# Dietary Soy and Isoflavone Intake and Risk of Colorectal Cancer in the Japan Public Health Center–Based Prospective Study

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## Abstract

**Several experimental studies have reported that the anticarcinogenic properties of dietary soy play an important role in preventing colorectal cancer. However, few epidemiologic studies have examined this association in general populations and their findings have been inconsistent. We investigated the association between dietary soy and isoflavone intake and incidence of colorectal cancer in a prospective cohort study of 83,063 Japanese men and women, ages 45 to 74 years. Dietary soy and isoflavone intake was measured through a validated food frequency questionnaire in 1995 and 1998. Throughout 2004, a total of 886 cases of colorectal cancer were newly identified (291 proximal colon, 286 distal colon, and 277 rectum). The hazard ratios and 95% confidence intervals (95% CIs) were estimated by fitting a Cox proportional hazards model. The intake of isoflavones, miso soup, and soy food was not associated with colorectal cancer in either men or women. By colorectal cancer subsite, the risk of proximal colon cancer in men decreased with increasing consumption of isoflavones, miso soup, and soy food. Compared with men in the lowest quartiles of isoflavones, miso soup, and soy food intake, the hazard ratios in the highest quartiles were 0.55 (95% CI, 0.33-0.92), 0.72 (95% CI, 0.43-1.21), and 0.51 (95% CI, 0.30-0.87), respectively. The results showed no association for distal colon and rectal cancer in men or for subsites of colorectal cancer in women. These findings suggest that the intake of isoflavones, miso soup, and soy food has no substantial effect on the risk of colorectal cancer in Japanese men and women.** (Cancer Epidemiol Biomarkers Prev 2008;17(8):2128–35)

## Introduction

Colorectal cancer is already one of the most common cancers in Western populations and is also rapidly increasing in Asian countries, particularly in Japan (age-adjusted incidence rate, 49.3 per 100,000 in men and 26.5 per 100,000 in women; ref. 1). This rapid increase is thought to be strongly influenced by several environmental exposures, including aging, sedentary lifestyle, and westernization of the diet over the past few decades. Against this background, evidence also exists to suggest that a high intake of dietary soy and isoflavones reduces the risk of colorectal cancer in animal studies (2).

Soy foods are traditional food products that have been consumed in certain Asian countries for centuries (3). The frequent constituents of these foods include a group of phytoestrogens called isoflavones, of which genistein accounts for two thirds or more by consumption, followed by daidzein and very small amounts of glycitein (2). Convincing evidence indicates that the antiestrogenic, anticarcinogenic, anti-inflammatory, and antioxidative properties of isoflavones favorably influence the risk of several cancers in Asian countries as opposed to Western countries, where soy foods are typically not consumed in large amounts (4, 5). Given the low breast and prostate cancer mortality rates in soy food–consuming countries like Japan, investigations have understandably focused on these two hormone-dependent malignancies (6). The similar chemical structure of soybean and soy food isoflavones to that of the mammalian hormone estrogen gives these compounds an antiestrogenic effect and possibly, in turn, an anticarcinogenic effect (7). Several experimental studies have shown that genistein has a direct inhibitory effect on large-bowel cancer cell growth via its activation of estrogen receptor-β as well as blocking of tyrosine protein kinases and DNA topoisomerases. Other anticancer activities included a decrease in abnormal cellular proliferation and the induction of apoptosis and inhibition angiogenesis (7, 8). However, these mechanisms have been less well studied in colorectal cancer.

Epidemiologic data on dietary soy and isoflavone intake in relation to the risk of colorectal cancer have been mixed. To date, 14 studies (9-22) have evaluated the association. Among the results from Western countries, two case-control studies (9, 10) reported an inverse association between dietary soy intake and colorectal

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cancer, whereas two other case-control studies (11, 12) and a randomized control trial (13) found no such association. Among studies in Asian populations, one cohort and one case-control study in Japan (14, 15) and one case-control study each in China (16) and Hong Kong (17) found an inverse association. In contrast, one cohort (18) and three case-control studies (19-21) in Japan and one case-control study (22) in Singapore found no such association. Although these limited epidemiologic data provide modest support for an inverse association, many of the studies have important limitations, including the common issues of sample size (9, 11, 15, 16, 19, 21, 22), recall bias in case-control studies (9-12, 15-17, 19-22), dietary measurement error (9, 11, 18, 19, 21, 22), and questions on whether the study was specifically and appropriately designed to address the soy isoflavone–colorectal cancer hypothesis (9, 11, 12, 15, 16, 18, 20, 21). Against this background, further confirmation of the effect on colorectal cancer risk is needed from general populations, in particular those having a variety of dietary soy and isoflavone intake levels.

