Table 1. Baseline characteristics of the study population according to level of coffee consumption

(Mean values and standard deviations or percentages)

	Men (*n* 5897)						Women (*n* 7643)					
	Never or almost never (*n* 931)		Once/month to six times/week (*n* 2402)		Once/d or more (*n* 2564)		Never or almost never (*n* 1398)		Once/month to six times/week (*n* 3312)		Once/d or more (*n* 2933)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	56·7	8·0	53·1	8·7	48·9	8·6	56·4	8·7	52·5	8·9	48·0	8·1
BMI (kg/m^2)*	22·3	2·6	22·7	2·6	22·6	2·7	21·9	2·9	22·3	2·7	22·0	2·7
Smoking status (%)†												
Never	23·4		21·9		11·7		79·8		84·4		76·1	
Current	39·0		44·0		65·5		5·9		5·3		15·5	
Past	34·8		32·7		21·4		2·4		3·1		3·7	
Currently married (%)	95·0		93·9		94·5		81·9		86·8		85·9	
Education 12 years or longer (%)	30·9		44·9		57·3		24·2		37·7		51·1	
Physical activity (metabolic equivalents/h per week)	26·6	39·8	31·1	43·3	28·0	42·1	18·0	26·8	22·6	33·1	22·0	30·4
Postmenopausal (%)							74·3		58·5		38·4	
Current use of hormone replacement therapy (%)							2·2		1·7		1·4	
Daily dietary intake												
Total energy (kJ)	10 820	3438	11 059	3375	11 408	3640	8570	3160	9154	3058	9391	3232
Fat (g)	56·9	28·0	60·2	26·5	63·7	29·2	51·5	25·5	57·5	25·9	60·7	26·6
Carbohydrate (g)	349	105	366	107	388	118	304	108	321	102	327	111
Dietary fibre (g)	16·1	9·0	16·0	7·9	16·4	8·9	16·7	9·5	17·2	8·5	17·1	8·5
Mg (mg)	400	171	401	154	415	166	360	163	374	146	383	152
Caffeine (mg)	42	48	79	57	218	100	60	56	97	66	226	103
Alcohol (g)	50·7	44·1	44·5	40·5	41·0	39·1	6·2	13·9	6·8	14·1	9·5	17·5
Soda (servings)	0·08	0·21	0·15	0·28	0·22	0·39	0·08	0·24	0·10	0·23	0·13	0·28
Coffee, tea and chocolate consumption per d (servings)												
Coffee	0·0	0·0	0·3	0·3	1·8	0·9	0·0	0·0	0·3	0·2	1·6	0·8
Decaffeinated coffee	0·01	0·1	0·02	0·1	0·06	0·3	0·02	0·2	0·02	0·1	0·07	0·4
Green tea	1·2	1·4	1·3	1·4	1·3	1·3	1·7	1·4	1·8	1·4	1·6	1·3
Black tea	0·03	0·2	0·06	0·2	0·06	0·2	0·04	0·2	0·07	0·2	0·08	0·3
Oolong tea	0·2	0·6	0·3	0·6	0·3	0·7	0·3	0·8	0·4	0·8	0·5	0·9
Chocolate snack pieces	0·05	0·2	0·10	0·2	0·12	0·3	0·08	0·2	0·15	0·3	0·19	0·4

* For men, *n* 5677; for women, *n* 7416.

† Values do not add to 100 % because of missing data.

Table 2. Risk of diabetes incidence according to consumption of coffee and tea, and caffeine intake
(Hazard ratios (HR) and 95 % confidence intervals)

