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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The aldehyde dehydrogenase 2 (*ALDH2*) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer

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The impact of alcohol on the risk of stomach cancer is controversial. Although aldehyde dehydrogenase 2 (*ALDH2*) Glu504Lys (rs671) polymorphism has a strong effect on acetaldehyde metabolism, little is known about its impact on stomach cancer risk when combined with alcohol drinking. This case-control study included a total of 697 incident stomach cancer case subjects and 1372 non-cancer control subjects who visited Aichi Cancer Center between 2001 and 2005. We estimated odds ratios (OR) and 95% confidence intervals (CI) for ALDH2 genotypes and alcohol consumption using logistic regression models after adjustment for potential confounders, including *Helicobacter pylori* infection. The ALDH2 504Lys allele was associated with the risk of stomach cancer, with adjusted ORs of 1.40 (95% CI, 1.11–1.76) for Glu/Lys and 1.73 (1.12–2.68) for Lys/Lys compared with Glu/Glu. Heavy drinking was associated with risk (OR 1.72, 1.17–2.52) after adjustment for *ALDH2* genotype and other confounders. Moreover, ORs for heavy drinking were 1.28 (0.77–2.12) for those with *ALDH2* Glu/Glu and 3.93 (1.99–5.79) for those with the *ALDH2* Lys allele relative to non-drinkers with the Glu/Glu genotype (*P* for interaction = 0.0054). In conclusion, *ALDH2* and alcohol drinking showed interaction for risk factors of stomach cancer, indicating that acetaldehyde plays a role in stomach carcinogenesis.

Introduction

Alcohol consumption is an established risk factor for cancers of the upper aero-digestive tract (UADT) (1–3), majority of them are squamous cell carcinoma. One major hypothesized mechanism behind alcohol-related carcinogenesis in the UADT is the involvement of acetaldehyde, a metabolite of ethanol. Aldehyde dehydrogenase 2 (ALDH2) is a key enzyme in acetaldehyde metabolism, and molecular epidemiologic studies in East Asia (4–11), where the functional *ALDH2* Glu504Lys (rs671) polymorphism is prevalent, have contributed to the conclusion that acetaldehyde has a substantial impact on carcinogenesis in humans as a result of its strong interaction with alcohol drinking (3).

To date, the association between alcohol consumption and gastric cancer, of which majority are adenocarcinoma, has been controversial. A recent meta-analysis showed no appreciable association of moderate alcohol drinking with stomach cancer, but it did find a suggestive association between heavy drinking and non-cardia adenocarcinoma (12). Although it has been hypothesized that acetaldehyde contributes to gastric carcinogenesis, as it does for UADT cancer (13,14), evidence for this association to date has been limited (15–18). Taken evidences of no association between esophageal adenocarcinoma risk and alcohol in mind (19,20), there may not be neither association nor interaction. Anyhow, it is worth to be evaluated in the population in which functionally validated *ALDH2* polymorphism is prevalent.

In this study, we investigated the association between *ALDH2* Glu504Lys (rs671) polymorphism and alcohol consumption and risk of stomach cancer in Japanese population.

Abbreviations: AG, atrophic gastritis; ALDH2, aldehyde dehydrogenase 2; OR, odds ratios; CI, confidence intervals; PG, pepsinogen; PY, pack years; UADT, upper aero-digestive tract.

Materials and methods

Study population

The case participants were 697 patients with no history of cancer who were histologically diagnosed with stomach cancer between January 2001 and December 2005 at Aichi Cancer Center Hospital in Japan. All participants were recruited under written informed consent within the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (21–23), and all provided blood samples. Among the 697 subjects, 684 (98.1%) were histologically confirmed as adenocarcinoma. Among 684 cases, 379 were diffuse type and 305 were intestinal type.

The control subjects were 1372 first-visit outpatients during the same period who were confirmed to have no cancer and no history of neoplasms. Non-cancer status was confirmed by medical examinations, including radiographic examinations, with participants suspected of having stomach cancer first examined by physical or endoscopic inspection, and subsequently radiographically when indicated. Controls were selected randomly and were individually matched by age (±5 years) and sex (male and female) with a case-control ratio of 1:1–2. A total of 2069 participants (697 cases and 1372 controls) were included in this study. Response rate was over 95% for both case and control subjects. The study was approved by the institutional ethical committee of Aichi Cancer Center.

