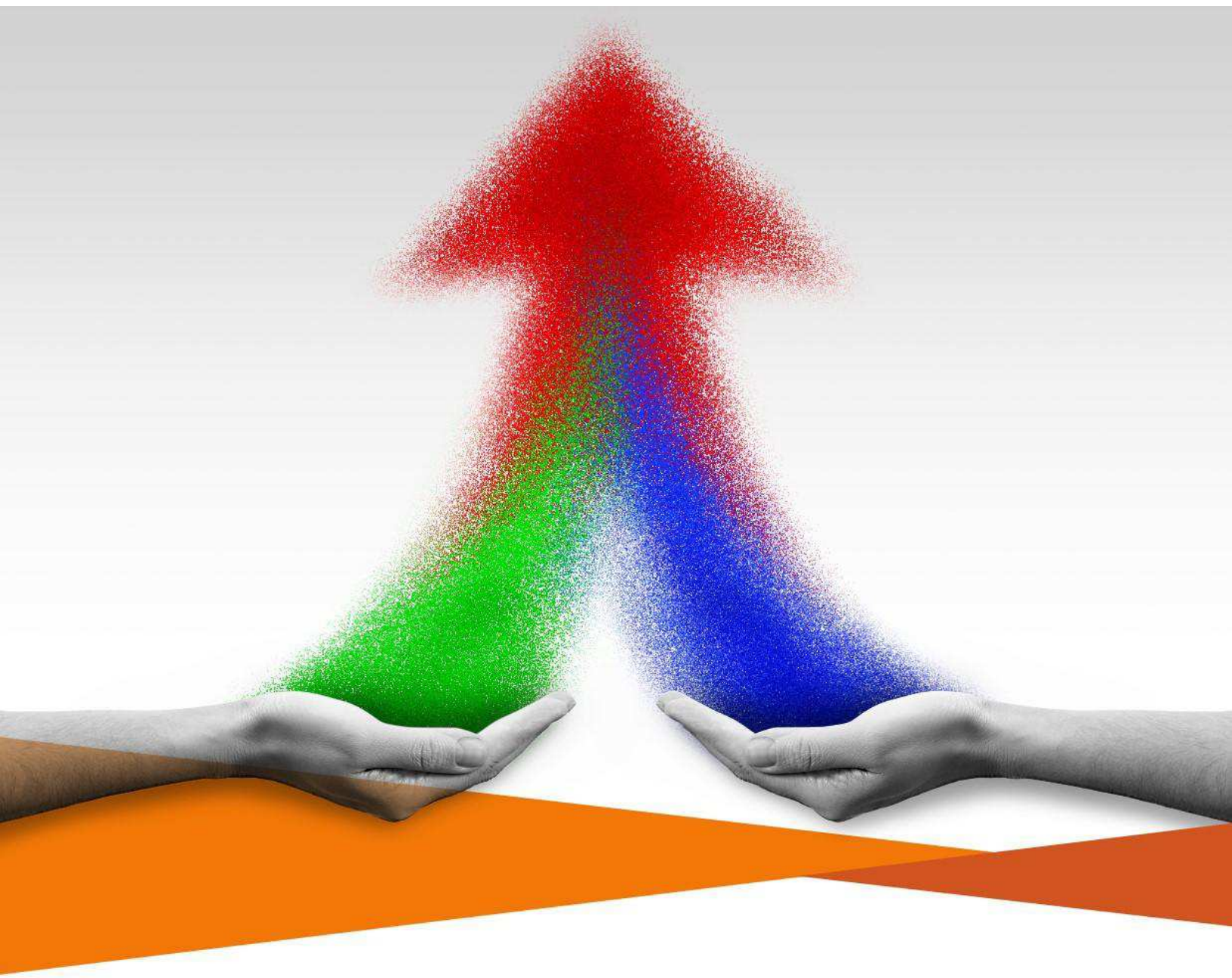

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Soy isoflavone intake and stomach cancer risk in Japan: From the Takayama study