	Men						Women					
	Subjects (*n*)	Cases (*n*)	HR (adjusted for age)	95 % CI	HR (multivariate adjustment)*	95 % CI	Subjects (*n*)	Cases (*n*)	HR (adjusted for age)	95 % CI	HR (multivariate adjustment)*	95 % CI
Coffee												
Never or almost never	931	56	1·00	–	1·00	–	1398	39	1·00	–	1·00	–
Once/month to six times/week	2402	107	0·74	0·53, 1·03	0·69	0·50, 0·97	3312	92	1·10	0·75, 1·60	1·08	0·74, 1·60
Once/d or more	2564	115	0·73	0·52, 1·03	0·69	0·49, 0·98	2933	44	0·73	0·46, 1·15	0·70	0·44, 1·12
P value for trend			0·35		0·32				0·04		0·03	
Caffeine intake												
1st tertile	1966	98	1·00	–	1·00	–	2553	58	1·00	–	1·00	–
2nd tertile	1967	81	0·81	0·60, 1·09	0·81	0·60, 1·10	2547	66	1·35	0·94, 1·94	1·26	0·88, 1·82
3rd tertile	1964	99	1·00	0·75, 1·35	0·95	0·69, 1·30	2543	51	1·18	0·79, 1·75	0·95	0·63, 1·43
P value for trend			0·77		0·94				0·55		0·53	
Green tea												
Never or almost never	2131	104	1·00	–	1·00	–	1539	32	1·00	–	1·00	–
Once/month to six times/week	801	48	1·30	0·92, 1·84	1·23	0·87, 1·76	1075	24	0·92	0·54, 1·58	0·90	0·52, 1·54
Once/d	616	28	0·94	0·61, 1·43	0·97	0·63, 1·49	778	14	0·94	0·50, 1·77	1·00	0·53, 1·89
Twice/d or more	2349	98	0·91	0·69, 1·20	0·94	0·71, 1·26	4251	105	1·07	0·72, 1·60	1·03	0·69, 1·55
P value for trend			0·20		0·38				0·51		0·64	
Oolong tea												
Never or almost never	2245	95	1·00	–	1·00	–	2702	52	1·00	–	1·00	–
Once/month to six times/week	2997	142	1·17	0·90, 1·52	1·05	0·80, 1·37	3696	77	1·05	0·74, 1·51	0·89	0·62, 1·28
Once/d or more	655	41	1·39	0·96, 2·02	1·12	0·77, 1·64	1245	46	2·00	1·34, 3·00	1·37	0·90, 2·07
P value for trend			0·12		0·58				0·0001		0·03	
Decaffeinated coffee												
Never or almost never	5394	249	1·00	–	1·00	–	6931		1·00	–	1·00	–
Once/month or more	503	29	1·21	0·82, 1·78	1·09	0·73, 1·61	712	164	0·74	0·40, 1·36	0·66	0·36, 1·23
P value for trend			0·34		0·69			11	0·33		0·19	
Black tea												
Never or almost never	4225	205	1·00		1·00		4586	98	1·00		1·00	
Once/month or more	1672	73	0·91	0·70, 1·19	0·88	0·67, 1·16	3057	77	1·29	0·96, 1·74	1·30	0·95, 1·77
P value for trend			0·48		0·37				0·10		0·11	
Chocolate snack pieces												
Never or almost never	2825	149	1·00	–	1·00	–	2494	74	1·00	–	1·00	–
Once/month to less than once/week	2199	98	0·83	0·64,1·07	0·84	0·65, 1·09	3546	67	0·68	0·49, 0·94	0·70	0·50, 0·98
Once/week or more	873	31	0·68	0·46, 1·00	0·65	0·43, 0·97	1603	34	0·79	0·53, 1·19	0·73	0·48, 1·13
P value for trend			0·06		0·04				0·53		0·32	

*Adjusted for age, smoking status, BMI, physical activity, length of education in years, alcohol consumption, total energy intake, fat intake and women's menopausal status to examine beverage and chocolate snacks, respectively.

association between coffee consumption and risk of diabetes was present even after controlling for caffeine intake in the present study.

