Isoflavone intake and risk of gastric cancer: a population-based prospective cohort study in Japan[1–3]

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ABSTRACT

Background: Isoflavones are structurally similar to 17β-estradiol and may be able to prevent gastric cancer. However, there is contradictory evidence concerning the relation between the intake of soy food, which is rich in isoflavones, and gastric cancer. The association with gastric cancer might differ between isoflavones and soy foods, and research on the effects of isoflavone intake alone on gastric cancer is needed.

Objective: We investigated the association between isoflavone intake and the incidence of gastric cancer.

Design: We conducted a large, population-based prospective study of 39,569 men and 45,312 women aged 45–74 y. Dietary soy and isoflavone intakes were measured by using a validated food-frequency questionnaire in 1995 and 1998.

Results: During 806,550 person-years of follow-up, we identified 1249 new gastric cancer cases. Isoflavone intake was not associated with gastric cancer in either men or women. Compared with the lowest quartile, the HR and 95% CI for developing gastric cancer in the fourth quartile of isoflavone intake was 1.00 (0.81, 1.24) for men and 1.07 (0.77, 1.50) for women. In a stratified analysis by exogenous female hormones (women only), however, we found an increasing trend in risk of gastric cancer associated with higher isoflavone intakes among exogenous female hormone users (P-trend = 0.03) but not for nonusers (P-interaction = 0.04).

Conclusion: The current study does not support the hypothesis that higher intakes of isoflavones prevent gastric cancer in either men or women. *Am J Clin Nutr* 2012;95:147–54.

INTRODUCTION

Although its incidence and mortality rate have been declining over the years (1), GC[4] is still the most common cancer in Japan and the second leading cause of death from cancer globally. Prevention of GC is one of the most important elements for cancer control strategy both in Japan and around the world.

Sex-based discrepancies in GC are found throughout the world, and the incidence of GC in men is 2- to 3-fold that in women (2). This difference is consistent across international populations regardless of different prevalences of environmental risk factors, such as *Helicobacter pylori* infection, tobacco smoking, and different dietary patterns (1, 3). A possible explanation involves biologic differences related to sex hormones, such as estrogen (3).

Isoflavones are structurally similar to 17β-estradiol, have a particular affinity for the β-estrogen receptor (4), and may be able to prevent GC. Because isoflavones are phytoestrogenic compounds that are abundant in soybeans, soy products have been of considerable interest in the etiology of GC (5). However, evidence of the relation between soy food intake and GC is contradictory. Non-isoflavone aspects of soy food, such as salt intake and fermentation, might contribute to the different association with GC between soy food and isoflavones, because salt is a well-known risk factor for GC (6), and fermented soy foods may contain nitroso compounds, which have been reported to induce gastric carcinogenesis (7, 8). Therefore, the association of isoflavones with GC might be different from that of soy food, and further research on the effects of isoflavones alone on GC is needed. However, no large-scale prospective study to assess this association has been conducted.

Here, we investigated the association between isoflavone intake and risk of GC in a population-based, prospective, cohort study in Japan. Our hypothesis was that a higher intake of isoflavones would prevent GC because of their estrogen-like effects.

SUBJECTS AND METHODS

Study population

The JPHC-Based Prospective Study was started in 1990 for cohort I and in 1993 for cohort II. Subjects were all registered Japanese inhabitants in 11 public health center areas who were aged 40–69 y (cohort 1: 40–59 y; cohort 2: 40–69 y) at the beginning of each cohort's baseline survey. Details of the study

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[4] Abbreviations used: EFH, exogenous female hormones; FFQ, food-frequency questionnaire; GC, gastric cancer; JPHC, Japan Public Health Center.

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design were described previously (9). The institutional review board of the National Cancer Center, Tokyo, Japan, approved the study. The participants in the current study were subjects in the JPHC study who responded to a 5-y follow-up questionnaire in 1995–1999 at the age of 45–74 y. This follow-up survey was used as the starting point in the current study. The subjects from 2 public health center areas (Katsushika in Tokyo prefecture and Suita in Osaka prefecture) were excluded from the current analysis because the selection of subjects was different from that in other public health center areas, which left 116,896 subjects as the study population. After the exclusion of subjects with a non-Japanese nationality (n = 51), a late report of emigration occurring before the starting point (n = 168), or ineligibility due to incorrect birth date (n = 4) or duplicate enrollment (n = 4), we established a population-based cohort of 116,669 subjects. After the exclusion of 1625 subjects who had died, moved out of the study area, or were lost to follow-up before the starting point, 115,044 eligible subjects remained. Of these, 91,246 responded to the questionnaire, which yielded a response rate of 78.2%.

