boost in 1999 when the US Food and Drug Administration (FDA) approved a health claim for soy’s cardiovascular benefits (5). In 2004, the American Soybean Association also recommended the FDA support a health claim for the association between soy intake and risk of certain cancers, including breast cancer. This recommendation, however, has not been accepted (6). The dispute about soy and breast cancer will continue. Soyfood is a rich source of isoflavones, a group of phytoestrogens that have been hypothesized to reduce the risk of breast cancer. Daidzein, genistein and their glucosides account for the major portion of isoflavones (7). Besides the antiestrogenic properties of isoflavones in possibly preventing breast cancers, isoflavones are antioxidants and possess other antitumor activities, including the inhibition of angiogenesis, topoisomerase and tyrosine kinase (8).

Up until now, the results from human and animal studies that assessed the association between soyfood or isoflavone intake and breast cancer risk have varied. Given the increasing incidence of breast cancer and the ever more popular consumption of soyfoods worldwide, it is imperative to investigate whether soyfood has beneficial effects on breast cancer risk. To address this issue, we performed a meta-analysis and provided a quantitative evaluation using published observational epidemiological studies.
Table 1. Characteristics of published epidemiological studies on soyfood consumption and breast cancer in women.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Area (year of enrollment)</th>
<th>Type of control</th>
<th>Intake comparison</th>
<th>OR/RR (95% CI)</th>
<th>Matched or adjusted variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee HP (1991) (13)</td>
<td>Singapore (1986–1988)</td>
<td>Hospital</td>
<td>Soyfood, 5.4 vs. third tertile</td>
<td>0.76 (0.50–1.12)</td>
<td>1, 4, 8, 11, 25</td>
</tr>
<tr>
<td>Lee HP (1992) (14)</td>
<td>Singapore (1986–1988)</td>
<td>Hospital</td>
<td>Soy food, 5.4 vs. third tertile</td>
<td>0.74 (0.50–1.12)</td>
<td>1, 4, 8, 11, 25</td>
</tr>
<tr>
<td>Hirose K (1995) (15)</td>
<td>Japan (1988–1992)</td>
<td>Hospital</td>
<td>Tofu, 3.5 vs. ≤ 1.6 g/d</td>
<td>0.78 (0.52–1.20)</td>
<td>1, 2, 3, 8, 12</td>
</tr>
<tr>
<td>Yuan JM (1995) (16)</td>
<td>China (1984–1986)</td>
<td>Population</td>
<td>Soy protein, Per g</td>
<td>1.07 (0.94–1.22)</td>
<td>1, 2, 4, 7–9, 11, 13, 18, 22</td>
</tr>
<tr>
<td>Wu AH (1996) (17)</td>
<td>USA (1981–1987)</td>
<td>Population</td>
<td>Tofu, 55+ vs. ≤ 12/y</td>
<td>0.66 (0.50–0.88)</td>
<td>1, 10, 20</td>
</tr>
<tr>
<td>Witte JS (1997) (18)</td>
<td>USA, Canada (1970–1989)</td>
<td>Sister(s)</td>
<td>Tofu, ≤ 1/wk vs. none</td>
<td>0.5 (0.2–1.1)</td>
<td>1, 2, 4, 12, 13</td>
</tr>
<tr>
<td>Dai Q (2001) (19)</td>
<td>China (1996–1998)</td>
<td>Population</td>
<td>Soy protein, Weekly vs. occasionally</td>
<td>0.78 (0.52–1.16)</td>
<td>1–6, 8, 9, 11</td>
</tr>
<tr>
<td>Horn-Ross PL (2001) (20)</td>
<td>USA (1995–1998)</td>
<td>Population</td>
<td>Soy protein, 1/16.6 g/wk</td>
<td>0.46 (0.28–0.75)</td>
