# Soyfood Intake during Adolescence and Subsequent Risk of Breast Cancer among Chinese Women[1]

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## Abstract

**Many experimental but few epidemiological studies have suggested that soyfoods and their constituents have cancer-inhibitory effects on breast cancer. No epidemiological study has evaluated the association of adolescent soyfood intake with the risk of breast cancer. To evaluate the effect of soyfood intake during adolescence, one of the periods that breast tissue is most sensitive to environmental stimuli, on subsequent risk of breast cancer, we analyzed data from a population-based case-control of 1459 breast cancer cases and 1556 age-matched controls (respective response rates were 91.1% and 90.3%). Information on dietary intake from ages 13–15 years was obtained by interview from all study participants and, in addition, from mothers of subjects less than 45 years of age (296 cases and 359 controls). Odds ratios (ORs) and 95% confidence intervals (CIs) derived from unconditional logistic models were used to measure soyfood intake and breast cancer risk. After adjustment for a variety of other risk factors, adolescent soyfood intake was inversely associated with risk, with ORs of 1.0 (reference), 0.75 (95% CI, 0.60–0.93), 0.69 (95% CI, 0.55–0.87), 0.69 (95% CI, 0.55–0.86), and 0.51 (95% CI, 0.40–0.65), respectively, for the lowest to highest quintiles of total soyfood intake (trend test, $P < 0.001$). The inverse association was observed for each of the soyfoods examined and existed for both pre- and postmenopausal women. Adolescent soyfood intakes reported by participants' mothers were also inversely associated with breast cancer risk ($P$ for trend $< 0.001$), with an OR of 0.35 (95% CI, 0.21–0.60) for women in the highest soyfood intake group. Adjustment for rice and wheat products, the major energy source in the study population, and usual adult soyfood intake did not change the soyfood associations. Our study suggests that high soy intake during adolescence may reduce the risk of breast cancer in later life.**

## Introduction

The incidence rate of breast cancer varies worldwide, with the rate of Chinese and other Asian women only being one-third to one-half of that for Caucasian women (1). Migration and ecological studies have suggested that this variation is largely the result of environmental rather than genetic differences, and dietary variability has been implicated (2). Numerous epidemiological studies focusing on dietary fat and breast cancer association have found no or weak association between dietary fat intake and breast cancer risk (2). Evidence from animal, *in vitro*, and a few epidemiological studies, on the other hand, has been accumulating to suggest that soyfoods, which are consumed in significantly high quantities by Asian women, may contribute to the international variation of breast cancer risk (3–9).

Mammary glands develop primarily during the adolescent growth spurt (10). Adolescent mammary tissue is therefore probably more sensitive to carcinogenic insult than adult mammary tissue (11). Rats on soy-based diets during the prepubertal period or from puberty onward developed fewer chemically induced mammary tumors (4, 12). To our knowledge, no epidemiological study has been conducted to evaluate the association of soyfood intake during adolescence with the risk of breast cancer later in life. We report here results from the Shanghai Breast Cancer Study on the association between soyfood and other dietary intakes during adolescence and subsequent risk of breast cancer in adulthood.

## Materials and Methods

The Shanghai Breast Cancer Study, a population-based case-control study, was designed to recruit all women newly diagnosed with breast cancer between the ages of 25 and 64 years during the period from August 1996 to March 1998. All study subjects were permanent residents of urban Shanghai with no prior history of cancer and were alive at the time of interview. The human investigations were performed after approval by a local institutional review board and in accord with an assurance filed with and approved by the United States Department of Health and Human Services. Written informed consent was obtained from each study participant. Through a rapid case ascertainment system, supplemented by the population-based Shanghai Cancer Registry, 1602 eligible breast cancer cases were identified during the study period, and in-person interviews were completed for 1459 cases (91.1%). The major reasons for nonparticipation were refusal (109 cases, 6.8%), death before interview (17 cases, 1.1%), and inability to locate the subject (17 cases, 1.1%). All diagnoses were confirmed by two senior pathologists through the review of slides.