Here, to address the hypothesis that higher intake is associated with decreased risk, we examined dietary soy and isoflavone intake and colorectal cancer incidence in a cohort with a mean 7.6-year follow-up (1995-1998 through 2004) in a general population in Japan. This study was characterized by high dietary soy and isoflavone consumption in both sexes as well as the availability of detailed data on the consumption of a variety of soy foods and on a wide range of potentially confounding variables.

## Subjects and Methods

**Study Population.** The Japan Public Health Center (JPHC)–based prospective study is an ongoing cohort study of 140,420 subjects (68,722 men and 71,698 women) investigating cancer, cardiovascular disease, and other lifestyle-related diseases in 29 municipalities supervised by 11 prefectural public health center areas. Cohort I was established in 1990 and consisted of residents who had registered their addresses in five public health center areas in Iwate, Akita, Nagano, Okinawa, and Tokyo, whereas cohort II was established in 1993 and included residents who had registered their addresses in six public health center areas in Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka. The design of this prospective cohort study has been reported in detail elsewhere (23). The JPHC-based study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

**Five-Year Follow-up Questionnaire Survey.** We conducted 5-year follow-up self-administered questionnaire surveys in 1995 (cohort I) and 1998 (cohort II) among participants, ages 45 to 74 years, which assessed demographic characteristics, personal and family medical histories, anthropometric measurements, leisure time physical activity, history of smoking and alcohol drinking, menopausal status and exogenous female hormone use (women only), different food habits, and other lifestyle variables. The food frequency questionnaire used for dietary intake included 138 food (9 frequency categories) and beverage (10 frequency categories) items with standard portion sizes (24). Among the eligible subjects, 103,791 subjects (73.9%) returned usable questionnaires. In the present analysis, we excluded subjects living in Osaka, for whom a different definition of study population was used, and those in Tokyo, for whom incidence data were not available. After the survey, 224 subjects were found to be ineligible due to non-Japanese nationality ($n$ = 51), late report of emigration before the start of the follow-up period ($n$ = 166), incorrect birth date ($n$ = 3), and duplicate registration ($n$ = 4). The exclusion of those with a history of cancer at baseline and 5-year follow-up questionnaires and those with cancer diagnosed before the 5-year follow-up survey further reduced the total number of eligible subjects for analysis to 88,486. Finally, we excluded subjects who reported an extreme energy intake (upper and lower 2.5%) or submitted incomplete answers on dietary soy and isoflavone intake, leaving 83,063 subjects (39,069 men and 43,994 women) for the 5-year follow-up survey.

**Dietary Assessment.** In the 5-year food frequency questionnaire, the subjects were questioned about how often they consumed individual soy products (frequency of consumption) during the previous year as well as representative relative sizes compared with standard portions. Dietary soy intake was categorized into three item groups: consumption of isoflavones, miso soup, and soy food. Because the estimates of genistein and daidzein intake were highly correlated, the results for genistein are provided here as representative for isoflavones. The daily intake of dietary genistein and daidzein was calculated with the use of values in a specially developed food composition table for isoflavones in Japanese foods (25, 26). Other food and nutrient intakes per day were calculated with the use of the Fifth Revised and Enlarged Edition of the Japanese Standard Food Composition Table (27).

For the items, consumption of *miso* soup was regarded as that of fermented soybean paste, from which it is made. Other soy food items included *tofu* (soybean curd) for miso soup, *tofu* (boiled or cold) for other dishes, *yushidofu* (predrained tofu), *koyadofu* or *shimitofu* (freeze-dried tofu), *aburaage* (deep-fried tofu), *natto* (fermented soybean), and soymilk (soybean as major ingredient). The frequency of miso soup consumption was divided into six categories: almost never, 1 to 3 days per month, 1 to 2 days per week, 3 to 4 days per week, 5 to 6 days per week, and daily. The portion size was specified, with one bowl of miso soup equaling 150 mL, into nine categories: <1 bowl per day, 1 bowl per day, 2 bowls per day, 3 bowls per day, 4 bowls per day, 5 bowls per day, 6 bowls per day, 7 to 9 bowls per day, and ≥10 bowls per day. The frequency response choices for soy foods were never, 1 to 3 times per month, 1 to 2 times per week, 3 to 4 times per week, 5 to 6 times per week, once a day, 2 to 3 times per day, 4 to 6 times per day, and ≥7 times per day. The portion sizes were specified as 20 g (tofu for miso soup), 75 g (tofu for other dishes), 150 g (predrained tofu), 60 g (freeze-dried tofu), 2 g (deep-fried tofu), and 50 g (fermented soybean). The amounts were divided into three categories of less than half, the same as, and >1.5 times the reference portion size. Here, the portion size for deep-fried tofu was relatively small as it is used as a seasoning only in miso soup. For soymilk, 200 mL was used as portion size, and 10 frequency categories were established: almost never, 1 to 3 times per month, 1 to 2 times per week, 3 to 4 four times per week, 5 to 6 times per week, 1 glass per day, 2 to

3 glasses per day, 4 to 6 glasses per day, 7 to 9 glasses per day, and >9 glasses per day.