<td>13, 14, 17, 24</td>
</tr>
<tr>
<td>Li W (2001) (21)</td>
<td>China (1996–1998)</td>
<td>Population</td>
<td>Tofu, 1/1 vs. m0</td>
<td>0.83 (0.70–1.13)</td>
<td>1, 2, 4, 5, 7–13</td>
</tr>
<tr>
<td>Shu XO (2001) (22)</td>
<td>USA (1984–1986)</td>
<td>Population</td>
<td>Soy protein, Weekly vs. occasionally</td>
<td>0.70 (0.55–0.90)</td>
<td>17, 24</td>
</tr>
<tr>
<td>Hirose K (2003) (23)</td>
<td>Japan (1989–2000)</td>
<td>Hospital</td>
<td>Tofu, 5/1 vs. ≤ 1/wk</td>
<td>0.58 (0.27–1.16)</td>
<td>1, 2, 4, 5, 7–13</td>
</tr>
<tr>
<td>Peterson J (2004) (24)</td>
<td>Greece (1989–1991)</td>
<td>Hospital</td>
<td>Tofu, 3/d vs. 0</td>
<td>0.93 (0.73–1.21)</td>
<td>1, 2, 8, 9</td>
</tr>
<tr>
<td>Wu AH (2005) (25)</td>
<td>USA (1995–1998)</td>
<td>Population</td>
<td>Soy protein, Weekly vs. occasionally</td>
<td>0.40 (0.24–0.66)</td>
<td>1, 2, 5, 10, 12</td>
</tr>
<tr>
<td>Linseisen J (2006) (27)</td>
<td>China (1992–1995)</td>
<td>Population</td>
<td>Soy protein, Daily vs. ≤ 1/wk</td>
<td>1.0 (0.7–1.3)</td>
<td>1, 2, 7, 8, 13</td>
</tr>
<tr>
<td>Sanderson M (2008) (28)</td>
<td>USA (1996–1998)</td>
<td>Population</td>
<td>Soy protein, Daily vs. ≤ 1/wk</td>
<td>1.0 (0.7–1.3)</td>
<td>1, 2, 7, 8, 13</td>
</tr>
<tr>
<td>Lee MM (2005) (29)</td>
<td>Taiwan (1996–1999)</td>
<td>Hospital</td>
<td>Tofu, 3/d vs. 0</td>
<td>0.93 (0.7–1.2)</td>
<td>1, 2, 8, 9</td>
</tr>
<tr>
<td>Hirose K (2005) (31)</td>
<td>Japan (2001–2002)</td>
<td>Hospital</td>
<td>Soy protein, Daily vs. ≤ 1/wk</td>
<td>1.0 (0.7–1.3)</td>
<td>1, 2, 8, 9</td>
</tr>
<tr>
<td>Shannon J (2005) (32)</td>
<td>China (1995–2000)</td>
<td>Population</td>
<td>Soy protein, Daily vs. ≤ 1/wk</td>
<td>1.0 (0.7–1.3)</td>
<td>1, 2, 8, 9</td>
</tr>
<tr>
<td>Cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirayama T (1990) (33)</td>
<td>Japan (1960–1982)</td>
<td>Population</td>
<td>Soy or tofu, Daily vs. non-daily</td>
<td>0.85 (0.68–1.06)</td>
<td>1, 3</td>
</tr>
<tr>
<td>Greenstein J (1996) (34)</td>
<td>USA (1986–1993)</td>
<td>Population</td>
<td>Soy or tofu, Consumers vs. nonconsumers</td>
<td>0.76 (0.51–1.18)</td>
<td>1, 2, 3, 8, 12, 16</td>
</tr>
<tr>
<td>Key TJ (1999) (35)</td>
<td>Japan (1969–1993)</td>
<td>Population</td>
<td>Soy protein, Weekly vs. occasionally</td>
<td>1.07 (0.78–1.47)</td>
<td>1, 2, 3, 8, 12, 16</td>
</tr>
<tr>
<td>Horzu-Ross PL (2002) (36)</td>
<td>USA (1995–1998)</td>
<td>Teachers</td>
<td>Genistein, Fifth vs. first quintile</td>
<td>0.88 (0.69–1.12)</td>
<td>1, 2, 3, 8, 12, 16</td>
</tr>
<tr>
<td>Yamamoto S (2003) (37)</td>
<td>Japan (1990–1999)</td>
<td>Population</td>
<td>Tofu, 3 vs. 1 cup/d</td>
<td>0.81 (0.59–1.12)</td>
<td>1, 2, 3, 8, 12, 16</td>
</tr>
<tr>
<td>Keinan-Boker I (2004) (38)</td>
<td>Netherslandes (1993–2001)</td>
<td>Population</td>
<td>Soy or tofu, Daily vs. ≤ 1/wk</td>
<td>0.6 (0.4–0.9)</td>
<td>1, 2, 3, 8, 12, 16</td>
</tr>
<tr>
<td>Adebamowo CA (2005) (39)</td>
<td>USA (1991–1999)</td>
<td>Nurses</td>
<td>Beans or lentil, ≤ 1/wk vs. ≤ 2/wk</td>
<td>0.85 (0.57–1.00)</td>
<td>1, 2, 3, 8, 12, 16, 18, 25</td>
</tr>
</tbody>
</table>