Questionnaire

We asked the subjects to reply to a lifestyle questionnaire that covered sociodemographic characteristics, medical history, smoking and drinking habits, diet, and other characteristics. We designed the FFQ to estimate dietary intake from 138 food items and validated it for the estimation of various nutrients and food groups (10). The participants were asked about how often they consumed the individual food items (frequency of intake) and to estimate representative relative sizes compared with standard portions during the previous year (11). Of the 138 food items, 8 items (standard portion size) dealt specifically with consumption of soy and isoflavones: miso soup (150 g), soymilk (200 g), tofu for miso soup (20 g), tofu for other dishes (75 g), *yushidofu* (predrained tofu; 150 g), *koyadofu* (freeze-dried tofu; 60 g), *aburaage* (deep-fried tofu; 2 g), and *natto* (fermented soybeans; 50 g). These 8 items contributed 95.9% of the total genistein and daidzein intakes in the estimates from dietary records in our validation study (12). We defined fermented soy food as miso (for miso soup) and *natto*, whereas nonfermented soy food was defined as soymilk, tofu for miso soup, tofu for other dishes, *yushidofu*, *koyadofu*, *and aburaage* (13). We then estimated genistein and daidzein intakes from either fermented or nonfermented foods. For miso soup, the FFQ included questions on the frequency of consumption (almost never, 1–3 d/mo, 1–2 d/wk, 3–4 d/wk, 5–6 d/wk, or daily) and on the daily amount consumed (number of bowls: $<$1, 1, 2, 3, 4, 5, 6, 7–9, or $\geq$10). For soymilk, the FFQ included questions on 10 frequency categories only: almost never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 glass/d, 2–3 glasses/d, 4–6 glasses/d, 7–9 glasses/d, or $\geq$9 glasses/d. For other soy foods, the FFQ contained questions on frequency (almost never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 time/d, 2–3 times/d, 4–6 times/d, or $\geq$7 times/d) and sizes relative to a standard portion [small (50% smaller than standard), medium (same as standard), or large (50% larger than standard)].

The daily intake of each food item was calculated by multiplying the frequency by the standard portion and, if available, the relative portion size for each item in the FFQ. We calculated daily intakes of isoflavones (genistein and daidzein) using values in a specially developed food-composition table of Japanese foods (14), which contained measured values of soy foods (15, 16). This allowed for the effect of food processing on isoflavone content, including fermentation, to be taken into consideration when intakes were estimated. We did not collect information on the use of isoflavone supplements. Intake of food and nutrients was log transformed and adjusted for total energy intake by using the residual model (17). Because the estimates of genistein and daidzein intakes were highly correlated (Spearman's rank correlation coefficient = 0.997), the results for genistein are provided as representative for isoflavones.

The validity of the energy-adjusted genistein intake assessed from the 5-y FFQ was evaluated in a subsample with consecutive 14- or 28-d dietary records. Spearman's correlation coefficients between the energy-adjusted intake of genistein from the questionnaire and from dietary records was 0.65 (cohort I) and 0.48 (cohort II) for men and 0.55 (cohort I) and 0.45 (cohort II) for women (18–21). The reproducibility between the 2 questionnaires for energy-adjusted genistein intake assessed 1 y apart showed Spearman's correlation coefficients of 0.75 (men) and 0.69 (women) for cohort I and 0.51 (men) and 0.41 (women) for cohort II (18–21).

We excluded subjects with a diagnosis of GC or who reported having GC before the starting point (n = 746), who had missing data regarding isoflavone intake (n = 1115), or who reported extreme total energy intakes (upper: 2.5%; lower: 2.5%) (n = 4504). The final analysis included 84,881 subjects (39,569 men and 45,312 women).

Follow-up and identification of GC cases

We followed subjects from the 5-y follow-up survey until 31 December 2006. We identified changes in residence status, including survival, annually through the residential registry in each area or, for those who had moved out of the area, through the municipal office of the area to which they had moved. Mortality data for persons in the residential registry are forwarded to the Ministry of Health, Labor, and Welfare and are coded for inclusion in the national Vital Statistics database. Residency registration and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are thought to be complete. During the follow-up period in the current study, 9370 (11.0%) subjects died, 3675 (4.3%) moved out of the study area, and 305 (0.4%) were lost to follow-up.

We identified incident data for GC by active patient notification from major local hospitals in the study area and from data linkage with population-based cancer registries. We coded GC cases according to the International Classification of Diseases for Oncology, third edition (22) (C16.0–C16.9). Tumors located in the lower side of the stomach were classified as distal GC (noncardia; code C16.2–16.7) and in the upper side as proximal GC (cardia; code C16.0–16.1). Tumors that could not be classified because they were overlapping lesions (code C16.8) or because no information was available (code C16.9) were categorized as unclassified. Histologic classification was based on review of the record from the respective hospital as described previously (23) and divided into differentiated and undifferentiated types, corresponding to the intestinal type and diffuse type, respectively, in the Lauren classification (24). In our

cancer registry system, the proportion of cases for which information was available from death certificates was only 4.2%.

Statistical analysis

We calculated person-years of follow-up for each subject from the starting point to the date of GC diagnosis, date of emigration from the study area, date of death, or end of the follow-up (31December 2006), whichever came first. We censored subjects lost to follow-up at the last confirmed date of presence in the study area.