Green tea consumption was not associated with the risk of diabetes in the present study. A prospective study in Japan reported a significant inverse association between green tea consumption and diabetes risk, primarily among women[15]. Two other studies in Japan failed to find an association between green tea consumption and risk of diabetes[16,21], although these studies were cross-sectionally conducted. In the present study, a higher consumption of oolong tea raised the risk of diabetes among women. In our data, an especially high incidence of diabetes was observed among women who reported consuming oolong tea twice per d or more. We speculated that participants who were at risk for diabetes may have chosen to drink oolong tea because of its reputed ability to cleanse the body of extra fat, although an additional analysis showed that the association between oolong tea consumption and risk of diabetes among women remained after the exclusion of participants who developed diabetes within the first 2 years during the follow-up. A previously conducted clinical trial reported that oolong tea consumption decreased the plasma glucose level among patients with type 2 diabetes[34]. More observational studies are needed to evaluate the association of consumption of oolong tea with the risk of diabetes.

The consumption of chocolate snacks was inversely associated with a risk of diabetes among men, and the association was also implied among women. Several previous studies included chocolate snacks to estimate total caffeine intake and assessed it with the risk of diabetes[17–19], but to our knowledge, no previous observational study has shown an association between chocolate snacks alone and risk of diabetes. The finding must be, however, interpreted with caution and any benefit derived from a possible reduction in the risk might be outweighed by the increased health risks, such as obesity, caused by the regular consumption of the high-energy snacks. The finding still leaves room for further evaluation of their components such as polyphenols for possible protective effects, although the possible effect of caffeine content cannot be completely eliminated. A clinical trial testing the insulin response to an oral glucose tolerance test indicated that polyphenol-rich dark chocolate improved insulin sensitivity in healthy subjects, which may support our finding[35].

The use of self-reported status of diabetes may be one of the limitations of the present study. A previous study conducted in Japan reported a substantial agreement between diabetes reported in a questionnaire and its diagnosis; 82 % of cases of self-reported diabetes were confirmed by medical records[36]. Even so, we were not able to determine the proportion of the participants who had diabetes and did not report it. Those subjects have been classified as not having diabetes, and this may attenuate the true association, if it exists. There is a possibility that subjects whose socio-economic status was high and who were health conscious were more likely to respond to the follow-up questionnaire, having the fact that the respondents were more likely to have high education levels than non-respondents. Furthermore, other dietary items might have contributed to the caffeine intake. The present study did not discuss caffeine intake from the consumption of sodas, since the FFQ did not allow us to distinguish sodas with caffeine from those without caffeine. The consumption of sodas was relatively low in the current population, and it slightly increased with the level of coffee consumption, and hence it would not have much impact on the results. There still exists a possibility that the study results are influenced by some residual confounders, such as family history of diabetes, on which information is not available, which prevents us from making a definitive conclusion.

The present study has several advantages. First, it was a community-based study, and the participants were men and women from a general Japanese population. The risk of diabetes in relation to the consumption of coffee and tea was prospectively evaluated after controlling for potential confounders in a multivariate model. The values of nutrient intake and physical activity included in the model were measured with a validated questionnaire. We evaluated the association not only with coffee but also with other kinds of tea and foods containing caffeine, including green tea, which is commonly consumed in Japan. Caffeine intake was estimated from coffee, tea and chocolate snacks and was evaluated separately from coffee consumption.

In summary, a modest inverse association between coffee consumption and risk of development of diabetes was observed among men and women in a community-based cohort from the general Japanese population. Green tea consumption and total caffeine intake appeared to have no relationship with the risk of diabetes. It was suggested that the association of coffee consumption with risk of diabetes was separate from the influence of caffeine intake on the risk. Further studies may be needed to investigate which substances in coffee play a role in the beneficial effect on the risk of diabetes, as well as the association of tea and chocolate snack consumption with the risk.

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H. S. and C. N. designed the study and directed the study implementation. C. N., H. S. and N. T. supervised the field activities and collected data. S. O. conducted the statistical analysis and all authors interpreted the analysis results. S. O. and C. N. initially drafted all the sections of the text, and K. N., K. F., T. K., N. T. and H. S. were responsible for critical revision of the manuscript. All authors contributed to and approved the final version of the manuscript.

None of the authors has conflicts of interests.