adjusted estimate was chosen from each study. Some category of consumption were extracted, and the most and 95% CI for the highest vs. the lowest (the referent) was available to calculate these parameters. The OR/RR and its 95% confidence interval (CI), or have raw data studies (OR) or the relative risk in cohort studies (RR) analysis had to provide the odds ratio in case-control data were included. The studies included in this meta-
tions that reported the same item, only the most recent and breast cancer risk. In studies with multiple publica-
that evaluated the exposure to soyfood (or isoflavones) combined with breast cancer. Because some studies that included soy (bean, soybean, soyfood, tofu, miso) and traditional Japanese soyfood. Therefore, the search terms included soy (bean, soybean, soyfood, tofu, miso) and isoflavone (phytoestrogen, daidzein, genistein) combined with breast cancer. Because some studies that may have presented data on the soyfood (isoflavone) intake may not have included these specific terms in the abstracts, we also carried out a broader search for all intake may not have included these specific terms in the abstracts, we also carried out a broader search for all kinds of isoflavones were observed across the studies. For example, tofu (bean curd) is a soyfood commonly consumed by Asian people, and miso (fermented soybean paste) is a traditional Japanese soyfood. Therefore, the search terms included soy (bean, soybean, soyfood, tofu, miso) and isoflavone (phytoestrogen, daidzein, genistein) combined with breast cancer. Because some studies that may have presented data on the soyfood (isoflavone) intake may not have included these specific terms in the abstracts, we also carried out a broader search for all studies that looked at diet and breast cancer. For completeness, we reviewed references listed in the available publications to identify additional studies. Soy, bean, soy products and soy food used in the original studies were defined as soyfood in the present analysis.
The studies considered in this meta-analysis were epidemiological studies (case-control or cohort studies) that evaluated the exposure to soyfood (or isoflavones) and breast cancer risk. In studies with multiple publications that reported the same item, only the most recent data were included. The studies included in this meta-analysis had to provide the odds ratio in case-control studies (OR) or the relative risk in cohort studies (RR) and its 95% confidence interval (CI), or have raw data was available to calculate these parameters. The OR/RR and 95% CI for the highest vs. the lowest (the referent) category of consumption were extracted, and the most adjusted estimate was chosen from each study. Some studies separated the risk estimates according to the menopausal status. In this situation, we pooled the risk estimate of premenopausal women and postmenopausal women, weighed by the inverse of the variance. In the present meta-analysis, OR and RR were combined to calculate the pooled RR. In practice, the OR and RR yield a similar risk estimate, because breast cancer is a rare occurrence. Two researchers performed data extraction independently. Differences in data extraction were resolved by discussion.
The pooled RR was calculated using the DerSimonian-Laird method, and the homogeneity was tested using the Q test (9). Because the estimate from the random-effects considers both intra- and inter-study variation (10), it is more conservative and hence more appropriate than that from the fixed-effects model. Thus, we showed the results from the random-effects model, regardless of their condition of homogeneity. In fact, the fixed effects and the random effects provide similar results across homogenous studies. The detailed calculation formulas have been described in our previous study (11). The results of meta-analysis may be biased if published studies are dependent on results. This bias was evaluated using the funnel plot and the Egger regression asymmetry test (12).