Received 10/12/00; revised 2/7/01; accepted 2/26/01.
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[1] Supported by USPHS Grant RO1CA64277 from the National Cancer Institute.
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The Shanghai Resident Registry, which registers all permanent residents in urban Shanghai, was used to randomly select controls from female residents who were frequency-matched to cases by age (5-year interval). The number of controls in each age-specific stratum was determined in advance according to the age distribution of the incident breast cancer cases reported to the Shanghai Cancer Registry from 1990–1993. Only women who lived at the registered address during the study period were considered to be eligible for the study. In-person interviews were completed for 1556 (90.3%) of the 1724 eligible controls identified. Reasons for nonparticipation included refusal (166 controls, 9.6%) and death or a prior cancer diagnosis (2 controls, 0.1%).

In addition to measurement of current weight, circumferences of the waist and hips, and sitting and standing heights, all study participants were interviewed face to face by trained interviewers. A structured questionnaire was used to elicit detailed information on demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight, and family history of cancer. Information on usual adult dietary intake was collected using a detailed quantitative FFQ,[3] including 76 raw food items/groups). Dietary intake during adolescence (between the ages of 13 and 15 years) was ascertained using a brief FFQ (17 raw food items/groups), and the following soyfood items were included: (*a*) tofu; (*b*) soymilk; and (*c*) soy products other than tofu (mainly dried/pressed tofu, bean cured cake or noodle, and fried tofu). In addition, subjects were asked about their consumption of fresh legumes (mostly peas and string or kidney beans and less often soy beans in the study population) and dried legumes (mostly soy beans, mung beans, and red beans). Using the adult FFQ, data on usual consumption of tofu, soy products other than tofu, soymilk, fresh and dried soy beans, mung beans, red beans, peas, string beans, kidney beans, and other fresh legumes during adulthood were specifically collected.

During the interview, each study participant was first asked how frequently she consumed a specific soyfood or group of soyfoods (daily, weekly, monthly, yearly, or never), followed by a question on how many lians (=50 grams) or jins (=500 grams) she ate per unit of time (day, week, month, or year). For example, when study participants were queried regarding consumption of tofu, they were first asked how often they ate tofu (daily, weekly, monthly, yearly, or never). If a study participant ate tofu on a weekly basis, she would be asked how many grams of tofu she ate each week. This method was used for collecting both adult and adolescent consumption data. For fresh legumes, subjects were asked to describe their consumption when the food was available on the market.

In addition to the self-reported adolescent dietary intake, biological mothers of all study participants under the age of 45 years who were alive and resided in urban Shanghai were approached to obtain their assessment of the index daughter's dietary intake from the age of 13–15 years, as well as *in utero* and early life exposures. The maternal questionnaire included the brief adolescent FFQ, perceived weight and height, physical activity of the index daughter during adolescence, exposures during mother's index pregnancy and breastfeeding, and birth weight. Of the 569 cases and 659 controls who reported being <45 years of age at interview, 372 case mothers and 439 control mothers were eligible for the substudy of adolescent and early life exposure. In-person interviews were completed for 296 (79.6%) case mothers and 359 (81.8%) control mothers. Forty-seven case mothers (12.6%) and 36 control mothers (8.2%) refused to participate in the study. Other reasons for nonparticipating include dementia (1.6%), health problems (3.5%), inability to locate the case mother (2.4%), and other miscellaneous reasons (0.3%) for case mothers. The corresponding rates were 2.5%, 4.6%, 1.1%, and 1.8% for control mothers. Daughter-mother pairs were interviewed on same day for 37% of subjects (41% cases and 33% controls), within 2 days for 25% subjects (24% cases and 26% controls), and within 1 month for 55% (49% cases and 60% controls). The vast majority (96.5%) of the mother-daughter pairs were interviewed by the same interviewer.

Dietary intake data were analyzed by individual food items and food groups for all subjects combined and separately for premenopausal women and postmenopausal women. Menopause was defined as cessation of menstrual period (excluding that caused by pregnancy and nursing) for at least 12 months before the interview date. Total soyfood consumption was measured by adding the soy protein of each specific soyfood. Quintile distributions among controls were used to categorize the dietary intake variables (soy protein contents and cut points are provided in the footnotes of Table 2). Adolescent intake of fresh and dried legumes was not included in the total soyfood because it was mixed with soy beans and other legumes. ORs were used to measure the association of breast cancer risk with adolescent dietary intake. Unconditional logistic regression models were used to obtain maximum likelihood estimates of the ORs and their 95% CIs after adjusting for potential confounding variables (13). Age was included as a continuous variable throughout, and categorical variables were treated as dummy variables in the model. Tests for linear trends were performed by entering the categorical variables as continuous parameters in the models. All statistical tests were based on two-sided probability using SAS 8.01.

