Table 2. *Continued*

References	Study time	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
Author		Type and source	Definition	No. of cases	No. of controls					
Inoue et al. (19)	1990–95	Hospital-based (Aichi Cancer Center)	Cases: Histologically diagnosed cases of gastric cancer at the Institute	893	21 128	Green tea				
						Rarely	1.00		Coffee intake, black tea intake, gender, age, year and season at first hospital visit, habitual smoking, habitual alcohol drinking, regular physical exercise, fruit intake, rice intake, and beef intake	
						Occasional	1.00 (0.77–1.44)			
						Daily				
			Controls: Outpatients without cancer			1–3 cups/day	0.96 (0.70–1.32)			
						4–6 cups/day	1.01 (0.74–1.39)			
						≥7 cups/day	0.69 (0.48–1.00)‡			

NS, not significant.
*$P < 0.05$.
†$P = 0.007$.
‡$P < 0.05$.

control studies consistently showed a weak negative association between intake of green tea and risk of gastric cancer (Table 4). Among them, when using the general population as a control setting, Kono et al. (18) observed a strong negative association between green tea intake and gastric cancer risk.

During the review process, we were aware of the difference in effect by sex. In all studies that presented the analysis for men and women separately, although not statistically significant, the point estimate of highest category of green tea intake for women was consistently lower than that for men; i.e. based on incidence data, compared with <1 cup/day, the RRs of drinking ≥5 cups/day for men and women were estimated as 1.5 and 0.8 (9) and 0.98 and 0.67 (11), respectively (Table 1). Based on mortality data, the corresponding values for men and women were estimated as 1.0 and 0.7 (<1 vs. ≥10 cups/day) (10), and 1.1 and 0.7 (less than several times per month vs. more than several times per week) (12), respectively (Table 1). These results suggest a small protective effect, if any, of green tea intake and development of gastric cancer for women. However, applying our definition of magnitudes of association, they slightly failed to reach the level of weak association (weak association for 0.5 to <0.67, not significant). The null association observed among men may, in part, reflect insufficient adjustment for confounding factors such as cigarette smoking. Likewise, differences in the effect of green tea by subsite may point to an inconsistent effect on gastric cancer overall (11). However, evidence for such specific issues is sparse, probably due to the relatively small number of gastric cancer cases occurring in the upper subsite among cohorts, particularly in women. Results from pooled analysis may lead to a better understanding of these unresolved issues.

In a pooled analysis of six cohort studies (9–11,13,20,21) involving total of 219 080 subjects and 3577 gastric cancer cases, the role of green tea intake and gastric cancer risk was analyzed for men and women separately, with consideration of smoking status, anatomic subsite and so on (16). As a result, a statistically significant, weakly decreased risk of gastric cancer with ≥5 cups/day of green tea intake among women was observed [hazard ratio (HR) = 0.79, 95% confidence interval (CI) 0.65–0.96], although no association was observed among men (Tables 1 and 3). When the anatomic subsite was considered among four cohort studies in which the data were routinely collected, the risk reduction among women was more prominent in the distal gastric region (HR = 0.70, range 0.50–0.96; *P* for trend = 0.04). Together with the results of the systematic review, this finding from the pooled analysis was also considered to finally evaluate the evidence for green tea intake and gastric cancer risk in Japanese.

A difference in the effect of green tea intake by sex has also been observed for cardiovascular disease (14,22,23). The exact reason for the difference is unknown but may be explained, in part, by residual confounding effects of

smoking, phytoestrogens in tea and so on. It was suggested in some studies (9,14), but not all (16), that cigarette smoking might modify the effect of green tea. Tsubono et al. (9) observed a trend toward a positive association between green tea consumption and the risk of gastric cancer in subjects currently smoking ≥20 cigarettes/day (P for trend = 0.06), but not in other groups (P for the interaction term = 0.17). A similar interaction was suggested among studies investigating green tea intake and risk for cardiovascular disease (14). Higher rates of smoking may mask the effect of green tea consumption in men. Tea flavonoids such as kaempferol have been shown to exhibit estrogenic activity *in vitro* (24). In addition, tea contains lignan polyphenols, such as secoisolaracinol, which are considered phytoestrogenic (25). The phytoestrogens in tea might also partly account for the stronger protective effect of green tea in women than in men (26,27), although an estrogen-related protective mechanism against gastric cancer, if any, warrants further investigation.

Several aspects need to be discussed in relation to interpreting the present findings. Although cigarette smoking, which is suggested to have an interactive effect with green tea, was adjusted in most studies, *H. pylori* infection, a Group 1 carcinogen recognized by the International Agency for Research on Cancer (IARC), was not considered in any study. Based on the same origin of cohort study (10), Hoshiyama et al. (28) investigated whether green tea has any association with gastric cancer risk with considering *H. pylori* infection in a nested case–control study design within 157 incidence cases and 285 controls. They found that green tea intake had no protective effect against gastric cancer even after controlling for *H. pylori* infection. A previous nested case–control study that investigated plasma tea polyphenols and risk for gastric cancer reported that the decreased risk of gastric cancer by intake of tea polyphenols observed among women in the study remained even after adjusting for *H. pylori* infection (29). Some researchers used an animal model to report the inhibition of *H. pylori* urease by green tea extract (30) and the bactericidal effect on *H. pylori* infection by green tea catechins (31). A long-term habit of drinking green tea might lead to the elimination of *H. pylori*; if this is true, *H. pylori* may act as an intermediate rather than a confounding factor in the relationship between green tea and gastric cancer.