### METHODS

To identify the studies of interest, we conducted a computerized search of the Medline (January 1966 to April 2006) literature. Since soyfood is a traditional food in Japan and China, there should be some studies that were published in these two languages. Thus, we also searched in Japan Centra Revuo Medicina (ichushi) for studies written in Japanese and Chinese Journal Database (CNKI) for studies in Chinese. Different types of soyfoods and different kinds of isoflavones were observed across the studies. For example, tofu (bean curd) is a soyfood commonly consumed by Asian people, and miso (fermented soybean paste) is a traditional Japanese soyfood. Therefore, the search terms included soy (bean, soybean, soyfood, tofu, miso) and isoflavone (phytoestrogen, daidzein, genistein) combined with breast cancer. Because some studies that may have presented data on the soyfood (isoflavone) intake may not have included these specific terms in the abstracts, we also carried out a broader search for all studies that looked at diet and breast cancer. For completeness, we reviewed references listed in the available publications to identify additional studies. Soy, bean, soy products and soy food used in the original studies were defined as soyfood in the present analysis.
The studies considered in this meta-analysis were epidemiological studies (case-control or cohort studies) that evaluated the exposure to soyfood (or isoflavones) and breast cancer risk. In studies with multiple publications that reported the same item, only the most recent data were included. The studies included in this meta-analysis had to provide the odds ratio in case-control studies (OR) or the relative risk in cohort studies (RR) and its 95% confidence interval (CI), or have raw data was available to calculate these parameters. The OR/RR and 95% CI for the highest vs. the lowest (the referent) category of consumption were extracted, and the most adjusted estimate was chosen from each study. Some studies separated the risk estimates according to the menopausal status. In this situation, we pooled the risk estimate of premenopausal women and postmenopausal women, weighed by the inverse of the variance. In the present meta-analysis, OR and RR were combined to calculate the pooled RR. In practice, the OR and RR yield a similar risk estimate, because breast cancer is a rare occurrence. Two researchers performed data extraction independently. Differences in data extraction were resolved by discussion.
The pooled RR was calculated using the DerSimonian-Laird method, and the homogeneity was tested using the Q test (9). Because the estimate from the random-effects considers both intra- and inter-study variation (10), it is more conservative and hence more appropriate than that from the fixed-effects model. Thus, we showed the results from the random-effects model, regardless of their condition of homogeneity. In fact, the fixed effects and the random effects provide similar results across homogenous studies. The detailed calculation formulas have been described in our previous study (11). The results of meta-analysis may be biased if published studies are dependent on results. This bias was evaluated using the funnel plot and the Egger regression asymmetry test (12).

### RESULTS

We found 27 epidemiological publications in English examining the association between soyfood consumption (or isoflavone intake) and breast cancer risk (Table 1) (13–39). There were 4 studies each published in Japanese and in Chinese (Table 2) (40–47). As for those studies, they were conducted in one city or area either in Japan or China. Two of the Japanese studies were cohort studies and all of Chinese studies were case-control studies. Generally speaking, these studies contained small numbers of participants and less adjusted variables. Considering the low quality of these studies, we will focus on the analysis of studies written in English,
unless otherwise indicated.

In 1991, Lee et al. reported their observations for premenopausal women (13), and then added the data from postmenopausal women in 1992 (14). The latter was retained in this analysis. Hirose et al. reported their study 10 y ago (15), and these cases were included in a 2003 publication (23). Thus, the former was excluded from the meta-analysis. However, a recent publication from the same project used the cases who were diagnosed in 2001–2002 (31), differing from the former in 1989–2000 (23). We considered it to be an independent study because of the non-overlap of cases. Similarly, Wu et al. separately collected cases who were diagnosed in 1983–1987 (17) and 1995–1998 (22, 25). They were two independent studies in our meta-analysis. In addition, three publications shared the data from the Shanghai Breast Cancer Study, with almost the same cases (19, 21, 32). Two publications from a randomized trial of breast self-examination in Shanghai had to be considered as one study (28, 30). However, two studies reported by Horn-Ross et al. originated from different projects: the Bay Area Breast Cancer Study (case-control study) (20) and the California Teachers Study (cohort study) (36).

Finally, 14 independent case-control studies and 7 cohort studies entered our analysis. Among these studies, 10 were conducted in Asia (Japan, China and Singapore). Seven studies were carried out in the USA, and 4 in Europe. However, the population in two USA studies (17, 25) and one European study (26) were Asian migrant women. Seven studies did not provide histological information (18, 20, 22, 25, 26, 35, 38), and described disease as incident (primary) breast cancer or identification by the cancer registry. Witte’s study collected the cases with bilateral breast cancer (18). In addition, one study restricted the cases to invasive breast cancer (36). All studies used food frequency questionnaires (FFQ) to quantify soyfood and isoflavone intake, of which 14 studies claimed to have validated FFQ. In general, dietary information was collected by interview in the case-control studies, and by mail in the cohort studies. Age was matched or adjusted in each study. The more recent studies usually incorporated more adjustments in their design.