Information on alcohol consumption

Information on alcohol consumption was collected from first-visit outpatients aged 20–79 years using a self-administered questionnaire. Each participant was asked at the time of first visit to our hospital about their alcohol consumption before the development of the current symptoms, which made them visit our hospital. For the present analyses, lifetime alcohol consumption of various common beverages (Japanese sake, beer, shochu, whiskey and wine) was determined in terms of the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent measure of 180 ml; termed a *go*, this is standard measure in Japan and contains 23 g of ethanol. Drinking status was classified into the four categories of never drinker, light drinker (fewer than 5 days per week, fewer than 2 go per day), moderate drinker (5 or more days per week, fewer than 2 go per day) and heavy drinker (5 or more days per week, 2 or more go per day).

Evaluation of other lifestyle factors

Information on smoking status was obtained in the three categories of non-smoker, former smoker and current smoker, with former smokers defined as those who had quit smoking at least 1 year before study enrolment. Cumulative exposure to smoking was categorized into five groups by pack years (PY), the product of the number of packs of cigarettes smoked per day and the number of years of smoking, namely as never, PY < 20, PY < 40, PY < 60 and PY 60 or more. Consumption of fruits and vegetables was determined using a food frequency questionnaire, which included 43 single food items in eight frequency categories (24). The food frequency questionnaire was validated using a 3 day weighed dietary record as standard, which showed that reproducibility and validity were satisfactory (25,26). Participants were divided into three groups based on the distribution of fruit and vegetable consumption among controls (tertiles).

Assessment of Helicobacter pylori infection and atrophic gastritis

All cases were examined for plasma IgG levels for *Helicobacter pylori (H.pylori)* using a commercially available direct enzyme-linked immunosorbent assay

kit ('E Plate "Eiken" *H.pylori* Antibody'; Eiken Kagaku, Tokyo, Japan). This enzyme-linked immunosorbent assay kit was developed in Japan using an antigen extracted from the domestic strain in Japan and is commonly used in medical studies in this country (27,28). A positive status for *H.pylori* infection was defined as an *H.pylori* IgG antibody level >10 U/ml in serum (27,28). Serum pepsinogens (PGs) were measured by chemiluminescence enzyme immunoassay, and gastric mucosal atrophy was defined by a PG I value ≤70 ng/ml and PG I/PG II ≤ 3 ng/ml (29–31).

Examination of ALDH2 Glu504Lys (rs671) polymorphism

DNA of each subject was extracted from the buffy coat fraction using a DNA blood mini kit (Qiagen). Genotyping for the *ALDH2* Glu504Lys polymorphism (rs671) was based on TaqMan Assays by Applied Biosystems (Foster City, CA). In our laboratory, the quality of genotyping is routinely assessed statistically using the Hardy–Weinberg test and by retyping of a random sampling of 5% of subjects.

Data analyses

To assess the association between ALDH2 polymorphism and alcohol consumption in the risk of stomach cancer, we estimated the odds ratios (OR) and corresponding 95% confidence intervals (CI) using multiple logistic regression models. First, we evaluated the impact of ALDH2 polymorphism and alcohol drinking separately using all subjects. For this analysis, conditional logistic regression models included terms for cumulative exposure to smoking, fruit/vegetable intake and *H.pylori* infection. We examined a model that separately evaluated ALDH2 genotype and alcohol drinking and a second model that included both. Further, we evaluated possible effect modification by ALDH2 polymorphism on the impact of alcohol consumption; for this analysis, we used unconditional logistic regression models adjusted for the same covariates as for the overall analysis. Effect modification was assessed by the likelihood ratio test between the models with and without interaction terms between the *ALDH2* polymorphism and alcohol consumption. We defined interaction term as a product of ALDH2 polymorphism (Lys allele carrier = 1 and wild-type homozygote = 0) and alcohol consumption as a continuous variable (never = 0, low = 1, moderate = 2 and heavy = 3); therefore, degree of freedom in the tests was 1. Consistency of the interaction between *ALDH2* polymorphism and alcohol consumption was assessed by stratified analysis according to the strata of the particular covariate considered with the model including three-way interaction term among ALDH2 polymorphism, alcohol consumption and stratifying factor. Association between the combination of *ALDH2* polymorphism and alcohol consumption and atrophic gastritis (AG) was evaluated in a multivariate unconditional logistic model among control subjects. Covariates considered in the model were the same as that for stomach cancer risk, except with regard to the status of AG. Missing values for covariates were treated as dummy variables in the models. All analyses were performed using Stata SE version 11.2 (STATA Corp, College Station, TX).

