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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Combined impact of five lifestyle factors and subsequent risk of cancer: The Japan Public Health Center Study

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ABSTRACT

Objective. To evaluate whether 5 combined healthy lifestyle factors (not smoking, moderate drinking, eating minimum salt-preserved foods, being physically active, and having appropriate body mass index) are associated with reduced risk of cancer.

Methods. Participants were enrolled in the Japan Public Health Center Study and responded to the 5-year follow-up questionnaire covering lifestyle factors in 1995–1999 at ages 45–74 years. During follow up through December 31, 2006, 3451 and 2125 cases of cancer were newly identified in men and women, respectively. For men and women, a factor-dependent risk reduction was observed for healthy lifestyles and cancer development. Compared to 0–1 healthy lifestyle factors, the adjusted RRs and 95% CIs for adherence to 2, 3, 4, and 5 healthy factors were 0.86 (0.78–0.95), 0.72 (0.65–0.80), 0.61 (0.54–0.69), and 0.57 (0.45–0.72), respectively, for men (P for trend<0.0001) and 0.86 (0.53–1.40), 0.73 (0.46–1.16), 0.68 (0.42–1.08), and 0.63 (0.39–1.01), respectively, for women (P for trend = 0.0003). Risk was reduced 14% and 9% by each one healthy lifestyle for men and women, respectively. Risk reduction was more pronounced among elderly women.

Conclusion. These combined lifestyle factors have a considerable impact on preventing cancer.

Introduction

Lifestyle factors such as cigarette smoking, alcohol consumption, diet, physical activity, and relative weight (body mass index [BMI]) are considered important core factors for preventing cancer (Secretan et al., 2009; World Cancer Research Fund/American Institute for Cancer Research, 2007). In fact, "Cancer Prevention for Japanese," one of the cancer prevention guidelines existing in Japan, which was proposed based on systematic review of epidemiologic studies by the Research Group for the Development and Evaluation of Cancer Prevention strategies in Japan (the 3rd term of 10-year comprehensive strategy for cancer control from the Ministry of Health, Labor and Welfare (MHLW)) (National Cancer Center [NCC web site], 2003: http://epi.ncc.go.jp/can_prev/93/180.html), presents these factors as recommended key aspects for cancer prevention, in addition to checking the status of infection. Although the individual effect of these factors on cancer has been well documented, their combined effect is not well known.

Based on projection models, we have shown that lifestyle factors of current smoking, excessive alcohol drinking, and obesity are suggested as common risk factors for cancer and cardiovascular disease (CVD), particularly in men (Tanaka and for the JPHC Study Group, 2009).

In this study that considered more factors, we evaluated the extent to which the combined 5 lifestyle factors are associated with reduced risk of cancer in a Japanese population.

Methods

Study population

Details of the study design have been described previously (Tsugane and Sobue, 2001). The participants in the present study were Japanese residents included in the Japan Public Health Center (JPHC)-Based Prospective Study who responded to the 5-year follow-up questionnaire covering lifestyle factors during 1995–1999 at ages 45–74 years. Subjects were followed from the starting point for the present analysis (1995–1999) until December 31, 2006. The institutional review board of the National Cancer Center, Tokyo, Japan, approved the study. We identified 133,323 subjects as the study population.

Follow-up and identification of cancer cases

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 present study, 11,073 subjects died, and 4904 moved away from the study area, and were lost to follow-up.

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We identified incident data for cancer by active patient notification from major local hospitals in the study area and from data linkage with population-based cancer registries. We coded cancer cases according to the *International Classification of Diseases for Oncology*, 3rd edition (World Health Organization, 2000). In our cancer registry system, the proportion of cases for which information was available from death certificates only was 6.1%.

Questionnaire

The questionnaire covered sociodemographic characteristics, medical history, smoking and drinking habits, diet, physical activity, and so on. The validated FFQ asked subjects about their usual intake of food during the previous year in standard portions/units and 9 frequency categories. (Tsubono et al., 1996). Salt-preserved foods and their salt content included in the questionnaire were: pickled vegetables (1.5–7.6%), dried and salted fish (1.7–4.1%), salted fish roe *tarako* (salted Alaska pollack roe) or suziko (salted salmon roe) (4.6–4.8%), and miso soup (1%) (Resource Council, 2002).

Subjects were asked about the average amount of time spent per day in three types of physical activity: heavy physical work or strenuous exercise, sitting, and standing or walking. MET-h/d were estimated by multiplying the daily time score for each activity by the MET intensity of that activity (Ainsworth et al., 2000; Inoue et al., 2008).

After excluding subjects with non-Japanese nationality (51), emigration occurring before the starting point (183), ineligibility due to incorrect birth date (7), or duplicate enrollment (4), we established a population-based cohort of 133,076 subjects. After exclusion of 12,067 subjects who had died (3432), moved away from the study area (8231), or been lost to follow-up before the starting point (304), and 121,009 eligible subjects remained. Among them, 98,456 responded to the questionnaire, yielding a response rate of 81.4%. We excluded subjects who had been diagnosed or reported as having cancer (2156), CVD (1188), or ischemic heart disease (1471) before the starting point, who had missing data regarding smoking (4702), alcohol (2439), physical activity (4490), missing or inadequate data for BMI (2822), or who reported extreme total energy intake (upper 2.5% or lower 2.5% for each sex). The final analysis included 78,548 subjects (36,964 men and 41,584 women).

Scores for lifestyle factors

The participants were regarded as adhering to the healthy lifestyle if they were nonsmokers (never smoked), drinking in moderation (drinking with <150 g/week), eating minimum salt-preserved foods (eating fish roe <0.67 g/week), being physically active (≥37.5 metabolic equivalents [MET]-h/d for men and ≥31.9 MET-h/d for women), having an adequate BMI (within 21–27 for men and 19–25 for women). The threshold was identified for each factor by means stated in the guideline or by the means used in our previous observation (Inoue et al., 2008; Takachi et al., 2010). Cut-off points for BMI were derived from the guideline, based on Japanese data representative at the time the guideline was reported (Inoue et al., 2004a). Based on our previous report, salted fish roe, but neither other salt-preserved foods nor total sodium intake, was associated with total cancer (Takachi et al., 2010). Pickled vegetables, dried and salted fish, and miso soup also include vitamins, n-3 fatty acids, and isoflavone, respectively, which may have beneficial effects on cancer. However, the elevated risk of total cancer by salted fish roe might be explained by destruction of the mucosal barrier by a high salt concentration, which leads to inflammation, diffuse erosion, and degeneration (Takachi et al., 2010). In the report, elevated risk was observed above the 4th quintile group, which corresponds to >0.67 g/d in the present data set. This corresponds to eating salted fish roe at a portion size once a month. Similarly, we have reported reduced risk of total cancer among the highest quartile group of total MET-h/d (Inoue et al., 2008). This corresponds to ≥37.5 MET-h/d for men and ≥31.9 MET-h/d for women in the present data set. For example, heavy physical work or strenuous exercise ≥1 h, sitting ≥8 h, and standing or walking ≤1 h can be calculated as 37.5 MET-h/d. This is typical for office workers with some active daily activity added. Similarly, no heavy physical work or strenuous exercise, sitting ≤3 h, and standing or walking ≤3 h is calculated to 31.4 MET-h/d, which is typical of the daily activity of housekeepers. We combined past smokers with current smokers because their risk of developing cancer was similar to current smokers, especially in women, based on our previous report (Inoue et al., 2004b). The general approach consisted of attributing a score of 1 to subjects who met the criteria for healthy lifestyle and 0 for not. Table 1 summarizes the definition of adherence to each lifestyle factor and the distribution by gender. More than 90% of women adhered to not smoking and moderate drinking, whereas fewer than 50% of the men did so. Due to the big difference in distribution of adherence to healthy lifestyle factors by gender, all the analyses were conducted separately for men and women.