Discrepancies were noted in the effects of green tea on gastric cancer risk between case–control studies and cohort studies. The discrepancies were quantitatively shown from a recent meta-analysis of green tea intake and gastric cancer risk based on 13 studies from Japan and China (32). Compared with the lowest level of green tea intake, the RR of gastric cancer for the highest level of green tea intake was 0.73 (95% CI 0.64–0.83) for case–control studies, whereas no association was observed for cohort studies (RR = 1.04, 95% CI 0.93–1.17). The discrepancy may be partially explained by recall or selection biases that are inevitable in case–control studies. For example, it is possible that individuals with gastric cancer reduce their green tea intake due to their gastric symptoms. In fact, it has been reported that among those with gastric cancer, black tea consumption was reduced even up to 2 years before their diagnosis was made (33). Therefore, the green tea intake for gastric cancer cases among case–control studies might be partly underreported. Another point is the variation of gastric cancer mortality rates across the country. The age-adjusted gastric cancer mortality rate under age 75 in 2009 in Japan was 11.8/100 000 and ranged from 6.3 (Okinawa prefecture) to 15.7 (Akita prefecture) (34). It is interesting that gastric cancer mortality rates in the two prefectures in the case–control studies are higher than the average level, whereas the situation for cohort studies is mixed. On the basis of wide variation in gastric cancer mortality rates by area, the approach such as pooled analysis might be important.

However, the null results in cohort studies also contradict the results of previous experimental studies that suggested the protective effect of tea polyphenols on gastric cancer using *in vivo* animal models and *in vitro* cancer cell lines (3). In most of the cohort studies where the validity of green tea intake was examined, a moderate validity was shown; the Spearman coefficient for the correlation between the green tea intake according to the questionnaire and the amounts consumed according to the food records ranged from 0.29 to 0.71 (9–11,13,14). However, in all epidemiologic studies investigating green tea intake and gastric cancer risk, green tea consumption was determined only in terms of self-reported frequency of drinking, and the size of the cup was not ascertained. Furthermore, the amount of tea polyphenols in one cup varies according to preparation, i.e. the type and amount of green tea leaves, the frequency of renewing a tea batch in the pot, the temperature of boiled water or time to brew the tea and so on. A number of studies have found that hot drinks have an effect on the risk for esophageal cancer (35). Yu et al. (36) also showed that boiling hot tea had a non-significant increased risk of causing gastric cancer (odds ratio = 1.18). The risk estimates for the cardia, pylori and antrum sites regarding boiling hot tea were 2.09, 0.56 and 0.82, respectively. Furthermore, the term 'green tea' might be ambiguous because some participants may include only 'sencha', which looks green, or others may also include 'bancha/houjicha/genmaicha', which is also a commonly consumed Japanese tea but looks brown. Sencha, one of the most popular green teas in Japan, contains higher levels of tannin, vitamin C and folate than bancha/houjicha/genmaicha (37). Inaccurate measurement of green tea consumption in epidemiologic studies necessarily attenuates the small effect of green tea. It is interesting that both studies using biomarkers of green tea intake showed a statistically significant association with gastric cancer. Sun et al. (38) reported that urinary (−)-epigallocatechin (EGC) showed a statistically significant inverse association with gastric cancer. In a case–control study nested within a cohort study (11), a high plasma level of EGC was associated with an increased risk of gastric cancer in men, whereas a high plasma level of

Table 3. Summary of associations between gastric cancer risk and consumption of green tea in cohort studies of Japanese populations

References			Study period	Study subjects					Strength of association
Author	Year	Ref. no.		Sex	No. of subjects	Age range	Event	No. of cases	
Nakachi et al.	2000	8	1986–99	Men and women	8552	40+	Death	140	–
Tsubono et al.	2001	9	1984–92	Men	11 902	40+	Incidence	296	↑
				Women	14 409			123	–
Hoshiyama et al.	2002	10	1988–97	Men	30 370	40–79	Death	240	–
				Women	42 481			119	–
Sasazuki et al.	2004	11	1990–2001	Men	34 832	40–59	Incidence	665	–
				Women	38 111			227	– (distal ↓↓)
Khan et al.	2004	12	1984–2002	Men	1524	40+	Death	36	–
				Women	1634			15	–
Sauvaget et al.	2005	13	1980–99	Men and women	38 576	34–98	Incidence	1270	–
Kuriyama et al.	2006	14	1995–2001	Men	19 060	40–79	Death	138	–
				Women	21 470			55	–
Suzuki et al.	2009	15	1999–2006	Men and women	12 251	65–84	Death	68	–
Pooled analysis of 6 cohort studies including those listed above (9,10, cohort I of 11, cohort II of 11) or mentioned in the text (20 and 21)									
Inoue et al.	2009	16	1985–2004	Men	100 479	40–103	Incidence	2495	–
				Women	118 601			1082	↓

Explanation for each symbol is as follows when statistical significance (SS) or no statistical significance (NS), strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS).

Table 4. Summary of associations between gastric cancer risk and consumption of green tea in case–control studies of Japanese populations

References			Study period	Study subjects				Strength of association
Author	Year	Ref. no.		Sex	Age range	No. of cases	No. of controls	
Tajima and Tominaga	1985	17	1981–83	Men and women	40–70	93	186	↓
Kono et al.	1988	18	1979–82	Men and women	20–75	139	Hospital 2547	↓
							General population 278	↓↓↓
Inoue et al.	1998	19	1990–95	Men and women	40+	893	21 128	↓

Explanation for each symbol is as follows when statistical significance (SS) or no statistical significance (NS), strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS).

(−)-epicatechin-3-gallate was associated with a statistically significant decreased risk of gastric cancer in women (29).

In conclusion, we found no preventive effect on gastric cancer for green tea intake in cohort studies, which have fewer biases and are more persuasive than case–control studies, where risk reduction was shown. However, a small, consistent risk reduction limited to women was observed, which was confirmed by pooling data from six cohort studies.

EVALUATION OF EVIDENCE ON GREEN TEA CONSUMPTION AND GASTRIC CANCER RISK IN JAPANESE

From the results of the systematic review and pooled analysis of green tea intake and gastric cancer risk and on the basis of assumed biologic plausibility, we conclude that green tea possibly decreases the risk of gastric cancer in women. However, epidemiologic evidence is still insufficient to demonstrate any association in men.