## Results

Comparisons of cases and controls on demographic factors and traditional breast cancer risk factors, as well as usual adult energy and total fat intake, are presented in Table 1. Compared with controls, cases were slightly older (mean ages, 47.9 and 47.3 years for cases and controls, respectively; $P < 0.05$) and had an earlier age at menarche, a later age at menopause, and a later age at first live birth. Cases were more likely to have a higher education, a family history of breast cancer among first-degree relatives, a history of breast fibroadenoma, a higher body mass index, and a higher WHR and were less likely to exercise regularly than controls. All subsequent analyses included all these variables and ages in the logistic models to control for their potential confounding effects. There were no significant differences between cases and controls in parity, months of breastfeeding, family income (after adjusted for education), alcohol consumption, use of oral contraceptives, hormone replacement therapy, adult height, or usual intake of energy and fat during adulthood.

Breast cancer cases reported a lower soyfood intake than controls during adolescence (ages 13–15 years). The mean soy protein intake per day was 6.45 and 7.23 grams (medium, 4.8 and 5.4 grams), respectively, for cases and controls ($P = 0.002$). After adjusting for rice and wheat product intake (the major sources of energy intake in the study population) and other factors noted above, the ORs associated with soyfood

[3] The abbreviations used are: FFQ, food frequency questionnaire; OR, odds ratio; CI, confidence interval; WHR, waist:hip circumference ratio; TEB, terminal epithelial bud.

*Table 1* Comparison of demographics and selected breast cancer risk factors of cases and controls, The Shanghai Breast Cancer Study, 1996–1998

Subjects with missing values were excluded from the analysis.

| | Cases[a] ($n$ = 1459) | Controls[a] ($n$ = 1556) | $P$ |
|---|---|---|---|
| Age (yrs) | 47.8 ± 8.0 | 47.2 ± 8.8 | 0.03 |
| Education (%) | | | |
| No formal education | 3.6 | 5.5 | |
| Elementary school | 8.5 | 8.4 | |
| Middle + high school | 74.3 | 75.4 | |
| Professional education, college and above | 13.6 | 10.7 | 0.01 |
| Per capita income (Yuan) (%) | | | |
| <4000 | 19.8 | 18.2 | |
| 4000–5999 | 31.7 | 31.9 | |
| 6000–7999 | 13.0 | 13.9 | |
| 8000–8999 | 20.2 | 23.5 | |
| ≥9000 | 15.2 | 12.4 | 0.05 |
| Breast cancer in first-degree relatives (%) | 3.7 | 2.4 | 0.05 |
| Ever had breast fibroadenoma (%) | 9.6 | 5.0 | <0.01 |
| Regular alcohol drinker (%) | 4.0 | 4.1 | 0.99 |
| Ever used oral contraceptives (%) | 21.9 | 20.9 | 0.51 |
| Ever used hormone replacement therapy (%) | 2.9 | 2.7 | 0.76 |
| Exercised regularly (%) | 18.8 | 25.2 | <0.01 |
| Body mass index | 23.5 ± 3.4 | 23.1 ± 3.4 | <0.01 |
| WHR | 0.81 ± 0.06 | 0.80 ± 0.06 | <0.01 |
| Nulliparous (%) | 5.1 | 3.9 | 0.13 |
| No. of live births[b] | 1.5 ± 0.85 | 1.5 ± 0.86 | 0.54 |
| Age at first live birth[b] (yrs) | 26.8 ± 4.2 | 26.2 ± 3.9 | <0.01 |
| Months of breastfeeding[c] | 15.1 ± 13.1 | 15.9 ± 14.0 | 0.81 |
| Menarcheal age (yrs) | 14.5 ± 1.6 | 14.7 ± 1.7 | <0.01 |
| Menopausal age[d] (yrs) | 48.1 ± 4.6 | 47.5 ± 4.9 | 0.02 |
| Height (cm) | 158.9 ± 5.10 | 158.5 ± 5.37 | 0.07 |
| Adult usual energy intake (kcal/day) | 1865.9 ± 464.2 | 1839.9 ± 464.2 | 0.12 |
| Adult usual fat intake (grams/day) | 36.3 ± 17.4 | 35.3 ± 16.2 | 0.08 |