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Although several experimental studies suggested that soy isoflavone intake inhibits the growth of stomach cancer, previous epidemiological studies have observed inconsistent results. We evaluated the associations of soy or isoflavone intake with stomach cancer incidence after considering several lifestyle factors, including salt intake, in a population-based prospective cohort study in Japan. Subjects were 14,219 men and 16,573 women aged 35 years or older in September 1992. Soy and isoflavone intakes, assessed with a validated food-frequency questionnaire, were controlled for the total energy intake. Cancer incidence was mainly confirmed through regional population-based cancer registries. Until March 2008, 441 men and 237 women developed stomach cancer. After adjustments for multiple confounders, a significantly decreased relative risk of stomach cancer was observed in the highest *vs.* lowest quartile of soy intake; the estimated hazard ratios were 0.71 (95% CI: 0.53, 0.96) for men (p for trend = 0.039) and 0.58 (95% CI: 0.36, 0.94) for women (p for trend = 0.003). Similar inverse associations between isoflavone intake and stomach cancer risk were also observed in women. Higher intake of non-fermented soy foods was significantly associated with a lower risk of stomach cancer (p for trend: 0.022 in men and 0.005 in women), whereas there was no significant association between the intake of fermented soy foods and a risk of stomach cancer. These results suggest that a high intake of soy isoflavone, mainly nonfermented soy foods, have a protective effect against stomach cancer.

The Japanese population has a higher incidence of stomach cancer than Western populations. Although *Helicobacter pylori* (*H. pylori*) is a strong and established risk factor of stomach cancer, environmental factors including smoking and diet might be involved in its development.[1–3] High consumption of salts has shown to be a probable risk factor for stomach cancer,[3–5] and higher intake of fruit and vegetables was reported to be protective against stomach cancer.[3,6]

Although the Japanese, who have a high risk of stomach cancer, consume higher amounts of soy foods, an inverse ecological correlation was reported between soy isoflavone intake and stomach cancer deaths in 47 Japanese prefectures.[7] Soy foods are a good source of isoflavones, which have been reported to have antioxidative and anticancer properties.[8–13] Thus, it is possible that soy has a preventive effect against stomach cancer. Kim *et al.* conducted a meta-analysis from 10 cohort and 16 case-control studies of Japanese and Korean subjects and found that a decreased risk of stomach cancer was associated with high intake of nonfermented soy foods, whereas high intake of fermented soy foods was associated with an increased risk of stomach cancer.[14] However, their analysis mainly consisted of previous studies, which covered a limited number of soy-based items without fully considering the possible lifestyle confounders, including the effects of salt. Common fermented soy foods, such as miso (soy paste) and natto (fermented soybeans), generally contain high amounts of salts, which might have contributed to the results as a confounder.

We previously reported an inverse association between overall intake of soy products and stomach cancer death from the Takayama study, a prospective study in Japan.[15] In this report, we evaluated the associations of soy or isoflavone intake with stomach cancer incidence after considering several lifestyle factors, including salt intake. We further examined whether or not the associations with stomach cancer were different between fermented and nonfermented soy foods.

Material and Methods

Participants and design

Participants were residents of Takayama City, Gifu, Japan, in September 1992. Among them, 36,990 persons aged 35 years

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What's new?

Soy food is a good source for isoflavones, which are substances with known anti-oxidative and cancer-protective properties. In this prospective epidemiological study conducted in Japan, the authors detected a lower risk of stomach cancer in people who consumed larger amounts of soy food and thus isoflavones, underscoring how diet can influence this frequent cancer type in Japan. Interestingly, a reduction in cancer risk was only observed for nonfermented and not for fermented soy foods. Fermented soy food, *i.e.*, miso, is rich in salt, itself a possible cause of stomach cancer and the authors speculate that this could have confounded previous studies yielding ambiguous results.

or older who were not hospitalized were eligible to be subjects in the Takayama study, a population-based cohort study. The details of the Takayama study have been described previously elsewhere.[16] A total of 31,552 residents (85.3%) completed a baseline self-administered questionnaire in the baseline survey (September 1, 1992).