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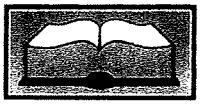

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Diet Based on the Japanese Food Guide Spinning Top and Subsequent Mortality among Men and Women in a General Japanese Population

SHINO OBA, PhD; CHISATO NAGATA, MD; KOZUE NAKAMURA, MD; KAORI FUJII; TOSHIAKI KAWACHI; NAOYOSHI TAKATSUKA, MD; HIROYUKI SHIMIZU, MD

ABSTRACT

Background The Japanese Food Guide Spinning Top was developed by the Japanese Ministry of Health, Labor, and Welfare and the Ministry of Agriculture, Forestry, and Fishery to promote healthful diets.

Objective Adherence to the Japanese Food Guide Spinning Top was evaluated in terms of future mortality in a prospective cohort study.

Design A prospective cohort study among men and women in a general Japanese population.

Subjects/setting The cohort consisted of 13,355 men and 15,724 women residing in Takayama, Japan, in 1992. At baseline, a food frequency questionnaire was administered, and adherence to the food guide was measured based on consuming the recommended number of servings of grains, vegetables, fish and meat, milk, and fruits, as well as total daily energy intake and energy from snacks and alcoholic beverages. Higher scores indicated better adherence to the recommendations on a scale of 0 to 70. Based on data obtained from the Office of the National Vital Statistics, deaths occurring among members of the cohort were prospectively noted from 1992 to 1999.

Statistical analyses performed To assess the magnitude of association of adherence scores with subsequent mortality, a Cox proportional hazard model was applied to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

Results Among women, the adherence score was significantly associated with a lower risk of mortality from all causes (comparing highest and lowest quartiles of the score, HR 0.78, 95% CI 0.65 to 0.94, *P* for trend 0.01) in a multivariate analysis; noncardiovascular, noncancer causes (HR 0.69, 95% CI 0.50 to 0.96, *P* for trend 0.04) and cardiovascular disease (HR 0.76, 95% CI 0.56 to 1.04, *P* for trend 0.05). No statistically significant association was observed between the adherence score and mortality among men.

Conclusions The results suggest that diets based on the food guide have the benefit of reducing future mortality in women.

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Japanese diets have attracted considerable attention in Western countries because of the low rate of coronary heart disease and the long life expectancy in Japan (1-3). The Japanese Food Guide Spinning Top was introduced in 2005 by the Japanese Ministry of Health, Labor, and Welfare and the Ministry of Agriculture, Forestry, and Fishery (see the Figure). This pictorial food guide is based on the *Dietary Guidelines for Japanese*, which was drawn up in 2000 by the former Ministry of Education, the former Ministry of Health and Welfare, and the Ministry of Agriculture, Forestry and Fishery. The aim of the Japanese Food Guide Spinning Top is to provide recommended food choices and quantities for a healthful diet that can be easily adopted by the Japanese public (4,5). The food guide may be developed based on a common Japanese meal consisting of rice (*gohan-mono*),