According to our criteria described above, nine studies chose soyfood as a dietary item (14, 21, 25, 28, 29, 31, 34, 37, 39), where four studies found the significant inverse association with breast cancer risk. When combining these studies, the pooled RR was 0.75 with a 95% CI of 0.59–0.95. As the main types of soyfood, the pooled RRs of tofu and miso were 0.78 (95% CI 0.69–0.88) and 0.88 (95% CI 0.78–1.00), respectively, which suggested clear protective effects (Fig. 1). Only three studies listed soy protein as the item in five publications (13, 14, 16, 19, 28) and it was weakly convincing even when combined.

In our meta-analysis, there were two studies that observed soyfood consumption in American women (34, 39). Moreover, the item was termed “soy or tofu” or “beans or lentils,” neither having a detailed explanation. Thus, these two American studies were inappropriate to combine with Asian studies, since Chinese and Japanese have similar traditional habits of soyfood consumption. When these two studies were excluded, the pooled RR showed a slightly stronger decrease of breast cancer risk with 0.71 (95% CI 0.59–0.95), 0.78 (95% CI 0.69–0.88) and 0.88 (95% CI 0.78–1.00), respectively.
RR in premenopausal women. which is slightly less strong than their corresponding
by 36% (RR = 0.88) (95% CI 0.72–0.96) (17, 21, 23, 29, 31). In addition, the
soyfood (miso) and breast cancer risk. To our surprise, all of studies written in
Chinese found an inverse association between soyfood (tofu) and breast cancer risk (Table 2). When these studies were combined with the
English, the inverse association became slightly stronger in the studies of soyfood and tofu. However, the association between miso and breast cancer risk disappeared (Table 4).

Although three cohort studies combined showed no association (RR = 0.81, 95% CI 0.59–1.01), we should note that two of them were conducted in Western women, where soyfood consumption is very low (14, 39).

Besides the analysis of stratification, we also performed a sensitivity analysis. We calculated pooled RR after excluding the study with the largest weight, with the largest or smallest RR. For soyfood and tofu, none of the pooled RR changed by greater than 0.03 and no confidence intervals changed in a way that would affect interpretation. However, the inverse association disappeared in miso study after excluding the study with the largest weight (pooled RR = 0.88 with a 95% CI 0.72–1.06) or excluding the study with the smallest RR (pooled RR = 0.90 with a 95% CI 0.78–1.03).

Isoflavones, such as daidzein and genistein, were observed in the studies conducted mostly in the Western countries (20, 22, 24, 26, 27, 37, 38). Isoflavone intake resulted in a 20% decrease of risk, with a significant difference (RR = 0.81, 95% CI 0.67–0.99). Daidzein and genistein intakes showed similar pooled RRs, with a larger 95% CI than isoflavone (Table 3).

Among eight studies published in Japanese and Chi-

Table 3. The pooled relative risk of breast cancer for isoflavone intakes.

<table>
<thead>
<tr>
<th>Isoflavone</th>
<th>No. of studies</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.81</td>
<td>0.67–0.99</td>
</tr>
<tr>
<td>Daidzein</td>
<td>4</td>
<td>0.82</td>
<td>0.62–1.09</td>
</tr>
<tr>
<td>Genistein</td>
<td>4</td>
<td>0.76</td>
<td>0.55–1.05</td>
</tr>
</tbody>
</table>

Table 4. The pooled relative risk and its 95% confidence interval with and without the addition of studies published in Japanese and Chinese.

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soyfood</td>
<td>0.75</td>
<td>0.59–0.95</td>
</tr>
<tr>
<td>Tofu</td>
<td>0.78</td>
<td>0.70–0.88</td>
</tr>
<tr>
<td>Miso</td>
<td>0.88</td>
<td>0.78–1.00</td>
</tr>
</tbody>
</table>