Baseline questionnaire

The baseline questionnaire included questions on demography, anthropometric characteristics, medical history, smoking status, physical activity and diet. For women, reproductive characteristics including age at menarche, age at first delivery, menopausal status, parity number and history of hormone replacement therapy were inquired. Smokers were defined as people who had smoked a total of at least 20 packs of cigarettes in their life. For former and current smokers, information was obtained on cumulative years for smoking. Physical activity was assessed by asking participants how much time on average they spent on the listed activities of strenuous sports, vigorous work and moderate activities during the past year. The number of hours per week spent at each activity was multiplied by the corresponding energy expenditure, expressed as a metabolic equivalent (MET) and the sum of the product was counted as the physical activity score (MET·hr/week). The details including its validity are described elsewhere.[17]

Dietary data, including soy intake, were assessed using a 169-item semiquantitative food frequency questionnaire (FFQ). In FFQ, participants were asked how often on average they consumed each of the food items listed and what the usual serving size of each item was during the past year. Nine food items for soy products [miso soup, tofu (soy bean curd), deep-fried tofu, fried tofu, freeze-dried tofu, natto, houba-miso, soymilk and boiled soy beans] were included. These food items and some other dishes including soy products as ingredients were used to obtain the estimates for soy and isoflavone intake. Miso and natto were defined as fermented soy food. The other soy foods were defined as nonfermented soy food. Each intake of nutrients was estimated from the frequency of ingestion and portion size using the Japanese Standard Table of Food Composition (fifth revised and enlarged edition), published by the Science and Technology Agency of Japan.[18] The isoflavone (the sum of daidzein and genistein) from soy products was estimated on the basis of previously published data on isoflavone concentrations in soy foods, summarized by Wakai *et al.*[19] The validity and reproducibility of the questionnaire were previously reported to be reliable.[20] Spearman correlation coefficients between the FFQ and 12-day diet records kept over a 1 year period for intakes of total energy, soy food, isoflavone, alcohol and salt were 0.44, 0.75, 0.75, 0.72 and 0.49, respectively, for men. Corresponding values for women were 0.53, 0.68, 0.62, 0.64 and 0.54, respectively. The FFQ was designed to measure an individual's relative intake of foods and nutrients, rather than absolute values. The values of soy isoflavone intake may have been overestimated by the FFQ.

Outcomes and follow-up

After the exclusion of 760 who were diagnosed with stomach cancer before the baseline and/or reported a positive history of any cancers at the baseline, a follow-up was conducted until the end of March 2008. Consequently, our analysis included 14,219 men and 16,573 women and during the period, 441 men and 237 women developed stomach cancer.

Migration data were obtained from the residential registers. During the study period, 1,812 persons (5.9%) moved out of the study area and the date of emigration was unknown for 242 subjects (0.8%). The incidence of cancer was mainly confirmed through two regional population-based cancer registries in Gifu. Information was also collected from a local base hospital, which had played a leading role in providing medical care for the residents in the study area. The causes of cancer were coded according to the International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10). Stomach cancer was defined as code C16. The mortality-to-incidence ratio for stomach cancer was 0.44 and 15.3% of patients were ascertained by death certificate-only registration. As for cases that were recognized by death certificates, the cancer registries made a backward tracking review of cancer incidence and determined the patients' incidence date based on the description in the death certificate. As a result, only 6.9% of patients had an unknown incidence date before date of death, indicating satisfactory completeness of cancer registration in this cohort. This study was approved by the ethical board of the Gifu University Graduate School of Medicine.

Statistical analyses

Soy and isoflavone intake were controlled for the total energy intake by using the residual method proposed by Willett.[21] In the model, the energy-adjusted nutrient intake was computed

as a sum of the residual from the regression model with total energy intake as the independent variable and absolute nutrient intake as the dependent variable and the expected nutrient intake for the mean caloric intake of the study population. Study participants were categorized into quartile groups (Q1, Q2, Q3 or Q4) according to their energy-adjusted intakes of soy and isoflavone. The characteristics of participants were calculated as the mean (standard deviation) or number (percentage) of each category, according to the quartile groups of soy intake for each sex. To compare the characteristics of participants by the quartile of soy intake, one-way analysis of variance for continuous variables and χ^2 test for categorical variables were used.