Results

Demographic characteristics and selected lifestyle habits of participants are shown in Table I. Age and sex were appropriately matched. The proportion of smokers was higher in cases than in controls. Cases were exposed to a higher smoking dose than controls. Prevalence of *H.pylori* infection was 82.2% in cases and 54.2% in controls. Fruit/vegetable intake between the two groups showed no apparent marked difference (27,28).

Table II presents the association between alcohol drinking and ALDH2 rs671 polymorphism and stomach cancer. We explored three models: model 1, a crude model; model 2, a confounder-adjusted model that evaluated alcohol drinking and *ALDH2* rs671 polymorphism separately and model 3, a complete model that included alcohol drinking and *ALDH2* polymorphism together. In model 3, ORs for drinking relative to non-drinking were 1.04 (0.77–1.40) for light, 1.15 (0.82–1.61) for moderate and 1.72 (1.17–2.52) for heavy drinking, indicating a dose-dependent positive association. This association remained significant after the exclusion of former drinkers from analysis (data not shown). The association between ALDH2 rs671 polymorphism was significant in model 3, with ORs relative to Glu/Glu, the normal enzyme activity genotype, of 1.40 (1.11–1.76) for Glu/Lys, 1.73 (1.12–2.68) for Lys/Lys and 1.42 (1.13–1.79) for the Lys allele carrier after adjustment for alcohol drinking. Although smoking and *H.pylori* status are potential sources of confounding for the effect of alcohol drinking, we did not observe clear evidence of confounding between these factors and ALDH2 rs671 polymorphism.

Table I. Subject characteristics

Overall	Cases		Controls	
	No. 697	%	No. 1372	%
Sex				
Male	521	74.7	1028	74.9
Female	176	25.3	344	25.1
Age (years)				
<40	34	4.9	146	10.6
40–49	72	10.3	154	11.2
50–59	245	35.2	429	31.3
60–69	210	30.1	435	31.7
>70	136	19.5	208	15.2
Smoking status				
Never	222	31.9	538	39.2
Former	181	26	403	29.4
Current	294	42.2	430	31.3
Unknown	0	0	1	0.1
PY				
Never	222	31.9	539	39.3
<20	99	14.2	286	20.9
<40	160	23.0	272	19.8
<60	117	16.8	153	11.2
60 or more	92	13.2	113	8.2
Unknown	7	1.0	9	0.7
Alcohol consumption				
Never	228	32.7	452	32.9
Light	167	24.0	412	30.0
Moderate	159	22.8	316	23.0
Heavy	132	18.9	177	12.9
Unknown	11	1.6	15	1.1
Fruit/vegetable intake				
Lowest tertile (<114.0 g/day)	263	37.7	446	32.5
Middle tertile (<199.96 g/day)	208	29.8	445	32.4
Highest tertile (≥199.96 g/day)	209	30	445	32.4
Unknown	17	2.4	36	2.6
Family history of gastric cancer				
Yes	153	22	239	17.4
No	544	78	1133	82.6
H.pylori IgG test				
Positive	124	17.8	628	45.8
Negative	573	82.2	744	54.2
AG defined by PG testing				
Negative	262	37.6	893	128.1
Positive	434	62.3	479	68.7
Unknown	1	0.1	0	0
Histologic classification				
Diffuse	379	54.4	—	
Intestinal	305	43.8	—	
Unknown	13	1.9	—	