We also conducted a weighted score approach based on factor response observed in our cohort previously. Coefficients of relative risks (RRs) derived from our previous publication regarding each lifestyle factor (Inoue et al., 2004a,b, 2005, 2008; Takachi et al., 2010) were multiplied by 10 and summed to present a risk score (Steyerberg, 2009).

Statistical analysis

We calculated person-years of follow-up for each subject from the starting point to the date of cancer diagnosis, date of emigration from the study area, date of death, or end of the follow-up (December 31, 2006), whichever came first. RRs and 95% confidence intervals (CIs) of developing cancer were estimated by 5 lifestyle factors individually and in combination. We used Cox proportional hazards models with adjustment for potential confounding variables such as age in years (<49, 50–54, 55–59, 60–64, 65–69, and >70), public health center area, and past history of diabetes mellitus (yes/no) by the SAS PHREG procedure (SAS Institute, Cary, NC). In the report on salt or salt-preserved foods from this cohort, the public health center area was not adjusted because consumption of these foods was defined by area, and adjustment masked their true influence on cancer (Takachi et al., 2010). Therefore, the public health center area was not adjusted in the individual analysis for salt-preserved food (Table 2).

We calculated population attributable fraction (PAF) (Miettinen, 1974) that might be associated with lack of adherence to all the recommendations, that is, the preventable fraction when all subjects would have adhered to all 5 healthy lifestyle factors as:

$$PAF_{ALL} = \sum P_i[HR_i - HR_5]\}/(1 \times HR_5 + \sum P_i[HR_i - HR_5]) \times 100,$$

and furthermore, the preventable fraction when subjects would have adhered to one additional healthy lifestyle for the entire cohort except the healthiest group was calculated as

$$PAF_{+1} = \sum P_i[HR_i - HR_{i+1}]\}/(1 \times HR_5 + \sum P_i[HR_i - HR_{i+1}]) \times 100,$$

Table 1
Adherence to 5 lifestyle factors among 78,548 Japanese subjects (1995).

Healthy lifestyle factors	Men (n=36,964)	Women (n=41,584)
Nonsmoking		
0 (current smoking or past smoking)	24,205 (65.5%)	2821 (6.8%)
1 (never smoking)	12,759 (34.5%)	38,763 (93.2%)
Moderate drinking		
0 (drinking alcohol ≥150 g/week)	18,658 (50.5%)	1252 (3.0%)
1 (drinking alcohol <150 g/week)	18,306 (49.5%)	40,332 (97.0%)
Eat minimum salt-preserved foods		
0 (eating fish roe at ≥0.67 g/d)[a]	7834 (21.2%)	8997 (21.6%)
1 (eating fish roe at 0–0.67 g/d)[a]	29,130 (78.8%)	32,587 (78.4%)
Being physically active		
0 (men, <37.5 MET-h/d[b]; women, <31.9 MET-h/d[c])	27,752 (75.1%)	23,981 (57.7%)
1 (men, ≥37.5 MET-h/d[b]; women, ≥31.9 MET-h/d[c])	9212 (24.9%)	17,603 (42.3%)
Maintaining adequate/appropriate BMI		
0 (men, <21, ≥27; women, <19, ≥25)	10,929 (29.6%)	14,104 (33.9%)
1 (men, 21–27; women, 19–25)	26,035 (70.4%)	27,480 (66.1%)

[a] The amount 0.67 g/d corresponds to eating salted fish roe at a portion size (quarter of *tarako* (Alaska pollack roe; salt content 4.6–4.8%) which is about 20 g) once a month.
[b] Physical activity level of 37.5 MET-h/d corresponds to for example, typical type of office worker with some active daily activity added. (Heavy physical work or strenuous exercise>=1 h, sitting>=8 h, and standing or walking <1 h).
[c] Physical activity level of 31.9 MET-h/d corresponds to for example, typical type of daily activity of house keeper. (Heavy physical work or strenuous exercise none, sitting <3 h, and standing or walking 3<=h can be calculated to be 31.4 MET-h/d).

Table 2
Independent relative risk (RR) of cancer incidence for individual healthy lifestyle factors among Japanese subjects (1995–2006).

Lifestyle factor	Men		Women	
	RR (95% CI)[a]	*P*	RR (95% CI)	*P*
Nonsmoking versus current smoking (including past smoking)	0.67 (0.62–0.72)	<0.0001	0.76 (0.64–0.90)	0.002
Moderate drinking versus not moderate (≥150 g/week) drinking	0.89 (0.83–0.96)	0.001	0.92 (0.70–1.21)	0.56
Eating minimum salt-preserved foods versus not	0.91 (0.84–0.96)	0.02	0.94 (0.85–1.04)	0.20
Physically active versus inactive	0.88 (0.81–0.95)	0.002	0.87 (0.80–0.95)	0.002
BMI adequate versus not adequate	0.97 (0.90–1.04)	0.33	0.91 (0.84–1.00)	0.04

RR: relative risk, CI: confidence interval, BMI: body mass index.
[a] Adjusted for age, area (not for salt-preserved foods), past history of diabetes mellitus, and all listed lifestyle factors.

where P_i is the prevalence of the subjects for each group i at baseline and HR_i and HR_{i+1} is the age-adjusted HR of group i and group i + 1, respectively.

Trend *P* was tested by assigning ordinal numbers to each group. All *P* values are two-sided, and statistical significance was determined at the $P<0.05$ level. We performed all statistical analyses with SAS software, version 9.1.

Results

During 727,162 person-years of follow up, we identified 3451 and 2125 new cases of cancer in men and women, respectively.

Table 2 gives the main effect of individual lifestyle factors on the development of cancer. Adherence to not smoking showed the largest risk reduction among the 5 lifestyle factors for both sexes, which was followed by being physically active, moderate drinking and eating minimum salt-preserved foods (men), and adequate BMI (women). Nonsignificant reduced risk was shown for adequate BMI in men and moderate drinking and eating minimum salt-preserved foods in women.

Table 3 shows the baseline characteristics of subjects according to the number of healthy lifestyles. Because the numbers of subjects who had 0 or 1 healthy behaviors were limited, especially in women (1.1%), these categories were combined as a single group. Those who adhered to many healthy lifestyles were older, ate more vegetables and fruits, had lower salt intake, and higher total energy.

Table 4 shows the RRs and 95% CIs of developing cancer according to the number of healthy lifestyles. For both men and women, a factor-dependent risk reduction was observed among healthy lifestyles and cancer development. Compared to 0–1 healthy lifestyle factors, the adjusted RRs and 95% CIs of adherence to 2, 3, 4, and 5 factors were 0.86 (0.78–0.95), 0.72 (0.65–0.80), 0.61 (0.54–0.69), and 0.57 (0.45–0.72) for men (*P* for trend<0.0001) and 0.86 (0.53–1.40), 0.73 (0.46–1.16), 0.68 (0.42–1.08), and 0.63 (0.39–1.01) for women (*P* for trend = 0.0003). The risk was reduced 14% and 9% by each one healthy lifestyle for men and women, respectively. When stratified by age, the risk reduction was more pronounced among women older than 60; 0.44 (0.21–0.94) for 5 lifestyles (*P* for trend = 0.0005), whereas the risk reduction remained marginally significant among women younger than 60; 0.78 (0.42–1.42; *P* for trend = 0.08). The results were similar after excluding early onset of cancer (data not shown). The PAF_{ALL} and PAF_{+1} was more than double for men compared to women; the corresponding values were 26.7% and 16.3% in men and 11.0% and 7.8% in women, respectively.