Relative risks and 95% confidence intervals (CIs) for stomach cancer were estimated for the quartile groups of soy and isoflavone intake using the Cox proportional hazards regression model. The end of follow-up was determined as the date of stomach cancer diagnosis, the date of emigration from the study area, the date of death or the end of the study, whichever came first. For subjects who emigrated, their move-out date was entered from the residential registers. For subjects who moved away on a date unknown ($n = 242$), their last date of residence in the study area was confirmed by an inquiry survey in 2002 or the cancer registries. The reference group was set as the lowest quartile (Q1) of soy and isoflavone intake. Covariates included in the models were the following potential confounders; For men, age (years, continuous), body mass index (quartiles), physical activity score (continuous), smoking status (never, past, current smoker who had smoked for 30 years or less, current smoker who had smoked for 31 years or more), alcohol consumption (g/day), energy-adjusted salt intake (g/day) and years of education (=<8 years, 9–11 year, 12 − 14 years, >=15 years) were included. For women, age, body mass index, physical activity score, smoking status (never, past and current smoker), alcohol consumption, energy-adjusted salt intake, years of education and menopausal status (premenopausal, postmenopausal) were used. These confounders were known or suggested risk factors of stomach cancer in previous studies and/or were associated with soy food intake or stomach cancer risk among our subjects. Spearman's correlation coefficients between soy intakes and salt intake were 0.55 ($p < 0.001$) for men and 0.53 ($p < 0.001$) for women. Indicator terms were specifically created for missing data of categorical covariates. Tests for a linear trend were conducted in the Cox model by treating soy and isoflavone intake as continuous variables. Tests for interaction were performed using the likelihood ratio test.

All analyses were conducted using the SAS computer program, version 9.3 (SAS Institute). p values were calculated by a two-sided test. A p values <0.05 was considered statistically significant in all analyses.

Results

The characteristics of participants were shown according to the quartile groups of energy-adjusted soy intake in Table 1. Male and female subjects in the higher quartile of soy intake were both older at baseline. The persons among the lowest quartile of soy intake tended to be ever smoked and to have high consumption of alcohol. The level of education was higher among subjects with a lower soy intake. Women with a lower soy intake tended to be premenopausal.

In the multivariate-adjusted model, a significantly decreased relative risk of stomach cancer was observed in the highest group of soy intake in both men and women (Table 2). The estimated hazard ratios (HRs) of Q4 were 0.71 (95% CI: 0.53, 0.96) for men and 0.58 (95% CI: 0.36, 0.94) for women. The linear trend in the association was statistically significant for both men ($p = 0.039$) and women ($p = 0.003$). As for isoflavone intake, a significantly decreased risk of stomach cancer among the group with the highest isoflavone intake was observed in women [HR: 0.60 (95% CI: 0.37, 0.98)], although the association was not significant in men. The p values for interaction by sex on the association with stomach cancer were 0.076 for soy food intake and 0.041 for isoflavone intake.

Soy foods were possible to be taken in place of the other protein resources such as meat and fish. The energy-adjusted meat intake was inversely correlated with the soy intake (Spearman's correlation coefficient: −0.07 for men and −0.08 for women) and the energy-adjusted fish intake was positively correlated with the soy intake (Spearman's correlation coefficient: 0.19 for men and 0.16 for women). When additional adjustments for meat and fish were conducted, the estimated HRs of stomach cancer were 0.85 (95% CI: 0.65, 1.10), 0.86 (95% CI: 0.65, 1.13) and 0.72 (95% CI: 0.54, 0.97), respectively, in Q2, Q3 and Q4 of soy food intake in men (p for linear trend = 0.049). Corresponding values were 1.07 (95% CI: 0.72, 1.60), 1.14 (95% CI: 0.76, 1.71) and 0.58 (95% CI: 0.36, 0.94), respectively, in women (p for linear trend = 0.004).

The subjects had about four times more intake of nonfermented soy foods than that of fermented soy foods; the means (standard deviations) of intake were 77.9 (54.8) mg/day for non-fermented soy foods and 19.5 (12.1) mg/day for fermented soy foods. In term of isoflavone intake, the means (standard deviations) were 27.7 (20.5) mg/day from nonfermented soy foods and 15.1 (9.1) mg/day from fermented soy foods. After being separately stratified to the intake of fermented and nonfermented soy foods at the baseline, the intake of nonfermented soy foods was inversely associated with a risk of stomach cancer (Table 3); HRs of stomach cancer among the highest quartile of nonfermented soy foods intake were 0.68 (95% CI: 0.50, 0.91) in men and 0.63 (95% CI: 0.40, 1.00) in women. The p values for linear trend in these associations were 0.022 for men and 0.005 for women. The intake of fermented soy foods was not associated with the risk of stomach cancer in either men or women. However, there was no significant difference between fermented and nonfermented soy foods in relation to stomach cancer risk in either men ($p = 0.37$) or women ($p = 0.47$).