Table III shows results for the interaction of ALDH2 rs671 polymorphism with alcohol consumption on the risk of stomach cancer. Among ALDH2 Glu/Glu, there was no statistically significant association. In contrast, heavy drinking among ALDH2 Lys allele carriers showed a statistically significant association, with ORs among *ALDH2* Lys+ subjects of 0.79 (0.55–1.11) for light, 1.18 (0.80–1.75) for moderate and 2.37 (1.37–4.12) for heavy drinking relative to non-drinking with *ALDH2* Glu/Glu. A significant interaction between drinking and *ALDH2 Lys* allele was seen (*P*-interaction = 0.0054). We further evaluated the consistency of the gene–environment interaction between the *ALDH2* Lys allele and alcohol drinking across strata of confounders. As shown in Table IV, interaction between the two factors was consistently observed, with some exception like fruit and vegetable consumption and *H.pylori* status.

Table II. Association between ALDH2 genotype and drinking and stomach cancer risk

	Case	Control	Model 1[a]	Model 2[b]	Model 3[c]
			OR (95% CI)[b]	OR (95% CI)[b]	OR (95% CI)[b]
Level of drinking					
Non-drinker	228	452	Reference	Reference	Reference
Ever drinker					
Light	167	412	0.81 (0.63–1.04)	0.89 (0.67–1.17)	1.04 (0.77–1.40)
Moderate	159	316	1.03 (0.79–1.34)	0.92 (0.68–1.24)	1.15 (0.82–1.61)
Heavy	132	177	1.52 (1.14–2.04)	1.29 (0.92–1.80)	1.72 (1.17–2.52)
Unknown subjects	11	15			
ALDH2 genotype[d]					
Glu/Glu	310	683	Reference	Reference	Reference
Lys+	386	689	1.24 (1.03–1.49)	1.27 (1.04–1.56)	1.42 (1.13–1.79)
Glu/Lys	323	580	1.23 (1.02–1.49)	1.25 (1.01–1.54)	1.40 (1.11–1.76)
Lys/Lys	63	109	1.27 (0.91–1.78)	1.42 (0.98–2.08)	1.73 (1.12–2.68)

[a]Crude ORs by the conditional logistic regression model.
[b]ORs were calculated by a conditional logistic regression model adjusted for PY of smoking, fruit/vegetable intake, family history of gastric cancer, gastric atrophy defined by serological PG testing and *H.pylori* status.
[c]ORs were calculated by unconditional logistic regression model adjusted for age, sex, PY of smoking, fruit/vegetable intake, family history of gastric cancer, gastric atrophy defined by serological PG testing, *H.pylori* status, levels of drinking and ALDH2 genotypes.
[d]One case was excluded because ALDH2 genotype was not defined.

Table III. Association between ALDH2 genotype and drinking and stomach cancer risk[a]

Level of drinking	ALDH2 Glu/Glu			ALDH2 Lys+			*P*-interaction
	Case	Control	OR (95% CI)[b]	Case	Control	OR (95% CI)[b]	
Non-drinker	49	112	Reference	179	340	1.24 (0.82–1.90)	0.0054
Ever drinker							
Light	87	208	1.07 (0.67–1.70)	80	204	1.03 (0.63–1.67)	
Moderate	79	208	0.89 (0.54–1.44)	80	108	1.57 (0.94–2.64)	
Heavy	87	145	1.28 (0.77–2.12)	44	32	3.03 (1.59–5.79)	
Unknown subjects	8	10		3	5		

[a]One case was excluded because ALDH2 genotype was not defined.
[b]ORs were calculated by an unconditional logistic regression model adjusted for age, sex, PY of smoking, fruit/vegetable intake, family history of gastric cancer, gastric atropy defined by serological PG testing and *H.pylori* status.

Table V explores the interaction between *ALDH2* genotype and alcohol drinking with regard to the prevalence of AG among non-cancer controls. Association with alcohol drinking was not significant. In analysis of the combination of *ALDH2* and alcohol drinking, heavy drinking with *ALDH2* Lys+ showed an OR of 4.50 (1.51–13.43, $P = 0.007$) relative to non-drinkers with *ALDH2* Glu/Glu, whereas that of heavy drinking with *ALDH2* Glu/Glu was 1.48 (0.74–2.98). The sources of confounding were age, sex, smoking status and *H.pylori* status.