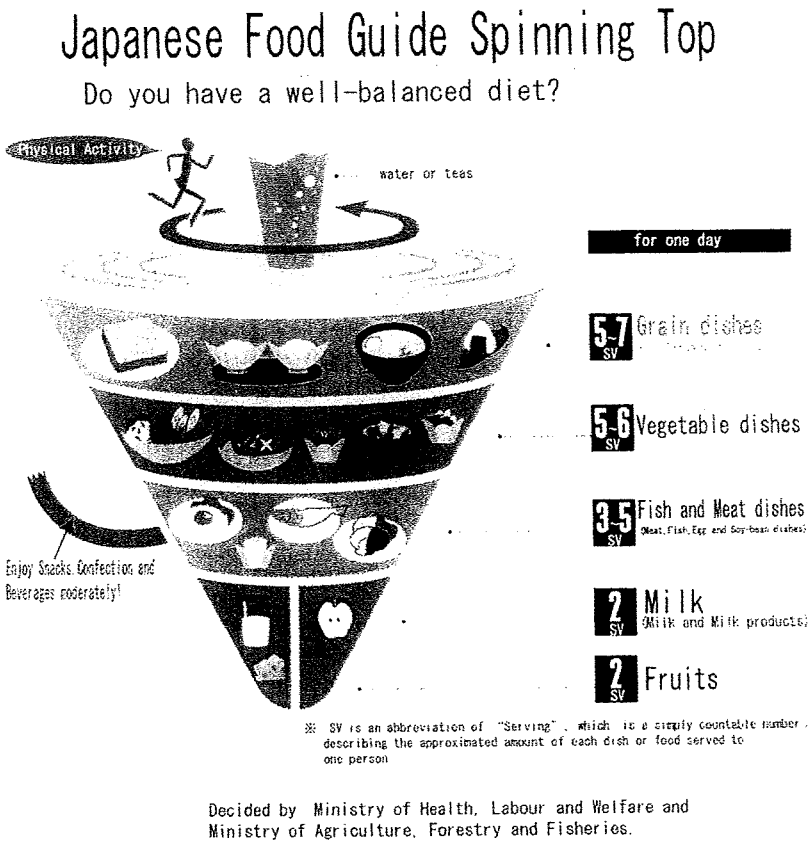

Figure. Graphic representation of the Japanese Food Guide Spinning Top. (Source: Japanese Ministry of Health, Labour and Welfare and Ministry of Agriculture, Forestry and Fisheries [4].) NOTE: This figure is available online at www.adajournal.org as part of a PowerPoint presentation.

soup (such as *miso* or *sumashi*), a main dish (*okazu*), and side dishes (*tsukeawase*). Although the guide was developed to promote healthful diets for Japanese people, the health benefits of following this guide have not been examined. The aim of our study was to evaluate whether diets based on the Japanese Food Guide Spinning Top are associated with reduced total mortality and mortality from cardiovascular disease, cancer, and noncardiovascular, noncancer causes in a prospective cohort study among men and women in a general Japanese population.

METHODS

Study Participants

The data were obtained from the Takayama Study in Japan, the details of which have been described elsewhere (6-8). Briefly, the study population was men and women residing in Takayama city who were aged 35 years or older in 1992. At the baseline, a self-administered questionnaire was distributed to 36,990 residents. Among them, subjects who left four out of nine two-page spreads or more all blank, who answered only 16 items or fewer out of 173 food items, who were regarded to be responded by the other person, who selected the food frequency category of "Never" for all food items, or who selected the food frequency category of "Once a day" or "Two or more times a day" for continuous 40 food items or over were excluded from the study (7). Furthermore, subjects who reported to have staple food (any kind of rice, bread, flour, or noodles) five times or more, meat seven times or more, fish seven times or more, or ethanol 400 mL or more per day were excluded (7). After the exclusion, the fixed cohort consisted of 31,552 subjects, 14,427 men and 17,125 women, yielding a response rate of 85.3%. Physician diagnoses of major diseases were reported in the questionnaire. For this study, those who reported cancer, myocardial infarction, angina, or stroke were excluded from the cohort, and the final cohort for the study consisted of 29,079 subjects, including 13,355 men and 15,724 women.

Definition of Scores and Data Collection

The Japanese Food Guide Spinning Top consists of five basic food group categories: grain dishes (including rice, bread, and noodles), vegetable dishes (including vegetables, mushrooms, potatoes, and seaweed), fish and meat dishes (including meat, fish, eggs, and soybeans), milk (milk and milk products), and fruits (fruits and 100% fruit juice counted as half the weight) (Figure). The amount of a particular type of food that counts as a serving is estimated in the food guide. One serving of grain dish is composed of about 40 g carbohydrates. In one serving of a vegetable dish, the main ingredient

Table 1. The recommended serving number and caloric intake per day for adults in the Japanese Food Guide Spinning Top