Table 1. Characteristics of study subjects at baseline in Takayama study

Quartile of soy food intake[1] (range)	Men					Women				
	Q1 (<=62 g)	Q2 (<=87 g)	Q3 (<=121 g)	Q4 (<=1051 g)	*p*	Q1 (<=62 g)	Q2 (<=87 g)	Q3 (<=121 g)	Q4 (<=1001 g)	*p*
n	4,519	3,325	3,062	3,313		3,179	4,873	4,636	4,385	
Age (y)[2]	51.1 (11.2)	55.6 (12.5)	57.2 (12.5)	58.3 (12.2)	<0.001	52.1 (12.2)	55.7 (13.5)	57.4 (13.2)	58.7 (12.8)	<0.001
Body mass index (kg/m^2)[2]	22.7 (2.8)	22.4 (2.7)	22.3 (2.8)	22.5 (2.9)	<0.001	22.1 (2.9)	21.8 (2.8)	21.9 (2.9)	22.1 (3.1)	<0.001
Diet intake[2]										
Total energy (kcal/day)	2789.7 (847.6)	2384.5 (784.4)	2412.5 (803.7)	2744.4 (966.1)	<0.001	2472.3 (857.8)	1984.0 (700.4)	1956.4 (694.3)	2197.1 (822.4)	<0.001
Soy food (g/day)	54.6 (26.6)	75.5 (29.5)	105.3 (31.3)	190.8 (89.9)	<0.001	48.1 (25.8)	61.6 (26.4)	88.1 (27.7)	163.2 (78.1)	<0.001
Isoflavone (mg/day)	26.0 (13.8)	34.9 (15.7)	47.1 (18.4)	77.4 (36.8)	<0.001	23.8 (14.0)	29.2 (14.2)	40.4 (16.0)	67.6 (32.8)	<0.001
Salt (g/day)	12.9 (5.7)	12.5 (5.4)	13.9 (5.7)	17.7 (7.4)	<0.001	12.7 (6.0)	11.4 (5.2)	12.4 (5.2)	15.6 (6.6)	<0.001
Alcohol consumption[2] (g/day)	47.6 (46.3)	37.2 (37.8)	36.6 (37.3)	40.6 (39.1)	<0.001	11.8 (24.3)	7.2 (15.0)	6.2 (13.1)	6.6 (14.7)	<0.001
Physical activity score[2] (METs·hr/week)	27.7 (42.5)	25.0 (38.7)	24.9 (38.7)	28.1 (43.5)	<0.001	18.6 (29.0)	17.8 (28.7)	18.6 (29.4)	18.8 (30.2)	0.42
Smoking status[3]					<0.001					<0.001
Never	675 (15.3%)	546 (16.9%)	504 (17.0%)	569 (17.8%)		2213 (75.0%)	3205 (81.4%)	3502 (85.0%)	3292 (86.2%)	
Past	1081 (24.4%)	966 (30.0%)	945 (31.9%)	1108 (34.7%)		158 (5.4%)	202 (5.1%)	170 (4.1%)	155 (4.1%)	
Current (<= 30 years)	1815 (41.0%)	986 (30.6%)	789 (26.7%)	739 (23.1%)		514 (17.4%)	456 (11.6%)	376 (9.1%)	292 (7.7%)	
Current (>= 31 years)	856 (19.3%)	726 (22.5%)	723 (24.4%)	782 (24.5%)		64 (2.2%)	75 (1.9%)	70 (1.7%)	79 (2.1%)	
Length of education[3]					<0.001					<0.001
<=8 years	673 (15.0%)	787 (24.0%)	799 (26.4%)	979 (29.9%)		568 (18.1%)	1139 (26.5%)	1368 (30.0%)	1504 (35.0%)	
9–11 years	1651 (36.9%)	1087 (33.2%)	1038 (34.3%)	1166 (35.7%)		1329 (42.3%)	1642 (38.2%)	1742 (38.2%)	1656 (38.5%)	
12–14 years	1536 (34.3%)	1040 (31.7%)	853 (28.2%)	842 (25.7%)		1080 (34.4%)	1297 (30.1%)	1252 (27.5%)	984 (22.9%)	
>=15 years	619 (13.8%)	363 (11.1%)	333 (11.0%)	284 (8.7%)		163 (5.2%)	225 (5.2%)	196 (4.3%)	158 (3.7%)	
Menopausal status[3] (premenopausal)						1706 (54.6%)	1800 (42.3%)	1626 (36.0%)	1241 (29.1%)	<0.001