Discussion

In this large case-control study, we found a significant interaction between the *ALDH2 Lys* allele and alcohol consumption after adjustment for *H.pylori* infection, cumulative exposure to smoking, and fruit/vegetable intake. Subjects with the *ALDH2* Lys allele who drank heavily showed a >2-fold higher risk than those with *ALDH2* Glu/Glu genotype who did not drink. A similar phenomenon was observed with regard to the prevalence of AG among non-cancer controls.

ALDH2 is a key enzyme that catalyzes acetaldehyde into acetate. The polymorphism Glu504Lys (rs671) has sufficient functional strength to influence many alcohol-related conditions (4,18,32). We first described a strong gene–environment interaction between alcohol drinking and the *ALDH2* Glu504Lys polymorphism in esophageal cancer risk (4), and subsequent studies, including our own, confirmed the same phenomenon in UADT cancers (5–11). This line of epidemiological evidence for an interaction between these two factors finally lead to the conclusion that 'acetaldehyde associated with alcoholic beverages' was Group 1 by the International Agency for Research on Cancer (3). Although the effect size of *ALDH2* or alcohol drinking was smaller than those for UADT cancers, our results are consistent with the phenomenon seen in UADT cancers, indicating the substantial attribution of acetaldehyde to stomach carcinogenesis, as previously hypothesized (13,14).

To date, several studies have evaluated the association between *ALDH2* rs671 polymorphism and risk of stomach cancer (15–18,33,34). However, these studies did not examine the interaction with detailed information on alcohol consumption. A recent study from Korea reported a similar phenomenon among 454 cases and 370 controls (17). Interestingly, a very recent study from Europe reported that a polymorphism in *ALDH2,* rs16941667, showed an allelic OR of 1.34 in a European population. But the interaction between rs16941667 and alcohol consumption is not remarkable, possibly because rs16941667 has less functional impact than rs671. In any case, their finding might indicate a substantial contribution of ALDH2 to stomach carcinogenesis across ethnicities. Clarification of the role of alcohol in gastric carcinogenesis awaits further studies of possible gene–gene interactions between the *ALDH2* and alcohol dehydrogenases genes.

In this study, we also explored the potential contribution of *ALDH2*–alcohol interaction in AG, which has been established as a pre-cancerous stage of stomach cancer (28,35,36). We defined AG status by PG I and II levels, which reflect the secretary function of gastric glands. We observed that the impact of heavy drinking was stronger in those with *ALDH2* Lys+ compared with *ALDH2* Glu/Glu, albeit that the statistical interaction was not significant. This finding might suggest that acetaldehyde plays a role in gastric carcinogenesis from the AG stage *via* induction of mutagenic adducts as reported (14) in the gastric mucosa. Against this, however, contradicting results have been reported from

Table IV. OR for heavy drinking compared with non-drinking stratified by potential confounders