We calculated HRs and 95% CIs of developing GC for the categories of energy-adjusted consumption of isoflavones, isoflavones from fermented soy food, isoflavones from nonfermented soy food, miso soup, and soy food in quartiles for men and women separately, with the lowest consumption category as the reference. We used Cox proportional hazards models with adjustment for potential confounding variables, such as age (in y), public health center area, BMI (in kg/m^2: $<$18.4, 18.5–19.9, 20–22.4, 22.5–24.9, 25–29.9, and $\geq$30), smoking status (never, past, and current), alcohol consumption (none and $<$150, 150–299, 300–449, and $\geq$450 g ethanol/wk for men and none and $<$150 and $\geq$150 g ethanol/wk for women), family history of GC, menopausal status (premenopausal, natural, or induced postmenopausal) and use of EFHs in women (never, past, and current), quartiles of total energy intake, and energy-adjusted intake of salt, vegetable, fruit, and fish.

We calculated *P* values for the analysis of linear trends by assigning ordinal values for categories of isoflavone intake and entering the number as a continuous term in the regression model. We also statistically evaluated the interactions between EFH use [never compared with ever (past and current)] and isoflavone in the risk of GC based on the likelihood ratio test with 1 df. Ordinal values were assigned to 2 categories of EFH (never compared with ever) and to 4 categories of isoflavone. An interaction term was then created by multiplying ordinal values for EFH by those for isoflavone. All *P* values are 2-sided, and statistical significance was indicated at the $P < 0.05$ level. We performed all statistical analyses with SAS software (version 9.1; SAS Institute Inc).

RESULTS

During 806,550 person-years of follow-up, we identified 1249 new GC cases (899 for men and 350 for women). The characteristics of participants according to isoflavone intake are shown in **Table 1**. Those with higher intakes were older, less likely to be current smokers and regular drinkers, and more likely to be postmenopausal and to consume more salt, vegetables, fruit, and fish. BMI was also distributed differently by isoflavone intake.

Associations of isoflavone, isoflavone from fermented soy food, isoflavone from nonfermented soy food, miso soup, and soy food for GC risk in men and women are shown separately for men (**Table 2**) and for women (**Table 3**). In an age- and area-adjusted model, no measurable associations were found between isoflavone, isoflavone from fermented soy food, isoflavone from nonfermented soy food, and soy food intakes and GC in either men or women, whereas the quartile category of miso soup intake was dose-dependently associated with an increased risk of GC in men and a decreased risk of GC in women (*P*-trend = 0.03 and 0.02, respectively); however, relations were not statistically significant in multivariate-adjusted models. Neither fermented soy food nor nonfermented soy food intake was associated with the risk of GC (data not shown). When isoflavone and soy food were respectively entered into the models as deciles of intakes, no substantial association was observed.

The results of stratified analysis by EFH use among women are shown in **Table 4**. We observed increased GC risks with isoflavone and soy food intakes among EFH ever users; compared with the lowest quartile, the HRs (and 95% CIs) of the second, third, and fourth quartiles of isoflavone intake were 1.25 (0.38, 4.06), 1.78 (0.58, 5.47), and 2.80 (0.93, 8.39) (*P*-trend = 0.03) and for soy food intake were 1.69 (0.48, 5.94), 3.20 (0.99, 10.3), and 3.76 (1.14, 12.4) (*P*-trend = 0.01). Among EFH never users, no association was observed between isoflavone and soy food intakes and GC risk, and a decreased GC risk with miso soup intake was observed. We found statistically significant interactions between isoflavone and soy food intakes and EFH (P = 0.04 and 0.02, respectively). Similar results were observed when we separately analyzed for isoflavone intakes from fermented and nonfermented soy food.

When cases were divided by histologic type, we observed no substantial association between isoflavone, miso soup, and soy food intakes and GC (data not shown). Stratified analyses by age, alcohol consumption, smoking status, salt intake, salted food (pickled vegetables, dried and salted fish, and salted fish roe) intake, and menopausal status also showed essentially the same results (data not shown). The association between daidzein intakes and GC risk was similar to that observed for genistein intake (data not shown).

DISCUSSION

In this large, population-based, prospective study, which was characterized by high soy food consumption, isoflavone intake overall was not found to be significantly associated with the risk of GC in either men or women. In a stratified analysis by EFH (women only), however, we found an increase in risk of GC associated with higher isoflavone intakes among EFH users. To our knowledge, this was the first large-scale prospective cohort study to examine the association of isoflavone intake with GC risk.