[1]Soy food intakes adjusted for total energy intake by Willett method were categorized into quartile groups.
[2]Mean (standard deviation).
[3]Number (percentage).

Table 2. Associations of soy food and isoflavone intake with stomach cancer incidence in Takayama study

	Soy food[1] (g/day)					Isoflavone[1] (mg/day)				
	Q1	Q2	Q3	Q4	*p* for trend	Q1	Q2	Q3	Q4	*p* for trend
Men										
Mean (range)	38.4 (<=62)	74.1 (<=87)	102.9 (<=121)	176.3 (<=1051)		17.6 (<=28)	33.5 (<=39)	45.4 (<=53)	75.5 (<=433)	
No. of incident cases	130	102	104	105		131	100	97	113	
Person-years	61,207	43,198	39,255	42,931		62,636	43,790	39,340	40,824	
Age-adjusted HR	1.00	0.85	0.87	0.75	0.051	1.00	0.86	0.83	0.83	0.13
(95% CI)	(Reference)	(0.65–1.10)	(0.67–1.13)	(0.58–0.97)		(Reference)	(0.67–1.12)	(0.63–1.08)	(0.64–1.08)	
Multivariate-adjusted HR[2]	1.00	0.84	0.85	0.71	0.039	1.00	0.85	0.82	0.81	0.098
(95% CI)	(Reference)	(0.64–1.09)	(0.65–1.12)	(0.53–0.96)		(Reference)	(0.65–1.11)	(0.62–1.08)	(0.60–1.09)	
Women										
Mean (range)	43.5 (<=62)	74.9 (<=87)	102.4 (<=121)	168.7 (<=1001)		20.1 (<=28)	33.8 (<=39)	45.6 (<=53)	72.6 (<=436)	
No. of incident cases	38	70	85	44		36	72	79	50	
Person-years	45,000	60,690	63,918	60,516		43,953	60,242	63,765	62,163	
Age-adjusted HR	1.00	1.10	1.17	0.60	0.002	1.00	1.16	1.06	0.64	0.002
(95% CI)	(Reference)	(0.74–1.64)	(0.80–1.72)	(0.39–0.93)		(Reference)	(0.78–1.73)	(0.71–1.58)	(0.42–0.99)	
Multivariate-adjusted HR[2]	1.00	1.08	1.15	0.58	0.003	1.00	1.13	1.02	0.60	0.001
(95% CI)	(Reference)	(0.72–1.62)	(0.76–1.72)	(0.36–0.94)		(Reference)	(0.75–1.69)	(0.67–1.54)	(0.37–0.98)	

[1]Soy and isoflavone intakes were adjusted for total energy intake by Willett method.
[2]Estimated hazard ratio after adjustments for age (years), body mass index, physical activity score, smoking status (never, past, current smoker for 30 years or less, current smoker for 31 years or more), alcohol consumption (g/day), salt intake (g/day) and education years (<=8 years, 9–11 year, 12–14 years, >=15 years) for men. For women, age, body mass index, physical activity score, smoking status (never, past, current smoker), alcohol consumption, salt intake, education years and menopausal status (premenopausal, postmenopausal).