We conducted additional analyses that examined the effect of adherence to 4 healthy lifestyles (moderate drinking, minimum salted foods, physical activity, and appropriate BMI) and cancer incidence when subjects were restricted to current or former smokers. The risk was reduced 10% (significantly for men and not significantly for women) by each one healthy lifestyle. Similar results were also shown when stratifications by other factors were conducted.

When the weighted score approach was applied, the results were essentially similar to those observed in the simple binary method.

Discussion

In this large-scale population-based prospective study, a clear linear reduction of cancer risk was observed according to the adherence to the 5 healthy lifestyle factors; the risk was reduced 10% by each one healthy lifestyle.

Table 3
Baseline characteristics of subjects according to the number of healthy lifestyle factors among Japanese subjects (1995).

	Number of healthy lifestyle factors									
	Men					Women				
	0–1	2	3	4	5	0–1	2	3	4	5
No.	5720	11,602	12,313	6296	1033	274	2574	11,918	18,476	8342
Age, y	55.6	56.0	56.6	57.2	57.1	54.2	56.1	56.7	56.8	56.3
Cancer screening, %	42.8	40.8	40.7	40.1	42.9	32.9	44.1	46.3	48.7	49.8
Past history of diabetes mellitus, %	5.6	6.4	6.4	6.9	4.6	1.5	4.7	3.5	3.0	2.3
Vitamin supplement use, %	9.6	9.9	10.6	10.5	10.8	18.6	15.2	14.0	15.6	15.9
Total energy, kcal/d	2396.8	2234.8	2134.6	2040.2	2105.4	2112.4	2007.1	1910.9	1849.3	1851.8
Total vegetable, g/d	204.2	193.2	202.8	210.1	230.0	215.8	240.1	239.7	234.8	246.6
Green-yellow vegetable, g/d	93.2	87.3	91.6	95.9	106.7	94.4	109.7	108.7	106.5	112.4
Fruit, g/d	175.1	168.4	184.5	198.6	228.4	218.1	265.2	258.8	248.4	258.2
Salt, g/d	13.7	12.4	12.1	11.7	12.3	13.1	13.5	12.5	11.7	11.9
Behaviors related to healthy lifestyle factors										
Current smoking, %	97.0	85.2	60.7	20.8	0.0	86.9	34.5	10.1	2.7	0.0
Heavy smoking[a] %	54.6	44.9	30.5	10.7	0.0	30.7	10.8	2.8	0.9	0.0
Alcohol drinking, ≥150 g/week, %	91.6	69.2	36.8	13.6	0.0	66.4	16.7	3.9	0.9	0.0
Heavy drinking[b] %	60.6	42.7	21.8	7.9	0.0	28.8	6.5	1.2	0.3	0.0
Fish roe, g/d	4.4	2.0	1.1	0.7	0.4	5.8	5.1	2.7	1.3	0.5
MET, MET-h/d	30.6	31.5	33.3	35.4	42.9	28.9	28.9	29.6	31.9	37.4
BMI, kg/m^2	23.0	23.5	23.8	23.8	23.9	23.7	25.0	24.5	23.1	22.3

BMI: body mass index. Values are means unless otherwise stated.
[a] Current smoking with ≥20 cigarettes/d.
[b] Alcohol drinking ≥300 g/week.

Table 4
Relative risk (RR) of cancer incidence by number of healthy lifestyle factors adjusted by age, area, and past history of diabetes mellitus among Japanese subjects (1995–2006).

No. of healthy lifestyle factors	Men				Women			
	No. of events	Person-y	RR (95% CI)[a]	*P* for trend	No. of events	Person-y	RR (95% CI)	*P* for trend
0–1	662	52,510	1.0		18	2494	1.0	
2	1142	104,140	0.86 (0.78–0.95)		166	24,616	0.86 (0.53–1.40)	
3	1077	111,433	0.72 (0.65–0.80)		657	113,387	0.73 (0.46–1.16)	
4	492	57,570	0.61 (0.54–0.69)		914	173,403	0.68 (0.42–1.08)	
5	78	9768	0.57 (0.45–0.72)	<0.0001	370	77,842	0.63 (0.39–1.01)	0.0003
RR at one score			0.86 (0.83–0.88)				0.91 (0.87–0.96)	
PAF_{ALL},%			**26.7**				**11.0**	
PAF_{+1}, %			16.3				7.8	
Stratification by age								
Age 60>								
0–1	303	37,553	1.0		11	1974	1.0	
2	511	71,628	0.92 (0.79–1.06)		91	16,606	0.94 (0.50–1.76)	
3	441	73,950	0.74 (0.64–0.86)		350	73,427	0.82 (0.45–1.49)	
4	175	36,470	0.58 (0.48–0.70)		471	112,050	0.74 (0.41–1.34)	
5	28	6222	0.55 (0.37–0.81)	<0.0001	225	51,881	0.78 (0.42–1.42)	0.08
RR at one score			0.85 (0.81–0.89)				0.94 (0.88–1.01)	
PAF_{ALL}, %			**32.7**				**2.5**	
Age 60≤								
0–1	359	14,957	1.0		7	520	1.0	
2	631	32,512	0.81 (0.71–0.93)		75	8010	0.71 (0.33–1.53)	
3	636	37,483	0.71 (0.62–0.81)		307	39,960	0.58 (0.27–1.23)	
4	317	21,100	0.63 (0.54–0.74)		443	16,353	0.56 (0.26–1.18)	
5	50	3546	0.58 (0.43–0.78)	<0.0001	145	25,961	0.44 (0.21–0.94)	0.0005
RR at one score			0.87 (0.83–0.90)				0.88 (0.81–0.94)	
PAF_{ALL}, %			**23.8**				**22.9**	

RR: relative risk, CI: confidence interval, PAF: population attributable fraction. PAF_{ALL}: PAF that might be associated with lack of adherence to all the recommendations, PAF_{+1}: the preventable fraction when subjects would have adhered to one additional healthy lifestyle for the entire cohort except the healthiest group.
[a] Adjusted for age, area, and past history of diabetes mellitus.

In an EPIC-Potsdam Study with 7.8 years of follow up and 868 cases of cancer incidence, Ford et al. (2009) showed a 36% reduction in cancer incidence for those with all 4 factors of interest. Using a chronic disease risk index that was created to summarize how well an individual adhered to recommended health guidelines, Meng et al. (1999) showed that cancer incidence was doubled in the highest risk index group compared to the lowest risk index group in a prospective study in Hawaii. Studies focused on colorectal (Kirkegaard et al., 2010) and pancreatic cancers (Jiao et al., 2009) also showed a clear risk reduction by combinations of healthy lifestyles. Other studies used mortality data, and among them, based on Japanese population 40–79 years old at baseline, Tamakoshi et al. (2009) showed a clear risk reduction of all-cause mortality by 6 lifestyle factors.