Two case-control studies have reported that isoflavone intake was not associated with GC. Nomura et al (25) showed no association between total isoflavone intake and gastric adenocarcinoma of the distal stomach among 300 cases and 446 population-based controls in Hawaii. Lagiou et al (26) reported that isoflavone intake was not associated with GC among 110 patients with incident stomach adenocarcinoma and 100 control patients in Greece. Our results, from a large population-based cohort study, support these previous case-control studies. As for the different exposure estimates, one small nested case-control study reported that high plasma concentrations of isoflavones were associated with a decreased risk of GC from 131 cases and 393 matched controls (27). Differences from our exposure estimates might explain the conflicting results. Alternatively, plasma concentrations of isoflavones might be better measurements of bioactive or bioavailable isoflavones, thus explaining the respective findings arising from the different approaches. The concentration of isoflavone in blood reflects individual differences in absorption and metabolism, in which intestinal microflora play an important

TABLE 1
Characteristics of the study subjects on the 5-y follow-up survey according to quartile of energy-adjusted intake of isoflavone (genistein) in the Japan Public Health Center–Based Prospective Study

	Quartile of energy-adjusted intake of isoflavone (genistein)									
	Men (n = 39,569)					Women (n = 45,312)				
	Lowest	Second	Third	Highest	P^1	Lowest	Second	Third	Highest	P^1
No. of subjects (%)	9892	9892	9893	9892		11,328	11,328	11,328	11,328	
Age (y)	56.2 ± 0.08[2]	56.4 ± 0.08	56.5 ± 0.08	57.5 ± 0.08	<0.0001	56.9 ± 0.08	56.7 ± 0.07	57.0 ± 0.07	57.7 ± 0.07	<0.0001
BMI ≥ 25 kg/m^2 (%)	28.7	27.9	27.5	28.3	<0.0001	28.9	27.7	28.4	29.8	<0.0001
Current smoker (%)	46.3	45.0	43.4	38.5	<0.0001	5.7	4.3	3.8	3.7	<0.0001
Regular drinker, ≥150 g ethanol/wk (%)	50.2	50.4	48.9	44.5	<0.0001	3.4	2.4	2.1	2.0	<0.0001
Family history of gastric cancer (%)	5.3	5.6	5.5	5.8	0.6	5.2	6.1	6.3	5.7	0.003
Postmenopausal status (%)	—	—	—	—		67.7	70.9	74.4	76.2	<0.0001
Exogenous female hormones, ever user (%)	—	—	—	—		12.3	12.4	13.4	13.6	<0.0001
Dietary intake[3]										
Energy (kcal/d)	2165 ± 6.8	2155 ± 6.4	2206 ± 6.7	2146 ± 6.4	<0.0001	1848 ± 5.6	1857 ± 5.4	1888 ± 5.4	1824 ± 5.1	<0.0001
NaCl deducted from Na content (g/d)	10.1 ± 0.04	11.8 ± 0.03	12.7 ± 0.04	13.4 ± 0.04	<0.0001	10.3 ± 0.1	11.6 ± 0.1	12.1 ± 0.03	12.7 ± 0.03	<0.0001
Pickled vegetables (g/d)	24.8 ± 0.4	30.3 ± 0.4	32.5 ± 0.4	36.2 ± 0.4	<0.0001	30.8 ± 0.4	35.5 ± 0.4	37.8 ± 0.4	39.7 ± 0.4	<0.0001
Dried and salted fish (g/d)	15.4 ± 0.2	17.0 ± 0.2	18.6 ± 0.2	20.0 ± 0.3	<0.0001	16.3 ± 0.2	17.4 ± 0.2	18.6 ± 0.2	18.9 ± 0.2	<0.0001
Salted fish roe (g/d)	1.0 ± 0.04	1.6 ± 0.03	2.0 ± 0.04	2.0 ± 0.03	<0.0001	1.1 ± 0.03	1.7 ± 0.04	1.9 ± 0.03	1.9 ± 0.03	<0.0001
Vegetables (g/d)	167 ± 1.3	188 ± 1.2	200 ± 1.2	221 ± 1.4	<0.0001	201 ± 1.2	223 ± 1.2	233 ± 1.1	245 ± 1.3	<0.0001
Fruit (g/d)	148 ± 1.5	168 ± 1.5	178 ± 1.4	190 ± 1.5	<0.0001	220 ± 1.8	232 ± 1.5	237 ± 1.5	240 ± 1.5	<0.0001
Fish (g/d)	81.9 ± 0.6	86.7 ± 0.5	92.1 ± 0.5	93.0 ± 0.5	<0.0001	79.7 ± 0.5	83.7 ± 0.4	86.1 ± 0.4	86.1 ± 0.5	<0.0001
Miso soup (mL/d)	144 ± 1.1	257 ± 1.5	297 ± 1.7	316 ± 1.9	<0.0001	124 ± 0.9	212 ± 1.3	245 ± 1.4	264 ± 1.5	<0.0001
Soy food (g/d)[4]	34.0 ± 0.1	63.3 ± 0.2	90.4 ± 0.3	163.6 ± 1.2	<0.0001	34.2 ± 0.1	63.0 ± 0.2	89.1 ± 0.3	164.1 ± 1.1	<0.0001
Daidzein (mg/d)	5.6 ± 0.02	11.0 ± 0.01	16.4 ± 0.02	29.7 ± 0.1	<0.0001	5.6 ± 0.01	10.9 ± 0.01	16.3 ± 0.02	29.1 ± 0.1	<0.0001
Genistein (mg/d)	8.8 ± 0.03	17.2 ± 0.02	26.2 ± 0.03	48.8 ± 0.2	<0.0001	8.9 ± 0.02	17.3 ± 0.02	26.2 ± 0.03	48.1 ± 0.2	<0.0001
Genistein from fermented soy food (mg/d)[5]	4.5 ± 0.03	9.6 ± 0.04	15.1 ± 0.06	27.2 ± 0.2	<0.0001	4.3 ± 0.03	9.2 ± 0.04	14.8 ± 0.06	25.9 ± 0.2	<0.0001
Genistein from nonfermented soy food (mg/d)[6]	4.3 ± 0.03	7.6 ± 0.04	11.1 ± 0.06	21.6 ± 0.2	<0.0001	4.6 ± 0.02	8.1 ± 0.04	11.4 ± 0.06	22.2 ± 0.2	<0.0001