[a] Unless otherwise specified, mean ± SD are presented.
[b] Among women who had live births.
[c] Among women who ever breastfed their children.
[d] Among menopausal women.

intake during adolescence were 0.75 (95% CI, 0.57–0.93), 0.69 (95% CI, 0.55–0.87), 0.69 (95% CI, 0.55–0.86), and 0.51 (95% CI, 0.40–0.65) for the second quintile to the highest quintile of soyfood intake compared with the lowest quintile of intake ($P$ for linear trend test = 0.0001). The dose-response relationship was observed for all three commonly consumed soyfoods (tofu, soy milk, and soy products other than tofu; Table 2). Consumption of fresh legumes, which included mainly peas, string beans, and kidney beans and, to a lesser extent, soy and other beans, was unrelated to the risk of breast cancer. On the other hand, high intake of dried legumes (mainly soy beans, red beans, and mung beans) was related to a significantly reduced risk (OR = 0.75 and 95% CI = 0.59–0.95 for the highest quartile of intake compared with the lowest quartile of intake).

Breast cancer risk was inversely associated with consumption of rice and wheat products (trend test, $P$ = 0.03) and milk ($P$ = 0.03) during adolescence after adjusted for soyfood intake and other nondietary breast cancer risk factors (Table 2). The association of soyfood intake and breast cancer risk remained unchanged when intake of both rice/wheat products and milk was adjusted. Consumption of meats, fruits, vegetables, sea foods, eggs, or preserved foods during adolescence was not associated with the risk of breast cancer.

The inverse association between adolescent soyfood intake and breast cancer was observed for both premenopausal (trend test, $P$ = 0.0001) and postmenopausal women ($P$ = 0.006). Similarly, fresh legume consumption was not related to risk, whereas dried legume intake was inversely related to breast cancer risk (trend test $P$ = 0.07 and 0.03 for pre- and postmenopausal women, respectively; Table 3).

Among a subgroup of young women (age < 45 years) for whom maternally reported data on adolescent diet were available, the two reports of soyfood intake produced correlation coefficients of 0.29 ($P$ < 0.01) and 0.30 ($P$ < 0.01), respectively, for the case and control groups. For the maternal data, ORs were 0.70 (95% CI, 0.45–1.09), 0.59 (95% CI, 0.32–1.07), 0.60 (95% CI, 0.37–0.99), and 0.35 (95% CI, 0.21–0.60) for the second quintile to the highest quintile of soyfood intake compared with the lowest quintile of intake (trend test, $P$ = 0.0002). A statistically significant inverse association was observed for both tofu and other soy products, but not for soy milk. Again, for the maternal data, risk also decreased with increased dry legume intake but was not related to fresh legume consumption (Table 3). Further analysis stratified by usual adult soyfood consumption showed that the pattern of adolescent soyfood intake and breast cancer risk was relatively unaffected by adult consumption (data not shown).

## Discussion

Soyfoods are rich in isoflavones, primarily genistein and daidzein, that show potential as cancer-protective agents (8). Various anticancer effects of isoflavonoids have been demonstrated *in vitro* and in animal experiments, including inhibition of tumor formation and tumor cell growth stimulated by growth factors (9) and inhibition of DNA topoisomerase I and II (3),

*Table 2* Soy food and other dietary intake during adolescence and risk of breast cancer, The Shanghai Breast Cancer Study, 1996–1998