In our study, as in previous studies (Haveman-Nies et al., 2002; Khaw et al., 2008; Tamakoshi et al., 2009), risk reduction remained statistically significant among the elderly. However, results among women aged ≤60 failed to reach statistical significance. There was no difference in baseline characteristics based on adherence to healthy lifestyles in both age groups (data not shown). The leading sites of cancer were breast (21.3%), colorectum (19.3%), stomach (13.1%), and lung (7.5%) for age ≤60 and colorectum (20.5%), stomach (14.8%), lung (12.4%), and breast (11.6%) for age ≥60. Lifetime exposure to estrogen influenced by early menarche, late natural menopause, not bearing children, and late first pregnancy increase the risk of breast cancer. These factors are not included in the 5 lifestyle factors and, thus, the results among women aged ≤60 might not have been as clear as those in the elderly or in men.

Study limitations and strengths

Our study has several limitations. First, by using binary data for lifestyle factors, we lost information on any dose response. However, when a weighted score approach was applied, similar results were obtained, in line with other studies reporting both results (Jiao et al., 2009; Kirkegaard et al., 2010). Furthermore, when subjects were restricted to current or former smokers, an essentially similar risk reduction pattern was observed. The current approach was used for its simple method that is conceptually easy to understand and can used in clinical practice. Second, we used only one point for exposure assessment. However, subjects with a past history of cancer, CVD, and ischemic heart disease were eliminated from the main analyses and after excluding early onset of cancer, similar results were obtained. Random measurement error may attenuate any results. Third, the external validity is not tested regarding the present findings. For example, salted fish roe was used to represent total salt-preserved foods or sodium intake; however, this may not necessarily be applied to other populations. The strengths of our study are its prospective design. We selected subjects from the general population, we had a large sample size, the response rate for the questionnaire was acceptable for studies of this type, and the number of subjects lost to follow-up was negligible. In addition, the cancer registry was of sufficient quality to reduce misclassification of the outcomes.

Although further studies are needed to seek cancer-causing factors or the involved mechanisms, the present analysis presents an appropriate way to translate analytic epidemiologic studies to primary cancer prevention by examining the combined effects of known modifiable lifestyle factors.

Conclusion

The combined lifestyle factors including not smoking, drinking moderately, consuming a minimum of salted foods, being physically active, and maintaining an appropriate BMI have considerable impact on the prevention of cancer.

Conflict of interest statement

None of the authors had a conflict of interest.

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We thank all staff members in each study area for their painstaking efforts to conduct the survey and follow-up. The authors' responsibilities were as follows: ST was principal investigator; MI conducted the study, managed the data collection; and SS helped to conduct the study, analyzed and interpreted the data, and prepared the manuscript. MI, NS, TS, and TY helped to conduct the study and interpreted the data. All authors provided critical suggestions for revision of the manuscript.

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Appendix A

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Green Tea Consumption and Breast Cancer Risk in Japanese Women: A Case-Control Study

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Although many in vitro and animal studies have suggested a protective effect of green tea against breast cancer, only a few epidemiological studies have examined this association, and findings have been inconsistent. We examined the association between green tea consumption and breast cancer risk in consideration of the hormone receptor status of tumors and investigated whether the association was modified by dietary and genetic factors based on a hospital-based case-control study in Nagano, Japan. A total of 369 pairs completed a validated food frequency questionnaire and provided blood samples. Four single nucleotide polymorphisms (SNPs) were genotyped: *CYP19A1* (rs10046), *COMT* (rs4680), *MTHFR* C677T (rs1801133), and *MTHFR* A1298C (rs1801131). We found no inverse association between green tea consumption and breast cancer risk. Compared with women who drank less than 120 ml of green tea per day, the adjusted odds ratio for women who drank more than 600 ml was 1.27 (95% confidence interval = 0.75–2.14; *P* for trend = 0.20). We also found no inverse association for either tumor subtype. No substantial effect modification was observed for menopausal status, 4 SNPs, or dietary intake of folate or isoflavone. This study provides additional evidence that green tea consumption is not associated with a decreased risk.

Catechol-O-methyltrasferease

INTRODUCTION

Green tea is one of the most popular beverages in Japan and China, which have a lower risk of breast cancer than western countries (1). Because of its high levels of catechins, green tea has been hypothesized to have a protective effect against breast cancer (2). To date, 3 case-control and 5 cohort studies have investigated the association between green tea consumption and breast cancer risk, but findings have been inconsistent (3–10). A recent meta-analysis showed an inverse association for the case-control studies but no association for the cohort studies,

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with odds ratios (OR) for the highest vs. lowest group of 0.70 [95% confidence interval (CI) = 0.61–0.79] for the former and 1.06 (95% CI = 0.93–1.20) for the latter (2). This difference between study types might be explained by the influence of recall and selection bias stemming from the case-control design; by differences in the type of tea and drinking methods (10); or by differences in the distribution of effect modifiers. As examples of the influence of effect modifiers, a case-control study in Asian American residents of Los Angeles County observed a risk-reducing effect primarily among subjects whose soy intake was low (3), whereas a nested case-control study in Singapore showed a protective effect among women with high-activity genotypes for *methylenetetrahydrofolate reductase* (*MTHFR*) and *thymidylate synthase* (*TYMS*) (8), particularly among those whose dietary folate intake was low.

Proposed mechanisms for green tea's decrease in the risk of breast cancer include strong antioxidant activity, inhibition of cell proliferation and angiogenesis, and induction of apoptosis (11). Green tea catechins have antiestrogenic properties, with green tea extracts inhibiting aromatase (12) and [(-)-epigallocatechin-3-gallate (EGCG)] inhibiting the binding of estrogen to its receptor (13). In cross-sectional studies, green tea consumption has been associated with a lower level of estrogen among premenopausal Japanese women (14) and postmenopausal Chinese women in Singapore (15). Given that the putative effect of green tea on the development of breast cancer might be mediated by estrogen exposure, we hypothesized that green tea consumption would be more closely associated with hormone receptor-positive than -negative breast cancer. However, only a few studies have investigated the association between green tea consumption and the risk of hormone receptor-defined subtype (10).

Here, using data from a hospital-based case-control study in Nagano, Japan, we investigated the association between green tea consumption and breast cancer risk in consideration of the hormone receptor status of tumors. We also examined whether the association was modified by dietary and genetic factors, which have been suggested as potential effect modifiers by previous reports (3,8,9,16).

MATERIALS AND METHODS

Study Subjects

This multicenter, hospital-based case-control study was conducted from May 2001 to September 2005 at 4 hospitals in Nagano Prefecture, Japan. Details of the study design and methods have been described elsewhere (17,18). Briefly, eligible case patients were a consecutive series of female patients aged 20–74 yr with newly diagnosed and histologically confirmed invasive breast cancer among hospitalized patients at 4 hospitals in Nagano Prefecture during the study period. Of the 412 eligible patients, 405 (98%) agreed to participate. Eligible control subjects were selected from medical checkup examinees in 2 of the hospitals who were confirmed to not have any cancer, with 1 control matched with each case by age (within 3 yr) and residential area. One control whose date of medical checkup was closest to the date of our examination of the index case was recruited from potential controls. Among potential controls, one examinee refused to participate and 2 refused to provide blood samples. We accordingly obtained written informed consent from 405 matched pairs. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Data Collection

Participants were asked to complete a self-administered questionnaire, which contained questions on demographic characteristics, anthropometric factors, smoking habits, family history of cancer, physical activity, medical history, menstrual and reproductive history, and dietary habits. Information on estrogen receptor (ER) and progesterone receptor (PR) status was obtained from medical records. Hormone receptor status was determined by either enzyme-linked immunoassay or immunohistochemical assay. Hormone receptor positivity values were determined either as specified by the laboratory that performed the assay, or in accordance with the laboratory's written interpretation thereof, or both. Participants provided blood at the time they returned their self-administered questionnaire. Whole blood in 7 mL EDTA-2Na Vacutainer and serum samples were stored at −80°C until they are analyzed.