Age and Level of Physical Activity		Grain dishes	Vegetable dishes	Fish and meat dishes	Milk	Fruits	Total energy	Snacks and alcoholic beverages
Men	Women	← (serving) →					← (kcal) →	
70 y or older	70 y or older or 18-69 y with low physical activity	4-5	5-6	3-4	2	2	1,800±200	0-200
18-69 y with low physical activity	18-69 y with moderate or higher physical activity	5-7	5-6	3-5	2	2	2,200±200	0-200
18-69 y with moderate or higher physical activity	—	7-8	6-7	4-6	2-3	2-3	2,600±200	0-200

weighs about 70 g. One serving of a fish or meat dish contains about 6 g protein, and one serving of milk contains about 100 mg calcium. In one serving of fruits, the main ingredient weighs about 100 g (9). The recommended number of servings by food group and the recommended total energy intake are specified according to sex, age, and two levels of physical activity (Table 1). For this study, low physical activity was defined as a metabolic equivalents (METs)-hours per week level of less than 1.5 per week. About 25% of participants fell under this category, and all such participants had 0 METs-hours per week. Also in the food guide, the recommended number of kilocalories from snacks and alcoholic beverages together is set at 200 kcal/day for all people.

Based on the above recommended number of servings of the five food groups and two additional groups (energy from total diet and energy from snacks or alcoholic beverages), the scores measuring adherence to this food guide were retrospectively calculated from the information in food frequency questionnaire (FFQ). A person who consumed the recommended number of servings from any of five food groups or the recommended energy from either of the two additional groups received a score of 10 for that group. For a person who exceeded or fell short of the recommended servings or energy, the score was calculated proportionately between 0 and 10. For example, if a person consumed three of the recommended five to six servings of vegetables, the score was calculated as $(10\times3/5=6)$. Likewise, if a person consumed eight servings of fish and meat when the recommendation was three to five servings, the score was $(10-10\times[8-5]/5=4)$. When the calculation produced a negative score because of excess servings or energy, the score was converted to 0.

The FFQ was administered at the baseline of the cohort study in 1992. It was in a semiquantitative format measuring 169 food items, and validated for intake of major foods and nutrients (6). From the FFQ, total daily energy intake and intake of each nutrient and food item were estimated according to the Japanese Standard Tables of Food Composition, 5th edition, published by the Science and Technology Agency of Japan. Detailed information on the FFQ, including its validity and reproducibility, is described elsewhere (6-8). In a previous comparison of the outcomes of this FFQ with those of a 3-day food record, overestimates (meat, eggs, milk, vegetables, soy, as well as alcohol for men and women, and snacks for men), and underestimates (fish for men and snacks for women) of intake were observed. Such overestimations or underestimations were adjusted in the current data. Although the FFQ was administered at the baseline, the estimation of the score was conducted retrospectively because the food guide was issued after the cohort study was planned.

Information on baseline characteristics of the study cohort, such as age, height, weight, cigarette smoking, use of medication, and education level, was reported in the questionnaire at the baseline. For women, information about menopausal status was requested in the questionnaire. The level of regular physical activity was estimated based on the average hours per week spent performing various kinds of activities during the past year as reported in the questionnaire, and the number was translated into the METs-hours per week (10).

Ascertainment of Mortality

Deaths in the cohort were recorded between September 1992 and December 1999. After obtaining permission to review the death data from the Ministry of Internal Affairs and Communication, causes and dates of death were confirmed based on data from the Office of the National Vital Statistics. The Statistics and Information Department of the Japanese Ministry of Health and Welfare obtained all the causes of deaths, which were coded according to the International Classification of Diseases, 10th Revision. Those already coded according to the International Classification of Diseases, 9th Revision (1992-1994) were converted into International Classification of Diseases, 10th Revision. The major endpoint of this study was mortality from all causes, cardiovascular disease (I00 through I99 and Q25 through Q28), cancer (C00 through C97), and mortality from noncardiovascular, noncancer causes. This study was approved by the Ethics Committee at Gifu University Graduate School of Medicine.