| | Median intake among controls[a] | Adjusted ORs (95% CI) by quintile[b,c,d] | | | | | Trend test *P* |
|---|---|---|---|---|---|---|---|
| | | Q1 (low) | Q2 | Q3 | Q4 | Q5 | |
| Soy foods (total) | 5.4 | 1.00 | 0.75 (0.60–0.93) | 0.69 (0.55–0.87) | 0.69 (0.55–0.86) | 0.51 (0.40–0.65) | <0.01 |
| Bean curd (tofu) | 0.9 | 1.00 | 0.83 (0.68–1.02) | 0.88 (0.68–1.13) | 0.67 (0.54–0.84) | 0.70 (0.55–0.90) | <0.01 |
| Soy milk | 0 | 1.00 | 0.75 (0.64–0.88) | | | | <0.01 |
| Soy products other than tofu | 3.5 | 1.00 | 0.85 (0.67–1.08) | 0.79 (0.59–1.06) | 0.65 (0.50–0.85) | | <0.01 |
| Fresh legumes[e] | 35.6 | 1.00 | 0.95 (0.74–1.22) | 0.98 (0.80–1.19) | 0.83 (0.65–1.05) | 0.93 (0.74–1.16) | 0.27 |
| Dried beans[f] | 0.7 | 1.00 | 0.84 (0.69–1.01) | 0.78 (0.64–0.96) | 0.75 (0.59–0.95) | | <0.01 |
| Vegetables/fruits (total)[g] | 171.0 | 1.00 | 0.88 (0.70–1.12) | 0.85 (0.67–1.08) | 1.01 (0.81–1.27) | 0.95 (0.74–1.21) | 0.97 |
| Vegetables[g] | 150.0 | 1.00 | 0.87 (0.72–1.06) | 0.90 (0.68–1.19) | 1.17 (0.96–1.43) | 0.72 (0.50–1.03) | 0.56 |
| Fruits[g] | 4.9 | 1.00 | 0.90 (0.74–1.10) | 0.97 (0.78–1.22) | 0.99 (0.79–1.23) | | 0.96 |
| Rice/wheat products[g] | 400.0 | 1.00 | 0.95 (0.71–1.29) | 0.96 (0.78–1.18) | 0.86 (0.71–1.04) | 0.65 (0.46–0.93) | 0.03 |
| Meats (total)[g] | 14.2 | 1.00 | 0.94 (0.74–1.19) | 1.11 (0.87–1.41) | 1.00 (0.78–1.27) | 1.00 (0.78–1.29) | 0.83 |
| Pork[g] | 8.2 | 1.00 | 1.08 (0.84–1.38) | 1.15 (0.93–1.41) | 1.00 (0.78–1.29) | 1.11 (0.88–1.41) | 0.46 |
| Other meats[g] | 1.4 | 1.00 | 0.92 (0.75–1.12) | 0.96 (0.76–1.21) | 0.91 (0.74–1.13) | | 0.51 |
| Eggs[g] | 9.9 | 1.00 | 1.00 (0.80–1.25) | 1.01 (0.81–1.26) | 0.98 (0.78–1.24) | 0.86 (0.67–1.11) | 0.34 |
| Seafoods[g] | 14.2 | 1.00 | 0.86 (0.68–1.08) | 0.86 (0.67–1.10) | 0.89 (0.71–1.12) | 0.89 (0.67–1.17) | 0.47 |
| Milk[g] | 0 | 1.00 | 0.76 (0.59–0.98) | | | | 0.03 |
| Preserved foods (total)[g] | 19.2 | 1.00 | 1.08 (0.86–1.36) | 1.05 (0.83–1.32) | 0.89 (0.70–1.13) | 0.94 (0.73–1.20) | 0.27 |
| Preserved meat/fish[g] | 0.7 | 1.00 | 1.01 (0.83–1.24) | 1.24 (1.01–1.53) | 1.12 (0.90–1.38) | | 0.10 |
| Salted eggs[g] | 1.4 | 1.00 | 0.77 (0.63–0.95) | 1.00 (0.80–1.23) | 1.00 (0.80–1.24) | | 0.62 |
| Preserved vegetables[g] | 14.2 | 1.00 | 1.17 (0.93–1.47) | 1.08 (0.87–1.35) | 0.89 (0.70–1.12) | 0.97 (0.73–1.28) | 0.24 |