Exposure Assessment

The consumption of beverages during the previous year, including 2 items of green tea, namely *Sencha* (first or second flush of green tea, i.e., first seasonal picking)/*Bancha* (third or fourth flush of green tea, i.e., late seasonal picking) and *Houjicha* (roasted green tea, usually *Bancha*)/*Genmaicha* (blend of *bancha* and roasted brown rice); oolong tea; black tea; and coffee or canned coffee was assessed in terms of frequency and amount using the nine precoded categories of less than 1 cup per wk, 1–2 cups per wk, 3–4 cups per wk, 5–6 cups per wk, 1 cup per day, 2–3 cups per day, 4–6 cups per day, 7–9 cups per day, and 10 or more cups per day. The amount of *Sencha/Bancha* or *Houjicha/Genmaicha* consumed (ml per day) was computed by multiplying the frequency by the portion size for each beverage (120 ml per cup). Total green tea intake was defined as the sum of *Sencha/Bancha* and *Houjicha/Genmaicha* consumption.

Dietary habits were investigated using a 136-item semiquantitative food frequency questionnaire (FFQ) that was developed and validated in a Japanese population (19,20). In the FFQ, participants were questioned on how often they consumed the individual food items (frequency of consumption), as well as relative sizes compared to standard portions. Daily food intake was calculated by multiplying frequency by the standard portion and relative size for each food item in the FFQ. Daily intake of nutrients was calculated using the fifth revised and enlarged edition of the *Standard Tables of Food Composition in Japan* (21).

Genotyping

Genomic DNA samples were extracted from peripheral blood using Qiagen FlexiGene® DNA Kits (Qiagen K.K., Tokyo, Japan) according to the manufacturer's protocol. We selected 4 single-nucleotide polymorphisms (SNPs) in *aromatase* (*CYP19A1*), *catechol-O-methyltransferase* (*COMT*), and *MTHFR* (*CYP19A1* [rs10046], *COMT* [rs4680], *MTHFR* C677T [rs1801133], and *MTHFR* A1298C [rs1801131]) for the present study on the basis of suggestions that genotypes of *COMT* and *MTHFR* modify the association of green tea consumption and breast cancer (8,16). Genotyping of the 4 SNPs was performed by a commercial laboratory (Genetic Lab., Sapporo, Japan) using TaqMan SNP Genotyping Assays developed by Applied Biosystems (Foster City, CA).

Statistical Analysis

We excluded subjects who reported extremely low or high total energy intake (<500 or ≥4000 Kcal), had no information on green tea consumption or genotypes of the four SNPs, or had no DNA sample, leaving 369 pairs for use in the present analyses.

Baseline characteristics of cases and controls were compared by the Mantel-Haenszel test using matched-pair strata. Genotype frequencies were tested for deviation from the Hardy-Weinberg equilibrium by the chi-square test. We categorized subjects into 3 groups: 1–119 ml per day, 120–599 ml per day, and more than 600 ml per day based on total green tea consumption; and less than 1 cup per day, 1–3 cups per day, and 4 or more cups per day based on the frequency of *Sencha/Bancha* or *Houjicha/Genmaicha* consumption. Using a conditional logistic regression model, we calculated ORs and 95% CIs of breast cancer for green tea consumption. Stratified analyses by potential effect modifiers were performed using an unconditional logistic regression model. Associations between consumption and hormone receptor-defined breast cancer were assessed by an unconditional polytomous logistic regression model. The Wald test was used to test the null hypothesis that estimates were equal across hormone receptor-defined breast cancer subtypes. Linear trends for ORs were tested in the logistic regression model using the exposure categories as ordinal variables. Tests for interaction were performed based on the difference between 2 likelihood ratios of the models with and without the interaction terms between consumption and potential effect modifiers. In addition to matching factors, the following variables were adjusted as potential confounders: menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea intake (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea intake (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee intake (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee intake (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day). All reported P values are 2-sided, and significance level was set at $P < 0.05$. All statistical analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of case patients and control subjects are shown in Table 1. The proportion of premenopausal women, current smokers, and vitamin supplement users was higher in cases than in controls; and cases tended to have a family history of breast cancer and history of benign breast disease. Cases were less likely than controls to breastfeed and be physically active. Among 369 breast cancer cases, 138 (37.4%) cases were stage I and 190 cases (51.5%) were stage II based on the TNM classification of malignant tumors by the international union against cancer. Major histologic types were invasive ductal carcinoma (85.6%), invasive lobular carcinoma (4.1%), and mucinous carcinoma (3.8%). Genotype frequencies of each SNP were consistent with the Hardy-Weinberg equilibrium.

We found no inverse association between green tea consumption and the risk of breast cancer (Table 2). Compared with women who drank less than 120 ml of green tea per day, the adjusted OR for women who drank more than 600 ml was 1.27 (95% CI = 0.75–2.14; P for trend = 0.20). No substantial change was seen after further adjustment for other potential confounders, including education, age at menarche, age at menopause, age at first birth, history of breast feeding, body mass index, alcohol drinking, and vegetable and isoflavones intake (data not shown). We further categorized subjects into tertiles or quintiles based on distribution among the control group. However, no inverse association was observed regardless of categorization method (data not shown). Analyses based on the frequency of *Sencha/Bancha* or *Houjicha/Genmaicha* drinking also showed no inverse association: compared with women who drank less than 1 cup of *Sencha/Bancha* or *Houjicha/Genmaicha* per day, adjusted ORs for women who drank 4 or more cups were 1.15 (95% CI = 0.71–1.86; P for trend = 0.56) for *Sencha/Bancha* and 1.42 (95% CI = 0.74–2.69; P for trend = 0.12) for *Houjicha/Genmaicha* (data not shown in Table 2).

Information on the combined ER and PR status of tumors was available for 366 (99%) of 369 patients. The following subtypes were used for modeling in an unconditional polytomous logistic regression model: positive for both receptors (ER+/PR+), ER-positive and PR-negative (ER+/PR-), and negative for both receptors (ER-/PR-). ER-negative and PR-positive (ER-/PR+) cases were excluded owing to their small number ($n = 12$). We found no inverse association between green tea consumption and risk regardless of subtype (Table 2). Instead, women who drank more than 600 ml per day tended to be at higher risk of ER-PR- tumors, albeit without statistical significance.