Table 2. Baseline characteristics of 13,355 men and 15,724 women by quartile of the score on adherence to the Japanese Food Guide Spinning Top in Takayama Study, Japan

	Quartile of the Score				
	1	2	3	4	*P* value[a]
Men					
Median score	29.5	37.0	42.8	49.8	
	← *mean± standard deviation* →				
Age (y)	53.1±12.2	53.1±11.8	54.1±12.1	55.7±12.2	<0.01
Body mass index	22.7±2.9	22.6±2.7	22.4±2.7	22.3±2.8	<0.01
Physical activity (metabolic equivalents-h/wk)	31.2±46.4	27.2±41.0	25.4±40.1	24.4±37.8	<0.01
	← % →				
Currently married[b]	91.1	90.4	91.3	93.0	<0.01
Education 12 years or longer[b]	39.2	43.0	44.2	45.1	<0.01
Cigarette smoking status[b]					<0.01
Never smoker	12.3	15.0	18.0	22.0	
Current smoker	62.8	59.2	53.2	44.9	
Former smoker	25.0	25.8	28.9	33.2	
Aspirin use within half year	5.0	3.8	3.8	3.7	0.02
Hypertension	20.5	19.4	17.7	18.0	0.01
Diabetes	5.0	5.1	5.9	7.8	<0.01
Women					
Median score	33.0	41.8	47.4	53.6	
	← *mean± standard deviation* →				
Age (y)	54.5±13.0	54.7±13.3	55.2±13.0	56.1±12.7	<0.01
Body mass index	22.1±3.0	21.9±2.9	22.0±2.9	21.8±2.9	<0.01
Physical activity (metabolic equivalents-h/wk)	18.1±30.1	18.0±28.8	19.3±29.3	19.9±30.3	<0.01
	← % →				
Currently married[b]	74.4	75.9	75.4	75.1	0.51
Education 12 years or longer[b]	67.4	66.2	66.0	65.1	0.20
Cigarette smoking status[b]					<0.01
Never smoker	78.6	80.9	84.0	86.6	
Current smoker	17.1	14.3	11.5	9.5	
Former smoker	4.29	4.8	4.4	3.9	
Aspirin use within half year	8.8	6.9	6.4	4.9	<0.01
Hypertension	16.1	17.7	18.0	17.5	0.12
Diabetes	2.0	2.5	2.8	3.5	<0.01
Postmenopausal	55.7	56.5	59.9	63.4	<0.01

[a]One-way analysis of variance for continuous variables and χ^2 test for categorical variables.
[b]Only individuals whose information is available are included. Currently married: n=13,226 for men and n=15,469 for women, education in years: n=13,194 for men and n=15,477 for women, and current cigarette smokers: n=12,969 for men and n=14,090 for women.

Statistical Analysis

The scores on the food guide were analyzed by quartile. The intake of each nutrient was logarithmically transformed to approximately normalize the distribution and was adjusted for total energy intake using the regression analysis proposed by Willett (11) to minimize the effect of an association between total energy intake and mortality. While controlling for age, the partial correlation coefficients between the intake of each nutrient and the adherence score was calculated. The back-transformed (geometric) mean for each nutrient intake was obtained to determine differences in scores among quartiles.

To assess the magnitude of association of adherence scores with subsequent mortality, a Cox proportional hazard model was applied to estimate hazard ratios with 95% confidence intervals. To evaluate the linear trend with mortality, the adherence score was entered in regression models as a continuous variable. Both an age-adjusted model and a multivariate model adjusting for possible confounders: age, body mass index (in kilograms/meters^2, classified into quintile groups or a group of missing value), smoking status (current, past, never smoked, or status missing), physical activity, education (12 years or longer, or not), reported history of hypertension and diabetes, and women's menopausal status was considered. All the statistical analyses were performed with SAS software (version 9.1, 2004, SAS Institute Inc, Cary, NC).