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Conflict of interest statement

None declared.

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Appendix

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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

[1] From the Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan.

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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 ≥ 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 ≥ 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 ≥ 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 ≥30), smoking status (never, past, and current), alcohol consumption (none and <150, 150–299, 300–449, and ≥450 g ethanol/wk for men and none and <150 and ≥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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Diabetes mellitus and cancer risk: Pooled analysis of eight cohort studies in Japan

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Although a growing body of evidence suggests a link between diabetes and cancer, it is not clear whether diabetes independently increases the risk of cancer. We conducted a comprehensive assessment of the association between pre-existing diabetes and total and site-specific cancer risk based on a pooled analysis of eight cohort studies in Japan (>330 000 subjects). We estimated a summary hazard ratio by pooling study-specific hazard ratios for total and site-specific cancer by using a random-effects model. A statistically increased risk was observed for cancers at specific sites, such as colon (hazard ratio; HR = 1.40), liver (HR = 1.97), pancreas (HR = 1.85) and bile duct (HR = 1.66; men only). Increased risk was also suggested for other sites, and diabetes mellitus was associated with an overall 20% increased risk in total cancer incidence in the Japanese population. The association between these two diseases has important implications for reiterating the importance of controlling lifestyle factors and may suggest a possible strategy for cancer screening among patients with diabetes. Studies continuously investigating the risk factors for diabetes are also important. (*Cancer Sci* 2013; 104: 1499–1507)

In Japan, as in other countries, the increasing prevalence of diabetes presents a serious public health problem. The estimated numbers of persons with diabetes in 1997, 2002 and 2007 were 6.9 million (prevalence 5.5%), 7.4 million (prevalence 5.4%) and 8.9 million (prevalence 7.1%), respectively.[1]

A growing body of evidence suggests a link between diabetes and cancer. A recent meta-analysis showed that people with diabetes are at elevated risk for cancers of the liver,[2] biliary tract,[3] pancreas,[4] stomach,[5] colorectum,[6] kidney,[7] bladder,[8] breast[9] and endometrium,[10] but at decreased risk for prostate cancer.[11] Research suggests that hyperinsulinemia acting through aberrations in the insulin-like growth factor pathways or steroid hormone metabolism is involved in mitogenic actions. However, whether diabetes independently increases the risk of these cancers or whether cancer and diabetes simply share common risk factors, such as obesity or physical inactivity, is not clear; many of the studies included in the meta-analysis did not necessarily control for other lifestyle factors. Moreover, evidence from other cancer sites and the impact of diabetes on total cancer have not been elucidated completely.[12–14]

In the present study, we conducted a comprehensive assessment of the association between pre-existing diabetes and total and site-specific cancer by means of a pooled analysis of eight cohort studies in Japan (>330 000 subjects).

Patients and Methods

Study population. In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer and mortality in Japanese people. The following *a priori* inclusion criteria were set for the present purpose: the study had to be a population-based cohort study conducted in Japan starting in the mid-1980s to the mid-1990s, it had to include >30 000 participants, it had to have collected information on the history of diabetes in a questionnaire at baseline, and it had to have collected cancer incidence data during the follow-up period. Eight ongoing studies that met these criteria were identified: (i) the Japan Public Health Center-Based Prospective Study, Cohort I (JPHC-I);[15] (ii) the Japan Public Health Center-Based Prospective Study, Cohort II (JPHC-II);[15] (iii) the Japan Collaborative Cohort Study (JACC);[16] (iv) the Miyagi Cohort Study (MIYAGI);[17] (v) the Ohsaki National Health Insurance Cohort Study (OHSAKI);[18] (vi) the Three-Prefecture Cohort Study, Miyagi (3-pref MIYAGI);[19] the (vii) Three-Prefecture Cohort Study, Aichi (3-pref AICHI);[19] and (viii) the Takayama Study (TAKAYAMA).[20] When analyzing the individual results of each study, we excluded subjects who had a previous history of cancer and those for whom information on diabetes mellitus was missing. Table 1 profiles the studies included in the analysis. Each study was approved by the appropriate institutional review board.

Follow up. Subjects were followed from the baseline questionnaire (JPHC-I, 1990; JPHC-II, 1993–1994; JACC, 1988–1990; MIYAGI, 1990; OHSAKI, 1994; 3-pref MIYAGI, 1984; 3-pref AICHI, 1985; TAKAYAMA, 1992) to the last date of follow up in each study (JPHC-I, 2008; JPHC-II, 2008; JACC, 2009; MIYAGI, 2003; OHSAKI, 2005; 3-pref MIYAGI, 1992; 3-pref AICHI, 2000; TAKAYAMA, 2008). Residence status, including survival, was confirmed through the residential registry. Migration from a study area was treated as censoring at the date of migration. Among the eight cohorts, the percentage

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Table 1. Characteristics of the eight cohort studies included in a pooled analysis of diabetes mellitus and the risk of cancer incidence

Study	Population	Age (years) at baseline survey	Year(s) of baseline survey	Population size	Rate of response (%) to baseline questionnaire	Method of follow up	For the present pooled analysis						
							Age (years) Range	Last follow-up time	Mean duration of follow up (years)	Size of cohort		Number of cancer cases	
										Men	Women	Men	Women
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990	61 595	82	Cancer registries and death certificates	40–59	2008/12/31	16.4	20 288	21 806	2915	1949
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–1994	78 825	80	Cancer registries and death certificates	40–69	2008/12/31	13.3	29 217	32 484	4003	2370
JACC	Residents from 45 areas throughout Japan	40–79	1988–1990	110 792	83	Cancer registries (24 selected areas) and death certificates	40–79	2009/12/31	12.9	23 261	33 260	3432	2436
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47 605	92	Cancer registries and death certificates	40–64	2003/12/31	12.5	22 395	24 064	2335	1531
Ohsaki	Beneficiaries of National Health Insurance among residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	54 996	95	Cancer registries and death certificates	40–79	2005/12/31	8.9	23 003	25 080	3235	1786
3-pref MIYAGI	Residents of 3 municipalities in Miyagi Prefecture, Japan	40–98	1984	31 345	94	Cancer registries and death certificates	40–98	1992/12/31	7.5	13 734	17 070	1136	786
3-pref AICHI	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985	33 529	90	Cancer registries and death certificates	40–103	2000/12/31	11.5	10 846	12 231	1048	754
TAKAYAMA	Residents of Takayama, Gifu, Japan	35–	1992	31 552	85	Cancer registries and death certificates	35–101	2008/3/31	13.3	14 173	16 547	1974	1514
Total										156 917	182 542	20 078	13 126

JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; MIYAGI, Miyagi Cohort Study; Ohsaki, Ohsaki National Health Insurance Cohort Study; 3-pref MIYAGI, Three Prefecture Study – Miyagi portion; 3-pref AICHI, Three Prefecture Study – Aichi portion; TAKAYAMA, Takayama Cohort Study.

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ranged from 5.1% to 6.1% for five cohorts, from 14.0% to 19.0% for two cohorts, and was 28.4% for one cohort.

Assessment of exposure. All the studies included were population-based, and blood data were available for only a part of one study. Therefore, we used self-reported past history of diabetes. Information on a history of diabetes in the baseline questionnaire was obtained by using one of the following questions: "Has a doctor ever told you that you have any of the following diseases? – diabetes mellitus (JPHC-I, JPHC-II, 3-pref MIYAGI, TAKAYAMA: yes/no; 3-pref AICHI: current/past/never)" or "Have you ever suffered from any of the following diseases? – diabetes mellitus (JACC, MIYAGI and OHSAKI: no/yes-under medication/yes-cured/yes-not under medication)." Having diabetes currently or in the past, with or without medication, was defined as "diabetes" in the analysis.

Assessment of outcome. Study outcome was defined as the incidence of cancer (total and site-specific) during the follow-up period of each study. In all cohorts in the present study, cancer diagnoses were identified through population-based cancer registries and/or active patient notification from major local hospitals. Indices of data quality were available for seven cohorts. Although the quality and completeness of the case ascertainment varied by cohort in the range of 4.7–11.3% for Death Certificate Only (five cohorts), 23.0% for Death Certificate Notification (one cohort), and 41% for Mortality and Incidence ratio (one cohort), we believe that the overall quality of cancer ascertainment was high enough to conduct the present analysis.

Statistical analysis. Follow-up time was calculated as the duration from the date of the baseline questionnaire in each study until the date of cancer incidence or the end of follow up, whichever came first. In each individual study, we estimated sex-specific hazard ratios (HR) and their 95% confidence intervals (CI) for total and site-specific cancer incidence for diabetes using the Cox proportional hazards model. In each study, two types of adjustment were performed for estimation of HR: age and area (applicable for JPHC-I, JPHC-II and JACC only) (HR1). We conducted further multivariate adjustments by including in the model covariates that were either known or suspected confounding factors: history of cerebrovascular disease, coronary heart disease, cigarette smoking, alcohol consumption, body mass index, leisure-time sports or physical exercise, green leafy vegetable consumption and coffee intake (HR2). We conducted an analysis excluding early diagnosis (within 3 years) from both the numerator and the denominator (HR3). The cut-off points of each covariate are listed in the footnotes of Tables 2–4. An indicator term for missing data was created for each covariate. SAS (version 9.1; SAS Institute, Cary, NC, USA) and STATA (version 11; Stata Corporation, College Station, TX, USA) statistical software packages were used for the HR estimations.

For each of the three developed models (HR1, HR2 and HR3), summary HR estimates were obtained using the DerSimonian and Laird random-effects model. Briefly, the summary estimates were calculated as a weighted sum of the study-specific HR, the weights being taken to be the sum of the study-specific HR variance estimates and an estimated between-study variance component. Statistical heterogeneity among studies was assessed by means of the I^2 statistics, which corresponds to the proportion of total variation in study estimates accounted for by between-study variation. The SAS and R software packages were used for meta-analysis.

Results

The present study included 339 459 subjects (156 917 men and 182 542 women) from eight ongoing large-scale population-based prospective studies in Japan (Table 1). During 4 156 262 person-years of follow up (mean 9.9 years/person), 33 204 incidences of cancer were identified (20 078 men and 13 126 women).

Results for men and women combined are shown in Table 2. Individuals who had a history of diabetes had a statistically significant increased risk of total cancer; when cases diagnosed within 3 years of the baseline were excluded, the hazard ratio was estimated as 1.19 (95% CI: 1.12–1.25). The association remained statistically significant even after exclusion of liver and pancreatic cancers, for which the risk was increased in individuals with diabetes (HR3 = 1.97 [1.65–2.36] and 1.85 [1.46–2.34], respectively).

The impact of diabetes on total cancer risk was similar in separate analyses of men and women. In men (Table 3), diabetes was associated with an increased risk of total cancer (HR3 = 1.19 [1.12–1.27]). Diabetes was also associated with a statistically significant increased risk of liver, pancreatic, colon and bile duct cancers; the HR were estimated as 2.07, 1.58, 1.58 and 1.66, respectively. An increased risk was also suggested for rectal, kidney and bladder cancers as well as for lymphoma, although these associations were not statistically significant. Diabetes was not associated with esophageal, stomach, lung or prostate cancer.