TABLE 1
Characteristics of case and matched control subjects

Characteristics	Case ($n = 369$)		Control ($n = 369$)		P^a
Age (yr), *M* (SE)	53.4	(0.53)	53.7	(0.53)	
Premenopausal women, *n* (%)	171	(46.3)	132	(35.8)	<0.01
Age at menopause (yr), *M* (SE)[b]	48.9	(0.30)	49.5	(0.27)	0.37
Age at menarche (yr), *M* (SE)[b]	13.4	(0.07)	13.2	(0.07)	0.24
Nulliparous women, n (%)	48	(13.0)	56	(15.2)	0.37
Number of births (≥ 4 births), *n* (%)	8	(2.2)	9	(2.4)	0.15
Age at first birth (yr), *M* (SE)[b, c]	27.0	(0.19)	26.4	(0.19)	0.41
Breast feeding (yes), *n* (%)[c]	283	(90.7)	297	(95.5)	0.03
Oral contraceptive use, *n* (%)	13	(3.5)	12	(3.3)	0.84
Family history of breast cancer, *n* (%)	43	(11.7)	24	(6.5)	0.02
History of benign breast disease, *n* (%)	45	(12.4)	27	(7.3)	0.03
Height (cm), *M* (SE)[b]	155.3	(0.27)	155.6	(0.27)	0.69
Body mass index (kg/m^2), *M* (SE)[b]	22.7	(0.17)	23.0	(0.17)	0.07
Smoking (current smoker), *n* (%)	29	(8.0)	19	(5.2)	<0.01
Alcohol drinking (regular drinker), *n* (%)	94	(25.5)	111	(30.1)	0.39
Moderate physical activity past 5 yr (yes), *n* (%)	116	(31.8)	146	(39.6)	0.03
Vitamin supplement use, *n* (%)	68	(18.4)	45	(12.2)	0.02
Sencha/Bancha, (≥4 cups per day), *n* (%)	114	(30.9)	120	(32.5)	0.41
Houjicha/Genmaicha, ≥4 cups per day), *n* (%)	27	(7.3)	24	(6.5)	0.33
Oolong tea, (≥1 cups per day), *n* (%)	51	(14.0)	46	(12.5)	0.59
Black tea, (≥1 cups per day), *n* (%)	18	(4.9)	19	(5.2)	0.97
Coffee, (≥1 cups per day), *n* (%)	185	(50.4)	204	(55.3)	0.39
Canned coffee, (≥1 cups per day), *n* (%)	9	(2.5)	5	(1.4)	0.07
Total energy intake (kcal/day), *M* (SE)[b]	1873.2	(28.1)	1960.2	(28.1)	0.19
Fish and shellfish intake (g/day), *M* (SE)[b]	87.1	(2.9)	95.5	(2.9)	0.09
Meat or red meat intake (g/day), *M* (SE)[b]	57.5	(2.0)	58.1	(2.0)	0.38
Vegetable intake (g/day), *M* (SE)[b]	254.2	(9.4)	311.6	(9.4)	<0.01
Fruit intake (g/day), *M* (SE)[b]	286.9	(10.4)	288.2	(10.4)	0.79
Isoflavone intake (mg/day), *M* (SE)[b]	43.1	(1.5)	46.1	(1.5)	<0.01

[a] *P* for Mantel-Haenszel test with matched-pair strata. [b] Adjusted for age. [c] Among parous women.

Moreover, no statistical difference in risk was observed across subtypes (*P* for heterogeneity = 0.08).

We examined whether the association between green tea consumption and breast cancer risk was modified by menopausal status, 4 SNPs of *CYP19A1*, *COMT*, and *MTHFR*, or dietary intake of folate and isoflavone (Table 3). None of the interactions was statistically significant. Furthermore, we investigated associations between green tea consumption, potential effect modifiers, and breast cancer risk by menopausal status (Table 4). No statistically significant interaction was seen for the 3 SNPs of *COMT* and *MTHFR* and dietary folate intake. Analyses by rs10046 polymorphisms in *CYP19A1* showed a decreased risk of breast cancer with increasing consumption among premenopausal women with the CC genotype only (OR for women who drank more than 600 ml vs. less than 120 ml per day = 0.22; 95% CI = 0.05–1.01; *P* for trend = 0.054) and a statistically significant interaction was seen for premenopausal women (*P* for interaction = 0.01). On the other hand, an increased risk with increasing consumption was seen among postmenopausal women with the CC genotype only (OR for women who drank more than 600 ml vs. less than 120 ml per day = 8.78; 95% CI = 1.01–76.44; *P* for trend = 0.04), but the test for interaction was not statistically significant (*P* for interaction = 0.70). Analyses by isoflavone intake showed that the risk of breast cancer tended to decrease with increasing consumption only among premenopausal women with lower isoflavone intake (OR for women who drank more than 600 ml vs. less than 120 ml per day = 0.41; 95% CI = 0.13–1.30; *P* for trend = 0.14), and *P* for interaction was marginally significant (*P* = 0.06). In contrast, risk increased with increasing consumption only among postmenopausal women with lower isoflavone intake (OR for women who drank more than 600 ml vs. less than 120 ml per

TABLE 2
Odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to green tea consumption

	Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
All breast cancer						
No. of cases/No. of controls	83/68	136/160		150/141		
OR (95% CI)	1.00	0.69	(0.46–1.04)	0.85	(0.56–1.31)	0.75
Adjusted OR (95% CI)[b]	1.00	0.86	(0.53–1.41)	1.27	(0.75–2.14)	0.20
ER+PR+ breast cancer						
No. of cases	54	77	74			
OR (95% CI)	1.00	0.62	(0.39–0.98)	0.70	(0.43–1.14)	0.23
Adjusted OR (95% CI)[c]	1.00	0.72	(0.43–1.18)	0.84	(0.50–1.43)	0.68
ER+PR- breast cancer						
No. of cases	12	20	31			
OR (95% CI)	1.00	0.68	(0.31–1.47)	1.12	(0.52–2.41)	0.50
Adjusted OR (95% CI)[c]	1.00	0.77	(0.32–1.82)	1.46	(0.62–3.45)	0.19
ER-PR- breast cancer						
No. of cases	13	33	40			
OR (95% CI)	1.00	1.06	(0.52–2.15)	1.42	(0.69–2.92)	0.27
Adjusted OR (95% CI)[c]	1.00	1.18	(0.54–2.54)	1.88	(0.86–4.14)	0.07

[a] Total green tea consumption was defined as the sum of Sencha/Bancha and Houjicha/Genmaicha consumption (ml per day). [b] Conditional model adjusting for menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day). [c] Unconditional model adjusting for matching factors (age and area), menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day).

day = 1.60; 95% CI 0.63–4.06; *P* for trend = 0.03), but *P* for interaction was not statistically significant ($P = 0.38$).

DISCUSSION

In this case-control study in Japanese women, we found no inverse association between green tea consumption and the risk of breast cancer. This lack of association is in general agreement with 5 prospective studies, including 3 Japanese cohort studies (6–10), but in disagreement with 3 case-control studies conducted outside Japan, which all showed an inverse association (3–5). We also found no inverse associations among tumor subtypes. Overall, no substantial effect modification was observed for menopausal status, 4 SNPs of *CYP19A1*, *COMT*, and *MTHFR*, or dietary intake of folate and isoflavone, which suggests that these factors might not be major explanation for the inconsistent findings among previous studies. Although many previous studies including our study have assessed green tea intake during adulthood, the timing of green tea exposure might be important and may account for the lack of association in previous studies. Therefore, further studies are needed to investigate the association between green tea intake during puberty and breast cancer risk, for example, given suggestions that some exposures during breast development are crucial to the development of breast cancer (22).