Stratified by	Glu/Glu				Lys+				*P*-heterogeneity
	Non-drinker	Light	Moderate	Heavy	Non-drinker	Light	Moderate	Heavy	
	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	
Overall	Reference	1.07 (0.67–1.70)	0.89 (0.54–1.44)	1.28 (0.77–2.12)	1.24 (0.82–1.90)	1.03 (0.63–1.67)	1.57 (0.94–2.64)	3.03 (1.59 (5.79)	
Sex									
Male	Reference	1.10 (0.45–2.69)	1.04 (0.43–2.52)	1.43 (0.59–3.47)	1.42 (0.59–3.38)	1.16 (0.48–2.82)	1.85 (0.76–4.52)	3.47 (0.76–4.52)	0.823
Female	Reference	1.38 (0.72–2.67)	0.69 (0.26–1.80)	3.72 (0.52–26.7)	1.29 (0.75–2.20)	1.02 (0.43–2.41)	1.13 (0.16–7.90)	2.63 (0.16–7.90)	
Age category									
<60	Reference	0.67 (0.34–1.34)	0.68 (0.34–1.38)	1.33 (0.64–2.76)	1.29 (0.70–2.39)	1.20 (0.60–2.40)	1.32 (0.61–2.87)	1.71 (0.67–4.37)	0.751
60 or more	Reference	1.64 (0.85–3.19)	1.07 (0.54–2.14)	1.18 (0.57–2.44)	1.17 (0.65–2.12)	0.81 (0.40–1.65)	1.82 (0.89–3.70)	4.99 (1.94–12.8)	
Smoking status									
Never	Reference	1.15 (0.65–2.06)	1.05 (0.53–2.07)	1.08 (0.42–2.77)	1.16 (0.71–1.89)	1.22 (0.61–2.43)	1.66 (0.65–4.25)	2.50 (0.69–9.06)	0.187
Ever	Reference	1.10 (0.39–3.09)	0.93 (0.33–2.61)	1.63 (0.58–4.56)	1.60 (0.58–4.39)	1.12 (0.40–3.13)	1.84 (0.65–5.18)	3.89 (1.27–11.9)	
Fruit/vegetable intake									
Lowest tertile	Reference	0.45 (0.19–1.04)	0.47 (0.19–1.20)	0.51 (0.21–1.21)	0.84 (0.38–1.86)	0.48 (0.20–1.16)	0.79 (0.31–1.99)	0.95 (0.31–2.84)	0.023
Middle tertile	Reference	1.69 (0.67–4.25)	1.59 (0.63–4.06)	2.42 (0.93–6.27)	1.42 (0.61–3.27)	1.99 (0.76–5.03)	1.67 (0.62–4.51)	4.94 (1.60–15.3)	
Highest tertile	Reference	1.36 (0.62–2.95)	0.89 (0.39–2.06)	1.64 (0.60–4.51)	1.58 (0.80–3.14)	1.27 (0.56–2.91)	2.78 (1.12–6.87)	9.89 (2.16–45.3)	
H.pylori									
Positive	Reference	1.21 (0.71–2.08)	1.14 (0.65–1.98)	1.49 (0.83–2.64)	1.60 (0.8–2.61)	1.12 (0.64–1.97)	2.44 (1.35–4.42)	3.87 (1.82–8.24)	0.097
Negative	Reference	0.79 (0.30–2.10)	0.52 (0.18–1.53)	0.87 (0.29–2.57)	0.57 (0.24–1.40)	0.79 (0.29–2.14)	0.43 (0.12–1.51)	1.89 (0.50–7.11)	
AG defined by PG test									
Positive	Reference	1.00 (0.53–1.89)	1.11 (0.58–2.13)	1.18 (0.59–2.35)	1.26 (0.71–2.23)	0.92 (0.47–1.82)	1.75 (0.87–3.54)	2.35 (0.99–5.58)	0.808
Negative	Reference	1.38 (0.67–2.83)	0.73 (0.33–1.63)	1.56 (0.72–3.37)	1.46 (0.76–2.82)	1.27 (0.61–2.66)	1.84 (0.82–4.15)	5.95 (2.17–16.3)	
Family history of gastric cancer									
Yes	Reference	0.58 (0.19–1.76)	0.47 (0.14–1.54)	1.40 (0.42–4.62)	0.64 (0.23–1.73)	0.45 (0.14–1.41)	1.30 (0.40–4.25)	3.42 (0.82–14.2)	0.483
No	Reference	1.24 (0.74–2.09)	1.01 (0.59–1.73)	1.22 (0.69–2.14)	1.44 (0.90–2.31)	1.23 (0.72–2.12)	1.58 (0.88–2.84)	2.86 (1.37–5.94)	
Histology[b]									
Diffuse	Reference	1.11 (0.64–1.95)	0.97 (0.54–1.76)	1.68 (0.92–3.08)	1.50 (0.92–2.46)	1.19 (0.66–2.13)	2.00 (1.07–3.74)	3.76 (1.74–8.14)	NE[c]
Intestinal	Reference	0.89 (0.44–1.79)	0.66 (0.32–1.35)	0.82 (0.39–1.73)	0.82 (0.43–1.58)	0.66 (0.31–1.37)	1.04 (0.49–2.20)	1.96 (0.81–4.71)	
Location of stomach cancer									
Upper[d]	Reference	0.48 (0.03–8.53)	0.89 (0.07–11.7)	2.25 (0.20–25.9)	1.47 (0.15–14.3)	3.57 (0.36–35.8)	1.45 (0.10–20.3)	4.32 (0.29–64.6)	NE[c]
Others	Reference	1.09 (0.68–1.75)	0.89 (0.55–1.46)	1.26 (0.76–2.10)	1.24 (0.81–1.90)	0.98 (0.60–1.60)	1.58 (0.94–2.67)	2.89 (1.51–5.56)	