In women (Table 4), as in men, diabetes was associated with an increased risk of total cancer (HR3 = 1.19 [1.07–1.31]). This association became borderline significant when both liver and pancreatic cancers were excluded. HR3 values for liver and pancreatic cancers were 1.71 and 2.48, respectively. For the uterine corpus, a statistically significant increased risk of cancer was observed (HR1 = 1.81); however, the association did not remain statistically significant when further variables were adjusted for (HR2 = 1.69 [0.87–3.31]) and when early cases were omitted (HR3 = 1.84 [0.90–3.76]). Alternatively, for cancers of the cervix and esophagus, HR were statistically significant only in HR2 and HR3. An increased risk was also suggested for stomach, rectal, bile duct, ovarian, kidney and bladder cancers, as well as lymphoma, although without statistical significance. No association was seen for colon, lung or breast cancer.

Discussion

To the best of our knowledge, this is the first examination of the association between diabetes and cancer incidence by means of pooled analysis, which allows for stable summary quantitative estimates. When we pooled eight ongoing prospective cohort studies (which included >330 000 subjects), we found that diabetes was moderately associated with an increase in total cancer risk. Studies conducted to date have tended to investigate the relationship between diabetes and cancer site specifically, and only a few studies have focused on total cancer.[12,21–24] Our results are in line with a recent systematic review and meta-analysis that revealed that diabetes was associated with a moderately increased risk of cancer incidence.[13,14]

The increased risks of liver cancer and pancreatic cancer seen in the present study are consistent with the increased risk observed for both sexes in previous studies:[2,4] on the basis of a meta-analysis of cohort studies, the summary estimates for heptatocellular carcinoma and pancreatic cancer were 2.01[2] and 1.94,[4] respectively, which are similar to our quantitative estimate. From a combination of 30 cohort studies, diabetes was shown to be associated with a 27% increase in the risk of colorectal cancer incidence with evident heterogeneity among studies.[6] Our results for colon cancer in men support this finding, although data for women and for rectal cancer did not show a clear association.

Table 2. Summary hazard ratios (HR) and 95% confidence intervals (CI) of history of diabetes for total and site-specific cancers: Men and women combined

Cancer site	Number of studies†	No diabetes		Diabetes		HR1‡ (95% CI)	HR2§ (95% CI)	HR3¶ (95% CI)	Between studies		
		Person-years of follow-up†	Number of cases†	Person-years of follow-up†	Number of cases†				Q†	P_{hetero}†	I^2 (%)†
All sites	8	3 963 570	30 634	192 691.6	2388	1.23 [1.18–1.28]	1.20 [1.15–1.26]	1.19 [1.12–1.25]	7.72	0.36	9.38
All sites excluding the liver	8	3 963 570	28 891	192 691.6	2120	1.18 [1.12–1.23]	1.15 [1.09–1.21]	1.14 [1.07–1.22]	9.56	0.22	26.76
All sites excluding the liver and pancreas	8	3 963 570	27 716	192 691.6	1987	1.14 [1.09–1.20]	1.12 [1.06–1.19]	1.11 [1.04–1.18]	8.78	0.27	20.24
Esophagus	7	3 572 768	841	176 490.6	66	1.12 [0.87–1.44]	1.04 [0.74–1.46]	1.03 [0.75–1.43]	5.23	0.51	0.00
Stomach	7	3 572 768	5939	176 490.6	438	1.09 [0.95–1.25]	1.05 [0.87–1.28]	1.06 [0.91–1.22]	7.69	0.26	21.95
Colon	6	2 874 063	2586	144 532.6	232	1.43 [1.25–1.64]	1.34 [1.15–1.54]	1.40 [1.19–1.64]	1.98	0.85	0.00
Rectum	6	2 874 063	1395	144 532.6	95	1.13 [0.92–1.39]	1.10 [0.86–1.41]	1.14 [0.87–1.50]	5.62	0.34	11.03
Liver	7	3 572 768	1593	176 490.6	251	2.36 [1.89–2.95]	2.15 [1.76–2.62]	1.97 [1.65–2.36]	2.85	0.83	0.00
Bile duct	7	3 572 768	832	176 490.6	72	1.32 [1.03–1.69]	1.29 [0.97–1.70]	1.35 [0.99–1.85]	5.34	0.50	0.00
Pancreas	7	3 572 768	1052	176 490.6	120	1.80 [1.49–2.18]	1.86 [1.50–2.30]	1.85 [1.46–2.34]	3.36	0.76	0.00
Lung	7	3 572 768	3359	176 490.6	233	1.00 [0.85–1.17]	1.01 [0.85–1.20]	1.00 [0.82–1.22]	7.79	0.25	23.02
Kidney	6	2 874 063	326	144 532.6	28	1.49 [0.78–2.85]	1.45 [0.76–2.77]	1.57 [0.62–3.94]	10.97	0.03	63.55
Bladder	7	3 572 768	701	176 490.6	56	1.16 [0.82–1.65]	1.22 [0.85–1.76]	1.28 [0.89–1.86]	5.61	0.35	10.92
Lymphoma	7	2 655 459	282	132 392.9	22	1.28 [0.83–1.98]	1.33 [0.83–2.13]	1.35 [0.82–2.22]	0.15	1.00	0.00

†Results given in this column are those pertaining to model HR3. ‡Adjusted for age (years, continuous) and area (applicable for JPHC-I, JPHC-II and JACC only). §Further adjusted for history of cerebrovascular disease (no, yes), coronary heart disease (no, yes), cigarette smoking (pack-years, 0/1–19/20–29/30–39/40 or more), alcohol consumption (ethanol equivalent g/week, continuous), body mass index (continuous), leisure-time sports or physical exercise (JPHC-I and II: less than monthly/1–3 days per month/more than weekly; JACC, MIYAGI and OHSAKI: almost none/more than 1 h per week; TAKAYAMA: none/vigorous exercise or activity, or moderate exercise 1 or more hours per week; 3-pref MIYAGI and AICHI: no information), green leafy vegetables (TAKAYAMA: <4 days per week/4–6 days per week/almost daily; other cohorts: <3 days per week/3–4 days per week/almost daily) and coffee intake (JPHC-I and II: almost none/1–2 days per week/3–4 days per week/1–2 cups per day/3–4 cups per day/5 or more cups per day; JACC: <2 cups per month/1–2 cups per week/3–4 cups per week/almost daily 1–2 cups/almost daily 3–4 cups/almost daily 5 or more cups; MIYAGI, OHSAKI, 3-pref MIYAGI and 3-pref AICHI: none/occasionally/1–2 cups per day/3–4 cups per day/5 or more cups per day; TAKAYAMA: less than once per week/1 day per week/2–6 times per week/daily/2–3 times per day/more than 4 times per day). ¶Adjusted for same covariates as HR2 and excluding early diagnosis within 3 years from the baseline.