**Validity and Reproducibility.** The validity of the energy-adjusted genistein intake assessed from the 5-year food frequency questionnaire was evaluated in a subsample with consecutive 14- or 28-day dietary records. Spearman's correlation coefficients between the questionnaire and the dietary records of energy-adjusted genistein was 0.65 (cohort I) and 0.48 (cohort II) for men (28, 29) and 0.55 (cohort I) and 0.45 (cohort II) for women (29).[1] The reproducibility between the two questionnaires for energy-adjusted genistein intake assessed 1 year apart showed rank correlation coefficients of 0.75 (men) and 0.69 (women) for cohort I (28)[2] and 0.51 (men) and 0.41 (women) for cohort II (29).

**Follow-up.** The subjects were followed from the date of the 5-year follow-up survey through December 31, 2004. Their residence status and survival were confirmed annually through the residential registers kept by each municipality in each of the study areas or, for those who had moved out of the study area, through the municipal office of the area they had moved to. Among the study participants, 6,315 subjects (7.6%) died, 2,881 (3.5%) moved out of the study area, and 303 (0.4%) were lost to follow-up during the study period. The persons who were lost to follow-up were censored on the last confirmed date of presence in the study area. The subjects who died were identified through mortality data obtained from the Ministry of Health, Labor, and Welfare, Japan. The incidence data for colorectal cancer were collected through continuous surveillance of major local hospitals and prefectural population-based cancer registries. In our cancer registry system, death certificate information was used as a supplementary information source. The proportion of cases of colorectal cancer first notified by death certificate during the follow-up period was 4.4%, and that of cases for which information was available from death certificate only was 2.0%.

**Identification of Colorectal Cancer.** Cancer site of origin and histologic type were coded with the use of the International Classification of Diseases for Oncology, 3rd edition: C180-189 (colon) and C199, 209 (rectum; refs. 30, 31). In subjects with multiple primary cancers of the colon or rectum at different times, the earliest date of diagnosis was used, whereas for cancers occurring simultaneously, the most advanced and most invasive type of tumor was used. Among the 83,063 subjects used in analysis, a total of 886 incident cases of colorectal cancer (291 cases of proximal colon, 286 distal colon, 277 rectum) were identified. On stratification of the colon into proximal (cecum to splenic flexure) and distal portions (descending colon to sigmoid colon), tumors with an overlapping (C18.8) or unspecified (C18.9) point of origin (32 cases) were excluded from the subsite-specific analyses but were included in the combined analyses. Among the incident cases of colorectal cancer, 770 (468 in men, 302 in women) were pathologically confirmed as adenocarcinoma. Information on depth of tumor invasion was available for 740 cases, with 217 intramucosal carcinomas corresponding to $T_{is}$ and 523 invasive carcinomas through the mucosal layer corresponding to $T_1$ or greater by the tumor-node-metastasis classification (32).

**Statistical Analysis.** We counted person-years of follow-up for each subject from the 5-year follow-up survey until the date of diagnosis of colorectal cancer, date of the subject's death, date of moving out of the study area, or end of the follow-up period (December 31, 2004), whichever occurred first. The total number of person-years was 632,728. Cox proportional hazards regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the incidence of colorectal cancer according to isoflavone, miso soup, and soy food intake with adjustment for potentially confounding variables. The StataSE version 9.2 data analysis and statistical software was used for analysis (Stata Corp. LP).

For primary outcome, we examined the association between the energy-adjusted quartiles of isoflavone, miso soup, and soy food intake and the risk of colorectal cancer incidence. The crude incidence rate for colorectal cancer was calculated by dividing the number of colorectal cancers by the number of person-years. The HRs were computed as the incidence rate among subjects for each category of isoflavone, miso soup, and soy food intake divided by the rate among those in the corresponding reference category. The reference category subjects are shown in Tables 2-4. We adjusted for the following variables as potential confounders: age (continuous); public health center area (9 public health centers); history of diabetes mellitus (yes or no); body mass index ($\leq$20, 21-22, 23-24, $\geq$25 kg/m$^2$); leisure time physical activity (rarely, 1-3 days per month, 1-2 days per week, frequently); cigarette smoking (never, past, current 1-19 cigarettes per day, $\geq$20 cigarettes per day); alcohol drinking (nondrinker, 1-3 days per month, <100 g ethanol per week, $\geq$100 g ethanol per week); and energy-adjusted quartiles of vitamin D, dairy products, meat, vegetable, fruit, and fish intake. We also adjusted for menopausal status (pre or post) and current use of female hormones (user or nonuser) in women only. Each dietary factor was adjusted by total energy with the use of the residual method (33-35) into the statistical model after log transformation. Isoflavone, miso soup, and soy food consumption were not included in the same models due to colinearity. Tests for linear trend were estimated with the median value of isoflavone, miso soup, and soy food intake, treating this variable as continuous. All statistical tests were two tailed, and $P$ <0.05 for trend was considered statistically significant.