[1] ANOVA or chi-square-test.
[2] Mean ± SE (all such values).
[3] All mean total intakes of food and nutrition are energy adjusted.
[4] Total of fermented and nonfermented soy food.
[5] The consumption of miso (for miso soup) and *natto*.
[6] The consumption of soymilk, tofu for miso soup, tofu for other dishes, *yushidofu*, *koyadofu*, and *aburaage*.

role (28). In particular, most likely because of differences in intestinal bacteria, only 30–50% of adults have the capacity to metabolize daidzein into equol—a compound known to have stronger estrogenic activity than daidzein (29). This might be relevant because the effect of isoflavones may be modulated by endogenous concentration of estrogens. However, the evidence was insufficient, both in the association between serum isoflavone concentrations and GC risk and that between isoflavone intake and GC risk. Moreover, our validation study, which used a subsample of the cohort, yielded satisfactorily high correlation coefficients for genistein estimates from dietary records measured repeatedly for 1 y, a fasting serum sample, and a single FFQ (dietary records compared with serum: 0.33; dietary records compared with. FFQ: 0.59) (12). Furthermore, we previously reported an association between plasma isoflavone concentrations and breast, prostate, and lung cancer risk from nested case-control studies within the JPHC Study (30–32) and found results similar to those we previously obtained in the JPHC Study using an FFQ (18, 20, 33). Further large prospective studies are needed to confirm the relation between isoflavones and GC risk.

As for soy food intake, several studies have examined the association with the risk of GC, but results have been varied: some epidemiologic studies reported that soy products significantly decrease the risk of GC (5, 34, 35), whereas others reported an increased risk of GC (6, 36) or no significant association (6, 36–38). A recent meta-analysis reported that a high intake of fermented soy foods is associated with an increased GC risk, whereas a high intake of nonfermented soy foods is associated with a decreased GC risk (13). However, because the possible confounding effects of salt, vegetable, fruit, and other dietary factors had not been considered in the soy product analysis in most studies included in the meta-analysis, the effects of these uncontrolled factors cannot be ruled out (5, 35). In the current study, we adjusted for these dietary factors and found no association between isoflavone, miso soup, and soy food intakes and the risk of GC.

We observed an increased risk of isoflavone and soy food intakes for GC among women with ever EFH use, although no association was found for isoflavone and soy food intakes among women with never EFH use. Such a differential association between isoflavone or soy food intake and GC by EFH status has not been documented previously. Our previous study showed that

TABLE 2
HRs and 95% CIs of gastric cancer according to quartile of energy-adjusted intake of isoflavone (genistein), miso soup, and soy food among men[1]