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Table 3. Summary hazard ratios (HR) and 95% confidence intervals (CI) of history of diabetes for total and site-specific cancers in men

Cancer site	Number of studies†	No diabetes		Diabetes		HR1‡ (95% CI)	HR2§ (95% CI)	HR3¶ (95% CI)	Between studies		
		Person-years of follow-up†	Number of cases†	Person-years of follow up†	Number of cases†				Q†	P_{hetero}†	I^2 (%)†
All sites	8	1 763 653	18 227	115 620.5	1748	1.24 [1.18–1.30]	1.21 [1.15–1.28]	1.19 [1.12–1.27]	5.20	0.64	0.00
All sites excluding the liver	8	1 763 653	17 062	115 620.5	1532	1.16 [1.10–1.22]	1.15 [1.08–1.22]	1.13 [1.06–1.21]	5.09	0.65	0.00
All sites excluding the liver and pancreas	8	1 763 653	16 466	115 620.5	1453	1.14 [1.07–1.22]	1.13 [1.06–1.20]	1.12 [1.05–1.19]	5.45	0.61	0.00
Esophagus	7	1 592 174	740	105 219.5	63	1.14 [0.87–1.47]	1.07 [0.79–1.44]	1.02 [0.73–1.42]	4.51	0.61	0.00
Stomach	7	1 592 174	4089	105 219.5	340	1.05 [0.89–1.24]	1.03 [0.84–1.25]	1.02 [0.88–1.17]	4.54	0.60	0.00
Colon	6	1 309 293	1494	88 263.5	175	1.55 [1.33–1.82]	1.58 [1.32–1.89]	1.58 [1.31–1.90]	3.34	0.65	0.00
Rectum	6	1 309 293	885	88 263.5	70	1.11 [0.86–1.43]	1.05 [0.80–1.36]	1.12 [0.84–1.50]	3.83	0.57	0.00
Liver	7	1 592 174	1078	105 219.5	201	2.40 [1.94–2.97]	2.25 [1.83–2.76]	2.07 [1.70–2.53]	2.79	0.83	0.00
Bile duct	6	1 498 794	362	98 182.7	44	1.52 [1.08–2.16]	1.52 [1.07–2.15]	1.66 [1.14–2.41]	1.83	0.87	0.00
Pancreas	7	1 592 174	533	105 219.5	70	1.75 [1.36–2.25]	1.72 [1.30–2.28]	1.58 [1.15–2.17]	3.01	0.81	0.00
Lung	7	1 592 174	2429	105 219.5	189	0.97 [0.83–1.14]	1.01 [0.83–1.22]	1.01 [0.82–1.25]	7.63	0.27	21.39
Prostate	6	1 309 293	1273	88 263.5	98	1.02 [0.79–1.31]	0.98 [0.70–1.36]	0.96 [0.64–1.43]	11.33	0.05	55.88
Kidney	4	1 027 108	154	67 821.9	20	1.55 [0.82–2.94]	1.48 [0.67–3.29]	2.25 [0.82–6.14]	8.02	0.05	62.58
Bladder	6	1 483 120	485	93 216.8	46	1.22 [0.83–1.79]	1.30 [0.89–1.91]	1.32 [0.90–1.96]	5.40	0.37	7.39
Lymphoma	3	764 797	118	54 004.7	13	1.33 [0.76–2.32]	1.73 [0.94–3.18]	1.60 [0.82–3.10]	0.41	0.81	0.00

†Results given in this column are those pertaining to model HR3. ‡Adjusted for age (years, continuous) and area (applicable for JPHC-I, JPHC-II and JACC only). §Further adjusted for history of cerebrovascular disease (no, yes), coronary heart disease (no, yes), cigarette smoking (pack-years, 0/1–19/20–29/30–39/40 or more), alcohol consumption (ethanol equivalent g/week, continuous), body mass index (continuous), leisure-time sports or physical exercise (JPHC-I and II: less than monthly/1–3 days per month/more than weekly; JACC, MIYAGI and OHSAKI: almost none/more than 1 h per week; TAKAYAMA: none/vigorous exercise or activity, or moderate exercise 1 or more hours per week; 3-pref MIYAGI and AICHI: no information), green leafy vegetables (TAKAYAMA: <4 days per week/4–6 days per week/almost daily; other cohorts: <3 days per week/3–4 days per week/almost daily) and coffee intake (JPHC-I and II: almost none/1–2 days per week/3–4 days per week/1–2 cups per day/3–4 cups per day/5 or more cups per day; JACC: <2 cups per month/1–2 cups per week/3–4 cups per week/almost daily 1–2 cups /almost daily 3–4 cups/almost daily 5 or more cups; MIYAGI, OHSAKI, 3-pref MIYAGI and 3-pref AICHI: none/occasionally/1–2 cups per day/3–4 cups per day/5 or more cups per day; TAKAYAMA: less than once per week/1 day per week/2–6 times per week/daily/2–3 times per day/more than 4 times per day). ¶Adjusted for same covariates as HR2 and excluding early diagnosis within 3 years from baseline.