We tested for effect modification between energy-adjusted isoflavones and other covariates (age, body mass index, leisure time physical activity, cigarette smoking, and alcohol drinking) in colorectal cancer through the addition of multiplicative interaction terms into the model. No statistically significant $P$ for interaction was found.

## Results

At the time of the 5-year follow-up survey, Table 1 shows that both men and women in the highest quartile of

[1] Unpublished data.
[2] Unpublished data.

isoflavone intake were slightly older, more frequently had a history of diabetes mellitus, and consumed more vegetables than those in the other quartiles. In contrast, the proportion of current smokers (≥20 cigarettes per day) and meat intake increased as isoflavone consumption decreased in both sexes. Alcohol drinking (≥100 g ethanol per week) and postmenopausal status were high among women in the lowest and the highest quartiles of isoflavone consumption, respectively.

Table 2 presents multivariable-adjusted HRs and 95% CIs for colorectal cancer incidence in men and women according to the respective quartile of isoflavone, miso soup, and soy food intake. Colorectal cancer risk was slightly decreased among men in the higher quartiles of all three. The HRs for the highest compared with lowest quartile of isoflavone, miso soup, and soy food intake in men were 0.89 (95% CI, 0.67-1.17), 0.88 (95% CI, 0.64-1.10), and 0.89 (95% CI, 0.68-1.17). The *P* value for linear trends was not statistically significant. In women, no association was found for colorectal cancer risk and isoflavone, miso soup, and soy food consumption. The age-adjusted incidence rates for women varied widely for the quartile of miso soup consumption, from 6.60 to 9.22 per 1,000 person-years, compared with the isoflavone (7.09 to 9.34 per 1,000 person-years) and soy food consumption quartiles (7.42 to 9.04 per 1,000 person-years). With regard to menopausal status, no change was seen in the results for isoflavone, miso soup, and soy food consumption and colorectal cancer in premenopausal and postmenopausal women (data not shown).

In Table 3, we noted a nonsignificant inverse association between the quartiles of isoflavones, miso soup, and soy food intake and the risk of colon cancer in men. No association was found for rectal cancer in men and colon or rectal cancer in women.

Further stratified analyses were done according to risk of proximal and distal colon cancer (Table 4). The consumption of isoflavones, miso soup, and soy food decreased the risk of proximal colon cancer, although the linear trend was not statistically significant for miso soup. Compared with the lowest quartiles, the multivariate-adjusted HRs for the highest quartiles of isoflavones, miso soup, and soy food intake with proximal colon cancer were 0.55 (95% CI, 0.33-0.92), 0.72 (95% CI, 0.43-1.21), and 0.51 (95% CI, 0.30-0.87), respectively. The results for isoflavone, miso soup, and soy food intake showed no association for proximal or distal colon cancer in women.

## Discussion

In our study, we found that the intake of isoflavones, miso soup, and soy food was not clearly associated with overall colorectal cancer in either men or women. However, the risk of proximal colon cancer in men decreased with increasing consumption of isoflavones, miso soup, and soy food. In contrast, we found no association for distal colon or rectal cancer in men or women. To our knowledge, this is the first cohort study to investigate the association between a large variety of dietary soy foods and isoflavone intake and the risk of colorectal cancer, including anatomic subsites in a general population. These findings suggest that the intake of isoflavones, miso soup, and soy food may not be associated with the risk of colorectal cancer in Japanese men and women.

