Health Study) provides further evidence that isoflavones play a role in reducing the risk of breast cancer. We are also conducting a cohort study (Japan Nurses’ Health Study) (2), with a baseline population of 39,713, and analyzing the association between phytoestrogen intake and breast cancer history among 4,128 postmenopausal women. We identified 176 women who had a history of breast cancer and who answered a food frequency questionnaire in which we asked questions regarding intake of soy products (including intake of tofu, natto, and miso soup, separately) and history of female hormone use (including hormone replacement therapy). We computed the odds ratios (ORs) of breast cancer by using a logistic model. The following variables were included as potential confounders: age, body mass index, smoking history, number of pregnancies, age at menarche, hormone replacement therapy use, female hormone use, educational level, alcohol consumption, and food intake (three categories: ≤1 day/week, 2–5 days/week, and ≥6 days/week).

Compared with women with a low intake of miso soup (≤1 day/week), women with a high intake (≥6 days/week) had a statistically significantly reduced risk of breast cancer (OR = 0.51, 95% confidence interval [CI] = 0.30 to 0.84). This reduced risk remained statistically significant after adjusting for female hormone use and other variables. Natto intake was not statistically significantly associated with breast cancer (OR = 1.07, 95% CI = 0.61 to 2.00). However, women with a high intake of tofu had a statistically significantly increased risk of breast cancer (OR = 1.73, 95% CI = 1.02 to 3.02).

Why the association between intake of natto or tofu and breast cancer history is different than the association between intake of miso soup and breast cancer history is unclear. However, one possibility involves the chemical structure of isoflavones and the method of cooking. Isoflavone glucoside is easily altered during extraction, processing, and cooking. Hot aqueous extraction to produce tofu results in the formation of β-glucoside conjugates (3). Fermentation to produce miso and natto forms aglucones (4). Although the total isoflavones in food are not affected under usual cooking conditions, high temperature causes an increase in aglucones and a decrease in total isoflavones. Because aglucones are more potent and more rapidly absorbed than β-glucoside conjugates, fermentation products such as miso soup and natto may have more anticarcinogenic effects than glucoside conjugates. A second possibility is that women with a history of breast cancer at menopause may ingest more tofu than women with no history of breast cancer. A history of breast cancer is associated with an increase in use of dietary soy for menopause symptoms (5), and a main source of soy products is tofu (6). We found an association between high tofu intake and a history of breast cancer among women aged 50–55 years (OR = 2.09, 95% CI = 1.07 to 4.38). However, we found no association between other soy products (natto and miso soup) and breast cancer history by subgroup analysis. Our finding regarding tofu intake and breast cancer may be explained by this temporal increase of tofu intake around menopause. We caution that when analyzing the effects of soy product consumption for women nearing menopause, attention to the type of soy product and the temporal increase of soy product consumption, especially tofu intake, is needed.

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REFERENCES


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RESPONSE

In our article (1), we showed an association between breast cancer risk and intake of miso soup and isoflavones in a prospective cohort study of Japanese women. Furthermore, the association between breast cancer risk and soyfood and isoflavone intake was stronger for postmenopausal women than for premenopausal women.

From their cross-sectional analysis of their cohort, Fujimaki and Hayashi report a negative association between breast cancer history and miso soup intake, no association with natto intake, and a positive association with tofu intake. They speculated that the isoflavones included in miso soup and natto may be more anticarcinogenic because they are aglucones, which are more potent and more rapidly absorbed than β-glucoside–conjugated isoflavones, such as those found in tofu. Their interpretation is plausible based on that theory and on previous in vivo and in vitro studies, and it is an important to note that the effects of isoflavones may vary among soyfoods and those effects should be assessed in humans. Their results—that an inverse association was not observed for soyfoods but was observed for miso soup—are consistent with our results, especially if the majority of women with a history of breast cancer had breast cancer before menopause. How-
ever, we showed an inverse association between relative risk estimates for both miso soup and soyfoods and breast cancer, although that for soyfoods was not statistically significant. Because the items in our baseline questionnaire were too broad to investigate differences associated with specific soyfoods such as miso soup, natto, and tofu, we think the differences in our results between miso soup and soyfoods may arise from variations in exposure measurements rather than from variations in the effects of soyfoods. Possible differences associated with various soyfoods should be investigated using a more precise questionnaire (2).

Fujimaki and Hayashi suggested that their different results for miso soup and tofu may be due to the increase in tofu use for symptoms of menopause. However, the study they cite for increased use of dietary soy was conducted among American women (3). Such extrapolation may not necessarily apply to Japanese women because alternative therapies for symptoms of menopause can vary over time and among countries and ethnic groups. We know of no studies that examined the increase of soyfood use for symptoms of menopause in Japan. Our data did not show increased isoflavone intake for women of perimenopausal age but did show a linear increase according to age [Table 2 of (1)]. Their data show a positive association between tofu intake and breast cancer history but do not necessarily show increased tofu intake for women aged 50–60 years. In addition, results from the study by Fujimaki and Hayashi came from a cross-sectional analysis of their cohort, not from a prospective follow-up. Cross-sectional analyses may sometimes lead to erroneous cause-and-effect relationships because they analyze the exposure and the endpoint data collected simultaneously. For example, Fujimaki and Hayashi show that women who have a history of breast cancer consume more miso soup, but this observation may reflect the fact that the women changed their eating habits after they were diagnosed with breast cancer. Consequently, we might observe a spurious association implying that tofu intake increased the risk of breast cancer. To examine the possible increase of soyfood intake during the perimenopausal period, data for soyfood intake must be collected for pre-, peri-, and postmenopausal periods. In addition, the sensitivity of cancer diagnoses by self-report is low among Japanese women, although the sensitivity for breast cancer history is higher than that for other cancers (4). Therefore, results from cross-sectional studies, especially those that include self-reported cancer as an endpoint, should not be used in etiologic studies examining the association of cancer with diet.

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