Table 4. Summary hazard ratios (HR) and 95% confidence intervals (CI) of history of diabetes for total and site-specific cancers in women

Cancer site	Number of studies†	No diabetes		Diabetes		HR1‡ (95% CI)	HR2§ (95% CI)	HR3¶ (95% CI)	Between studies		
		Person-years of follow up†	Number of cases†	Person-years of follow up†	Number of cases†				Q†	P_{hetero}†	I^2 (%)†
All sites	8	2 199 917	12 407	77 070.4	640	1.19 [1.10–1.29]	1.18 [1.08–1.30]	1.19 [1.07–1.31]	5.52	0.60	0.00
All sites excluding the liver	8	2 199 917	11 829	77 070.4	588	1.16 [1.07–1.26]	1.16 [1.05–1.28]	1.16 [1.03–1.31]	8.41	0.30	16.78
All sites excluding the liver and pancreas	8	2 199 917	11 250	77 070.4	534	1.12 [1.02–1.22]	1.10 [0.99–1.22]	1.08 [0.97–1.22]	6.32	0.50	0.00
Esophagus	2	790 755	24	23 229.2	3	4.28 [0.80–22.90]	4.70 [1.12–19.71]	5.28 [1.48–18.86]	0.92	0.34	0.00
Stomach	7	1 980 594	1850	71 270.4	98	1.14 [0.90–1.44]	1.22 [0.95–1.57]	1.29 [0.97–1.72]	6.83	0.34	12.21
Colon	6	1 564 770	1092	56 268.4	57	1.13 [0.87–1.48]	0.92 [0.66–1.29]	0.99 [0.69–1.42]	1.90	0.86	0.00
Rectum	6	1 564 770	510	56 268.4	25	1.35 [0.81–2.25]	1.48 [0.76–2.89]	1.44 [0.66–3.14]	9.70	0.08	48.45
Liver	7	1 980 594	515	71 270.4	50	1.99 [1.41–2.81]	1.84 [1.30–2.60]	1.71 [1.14–2.57]	4.53	0.61	0.00
Bile duct	7	1 980 594	439	71 270.4	26	1.28 [0.85–1.91]	1.38 [0.85–2.24]	1.44 [0.77–2.70]	1.86	0.87	0.00
Pancreas	7	1 980 594	519	71 270.4	50	1.98 [1.33–2.94]	2.27 [1.33–3.85]	2.48 [1.48–4.16]	10.87	0.09	44.81
Lung	7	1 980 594	930	71 270.4	44	1.09 [0.80–1.47]	1.08 [0.76–1.54]	1.02 [0.68–1.51]	3.26	0.78	0.00
Breast	6	1 564 770	1380	56 268.4	43	0.95 [0.70–1.29]	0.98 [0.69–1.38]	1.03 [0.69–1.56]	5.55	0.35	9.87
Cervix	5	1 131 529	206	41 589.4	11	1.59 [0.90–2.80]	2.08 [1.02–4.27]	2.63 [1.20–5.80]	2.42	0.66	0.00
Uterine corpus	5	1 439 547	224	51 165.5	12	1.81 [1.01–3.27]	1.69 [0.87–3.31]	1.84 [0.90–3.76]	1.70	0.79	0.00
Ovary	3	773 230.7	127	32 026.7	7	1.32 [0.41–4.22]	1.68 [0.69–4.07]	1.22 [0.44–3.37]	0.32	0.85	0.00
Kidney	3	785 630.4	56	33 275	4	1.52 [0.60–3.86]	1.28 [0.46–3.55]	1.26 [0.30–5.28]	0.14	0.93	0.00
Bladder	3	944 409.6	94	36 264.2	7	1.14 [0.58–2.24]	1.45 [0.65–3.22]	1.63 [0.69–3.87]	0.01	0.99	0.00
Lymphoma	4	1 301 924	108	44 814.4	8	2.00 [0.91–4.38]	2.16 [0.88–5.32]	2.43 [0.93–6.37]	4.18	0.24	28.16

†Results given in this column are those pertaining to model HR3. ‡Adjusted for age (years, continuous) and area (applicable for JPHC-I, JPHC-II and JACC only). §Further adjusted for history of cerebrovascular disease (no, yes), coronary heart disease (no, yes), cigarette smoking (pack-years, 0/1–19/20–29/30–39/40 or more), alcohol consumption (ethanol equivalent g/week, continuous), body mass index (continuous), leisure-time sports or physical exercise (JPHC-I and II: less than monthly/1–3 days per month/more than weekly; JACC, MIYAGI and OHSAKI: almost none/more than 1 h per week; TAKAYAMA: none/vigorous exercise or activity, or moderate exercise 1 or more hours per week; 3-pref MIYAGI and AICHI: no information), green leafy vegetables (TAKAYAMA: <4 days per week/4–6 days per week/almost daily; other cohorts: <3 days per week/3–4 days per week/almost daily) and coffee intake (JPHC-I and II: almost none/1–2 days per week/3–4 days per week/1–2 cups per day/3–4 cups per day/5 or more cups per day; JACC: <2 cups per month/1–2 cups per week/3–4 cups per week/almost daily 1–2 cups/almost daily 3–4 cups/almost daily 5 or more cups; MIYAGI, OHSAKI, 3-pref MIYAGI and 3-pref AICHI: none/occasionally/1–2 cups per day/3–4 cups per day/5 or more cups per day; TAKAYAMA: less than once per week/1 day per week/2–6 times per week/daily/2–3 times per day/more than 4 times per day). ¶Adjusted for same covariates as HR2 and excluding early diagnosis within 3 years from baseline.