These epidemiologic findings for dietary soy and isoflavone intake and colorectal cancer risk are partially consistent with the results of a previous cohort study (14) in women, four case-control studies in men and women

**Table 1. Characteristics of study subjects at 5-y follow-up survey according to quartile of energy-adjusted intake of isoflavones in the JPHC study**

| | Quartile of energy-adjusted intake of isoflavones | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Men (*n* = 39,069) | | | | Women (*n* = 43,994) | | | |
| | Lowest | 2nd | 3rd | Highest | Lowest | 2nd | 3rd | Highest |
| No. subjects | 9,593 | 9,850 | 9,871 | 9,755 | 10,763 | 11,073 | 11,162 | 10,996 |
| Mean age (y) | 56.2 | 56.4 | 56.5 | 57.6 | 56.8 | 56.6 | 57.0 | 57.7 |
| History of diabetes mellitus (%) | 4.4 | 4.8 | 5.1 | 7.0 | 2.0 | 2.3 | 2.5 | 3.3 |
| Mean body mass index (kg/m$^2$) | 23.0 | 23.0 | 23.0 | 23.1 | 23.0 | 23.0 | 23.1 | 23.3 |
| Leisure time physical activity, 1-3 d/mo (%) | 16.9 | 19.1 | 19.3 | 18.0 | 9.7 | 11.1 | 11.1 | 10.1 |
| Current smoking, ≥20 cigarettes/d (%) | 37.7 | 34.8 | 31.8 | 28.4 | 2.5 | 1.8 | 1.5 | 1.3 |
| Alcohol drinking, ≥100 g ethanol/wk (%) | 16.5 | 21.6 | 23.6 | 20.9 | 1.2 | 0.94 | 0.94 | 0.90 |
| Mean total intake of energy (kcal/d) | 2,161.8 | 2,171.8 | 2,220.5 | 2,140.4 | 1,839.8 | 1,865.5 | 1,899.6 | 1,826.6 |
| Mean total intake of food and nutrition* | | | | | | | | |
| Meat (g/d) | 76.7 | 69.6 | 66.2 | 58.2 | 69.9 | 62.7 | 57.8 | 50.8 |
| Fish (g/d) | 90.0 | 95.1 | 101.4 | 102.6 | 87.9 | 92.4 | 95.2 | 94.9 |
| Vegetables (g/d) | 180.9 | 205.0 | 217.6 | 240.9 | 220.7 | 243.4 | 253.9 | 268.4 |
| Fruit (g/d) | 164.6 | 187.7 | 198.5 | 212.8 | 248.3 | 261.8 | 267.0 | 271.0 |
| Dairy products (g/d) | 165.3 | 166.8 | 169.7 | 185.7 | 153.4 | 152.5 | 152.0 | 152.5 |
| Vitamin D (μg/d) | 9.4 | 10.5 | 11.5 | 12.1 | 9.5 | 10.6 | 11.3 | 11.5 |
| Mean total intake of dietary soy | | | | | | | | |
| Genistein (mg/d) | 9.1 | 17.9 | 28.1 | 50.4 | 9.1 | 18.1 | 28.2 | 49.7 |
| Daidzein (mg/d) | 5.8 | 11.4 | 17.6 | 30.7 | 5.7 | 11.3 | 17.4 | 30.0 |
| Miso soup (mL/d) | 147.5 | 260.0 | 301.7 | 313.8 | 125.6 | 212.8 | 246.9 | 261.3 |
| Soy food (g/d) | 35.4 | 65.7 | 96.4 | 169.9 | 35.6 | 65.9 | 94.9 | 170.3 |
| Postmenopausal status (%) | — | — | — | — | 72.6 | 74.8 | 78.4 | 81.7 |
| Current use of exogenous female hormones (%) | — | — | — | — | 3.0 | 2.6 | 2.7 | 2.9 |

*All mean total intakes of food and nutrition are energy adjusted.

**Table 2. HRs and 95% CIs of colorectal cancer according to quartile of energy-adjusted intake of isoflavones, miso soup, and soy food in the JPHC study**