There is no strong evidence for publication bias for the consumption of soyfood, miso or isoflavone. Figure 2 shows the funnel plot of the all the independent English studies on soyfood consumption and isoflavone intake. The test of linear regression showed that the plots remained symmetrical for soyfood (intercept = 0.54, with a 95% CI = −0.54–1.63), for tofu (intercept = −0.72, with a 95% CI = −2.40–0.99), for miso (intercept = 0.27, with a 95% CI = −1.77–1.33) and for isoflavone (intercept = −0.54, with a 95% CI = −1.68–0.6). All of the p values were larger than 0.1. Although we did not find a publication bias visually or in formal statistical testing, these tests possess a relatively low power to detect real publication bias when the number of individual studies in the meta-analysis is small. We also tested publication bias with a method that we used in our previous study (48). It can be considered that studies with significant results were easier to be published than those with nonsignificant results. Thus, we randomly added the nonsignificant results shown in the analysis and calculated new pooled RR. Even if 30 of the nonsignificant results were added, the pooled RRs for soyfood, tofu, miso and isoflavones changed little. This suggested that unpublished studies, like these published studies with nonsignificant results, did not seem to influence this inverse association over a large range.
**DISCUSSION**

For a long time, it was considered that fat intake provided the strongest dietary link with breast cancer risk. This belief was based largely on the evidence that Asian women, with a low incidence of breast cancer, consume less fat than Western women, with a high incidence. However, more and more studies have failed to observe a strong positive association between fat intake and breast cancer risk (15, 16, 18, 32, 35, 36, 49). Thus, several alternative dietary hypotheses, including soyfood intake, have been extensively studied recently. Thirty years ago, a study conducted in Hawaii using Japanese migrants found that men whose wives were free from breast cancer ate more Japanese food, especially Japanese soup, than breast cancer spouses (50). In another early study carried out in Japan, the mortality rate from breast cancer was lower with the increase in soyfood intake, and it was not included under soyfood (34). Several studies, Yamamoto used miso as an independent item, whereas in the studies conducted in Asia, soyfood was generally included in soyfood in Japanese studies. For example, although soybean paste soup was consumed in Japan, the mortality rate from breast cancer was lower with the increase of soybean paste soup consumption (51). Soyfood has received a great attention since the publication of Lee’s study, showing a clear protective effect against breast cancer (13). Several subsequent studies, but not all, have showed the beneficial effects of soyfood, whereas there have been no epidemiological studies reporting adverse effects on breast cancer (Table 1). When combining these published epidemiological studies, we found that soyfood intake is related to a decreased risk of breast cancer. Women with the highest intake of soyfood were 25% more likely to inhibit breast cancer than women with the lowest intake. When the studies published in Japanese and Chinese were added, approximate 30% of breast cancer risk was protected by the highest intake of soyfood.

Historically, soyfood consumption varies widely between Asian countries and Western countries. The upper category of intake in Americans is still low compared to the lowest category of women in Asia in some studies. Even in the studies conducted in Asia, soyfood covers different kinds of food. For example, although miso was generally included in soyfood in Japanese studies, Yamamoto used miso as an independent item, and it was not included under soyfood (37). In addition, natto (fermented soybean) is a special Japanese soyfood and was not included in the FFQ for Chinese. Thus, we could not avoid the bias from the misclassification of soyfood because of the differences in the interviews and questionnaires among studies. To our surprise, soyfood was not included in the FFQ in Keinan-Boker’s study, where isoflavones were analyzed, although these foods are infrequently consumed in the Netherlands (38). On the other hand, modern soyfood (energy bar, soy milk), consumed mostly in Western countries, differs from traditional Asian soyfood (tofu, miso). The former contains considerable amounts of sugars and has a relatively high energy density, a potential risk factor for breast cancer (52). Although these confounding factors cannot be ruled out, most of the studies published in English adjusted for them, together with reproductive history, in multivariate analysis.

Unlike soyfood, tofu and miso are relatively homogenous components in each study. In our meta-analysis, tofu and miso showed 20% and 10% significant reductions for breast cancer, respectively. The weaker association of miso than tofu is possibly due to the high concentration of salt in miso soup (23). Furthermore, not every study published in Japanese found protective effects of miso and soyfood, while all of studies in Chinese found an inverse association between soyfood and breast cancer risk without the interference of miso, which is generally not consumed in China. Two studies collected tofu information from premenopausal women (18) or postmenopausal women (34). The pooled RR after the exclusion of these two studies was 0.79 with a 95% CI 0.69–0.90. This pooled RR also reflected the risk for Asian women because only these two studies were conducted in Western women.