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The association of diabetes with cancer at other sites of the gastrointestinal tract was unclear. Studies on the association of diabetes with biliary tract cancer have shown mixed results. The first systematic review, which was published recently, showed that diabetic individuals may have an approximately 50% increased risk of bile tract cancer.[3] Our results for men support this finding, but the association did not reach statistical significance for women. An analysis of 21 studies found that nondiabetic and diabetic individuals have similar risks of gastric cancer; however, a subgroup analysis found that diabetic women have an 18% increased risk of gastric cancer.[5] In line with this finding, we observed increased risk only among women, although the association did not reach the level of statistical significance (HR3 = 1.29 [0.97–1.72]). Some authors have suggested that the progression from diabetes to cancer may have different etiologies in men and women, perhaps owing to hormonal differences.[25] *Helicobacter pylori* may also play a key role in the association: in a 9-year cohort study of 2466 Japanese, fasting plasma glucose level was positively associated with the risk of developing gastric cancer;[26] however, the excess risk was observed only among *H. pylori*-positive subjects, which suggests that hyperglycemia may be a cofactor for both diabetes and gastric cancer. Evidence regarding the association between diabetes and the risk of esophageal cancer is contradictory.[27] Histologically, the major type of esophageal cancer in Japan and Taiwan is squamous cell carcinoma, but a recent case–control study conducted in Taiwan did not show any significant association between diabetes and esophageal cancer.[28] We observed no association among men, whereas a statistically significant excess risk was observed among women (HR2, HR3). However the 95% CI was wide, suggesting that the excess risk may have been a chance finding due to the small number of cases in women.

A recently published meta-analysis showed that diabetes is associated with increased risk of kidney and bladder cancers.[7,8] However, when studies were restricted to those with adjustments for body mass index or obesity, the association failed to reach the level of statistical significance for kidney cancer.[7] The evidence for a relationship between obesity and bladder cancer risk is limited and inconsistent.[8] Our pooled analysis of eight studies of populations of Japanese people, who are relatively lean compared with US and European populations, suggested a statistically insignificant elevated risk for kidney and bladder cancers. This result suggests that there may be some underlying mechanism common to both diseases that cannot totally be explained by obesity. In the first systematic review to evaluate the relationship between type 2 diabetes and non-Hodgkin lymphoma, Chao and Page[29] showed that the two diseases were positively associated, on the basis of 13 studies, including three prospective studies. However, the authors conclude that the evidence is inconclusive, owing to the methodological limitations of the included case–control studies, and note the need for more prospective studies with improved control of confounding. The elevated risk was more evident in prospective cohort studies, among women, in East Asian populations and in studies with adjustment for body mass index. This situation all meets to our present analysis with adjustment for body mass index and HR larger among women, although without statistical significance.

Increased exposure to estrogen as a result of diabetes is considered to be another factor affecting the relationship between site-specific cancers and diabetes. Our findings with regard to cancer of the cervix and uterine corpus contradict the findings reported for previous studies.[10] This difference may be due to the small sample size in our study, especially for HR2 and HR3. Our results for prostate cancer are in line with the results of previous studies showing a negative or null association.[11] Previous studies have been conducted mainly among white men. Race is reported to be one of the strongest risk factors for prostate cancer, and our pooled analysis adds important evidence from an Asian population. The suggested mechanism for the inverse association between diabetes and the risk of prostate cancer is the reduced level of testosterone, which is commonly seen in diabetic men or with obesity secondary to low levels of sex hormone-binding globulin. We found no association between breast cancer and diabetes, whereas previous studies have shown that diabetes is associated with an increased risk of breast cancer.[9] Epidemiologic studies have generally indicated a positive association between estrogen level and breast cancer risk in postmenopausal women. In this study, when women were stratified by menopausal status, similar results were observed; HR3 = 1.39 (0.57–3.40) and HR3 = 1.01 (0.63–1.60) for premenopausal and postmenopausal women, respectively. In a previous meta-analysis,[9] the relation between diabetes and breast cancer appeared to be confined to postmenopausal women, but the number of studies of premenopausal breast cancer was limited, and a test for difference in association by menopausal status was not statistically significant. To clarify whether the association varies by menopausal status, further investigations are warranted.

The most supported of the mechanisms suggested for the association between diabetes and cancer is insulin resistance with hyperinsulinemia, which may have a mitogenic effect by activating insulin-like growth factor.[30–32] Hyperinsulinemia and hyperglycemia have also been reported to promote tumor cell proliferation and metastasis in type 2 diabetes.[33,34] These mechanisms are supported by the fact that treatment with metformin, an insulin sensitizer, is associated with a lower risk of cancer among diabetic patients, compared to patients treated with insulin or sulfonylurea.[35,36] Furthermore, inflammatory cytokines produced by adipose tissues, such as interleukin-6, monocyte chemoattractant protein, and plasminogen activator inhibitor-1, may play important roles in carcinogenesis, cancer progression and poor prognosis.

It should be noted, however, that the relationship between diabetes and cancer may not be causal. First, confounding factors may obscure the relationship between these diseases. Although in the present analysis potential confounding factors were adequately adjusted across the study, it is possible that the effect of unadjusted (unmeasured, unknown) common factors cannot be totally excluded. Second, it is possible that cancer and diabetes simply share common risk factors, such as obesity or physical inactivity. As presented in Tables 2–4, for those HR showing significant results in model 1 (HR1), further adjustment for covariates including body mass index (relative marker of obesity) and physical activity, which are known risk factors for DM, slightly attenuated the results but remained statistically significant (HR2). This means that increased risk of cancer among diabetes is partially, but not fully, explained by these shared risk factors. Although several mechanism have been suggested for the association between diabetes and cancer, further studies using blood glucose or insulin level are needed to clarify the etiology. Third, detection bias may arise because diabetic subjects may receive medical care more frequently than nondiabetic subjects, leading to more frequent detection of cancer among diabetic subjects. Fourth, reverse causality may also exist. Cancer generally causes insulin resistance, and the resulting hyperglycemia may produce cytokines, such as tumor necrosis factor α.[37,38] In the present analysis, HR3 was calculated by removing early diagnosis within 3 years. Removing early diagnosis within 5 years from the analysis also did not alter the findings essentially, and the possibility of reverse causality might be minimized.

The present study has several limitations. First of all, we cannot exclude the possibility that there may be some chance