The present study does not support our hypothesis that green tea consumption is more closely associated with hormone receptor-positive than -negative breast cancer. Contrary to our expectation, consumption was associated with an increased risk of ER-PR- tumors, albeit without statistical significance. Among previous studies, an inverse association was found for both ER+PR+ and ER-PR- tumors in a case-control study of Asian Americans (2), whereas no inverse association for either subtype was seen in our cohort study in Japanese women (10). Overall, the findings of the few studies reported to date are inconsistent. A better understanding of the

TABLE 3
Odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to green tea consumption by potential effect modifiers

	Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
Menopausal status						
Premenopausal						
No. of cases/No. of controls	56/38	70/60		45/34		
Adjusted OR (95% CI)[b]	1.00	0.72	(0.38–1.35)	1.10	(0.54–2.23)	0.83
Postmenopausal						
No. of cases/No. of controls	27/30	66/100		105/107		
Adjusted OR (95% CI)[b]	1.00	0.83	(0.42–1.67)	1.42	(0.71–2.85)	0.08
	P for interaction = 0.56					
CYP19A1 gene (rs10046)						
CC						
No. of cases/No. of controls	31/19	46/56		39/42		
Adjusted OR (95% CI)[b]	1.00	0.57	(0.25–1.30)	0.82	(0.34–1.99)	0.82
CT + TT						
No. of cases/No. of controls	52/49	90/104		111/99		
Adjusted OR (95% CI)[b]	1.00	0.88	(0.51–1.51)	1.22	(0.70–2.14)	0.32
	P for interaction = 0.24					
COMT gene (rs4680)						
GG						
No. of cases/No. of controls	47/38	60/68		72/67		
Adjusted OR (95% CI)[b]	1.00	0.88	(0.46–1.68)	1.37	(0.71–2.65)	0.26
GA + AA						
No. of cases/No. of controls	36/30	76/92		78/74		
Adjusted OR (95% CI)[b]	1.00	0.68	(0.35–1.30)	0.88	(0.44–1.77)	0.98
	P for interaction = 0.77					
MTHFR gene (rs1801133)						
CC						
No. of cases/No. of controls	27/18	47/48		47/44		
Adjusted OR (95% CI)[b]	1.00	0.89	(0.37–2.12)	1.10	(0.45–2.66)	0.73
CT + TT						
No. of cases/No. of controls	56/50	89/112		103/97		
Adjusted OR (95% CI)[b]	1.00	0.89	(0.52–1.53)	1.21	(0.69–2.13)	0.37
	P for interaction = 0.46					
MTHFR gene (rs1801131)						
AA						
No. of cases/No. of controls	56/46	84/106		99/92		
Adjusted OR (95% CI)[b]	1.00	0.78	(0.45–1.36)	1.24	(0.70–2.18)	0.26
AC + CC						
No. of cases/No. of controls	27/22	52/54		51/49		
Adjusted OR (95% CI)[b]	1.00	0.80	(0.35–1.84)	0.79	(0.32–1.91)	0.64
	P for interaction = 0.54					
Folate intake						
Lower						
No. of cases/No. of controls	68/50	87/92		40/32		
Adjusted OR (95% CI)[b]	1.00	0.81	(0.47–1.39)	1.08	(0.54–2.13)	0.94
Higher						
No. of cases/No. of controls	15/18	49/68		110/109		
Adjusted OR (95% CI)[b]	1.00	0.82	(0.33–2.03)	1.22	(0.52–2.86)	0.26

(Continued on next page)

TABLE 3
Odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to green tea consumption by potential effect modifiers *(continued)*

	Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
	P for interaction = 0.28					
Isoflavone intake						
Lower						
No. of cases/No. of controls	46/29	71/88		84/67		
Adjusted OR (95% CI)[b]	1.00	0.60	(0.32–1.15)	1.05	(0.54–2.05)	0.45
Higher						
No. of cases/No. of controls	37/39	65/72		66/74		
Adjusted OR (95% CI)[b]	1.00	0.99	(0.51–1.93)	1.16	(0.58–2.35)	0.61
	P for interaction = 0.71					

COMT = catechol-O-methyltrasferease; CT + TT = ; AC + CC = .

[a] Total green tea consumption was defined as the sum of Sencha/Bancha and Houjicha/Genmaicha consumption (ml per day).[b] Unconditional model adjusting for matching factors (age and area), menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day).

protective role of green tea in the development of breast cancer will require further study aimed at clarifying the association between consumption and hormone receptor-defined subtype.

Given that the putative effect of green tea consumption on the development of breast cancer might be mediated by estrogen exposure, as mentioned in the **Introduction**, the association between consumption and risk may vary according to menopausal status or genetic polymorphisms in *CYP19A1*. A cohort study among Chinese women in Shanghai showed an association between green tea drinking and a decreased risk of breast cancer for premenopausal women but an increased risk for postmenopausal women (9). In the present study, no significant interaction between two strata was found, which is consistent with the results of 2 previous studies in our cohort study among Japanese women (10) and in a case-control study among Chinese women in Shanghai (5). To our knowledge, this is the first study to investigate effect modification of genetic polymorphisms in *CYP19A1* in the association between green tea consumption and breast cancer risk. We found a statistically significant interaction for the rs10046 polymorphisms in *CYP19A1* among premenopausal women. An inverse association between consumption and breast cancer risk was seen among premenopausal women with the CC genotype only. Give that the stratified analysis included only a relatively small number of cases and multiple comparisons were made, these findings might have been merely due to chance. Given that we genotyped only one SNP of *CYP19A1*, a full understanding of this gene–nutrient interaction awaits a more comprehensive evaluation of this gene. Replication of our findings would suggest that green tea might reduce the risk of breast cancer via a mechanism involving *CYP19A1*.

Isoflavones are classified as phytoestrogens, which are plant-derived nonsteroidal compounds with estrogen-like biological properties. Similarly to green tea, isoflavones have also been shown to inhibit aromatase (23). A meta-analysis reported an inverse association between isoflavone intake and breast cancer risk among Asian but not Western populations (24). A case-control study of Asian Americans found an inverse association between green tea consumption and breast cancer risk only among women whose soy intake was low (3), although this effect modification was not replicated by subsequent studies (5,7,10). In the present stratified analysis also, an inverse association between green tea consumption and breast cancer risk tended to be limited to premenopausal women with lower isoflavone intake, albeit it that this effect was not statistically significant and that the overall findings suggested that soy intake was unlikely to be an effect modifier. The different findings between the case-control study in Asian Americans and other previous studies might be explained by differences in the definition of soy intake and its level of consumption among studies; the former evaluated soy intake during both adolescence and adulthood (3), for

TABLE 4
Odds ratio (OR) and 95% confidence interval (CI) for associations between green tea consumption, potential effect modifiers and breast cancer risk by menopausal status

	Premenopausal women						Postmenopausal women					
	Green tea consumption[a]						Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
CYP19A1 gene (rs10046)												
CC												
No. of cases/No. of controls	23/10		26/22		12/12		8/9		20/34		27/30	
Adjusted OR (95% CI)[b]	1.00	0.20	(0.05–0.88)	0.22	(0.05–1.01)	0.054	1.00	4.21	(0.52–33.78)	8.78	(1.01–76.44)	0.04
CT + TT												
No. of cases/No. of controls	33/28		44/38		33/22		19/21		46/66		78/77	
Adjusted OR (95% CI)[b]	1.00	1.08	(0.49–2.37)	2.04	(0.83–5.04)	0.13	1.00	0.71	(0.31–1.67)	1.16	(0.51–2.65)	0.31
	P for interaction = 0.01						P for interaction = 0.70					
COMT gene (rs4680)												
GG												
No. of cases/No. of controls	35/22		30/25		20/21		12/16		30/43		52/46	
Adjusted OR (95% CI)[b]	1.00	0.67	(0.24–1.88)	0.81	(0.28–2.34)	0.68	1.00	0.98	(0.33–2.89)	2.12	(0.70–6.39)	0.06
GA + AA												
No. of cases/No. of controls	21/16		40/35		25/13		15/14		36/57		53/61	
Adjusted OR (95% CI)[b]	1.00	0.49	(0.18–1.31)	0.90	(0.26–3.09)	0.83	1.00	0.49	(0.17–1.43)	0.67	(0.23–1.93)	0.94
	P for interaction = 0.50						P for interaction = 0.24					
MTHFR gene (rs1801133)												
CC												
No. of cases/No. of controls	18/11		23/18		16/7		9/7		24/30		31/37	
Adjusted OR (95% CI)[b]	1.00	0.17	(0.03—0.92)	2.15	(0.40—11.60)	0.47	1.00	0.84	(0.19—3.71)	0.89	(0.21—3.71)	0.96
CT + TT												
No. of cases/No. of controls	38/27		47/42		29/27		18/23		42/70		74/70	
Adjusted OR (95% CI)[b]	1.00	0.81	(0.37—1.78)	0.85	(0.35—2.08)	0.72	1.00	0.80	(0.34—1.89)	1.71	(0.72—4.04)	0.048