			All gastric cancer			Upper third, including cardia		Distal	
Quartiles	Median	Person-years	No. of cases	HR1 (95% CI)[2]	HR2 (95% CI)[3]	No. of cases	HR2 (95% CI)[3]	No. of cases	HR2 (95% CI)[3]
Isoflavone (genistein) (mg/d)									
First	9.2	90,530	187	1.00 (reference)	1.00 (reference)	12	1.00 (reference)	121	1.00 (reference)
Second	17.2	92,407	219	1.01 (0.83, 1.23)	1.01 (0.82, 1.23)	32	2.28 (1.15, 4.52)	145	0.98 (0.76, 1.26)
Third	25.9	93,569	234	0.98 (0.80, 1.20)	0.99 (0.81, 1.23)	27	1.83 (0.89, 3.77)	167	1.02 (0.79, 1.31)
Fourth	42.3	92,078	259	0.98 (0.80, 1.20)	1.00 (0.81, 1.24)	33	2.00 (0.97, 4.12)	176	0.97 (0.74, 1.26)
P-trend				0.8	0.96		0.2		0.9
Isoflavone (genistein) from fermented soy food (g/d)[4]									
First	3.1	89,125	169	1.00 (reference)	1.00 (reference)	11	1.00 (reference)	106	1.00 (reference)
Second	8.3	92,699	201	1.04 (0.84, 1.29)	1.01 (0.82, 1.26)	22	1.63 (0.76, 3.49)	145	1.09 (0.83, 1.42)
Third	14.4	94,270	253	1.15 (0.92, 1.43)	1.13 (0.90, 1.41)	40	2.74 (1.28, 5.84)	163	1.02 (0.77, 1.35)
Fourth	26.7	92,490	276	1.09 (0.87, 1.36)	1.09 (0.86, 1.38)	31	1.95 (0.87, 4.35)	195	1.07 (0.80, 1.43)
P-trend				0.4	0.4		0.1		0.8
Isoflavone (genistein) from nonfermented soy food (g/d)[5]									
First	2.8	91,629	219	1.00 (reference)	1.00 (reference)	26	1.00 (reference)	145	1.00 (reference)
Second	6.1	92,384	244	1.05 (0.87, 1.26)	1.08 (0.89, 1.30)	21	0.81 (0.45, 1.45)	173	1.15 (0.92, 1.44)
Third	10.2	92,541	224	0.94 (0.78, 1.14)	0.97 (0.80, 1.18)	32	1.22 (0.71, 2.08)	150	0.99 (0.78, 1.25)
Fourth	20.2	92,031	212	0.91 (0.75, 1.10)	0.94 (0.77, 1.14)	25	0.95 (0.54, 1.69)	141	0.94 (0.74, 1.20)
P-trend				0.2	0.3		0.8		0.4
Miso soup (mL/d)									
First	63	88,482	177	1.00 (reference)	1.00 (reference)	19	1.00 (reference)	109	1.00 (reference)
Second	175	90,957	208	1.03 (0.84, 1.26)	1.02 (0.83, 1.26)	19	0.81 (0.43, 1.56)	145	1.14 (0.89, 1.47)
Third	294	94,149	232	1.08 (0.88, 1.33)	1.08 (0.87, 1.33)	29	1.10 (0.59, 2.05)	164	1.18 (0.91, 1.53)
Fourth	449	94,997	282	1.22 (1.00, 1.49)	1.17 (0.94, 1.47)	37	1.18 (0.61, 2.27)	191	1.22 (0.92, 1.61)
P-trend				0.03	0.1		0.4		0.2
Soy food (g/d)[6]									
First	33.4	89,909	192	1.00 (reference)	1.00 (reference)	14	1.00 (reference)	130	1.00 (reference)
Second	59.3	92,407	237	1.05 (0.87, 1.28)	1.06 (0.87, 1.29)	32	1.95 (1.02, 3.73)	152	0.95 (0.75, 1.21)
Third	86.1	93,669	241	1.01 (0.83, 1.23)	1.03 (0.84, 1.26)	28	1.64 (0.83, 3.24)	174	1.02 (0.80, 1.31)
Fourth	140.6	92,601	229	1.00 (0.81, 1.22)	1.02 (0.82, 1.25)	30	1.82 (0.92, 3.60)	153	0.95 (0.73, 1.22)
P-trend				0.8	0.99		0.2		0.8

[1] Cox proportional hazards models were used.
[2] HR adjusted for age and public center area.
[3] HR further adjusted for BMI, smoking status, ethanol intake, family history of gastric cancer, vegetable intake, fruit intake, fish intake, salt intake, and total energy intake.
[4] The consumption of miso (for miso soup) and *natto*.
[5] The consumption of soymilk, tofu for miso soup, tofu for other dishes, *yushidofu*, *koyadofu*, and *aburaage*.
[6] Total of fermented and nonfermented soy food.

EFH users had an increased risk of the differentiated type of GC compared with never users among postmenopausal women (39), although some studies reported that EFH reduced the risk of GC (40). It has been shown that the biologic behavior of isoflavones may be modulated by an individual's endogenous concentration of estrogens. In vitro studies have shown that isoflavones can act primarily as estrogen agonists in a low-estrogen environment, whereas they can act as estrogen antagonists in a high-estrogen environment (41). Therefore, it is possible that isoflavones worked as antagonists with a high-estrogen environment among EFH users. Meanwhile, compared with never EFH users, EFH users were more likely to have higher proportions of smoking, regular drinking, family history of GC, and screening examination for GC (data not shown), which suggests that an elevated risk among EFH users may be partly explained by characteristics that were not measured or could not be totally adjusted for in our study. Further studies are needed to confirm these findings.

The strength of the study was its prospective design, which enabled us to avoid exposure recall bias. We selected subjects from the general population, we kept the sample size large, the response rate for the surveys was acceptable for studies of settings such as this, and the loss to follow-up was negligible. Participants were recruited from the Japanese population, which has a relatively higher isoflavone intake than Western populations. Isoflavone intake was measured by a questionnaire with a reasonably high level of validity and reproducibility. In addition, the registry of cancer was of sufficient quality to reduce the misclassification of the outcome.