[a] Average daily intake in grams. Soy food intake was converted to soy protein equivalence (tofu, 6.2%; soy milk, 1.8%; and soy products other than tofu, 24.72%); Refs. 33–35.
[b] ORs were compared to the lowest quintile of intake and adjusted for intake level of rice and wheat products, age, education, family history of breast cancer, history of breast fibroadenoma, WHR, age at menarche, physical activity, ever had live birth, age at first live birth, menopausal status, and age at menopause. Quintile cutoffs are 0.44, 0.88, 1.32, and 2.2 gram(s)/day for tofu and 2.20, 4.41, 6.61, and 11.01 gram(s)/day for total soyfoods.
[c] Ever *versus* never for analyses of foods rarely consumed.
[d] Tertile distribution of intake for analyses of foods when a large number of subjects did not eat the foods. Tertile cutoffs are 3.52 and 5.28 grams/day for soy products other than tofu.
[e] Commonly consumed fresh legumes include peas, string beans, and kidney beans, and, less commonly consumed legumes include soy beans.
[f] Commonly consumed dry beans are soy bean seeds, mung beans, and red beans.
[g] Additionally adjusted for total soy food intake.

proteases (14), tyrosine kinases (3), inositol phosphate (15), and angiogenesis (3). Isoflavones may also affect breast cancer and other hormone-related cancers by competing with endogenous estrogens in the binding of estrogen receptors and nuclear type II estrogen-binding sites as well as by increasing the synthesis of sex hormone-binding globulin (lowering biological availability of sex hormones), inhibiting 17$\beta$-hydroxysteroid dehydrogenases [reducing estrogen synthesis (3, 16)], and increasing the clearance of steroids from the circulation (8). In addition, isoflavones possess other chemopreventive characteristics, such as antioxidation, antivirus, antibacteria, and immune enhancement (17, 18). It has been documented that genistein inhibits both estrogen- and growth factor-stimulated proliferation of human breast cancer cells (9). Administration of soyfoods or isoflavones to rats reduces the number of mammary tumors (3, 4, 19, 20).

An inverse association between soyfood consumption and breast cancer has also been suggested from population studies, both ecological/cross-sectional studies (8, 3) and analytic studies (6, 7, 21–23). Incidence of breast cancer has been low in China and Japan, where consumption of soyfoods is much higher than that in the United States (1), although some increases in consumption rates have been described recently (24). Case-control studies have found that soyfood intake was associated with a decreased risk of breast cancer among premenopausal Singapore women (7) and both pre- and postmenopausal Asian-American women (6). However, a Japanese case-control study found that consumption of bean curd but not miso soup was inversely associated with premenopausal breast cancer (25). An earlier Chinese study also failed to find any association between soyfood intake and breast cancer risk (26). That study, however, was not designed to evaluate the effect of soyfoods, and soyfood intake ascertainment was incomplete. The median soy protein intake among control women from Shanghai in the earlier study was 3.5 grams/day based primarily on intake of tofu, soy milk, and vegetarian chicken, whereas in the current study, the median soy protein intake in the usual adult diet was 10.3 grams/day. The median intake of soy protein from soy milk and tofu in the current study was 1.0 gram/day and 2.0 grams/day, respectively, accounting for only one-third of the total soy protein intake and close to the intakes reported in the earlier Chinese study. Cohort studies among Japanese, Japanese-American, and Caucasian-American women have provided some evidence that soyfoods may reduce the risk of breast cancer (21–23), although a recent prospective study in Japan failed to find any protective effect (27). A lower urine level of isoflavonoids among breast cancer patients compared with controls has also been reported previously (28, 29), including a study in Shanghai (29). To our knowledge, no epidemiological study has specifically evaluated the effect of soyfood intake during adolescence, a period when breast tissue is most sensitive to environmental stimuli, on subsequent risk of breast cancer.

The mammary primordium arises from solid terminal epithelial buds that branch during adolescence into a tree-like system of ducts (10). The hollowing of the TEBs occurs by extensive tissue remodeling and cell elimination. An alteration in tissue remodeling by changes in rates of cell proliferation or cell death could cause incomplete hollowing of TEBs, which in turn could result in an increase in ductal cells, a population of cells known to be susceptible to carcinogenic transformation (11). Animal studies have shown that mammary tissue is espe-