			P for interaction = 0.72						P for interaction = 0.15			
MTHFR gene (rs1801131)												
AA												
No. of cases/No. of controls	40/24		47/40		35/26		16/22		37/66		64/66	
Adjusted OR (95% CI)[b]	1.00	0.65	(0.30—1.41)	1.05	(0.45—2.44)	0.92	1.00	0.82	(0.32—2.06)	2.13	(0.85—5.36)	0.02
AC + CC												
No. of cases/No. of controls	16/14		23/20		10/8		11/8		29/34		41/41	
Adjusted OR (95% CI)[b]	1.00	0.71	(0.19—2.61)	0.96	(0.19—4.83)	0.88	1.00	0.61	(0.15—2.46)	0.75	(0.19—2.95)	0.95
			P for interaction = 0.88						P for interaction = 0.11			
Folate intake												
Lower												
No. of cases/No. of controls	46/31		52/42		13/15		22/19		35/50		27/17	
Adjusted OR (95% CI)[b]	1.00	0.76	(0.36—1.62)	0.76	(0.25—2.28)	0.52	1.00	0.74	(0.29—1.85)	1.27	(0.44—3.65)	0.59
Higher												
No. of cases/No. of controls	10/7		18/18		32/19		5/11		31/50		78/90	
Adjusted OR (95% CI)[b]	1.00	0.43	(0.08—2.18)	1.23	(0.29—5.21)	0.37	1.00	1.26	(0.32—4.98)	2.02	(0.53– 7.70)	0.11
			P for interaction = 0.18						P for interaction = 0.43			
Isoflavone intake												
Lower												
No. of cases/No. of controls	30/13		46/31		24/20		16/16		25/57		60/47	
Adjusted OR (95% CI)[b]	1.00	0.53	(0.18–1.53)	0.41	(0.13–1.30)	0.14	1.00	0.43	(0.16– 1.13)	1.60	(0.63–4.06)	0.03
Higher												
No. of cases/No. of controls	26/25		24/29		21/14		11/14		41/43		45/60	
Adjusted OR (95% CI)[b]	1.00	0.47	(0.17–1.27)	1.90	(0.62–5.82)	0.44	1.00	2.18	(0.65– 7.30)	1.59	(0.46–5.46)	0.93
			P for interaction = 0.06						P for interaction = 0.38			

CC = ; GA + AA; GG = ; COMT = catechol-O-methyltrasferease; CT + TT = ; AC + CC = .

Q3 [a]Total green tea consumption was defined as the sum of Sencha/Bancha and Houjicha/Genmaicha consumption (ml per day).

[b]Unconditional model adjusting for matching factors (age and area), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day).

example, whereas the latter assessed intake during adulthood only (5,7,10).

Factors related to the bioavailability of tea catechins may modify the association between green tea and breast cancer risk. One important conjugation reaction of these compounds is *O*-methylation by COMT (25). The AA genotype of rs4680 has been associated with a decrease in *COMT* enzyme activity (26) and may modify the association. Indeed, green tea drinking was associated with a decreased risk of breast cancer among carriers of low-activity *COMT* alleles in the case-control study in Asian Americans but not among those who possessed high-activity *COMT* alleles (16), whereas subsequent studies, including a large case-control (number of case = 1116) and the present study, did not detect such interaction (5). The folate pathway has been suggested as one mechanism through which green tea might protect against breast cancer, on the basis that EGCG inhibits dihydrofolate reductase (27). As mentioned in the Introduction, a nested case-control study in Singapore suggested that folate intake and genetic polymorphism of *MTHFR* and *TYMS* modified the association between green tea intake and breast cancer risk (8). The present and a previous study, however, found no effect modification of folate intake and genetic polymorphisms of *MTHFR* (5,10).

Several limitations of the present study warrant mention. First, green tea consumption was assessed after the diagnosis of breast cancer and is therefore sensitive to recall bias. If patients considered green tea as a healthy drink, even though a preventive effect on breast cancer has not been established, their consumption of green tea might be under- or overestimated. We cannot deny the possibility that such bias might have affected our findings. Second, although the substantially high participation rates among both eligible cases and controls minimized potential biases related to control selection, the use of controls from medical checkup examinees, whose dietary habits may differ from those of the general population due to health consciousness or disease, might have led to selection bias. Third, because the evaluation of interactions was performed in a relatively small number of cases, power to evaluate interactions was limited. This might have also limited the interpretability of the results.

Allowing for these methodological issues, we found that green tea consumption was not associated with a decreased risk of breast cancer. Overall, our stratified analyses suggested that there were no subgroups in which the risk of breast cancer decreased with increasing consumption of green tea. However, further larger studies are required to identify such subgroups.

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ORIGINAL PAPER

Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study

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Abstract
Background Epidemiological evidence for the impact of fruit and vegetable intake on breast cancer risk among the Japanese populations is scarce.
Objective The purpose of this study was to evaluate the association between fruit and vegetable intake and breast cancer risk among 47,289 Japanese women.
Design The study was conducted under a population-based prospective cohort design. Dietary assessment was performed using a validated food frequency questionnaire. A Cox proportional hazards regression model was used to calculate relative risks (RRs) and their corresponding 95 % confidence intervals (CIs).
Results During an average of 10.2 years of follow-up, 452 cases of breast cancer were newly diagnosed. No association with breast cancer risk was seen for intake of total fruits and vegetables, cruciferous vegetables, green-leaf vegetables, yellow vegetables, or tomato products in overall or postmenopausal women. Cruciferous vegetable intake was associated with a statistically significant decrease in risk of premenopausal breast cancer [multivariable-$RR_{Q4\ vs.\ Q1}$ = 0.64 (95 % CI = 0.38–1.10; p_{trend} = .046)] and showed a marginally inverse association with ER+ PR+ tumors [$RR_{per\ 100\ g\ increment}$ = 0.64 (95 % CI = 0.41–1.00)]. In contrast, positive associations were seen between intake of total fruits and citrus fruits and breast cancer risk in overall and premenopausal women. However, these associations for fruit were all attenuated with additional adjustment for vitamin C intake.
Conclusions Our results suggest an overall null association between total fruit and vegetable intake and breast cancer risk. Intake of cruciferous vegetable showed a statistically significant association with a decreased risk of breast cancer among premenopausal women.

Keywords Breast cancer · Fruits · Vegetables · Risk · Receptor

Abbreviations

BMI	Body mass index
CIs	Confidence intervals
ER	Estrogen receptor
EFH	Exogenous female hormones
FFQ	Food frequency questionnaire
The JPHC Study	The Japan Public Health Center-based Prospective Study
OC	Oral contraceptive
PR	Progesterone receptor
RR	Relative risk
SD	Standard deviation
DCN	Death certificate notification
DCO	Death certificate only

Introduction

In Japan, the incidence of breast cancer has continuously and steeply increased over the last three decades, and this

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