Table 3. Associations of intake of fermented or nonfermented soy foods with stomach cancer incidence in Takayama study

	Fermented soy foods[2] (g/day)					Nonfermented soy foods[2] (g/day)				
	Q1	Q2	Q3	Q4	*p* for trend	Q1	Q2	Q3	Q4	*p* for trend
Men										
Mean (range)	6.6 (<=11)	14.5 (<=18)	20.5 (<=24)	37.3 (<=112)		27.7 (<=47)	57.3 (<=68)	80.8 (<=96)	147.8 (<=1034)	
No. of subjects	3,907	3,387	3,304	3,621		4,662	3,331	2,978	3,248	
No. of incident cases	110	116	92	123		131	109	104	97	
Person-years	52,442	43,918	42,727	47,504		63,363	43,290	37,857	42,082	
Age-adjusted HR	1.00	1.14	0.85	1.02	0.84	1.00	0.91	0.90	0.71	0.027
(95% CI)	(Reference)	(0.88–1.48)	(0.64–1.12)	(0.79–1.32)		(Reference)	(0.70–1.17)	(0.69–1.16)	(0.54–0.93)	
Multivariate-adjusted HR[1]	1.00	1.13	0.84	1.02	0.78	1.00	0.90	0.88	0.68	0.022
(95% CI)	(Reference)	(0.87–1.47)	(0.63–1.12)	(0.77–1.34)		(Reference)	(0.69–1.16)	(0.67–1.16)	(0.50–0.91)	
Women										
Mean (range)	7.5 (<=11)	14.4 (<=18)	20.9 (<=24)	34.0 (<=104)		32.0 (<=47)	58.1 (<=68)	80.6 (<=96)	140.8 (<=992)	
No. of incident cases	56	62	67	52		39	63	83	52	
Person-years	52,681	59,581	61,290	56,572		43,203	60,700	64,729	61,491	
Age-adjusted HR	1.00	0.94	0.92	0.76	0.075	1.00	0.90	1.00	0.63	0.003
(95% CI)	(Reference)	(0.65–1.35)	(0.65–1.32)	(0.52–1.11)		(Reference)	(0.60–1.35)	(0.68–1.47)	(0.42–0.96)	
Multivariate-adjusted HR[1]	1.00	0.95	0.95	0.79	0.14	1.00	0.89	0.98	0.63	0.005
(95% CI)	(Reference)	(0.66–1.36)	(0.66–1.38)	(0.52–1.19)		(Reference)	(0.59–1.34)	(0.66–1.47)	(0.40–1.00)	

[1]Soy intakes were adjusted for total energy intake by Willett method.
[2]Estimated hazard ratio after adjustments for age (years), body mass index, physical activity score, smoking status (never, past, current smoker for 30 years or less, current smoker for 31 years or more), alcohol consumption (g/day), salt intake (g/day) and education years (<=8 years, 9–11 year, 12–14 years, >=15 years) for men. For women, age, body mass index, physical activity score, smoking status (never, past, current smoker), alcohol consumption, salt intake, education years and menopausal status (premenopausal and postmenopausal).

Nonfermented soy food intakes were positively correlated with the intakes of fruits and vegetables (Spearman's correlation coefficient: 0.31 for men and 0.26 for women). When we made additional adjustments for fruits and vegetables, the associations between soy or isoflavone and stomach cancer were not altered substantially for either men or women; estimated HRs of stomach cancer were 0.90 (95% CI: 0.69, 1.17), 0.89 (95% CI: 0.67, 1.16) and 0.68 (95% CI: 0.51, 0.92), respectively, in Q2, Q3 and Q4 of nonfermented soy foods intake in men (p for linear trend = 0.025). Corresponding values were 0.90 (95% CI: 0.60, 1.36), 1.00 (95% CI: 0.67, 1.50) and 0.65 (95% CI: 0.41, 1.03), respectively, in women (p for linear trend = 0.007).

To eliminate those who might have had stomach cancer but it was not noticed yet at baseline, we re-analyzed after excluding 78 patients who were diagnosed with stomach cancer in the first 2 years of follow-up. None of the results were substantially altered.