*Table 3* Soy food and other dietary intake during adolescence and risk of breast cancer, The Shanghai Breast Cancer Study, 1996–1998

| | Adjusted ORs (95% CI) by quintile[a,b,c] | | | | | Trend test *P* |
|---|---|---|---|---|---|---|
| | Q1 (low) | Q2 | Q3 | Q4 | Q5 | |
| A. Premenopausal women (952 cases and 990 controls) | | | | | | |
| Soy foods (total) | 1.00 | 0.75 (0.57–1.00) | 0.72 (0.54–0.96) | 0.64 (0.48–0.85) | 0.53 (0.39–0.72) | <0.01 |
| Bean curd (tofu) | 1.00 | 0.73 (0.56–0.92) | 0.87 (0.64–1.20) | 0.60 (0.45–0.79) | 0.79 (0.58–1.08) | 0.02 |
| Soy milk | 1.00 | 0.67 (0.55–0.82) | | | | <0.01 |
| Soy products other than tofu | 1.00 | 0.90 (0.65–1.23) | 0.76 (0.52–1.10) | 0.68 (0.48–0.96) | | 0.01 |
| Fresh legumes[d] | 1.00 | 1.04 (0.76–1.41) | 1.04 (0.82–1.33) | 0.86 (0.64–1.15) | 0.96 (0.72–1.29) | 0.51 |
| Dried beans[e] | 1.00 | 0.91 (0.72–1.15) | 0.85 (0.66–1.10) | 0.77 (0.57–1.05) | | 0.07 |
| B. Postmenopausal women (501 cases and 562 controls) | | | | | | |
| Soy foods (total) | 1.00 | 0.69 (0.48–1.01) | 0.65 (0.44–0.97) | 0.79 (0.54–1.16) | 0.49 (0.33–0.74) | <0.01 |
| Bean curd (tofu) | 1.00 | 1.10 (0.77–1.57) | 0.89 (0.58–1.38) | 0.82 (0.56–1.19) | 0.62 (0.41–0.93) | 0.01 |
| Soy milk | 1.00 | 0.98 (0.73–1.32) | | | | 0.89 |
| Soy products other than tofu | 1.00 | 0.77 (0.53–1.12) | 0.93 (0.57–1.53) | 0.62 (0.41–0.94) | | 0.05 |
| Fresh legumes[d] | 1.00 | 0.77 (0.50–1.19) | 0.92 (0.65–1.30) | 0.83 (0.55–1.27) | 0.96 (0.67–1.39) | 0.82 |
| Dried beans[e] | 1.00 | 0.70 (0.50–0.97) | 0.67 (0.46–0.95) | 0.76 (0.53–1.08) | | 0.03 |
| C. Data reported by mothers among women <40 years of age (296 cases and 359 controls) | | | | | | |
| Soy foods (total) | 1.00 | 0.70 (0.45–1.09) | 0.59 (0.32–1.07) | 0.60 (0.37–0.99) | 0.35 (0.21–0.60) | <0.01 |
| Bean curd (tofu) | 1.00 | 1.08 (0.70–1.65) | 0.72 (0.41–1.27) | 0.52 (0.31–0.85) | 0.65 (0.37–1.17) | <0.01 |
| Soy milk | 1.00 | 0.89 (0.61–1.31) | | | | 0.56 |
| Soy products other than tofu | 1.00 | 1.10 (0.67–1.79) | 0.72 (0.45–1.17) | 0.79 (0.46–1.33) | 0.44 (0.25–0.79) | <0.01 |
| Fresh legumes[d] | 1.00 | 0.52 (0.30–0.92) | 0.88 (0.57–1.38) | 1.05 (0.63–1.75) | 0.67 (0.40–1.12) | 0.55 |
| Dried beans[e] | 1.00 | 0.94 (0.62–1.44) | 0.73 (0.46–1.16) | 0.63 (0.40–1.01) | | 0.04 |

[a] ORs were compared to the lowest quintile of intake and adjusted for intake level of rice and wheat products, age, education, family history of breast cancer, history of breast fibroadenoma, WHR, age at menarche, physical activity, ever had live birth, menopausal status, and age at menopause.
[b] Ever *versus* never for analyses of foods rarely consumed.
[c] Tertile distribution of intake for analyses of foods when a large number of subjects did not eat the foods.
[d] Commonly consumed fresh legumes include peas, string beans, kidney beans, and, less commonly consumed fresh legumes include soy beans.
[e] Commonly consumed dry beans are soy bean seeds, mung beans, and red beans.

cially susceptible to carcinogens during puberty, a time when the mammary glands are highly proliferative, and hormonal changes are at their maximum (30). Epidemiological observations also suggested that earlier age at exposure to radiation, alcohol, and smoking was related to a higher risk of breast cancer (31). In the present large-scale population-based case-control study, we demonstrated, for the first time, a strong and consistent inverse association between adolescent soyfood intake and the risk of breast cancer in later life. Women whose consumption of soyfoods during adolescence was in the upper quintile had only half the breast cancer risk of those in the lowest quintile. The inverse association persisted after adjustment for adult soyfood intake.