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of colorectal cases | Person-years | Age-adjusted incidence rate (per 1,000) | HR (95% CI)* | No. of colorectal cases | Person-years | Age-adjusted incidence rate (per 1,000) | HR (95% CI)* |
| Isoflavones | | | | | | | | |
| Lowest | 116 | 70,269 | 12.50 | 1.00 (Reference) | 78 | 81,022 | 7.16 | 1.00 (Reference) |
| 2nd | 141 | 73,928 | 14.45 | 1.06 (0.82-1.36) | 77 | 85,947 | 7.09 | 0.88 (0.64-1.21) |
| 3rd | 140 | 75,207 | 14.25 | 0.98 (0.75-1.28) | 97 | 87,355 | 8.55 | 1.02 (0.74-1.40) |
| Highest | 131 | 73,033 | 13.12 | 0.89 (0.67-1.17) | 106 | 85,967 | 9.34 | 1.07 (0.78-1.47) |
| *P* for trend | | | | 0.25 | | | | 0.44 |
| Miso soup | | | | | | | | |
| Lowest | 113 | 68,201 | 12.17 | 1.00 (Reference) | 71 | 78,946 | 6.60 | 1.00 (Reference) |
| 2nd | 139 | 71,604 | 14.27 | 1.05 (0.81-1.35) | 83 | 82,288 | 7.65 | 1.04 (0.75-1.43) |
| 3rd | 145 | 76,172 | 14.66 | 0.98 (0.76-1.27) | 104 | 88,341 | 9.22 | 1.14 (0.84-1.56) |
| Highest | 131 | 76,460 | 12.76 | 0.88 (0.64-1.10) | 100 | 90,725 | 8.67 | 1.03 (0.75-1.43) |
| *P* for trend | | | | 0.13 | | | | 0.74 |
| Soy food | | | | | | | | |
| Lowest | 117 | 69,825 | 12.77 | 1.00 (Reference) | 82 | 80,510 | 7.64 | 1.00 (Reference) |
| 2nd | 146 | 74,366 | 15.03 | 1.06 (0.83-1.36) | 82 | 85,802 | 7.42 | 0.87 (0.64-1.18) |
| 3rd | 138 | 75,569 | 13.72 | 0.94 (0.73-1.22) | 91 | 88,201 | 8.10 | 0.90 (0.66-1.23) |
| Highest | 127 | 72,678 | 12.72 | 0.89 (0.68-1.17) | 103 | 85,787 | 9.04 | 1.04 (0.76-1.42) |
| *P* for trend | | | | 0.22 | | | | 0.69 |

*Adjusted for age (continuous); public health center area (nine centers); history of diabetes mellitus (yes or no); body mass index (<20, 21-22, 23-24, ≥25 kg/m$^2$); leisure time physical activity (rarely, 1-3 d per month, 1-2 d per week, frequently); cigarette smoking (never, past, current 1-19 cigarettes per day, current ≥20 cigarettes per day); alcohol drinking (nondrinker, 1-3 d per month, <100 g ethanol per week, ≥100 g ethanol per week); and intake of vitamin D, dairy products, meat, vegetable, fruit, and fish (energy-adjusted quartiles). Also adjusted for menopausal status (pre or post) and current use of female hormones (user or nonuser) in women only.

combined (9, 12, 15, 16), and one case-control study (17) in men and women separately. In the Takayama prospective study (14), soy products showed a dose-dependent inverse association with colon cancer risk. Witte et al. (9) reported that higher consumption of tofu was inversely associated with colorectal adenomatous polyps. The Ontario Familial Colorectal Cancer Registry found that isoflavones were associated with a decrease in colorectal cancer risk (12). A case-control study (15) found that soybean products, except miso soup, reduced colon and rectal cancer separately. Jingfu et al. (16) reported that decreased consumption of bean products was associated with an increase in risk for cancer of the rectum. The results from another case-control study (17) suggested an inverse association between colorectal cancer and soy consumption.

The association between dietary soy and isoflavone intake and colorectal cancer risk has been investigated from various standpoints. Soybean and soy food contain plant-derived phytoestrogens that have a similar molecular structure to the endogenous hormone estrogen and distinctly interact with estrogen receptors. At least two distinct estrogen receptors occur in humans, estrogen receptor-α and estrogen receptor-β (36), with estrogen receptor-β widely regarded as predominant in the normal human colon. Animal studies have found that phytoestrogens bind with high affinity to estrogen receptor-β and consistently inhibit cell proliferation in colon tumor cells. It has been suggested that estrogen receptor-β receptors mediate signals that protect the colon against tumorigenesis. In addition, genistein acts as a weak estrogen and is a potent inhibitor of tyrosine protein kinase, aromatase, and DNA topoisomerase. It also possesses antioxidant activity and inhibits cell cycle progression and angiogenesis in endothelial cells. A similar beneficial association between high intake of dietary soy products and colorectal cancer was expected in both men and women. We observed a statistically significant inverse association only in male proximal colon cancer. However, this may have been due to small numbers and chance because there was no such finding in women.

With regard to the possible estrogen-like effect of isoflavones in women, several observational studies investigating the relation between hormone replacement therapy and colorectal cancer have reported a protective effect on colorectal cancer in women (37-40). The Women's Health Initiative trial, which included healthy women who received a combined oral estrogen-progestin regimen, confirmed a reduced incidence of colorectal cancer (41, 42). These studies provide evidence that colorectal cancer is a hormone-sensitive malignancy and that phytoestrogens may play an important role in preventing colorectal cancer (7). However, our study showed no such decrease in colorectal cancer risk by plant estrogen (isoflavones) in either premenopausal or postmenopausal women as well as in women overall.