[a]ORs were calculated by an unconditional logistic regression model adjusted for age, sex, PY of smoking, fruit/vegetable intake, family history of gastric cancer, gastric atrophy defined by serological PG testing and *H.pylori* status.
[b]One case was excluded from analysis because of undefined histology.
[c]NE indicates not evaluable.
[d]Upper stomach cancer includes ICD O3T C16.0 (cardia, NOS, $n = 21$) and C16.1 (fundus of stomach, $n = 3$).

Table V. Associations between ALDH2 genotype and drinking and AG prevalence among controls

Level of drinking	Overall			Combined with ALDH2 genotype					
				ALDH2 Glu/Glu			ALDH2 Lys+		
	AG	Non-AG	OR (95% CI)[b]	AG	Non-AG	OR (95% CI)[b]	AG	Non-AG	OR (95% CI)[b]
Non-drinker	163	289	Reference	39	73	Reference	124	216	1.65 (0.92–2.93)
Ever drinker									
Light	128	284	0.99 (0.68–1.44)	68	140	1.71 (0.90–3.25)	60	144	1.27 (0.66–2.44)
Moderate	119	197	1.20 (0.81–1.79)	76	132	1.67 (0.88–3.17)	43	65	2.10 (1.00–4.41)
Heavy	66	111	1.19 (0.73–1.92)	51	94	1.48 (0.74–2.98)	15	17	4.50 (1.51–13.43)
Unknown subjects	3	12		1	9		2	3	

[a]One case was excluded because ALDH2 genotype was not defined.
[b]ORs were calculated by an unconditional logistic regression model adjusted for age, sex, PY of smoking, fruit/vegetable intake, family history of gastric cancer and *H.pylori* status.

Germany (37). In their population-based study in 9444 older adults, Gao *et al.* (37) found that alcohol drinking was associated with a reduced risk of AG, which they explained as due to the potentially bactericidal effect of alcohol. The attribution of *ALDH2* or alcohol consumption to gastric carcinogenesis thus remains to be elucidated.

This study had several methodological strengths. First, potential confounding by age, sex, smoking, fruit/vegetable intake, *H.pylori* infection and gastric atrophy status was considered by individual matching and statistical adjustment in the analyses. In particular, the consideration of *H.pylori* infection warrants the robustness of our observation. Second, as the *ALDH2* genotype does not change throughout life, we can assume that the impact of *ALDH2* polymorphism is subject to Mendelian randomization. Third, the size of the study was large, and the food frequency questionnaire was satisfactorily valid and reproducible (17,18). Potential limitations of this study also warrant mention. First, measurement of alcohol drinking might have been affected by the status of cases at recruitment. To avoid this, we asked about drinking behavior when the participants were healthy or before the current symptoms developed. Second, the control participants were selected from among non-cancer patients at our hospital. Because cases and controls were selected from the same hospital and almost all patients lived in the Tokai area of central Japan, the internal validity of this case-control study is likely acceptable (21). In addition, to dilute any bias that might have resulted from the inclusion of a specific diagnostic group that is related to the exposure, we did not set eligibility criteria for control diseases. Finally, it is difficult to completely rule out misclassification of *H.pylori* infection status or AG status by plasma measurement, or lifestyle factors considered as potential confounders based on self-reporting. If present, however, the effect of such misclassification in relation to possible under-adjustment would be limited, particularly considering the consistency of results across stratified analyses by several potential confounders.

In conclusion, we found that ALDH2 and alcohol drinking interact with each other in the risk of stomach cancer. This finding indicates a substantial role of acetaldehyde in carcinogenesis in the stomach, as has already been shown for cancers of the UADT.

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