Soyfood intake could be a dietary habit that develops in early life and continues throughout adult life. If this is true, our findings for the inverse association between adolescent soyfood intake and breast cancer risk could be the result of soy exposure during the prepuberty period, cumulative lifetime exposure, or both. We found that the inverse association between adolescent soyfood intake and breast cancer risk persisted after adjustment for usual soyfood intake in adults, suggesting that an effect of soyfood intake early in life is independent from adult soyfood intake. However, we could not disentangle the effect of soyfood intake during adolescence from soyfood intake before puberty or in the neonatal period because relevant information was not available. Animal studies have suggested that short-term neonatal or prepubertal exposure to dietary isoflavones decreases carcinogen-induced breast cancer by differentiation of the mammary gland cells (3, 4). Therefore, the inverse association found in the study could be the result of high soyfood consumption before puberty, early in life, or during both childhood and adolescence.

One of the major concerns in this study is the measurement error in ascertaining adolescent soyfood intake. Although recall errors are unavoidable in virtually all case-control studies, the error is more likely to be nondifferential in our study because any possible anticancer benefits of soyfood were not publicized in China during the period in which our study was conducted. To minimize interview biases, we implemented several measures in the study, including strict enforcement of the interview protocol, tape recording the interview, and blinding interviewers with study hypotheses. The correlation coefficients between self-reported and maternally reported soyfood intake during adolescence observed were virtually identical in cases and controls, providing additional assurance that the exposure measurement error in this study is unlikely to be differential. Because nondifferential error usually attenuates a true association toward null, the potential beneficial effect of soyfood intake during adolescence is likely to be underestimated.

Although we adjusted for major breast cancer risk factors throughout the analyses, we were also concerned about potential confounding from other aspects of adolescent lifestyle or nutrition. However, we did not find that adolescent intakes of meat or fruit, markers of an affluent lifestyle, were associated with breast cancer risk. Adjustment for other adolescent dietary intake did not alter the soyfood association. In addition, we found that soyfood intake was not related to the sitting:standing height ratio or to age at menarche, indirect measures of nutritional advantage during adolescence in populations with limited food supplies. These observations suggest that the inverse soyfood and breast cancer risk association is unlikely to be a result of confounding by adolescent lifestyle or nutrition. We found that soyfood intake was not correlated to women's education level or current family income.

In this study, we found that food groups containing the lowest amount of isoflavonoids [*i.e.*, fresh legumes (including primarily peas, string beans, and kidney beans and less often soy beans or other beans in the study population); Ref. 32] were

not related to the risk of breast cancer. Dried legumes (mixed with soybeans, mung beans, and other beans) were less strongly associated with the risk of breast cancer than pure soyfood items (total soyfoods, bean curd, soy milk, and soy products other than tofu). We also found that both self-reported and maternally reported soyfood intake were related to breast cancer in a dose-response pattern. Finally, the findings were consistent for all single soyfood items and existed for both pre- and postmenopausal women. These observations all argue against the possibility of a chance finding.

In summary, in the Shanghai Breast Cancer Study undertaken in a traditionally high soyfood-consuming population, we found that adolescent soyfood intake was inversely associated with the risk of breast cancer in adult life. The dose-response relationship, the biological plausibility, the specificity of the association, and the consistent relationship across a variety of strata and between data from mothers and daughters all strongly suggest an etiological association. Our finding suggests that a substantial difference in breast cancer incidence between Asian and Caucasian women and increasing breast cancer incidence among Asian-Americans may be explained, at least in part, by soyfood intake during adolescence. Our study again emphasizes the importance of initiating cancer intervention programs early in life (31).

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