TABLE 3
HRs and 95% CIs of gastric cancer according to quartile of energy-adjusted intake of isoflavone (genistein), miso soup, and soy food among women[1]

			All gastric cancer			Upper third, including cardia		Distal	
Quartile	Median	Person-years	No. of cases	HR1 (95% CI)[2]	HR2 (95% CI)[3]	No. of cases	HR2 (95% CI)[3]	No. of cases	HR2 (95% CI)[3]
Isoflavone (genistein) (mg/d)									
First	9.4	106,951	74	1.00 (reference)	1.00 (reference)	7	1.00 (reference)	46	1.00 (reference)
Second	17.3	109,818	83	1.03 (0.75, 1.41)	1.08 (0.78, 1.49)	6	0.72 (0.24, 2.20)	58	1.14 (0.77, 1.70)
Third	26.0	110,797	102	1.16 (0.85, 1.58)	1.23 (0.90, 1.70)	7	0.78 (0.26, 2.35)	75	1.33 (0.90, 1.97)
Fourth	41.8	110,399	91	0.99 (0.71, 1.37)	1.07 (0.77, 1.50)	13	1.43 (0.52, 3.95)	58	1.00 (0.66, 1.53)
P-trend				0.9	0.6		0.4		0.9
Isoflavone (genistein) from fermented soy food (g/d)[4]									
First	3.0	105,253	77	1.00 (reference)	1.00 (reference)	6	1.00 (reference)	48	1.00 (reference)
Second	8.0	110,124	80	0.86 (0.62, 1.19)	0.90 (0.65, 1.25)	7	0.76 (0.24, 2.37)	56	0.93 (0.62, 1.39)
Third	14.1	112,341	86	0.81 (0.57, 1.13)	0.87 (0.61, 1.23)	9	0.83 (0.26, 2.59)	63	0.90 (0.59, 1.37)
Fourth	25.6	110,247	107	0.91 (0.65, 1.28)	1.00 (0.71, 1.42)	11	0.89 (0.28, 2.80)	70	0.93 (0.61, 1.43)
P-trend				0.7	0.9		0.9		0.8
Isoflavone (genistein) from nonfermented soy food (g/d)[5]									
First	3.2	107,879	85	1.00 (reference)	1.00 (reference)	10	1.00 (reference)	53	1.00 (reference)
Second	6.5	109,703	87	1.02 (0.76, 1.38)	1.07 (0.79, 1.45)	7	0.71 (0.27, 1.91)	60	1.14 (0.79, 1.66)
Third	10.7	110,224	97	1.14 (0.85, 1.53)	1.20 (0.89, 1.61)	7	0.77 (0.28, 2.08)	69	1.29 (0.89, 1.86)
Fourth	20.6	110,159	81	0.99 (0.73, 1.35)	1.03 (0.75, 1.42)	9	1.06 (0.41, 2.70)	55	1.07 (0.72, 1.58)
P-trend				0.9	0.7		0.9		0.6
Miso soup (mL/d)									
First	47	104,994	92	1.00 (reference)	1.00 (reference)	6	1.00 (reference)	62	1.00 (reference)
Second	140	106,895	84	0.80 (0.59, 1.08)	0.85 (0.63, 1.14)	10	1.59 (0.57, 4.46)	49	0.70 (0.48, 1.02)
Third	244	111,927	92	0.79 (0.59, 1.07)	0.81 (0.59, 1.11)	9	1.04 (0.35, 3.15)	69	0.84 (0.58, 1.22)
Fourth	384	114,148	82	0.67 (0.49, 0.92)	0.71 (0.50, 1.01)	8	0.83 (0.25, 2.76)	57	0.69 (0.45, 1.05)
P-trend				0.02	0.06		0.6		0.2
Soy food (g/d)[6]									
First	33.6	106,148	84	1.00 (reference)	1.00 (reference)	8	1.00 (reference)	52	1.00 (reference)
Second	58.7	109,310	86	0.94 (0.69, 1.27)	0.99 (0.73, 1.35)	6	0.65 (0.22, 1.91)	59	1.04 (0.71, 1.52)
Third	85.2	111,361	99	1.05 (0.78, 1.41)	1.12 (0.83, 1.53)	10	1.09 (0.41, 2.90)	71	1.21 (0.83, 1.76)
Fourth	141.0	111,146	81	0.92 (0.67, 1.27)	0.99 (0.71, 1.38)	9	1.10 (0.39, 3.08)	55	1.02 (0.68, 1.53)
P-trend				0.8	0.8		0.6		0.8

[1] Cox proportional hazards models were used.
[2] HR adjusted for age and public center area.
[3] HR further adjusted for BMI, smoking status, ethanol intake, family history of gastric cancer, vegetable intake, fruit intake, fish intake, salt intake, and total energy intake.
[4] The consumption of miso (for miso soup) and *natto*.
[5] The consumption of soymilk, tofu for miso soup, tofu for other dishes, *yushidofu*, *koyadofu*, and *aburaage*.
[6] Total of fermented and nonfermented soy food.