The present prospective study has several methodologic advantages over previous epidemiologic studies. First, the subjects were enrolled from a large general population. The high response rate and negligibly low proportion of subjects lost to follow-up minimized selection bias, allowing the identification of a large number of cases within a mean 7.6-year study period. Second, information on dietary soy intake was collected before the subsequent development of colorectal cancer, diminishing the probability of recall bias. Third, the end point was the risk of colorectal cancer incidence rather

**Table 3. HRs and 95% CIs of colon and rectal cancer according to quartile of energy-adjusted intake of isoflavones, miso soup, and soy food in the JPHC study**

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Colon | | Rectum | | Colon | | Rectum | |
| | No. cases | HR (95% CI)* | No. cases | HR (95% CI)* | No. cases | HR (95% CI)* | No. cases | HR (95% CI)* |
| Isoflavones | | | | | | | | |
| Lowest | 83 | 1.00 (Reference) | 33 | 1.00 (Reference) | 54 | 1.00 (Reference) | 24 | 1.00 (Reference) |
| 2nd | 95 | 0.97 (0.72-1.31) | 46 | 1.28 (0.81-2.02) | 56 | 0.89 (0.61-1.31) | 21 | 0.85 (0.46-1.54) |
| 3rd | 89 | 0.85 (0.62-1.17) | 51 | 1.34 (0.84-2.13) | 67 | 0.96 (0.66-1.40) | 30 | 1.21 (0.68-2.15) |
| Highest | 83 | 0.76 (0.55-1.07) | 48 | 1.17 (0.72-1.91) | 82 | 1.11 (0.77-1.61) | 24 | 0.97 (0.52-1.79) |
| *P* for trend | | 0.08 | | 0.61 | | 0.43 | | 0.79 |
| Miso soup | | | | | | | | |
| Lowest | 77 | 1.00 (Reference) | 36 | 1.00 (Reference) | 54 | 1.00 (Reference) | 17 | 1.00 (Reference) |
| 2nd | 90 | 0.98 (0.72-1.33) | 49 | 1.19 (0.77-1.85) | 59 | 0.95 (0.65-1.38) | 24 | 1.31 (0.70-2.46) |
| 3rd | 92 | 0.90 (0.66-1.24) | 53 | 1.16 (0.75-1.80) | 77 | 1.05 (0.73-1.50) | 27 | 1.44 (0.77-2.69) |
| Highest | 91 | 0.85 (0.61-1.17) | 40 | 0.78 (0.49-1.26) | 69 | 0.88 (0.60-1.27) | 31 | 1.62 (0.87-3.02) |
| *P* for trend | | 0.27 | | 0.27 | | 0.60 | | 0.13 |
| Soy food | | | | | | | | |
| Lowest | 85 | 1.00 (Reference) | 32 | 1.00 (Reference) | 55 | 1.00 (Reference) | 27 | 1.00 (Reference) |
| 2nd | 101 | 0.99 (0.74-1.33) | 45 | 1.26 (0.79-2.00) | 60 | 0.91 (0.63-1.33) | 22 | 0.78 (0.44-1.39) |
| 3rd | 84 | 0.78 (0.57-1.07) | 54 | 1.40 (0.88-2.22) | 66 | 0.93 (0.64-1.34) | 25 | 0.87 (0.49-1.54) |
| Highest | 80 | 0.77 (0.55-1.06) | 47 | 1.20 (0.74-1.95) | 78 | 1.11 (0.77-1.60) | 25 | 0.90 (0.50-1.62) |
| *P* for trend | | 0.05 | | 0.47 | | 0.52 | | 0.82 |

*Adjusted for age (continuous); public health center area (nine centers); history of diabetes mellitus (yes or no); body mass index (<20, 21-22, 23-24, ≥25 kg/m$^2$); leisure time physical activity (rarely, 1-3 d per month, 1-2 d per week, frequently); cigarette smoking (never, past, current 1-19 cigarettes per day, current ≥20 cigarettes per day); alcohol drinking (nondrinker, 1-3 d per month, <100 g ethanol per week, ≥100 g ethanol per week); and intake of vitamin D, dairy products, meat, vegetable, fruit, and fish (energy-adjusted quartiles). Also adjusted for menopausal status (pre or post) and current use of female hormones (user or nonuser) in women only.

than death, allowing us to distinguish whether dietary soy was related to cancer incidence, cancer survival, or both. Incidence is a more direct measure of colorectal cancer risk than death because survival time to death is influenced by the treatment received. Finally, our sample came from Japanese populations with high consumption of dietary soy items, ~7 times that of other Asian countries (43) and 70 times that of Western countries (44), providing an ideal setting for determining whether an association exists.