The developmental period of women has been considered by some studies because the occurrence of breast cancer is related to hormonal levels (53). In addition to the premenopausal women showing a stronger association than postmenopausal women, two studies clearly indicated that soyfood intake during early life had a lasting protective effect on breast cancer (21, 22). This was supported by animal studies that early postnatal or prepubertal exposure to isoflavones was prone to reduce the susceptibility to mammary tumors in adult animals (54, 55). In contrast, isoflavones stimulated carcinogen-induced tumorigenesis in adult female rats at a dose that is comparable to the approximately daily consumption in Asian people (56, 57). This is why the positive effects of soy against breast cancer come primarily from Asian populations who have usually consumed soyfood since childhood.

In a meta-analysis conducted by Trock et al., high soy protein intake was associated with reduced breast cancer risk (pooled RR = 0.86, 95% CI 0.75–0.99) (58). Our analysis, with a stronger inverse association, is consistent with that analysis. Although the completion of our collection (to April 2006) was only one and half years later than that in Trock’s analysis (to December 2004), we found 9 recent studies that were not included in the Trock’s study. We also expanded the search to the studies published in Japanese and Chinese. Finally, the number of studies in our analysis was as twice as that in Trock’s analysis. In fact, the most important difference between the two analyses was the observational items. Trock tried to convert the different measures of exposure into the amount of soy protein. However, this exercise had to involve multiple assumptions (6). For FFQ data, the author created an equation based on data about tofu in Japan and America to calculate the amount of soy protein. Thus, this equation may not be appropriate when participants were not from Japan or America, or when the collective of soyfood was reported. For this reason, only three studies listed soy protein as an observational item. Therefore, we did not extract soy protein from the original data. Alternatively, we observed the effects of tofu and miso on the breast cancer risk, which was not done in Trock’s analysis. The other difference was that two
studies reporting urinary isoflavone levels were included in Trock’s study. Although the equation converting urinary isoflavone levels to soy protein was validated, the problem was that urinary isoflavone levels just reflect a short-term intake of soy, even the intake of the last meal. Thus, these two studies were not included in our meta-analysis, where all studies used FFQ to collect diet information.

In Trock’s study, the amount of isoflavone also was converted into the intake of soy protein. Our study used isoflavone as an item to observe its effect on breast cancer because almost all mechanistic studies relate specifically to the isoflavones in soyfood, which play anti-cancer roles in hormone-dependent and hormone-independent ways (8). Because food composition tables do not usually include the values for isoflavones, epidemiological studies that calculated isoflavones were not reported until 2001 (19, 20, 59). In general, the isoflavone intake in Western countries has been estimated to be an average of <1 mg/d (24, 27, 36), whereas it is as high as 50 mg/d in Chinese and Japanese populations (19, 59). Among five studies in non-Asian women, only one study found an inverse association between genistein or daidzein (not isoflavone) intake and breast cancer risk (27). When combining the studies of Western women, the association became negative (RR=0.95, 95% CI 0.76–1.19). Thus, the isoflavone intake in non-Asian women is too low to decrease the breast cancer risk (60). A study of first-generation of South Asian immigrants living in the UK showed an inverse relationship (26). In spite of low reported isoflavones, we speculated that the high intake of phytoestrogens, such as lignans, in their host countries may have contributed to these protective effects. Two studies in Asian populations, living in Japan (a prospective study) and the USA (a case-control study), both of which have a high intake of isoflavones, reported a strong inverse association with breast cancer risk (22, 37). Among the population with the high intake of soyfood, the urinary excretion of isoflavones was also associated with the reduction in breast cancer risk (61). Although the data of isoflavones was mostly obtained from Western women with a low intake, the pooled RR from the total information still suggested a decreased risk of breast cancer associated with a high intake of isoflavones. Because there were only four studies involved, the daidzein or genistein showed a weak inverse association with breast cancer. To increase the test power, more epidemiological studies with the observation of isoflavones in Asian women should be encouraged.

Although our meta-analysis has several limitations, which cannot be avoided in meta-analysis, our findings provide support for the hypothesis that high soyfood intake may be associated with a decreased risk of breast cancer due to the considerable amount of isoflavones. Further epidemiological studies should consider including more comprehensive information about soyfood, more accurate assessment of isoflavones and the different effects among age groups.

Acknowledgments

Li-Qiang Qin is funded by Japan Society for the Promotion of Science (JSPS) postdoctoral fellowship for foreign researchers.

REFERENCES