Several limitations of the study warrant mention. First, because we assessed isoflavone intake by using an FFQ, some misclassification of isoflavone intake may have arisen when the effect on GC risk was estimated. Such misclassification was likely nondifferential and would tend to result in an underestimation of the effect of isoflavone intake. Second, we did not collect information on isoflavone supplement use. However, a relatively recent 2006 survey on supplement use in Japan showed a low prevalence of isoflavone supplementation (<1.6%) (42); thus, intake from supplements is considered to be negligible. Third, it was not possible to distinguish hormone replacement therapy from oral contraceptives. This may have confounded any possible effect, particularly among those participants in menopause. Finally, we were unable to adjust for *H. pylori* infection. However, because we showed a high infection rate based on CagA and IgG positivity in an earlier published subset of the JPHC study participants, 99% among GC case and 90% among control (43), most participants could be regarded as being infected, and the difference of infection likely did not affect the results.

In conclusion, the current study found no evidence to support the hypothesis that higher intakes of isoflavone prevent GC in either men or all women. However, we did observe associations suggestive of a higher risk with isoflavone intake in women with EFH use. Our findings warrant further investigation.

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TABLE 4
HRs and 95% CIs of gastric cancer according to quartile of energy-adjusted intake of isoflavone (genistein), miso soup, and soy food by exogenous female hormones[1]

	EFH never user (n = 36,930)			EFH ever user (n = 5853)			
Quartile	Person-years	No. of cases	HR (95% CI)[2]	Person-years	No. of cases	HR (95% CI)[2]	P-interaction
Isoflavone (genistein)							
First	86,437	65	1.00 (reference)	13,906	5	1.00 (reference)	
Second	89,308	67	0.96 (0.68, 1.37)	14,593	7	1.25 (0.38, 4.06)	
Third	89,947	86	1.13 (0.80, 1.59)	15,823	11	1.78 (0.58, 5.47)	
Fourth	88,627	69	0.89 (0.61, 1.29)	16,203	17	2.80 (0.93, 8.39)	
P-trend			0.7			0.03	0.04
Isoflavone (genistein) from fermented soy food (g/d)[3]							
First	85,111	63	1.00 (reference)	13,267	6	1.00 (reference)	
Second	90,196	66	0.87 (0.60, 1.25)	14,354	9	1.22 (0.41, 3.66)	
Third	89,954	74	0.87 (0.59, 1.27)	16,833	7	0.78 (0.23, 2.60)	
Fourth	89,058	84	0.91 (0.62, 1.34)	16,071	18	2.02 (0.69, 5.97)	
P-trend			0.7			0.2	0.2
Isoflavone (genistein) from nonfermented soy food (g/d)[4]							
First	86,891	75	1.00 (reference)	14,037	5	1.00 (reference)	
Second	89,328	75	1.04 (0.75, 1.43)	15,254	6	1.17 (0.35, 3.91)	
Third	89,437	72	0.99 (0.41, 1.37)	15,712	18	3.27 (1.18, 9.12)	
Fourth	88,662	65	0.94 (0.67, 1.33)	15,522	11	2.05 (0.68, 6.18)	
P-trend			0.7			0.07	0.051
Miso soup							
First	85,458	79	1.00 (reference)	13,880	8	1.00 (reference)	
Second	87,746	65	0.74 (0.53, 1.04)	14,031	9	1.01 (0.38, 2.69)	
Third	90,907	76	0.75 (0.53, 1.05)	15,616	13	1.44 (0.54, 3.86)	
Fourth	90,207	67	0.65 (0.45, 0.96)	16,998	10	1.01 (0.33, 3.05)	
P-trend			0.04			0.8	0.62
Soy food[5]							
First	86,192	75	1.00 (reference)	13,577	4	1.00 (reference)	
Second	89,507	70	0.87 (0.62, 1.22)	14,622	7	1.69 (0.48, 5.94)	
Third	89,735	80	0.98 (0.70, 1.37)	16,006	14	3.20 (0.99, 10.3)	
Fourth	88,885	62	0.83 (0.58, 1.19)	16,319	15	3.76 (1.14, 12.4)	
P-trend			0.5			0.01	0.02

[1] Cox proportional hazards models were used. EFH, exogenous female hormones.
[2] Adjusted for age, public center area, BMI, smoking status, ethanol intake, family history of gastric cancer, vegetable intake, fruit intake, fish intake, salt intake, total energy intake, and menopausal status.
[3] The consumption of miso (for miso soup) and *natto*.
[4] The consumption of soymilk, tofu for miso soup, tofu for other dishes, *yushidofu*, *koyadofu*, and *aburaage*.
[5] Total of fermented and nonfermented soy food.

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