Several limitations of the study also warrant mention. First, measurement error in the food frequency

**Table 4. HRs and 95% CIs of proximal and distal colon cancer according to quartile of energy-adjusted intake of isoflavones, miso soup, and soy food in the JPHC study**

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Proximal colon | | Distal colon | | Proximal colon | | Distal colon | |
| | No. cases | HR (95% CI)* | No. cases | HR (95% CI)* | No. cases | HR (95% CI)* | No. cases | HR (95% CI)* |
| Isoflavones | | | | | | | | |
| Lowest | 38 | 1.00 (Reference) | 42 | 1.00 (Reference) | 26 | 1.00 (Reference) | 23 | 1.00 (Reference) |
| 2nd | 41 | 0.79 (0.50-1.25) | 51 | 1.15 (0.76-1.75) | 36 | 1.15 (0.69-1.91) | 19 | 0.70 (0.38-1.30) |
| 3rd | 30 | 0.49 (0.29-0.81) | 53 | 1.21 (0.78-1.86) | 42 | 1.18 (0.71-1.97) | 23 | 0.76 (0.41-1.39) |
| Highest | 36 | 0.55 (0.33-0.92) | 43 | 0.98 (0.61-1.57) | 42 | 1.10 (0.65-1.85) | 32 | 1.02 (0.57-1.84) |
| *P* for trend | | 0.007 | | 0.95 | | 0.79 | | 0.76 |
| Miso soup | | | | | | | | |
| Lowest | 30 | 1.00 (Reference) | 43 | 1.00 (Reference) | 30 | 1.00 (Reference) | 19 | 1.00 (Reference) |
| 2nd | 38 | 0.96 (0.59-1.56) | 47 | 0.98 (0.64-1.49) | 32 | 0.90 (0.54-1.48) | 22 | 1.04 (0.56-1.93) |
| 3rd | 42 | 0.91 (0.56-1.47) | 49 | 0.97 (0.63-1.49) | 40 | 0.91 (0.56-1.49) | 35 | 1.42 (0.80-2.54) |
| Highest | 35 | 0.72 (0.43-1.21) | 50 | 0.92 (0.60-1.43) | 44 | 0.90 (0.55-1.47) | 21 | 0.83 (0.44-1.60) |
| *P* for trend | | 0.20 | | 0.73 | | 0.74 | | 0.84 |
| Soy food | | | | | | | | |
| Lowest | 35 | 1.00 (Reference) | 47 | 1.00 (Reference) | 25 | 1.00 (Reference) | 24 | 1.00 (Reference) |
| 2nd | 44 | 0.91 (0.58-1.44) | 52 | 1.03 (0.68-1.54) | 39 | 1.25 (0.75-2.09) | 21 | 0.72 (0.40-1.31) |
| 3rd | 40 | 0.76 (0.47-1.22) | 41 | 0.80 (0.52-1.25) | 41 | 1.19 (0.71-2.00) | 21 | 0.67 (0.37-1.24) |
| Highest | 26 | 0.51 (0.30-0.87) | 49 | 1.01 (0.65-1.55) | 41 | 1.16 (0.69-1.97) | 31 | 1.08 (0.61-1.92) |
| *P* for trend | | 0.009 | | 0.77 | | 0.72 | | 0.73 |

*Adjusted for age (continuous); public health center area (nine centers); history of diabetes mellitus (yes or no); body mass index (<20, 21-22, 23-24, ≥25 kg/m$^2$); leisure time physical activity (rarely, 1-3 d per month, 1-2 d per week, frequently); cigarette smoking (never, past, current 1-19 cigarettes per day, current ≥20 cigarettes per day); alcohol drinking (nondrinker, 1-3 d per month, <100 g ethanol per week, ≥100 g ethanol per week); and intake of vitamin D, dairy products, meat, vegetable, fruit, and fish (energy-adjusted quartiles). Also adjusted for menopausal status (pre or post) and current use of female hormones (user or nonuser) in women only.

questionnaire due to changes in dietary habits during the study period may have resulted in the misclassification of individual intake and could have led to underestimation of the association between dietary soy intake and colorectal cancer risk. Nevertheless, the food frequency questionnaire used has been validated and reasonably reflects long-term dietary intake (28, 29). Second, although we adjusted for multiple potential confounding variables in the statistical model, including several dietary items, the possibility of residual confounding cannot be excluded. Third, we did not conduct analysis for soy sauce consumption or isoflavone supplement use and colorectal cancer risk because this information was not collected at 5-year follow-up survey.

In summary, this prospective study indicated that the intake of isoflavones, miso soup, and soy food has no substantial effect on the risk of colorectal cancer in Japanese men and women. Further large-scale epidemiologic studies from other populations are needed to elucidate this finding.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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