Discussion

Several epidemiological studies have examined the association between intake of some items of soy-based products and stomach cancer.[4,22–29] However, few studies have reported the associations between intakes of soy[3,5,15,27–29] or isoflavone[28–32] as a whole and stomach cancer. In this study, a decreased risk of stomach cancer was observed among the higher quartile of total soy intake in both men and women and similar inverse associations between isoflavone intake and stomach cancer risk were also observed in women. The inverse associations seemed to be linear in men, whereas in women a decreased risk of stomach cancer was mainly observed in the highest group of soy or isoflavone intake and not in the moderate group of soy or isoflavone intake. Three previous Western case-control studies and two Asian cohort studies that estimated dietary isoflavone reported no significant association with stomach cancer,[28–32] which is, in part, inconsistent with our results. However, case-control studies in China[3] and Korea,[27] and our report on this cohort[15] that estimated total soy intake, observed an inverse association with the risk of stomach cancer and had concordant results. Studies among Western populations[30–32] might not have detected significant associations due to the quite low intake of isoflavones among the majority of their participants (at most 10 mg/day), although estimates of nutrition intake should not be compared when calculated by different questionnaires. In addition, one nested case-control study that measured plasma isoflavone concentrations observed associations between a decreased risk of stomach cancer and higher blood levels of isoflavone in Koreans,[33] whereas another study of Japanese found no association.[34] The inverse associations between soy isoflavone and stomach cancer should be further verified in different epidemiological studies. Future studies might need to delineate the dose-response relationship of soy isoflavone and stomach cancer, considering sex differences.

Previous studies suggested that associations with stomach cancer for nonfermented soy products were affected by the confounding effects of fruit and vegetable intake and that the associations for fermented soy products were affected by the confounding effects of salt intake.[14,35] After considering these confounding effects, we observed a lower risk of stomach cancer among subjects with higher intake of non-fermented soy foods, although the association between the intake of fermented soy foods and a risk of stomach cancer did not obtain a statistical significance. The effects of soy intake on stomach cancer risk might differ depending on the preparation or fermentation of soy foods. As fermented soy foods may contain *N*-nitroso compounds as a result of their storage process, the potential carcinogenicity of *N*-nitroso compounds might counteract a protective effect of other ingredients of soy, including isoflavones. The isoflavone intake from nonfermented soy foods was considerably higher than that from fermented soy foods among our subjects, although fermented soy foods generally contains more isoflavones per gram than nonfermented soy foods. In contrast with non-fermented soy foods, high concentrations of salts in fermented soy foods also might have interrupted the effect of fermented soy beans on stomach cancer, even though the association was assessed after adjustments for salt intake as a confounder.

Although isoflavone, which is structurally similar to estrogens, may have protective effects on hormone-related cancers such as breast and prostate cancer, its effects on stomach cancer might be mediated by some mechanisms other than the estrogen pathway. In experimental studies *in vitro* and in animals, genistein reduced the growth and proliferation of gastric cancer cells by cell cycle arrest, induced increased apoptosis and inhibited angiogenesis.[8–10] It has anti-inflammatory and antioxidative effects.[11,12] Genistein also attenuated stem cell-like properties in gastric cancer cells and suppressed the tumor cell's invasive capacity that is required for its growth and metastasis.[13]

The strengths of our study included its prospective design, good participation rate, long follow-up, use of validated FFQ and the information on several confounders. The validated FFQ listed various types of soy foods, leading to precise estimates of soy or isoflavone intake. Although some dietary intake can be misclassified, recall bias in diet would not systematically occur at the baseline between subjects with stomach cancer and those without stomach cancer, since information on diet was collected before the diagnosis of stomach cancer. Although the exclusion of those who had died during the first two years of follow-up did not change the results, diet patterns might have changed due to preclinical signs. Another limitation of our study was the lack of information regarding infection with *H. pylori*. Although several lifestyle and reproductive factors were adjusted in the analyses, we could not fully exclude the possibility of residual confounders.

In conclusion, this prospective study in Japan demonstrated decreased risks of stomach cancer among people who had higher intakes of total soy and isoflavone. Higher intakes of nonfermented soy foods were associated with a lower risk of stomach cancer, whereas there was no significant associations between the intake of fermented soy foods and a risk of stomach cancer. These results suggest that higher intakes of soy isoflavone have a protective effect against stomach cancer. In addition, the risk reduction appeared to be more attributed to the intake of nonfermented soy foods than fermented soy foods.

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