Table 3. Daily nutrients intake by quartile of the score on adherence to the Japanese Food Guide Spinning Top in Takayama Study, Japan

	Men (n=13,355)					Women (n=15,724)				
	Geometric Mean[a]					Geometric Mean[a]				
	Quartile of the Score					Quartile of the Score				
	1	2	3	4	ρ^b	1	2	3	4	ρ^b
Total energy (kcal)[c]	3,182	2,598	2,370	2,294	−0.44	2,782	1,993	1,895	1,829	−0.58
Carbohydrate (g)	331	341	352	364	0.25	297	296	295	295	−0.03
Total fat intake (g)	51.0	52.7	55.3	58.7	0.19	46.8	49.1	50.9	51.9	0.17
Saturated fat (g)	13.5	14.2	15.3	16.8	0.27	12.9	13.4	14.1	14.7	0.17
Monounsaturated fat (g)	17.7	18.2	18.8	19.6	0.14	15.9	16.6	17.0	17.2	0.13
Polyunsaturated fat (g)	14.3	14.5	14.9	15.4	0.10	13.1	13.5	13.8	14.0	0.10
Salt (g)	12.8	12.6	13.0	13.6	0.06	11.6	11.7	12.1	12.6	0.10
Cholesterol (mg)	350	350	359	371	0.05	286	304	317	326	0.14
Protein (g)	84.7	84.7	87.2	90.4	0.12	73.4	74.8	76.8	77.9	0.13
Dietary fiber (g)	13.2	13.6	14.7	16.9	0.26	14.1	14.0	15.1	16.8	0.17
Calcium (mg)	568	595	666	776	0.33	581	601	663	725	0.22
Vitamin A (IU)	828	859	949	1,118	0.24	857	887	977	1,122	0.21
Vitamin C (mg)	110	118	129	151	0.25	118	120	130	147	0.17
Vitamin E (mg)	9.3	9.4	9.9	10.7	0.17	9.2	9.3	9.6	10.1	0.12
Folate (μg)	393	397	420	469	0.19	387	386	414	456	0.16

[a]Values for nutrient intake are energy adjusted.
[b]Correlation with the score on the food guide, partially controlling for age. Each nutrient intake was log transformed and adjusted for total energy intake.
[c]Arithmetic means of raw values.

RESULTS

The mean scores for adherence to the food guide were 39.6 among men and 43.6 among women. Baseline characteristics of the study participants across quartile categories for the adherence score on the food guide are presented in Table 2. Participants with high scores were less likely to smoke, more likely to have 12 or more years of education, and more likely to be diagnosed with diabetes. The adherence score on the food guide was significantly associated with age, and older participants were more likely to obtain a higher score. Daily servings of meat and fish were likely to exceed the recommended number (72% of men and 62% of women with exceeding the recommended number), whereas milk intake was less likely to reach the recommended serving number (79% of men and 64% of women with below the recommended serving number). Individuals with high physical activity levels have high total energy intake, especially among men (correlation coefficients between total energy intake and METs-hours per week were 0.16 among men and 0.08 among women). Table 3 presents the geometric mean of energy-adjusted nutrient intake for each quartile of the adherence score, and the correlation between nutrient intake and adherence score.

The relation of the adherence score to subsequent mortality is presented in Table 4. Among women, the risks of mortality from all causes, and noncardiovascular, noncancer causes were significantly lower for women in the highest quartile compared to those in the lowest quartile of the adherence score, and the analysis of linear trend also showed inverse associations. A significant association between the risk of mortality from cardiovascular diseases and the adherence score was also observed in the trend analysis among women. Such associations observed in the age-adjusted model were even stronger in the multivariate model. Among men, no significant association was observed between the adherence score and later mortality.

DISCUSSION

The results of this prospective study among a general Japanese population imply that diets based on the Japanese Food Guide Spinning Top have a beneficial influence on future mortality among women. With higher adherence scores among women, reductions in mortality from all causes and noncardiovascular, noncancer related causes were observed, and a weak reduction in mortality from cardiovascular disease was also observed. No relation to mortality from cancer was observed among men or women.

The Healthy Eating Index (HEI) is an index of overall diet quality, developed in the United States based on 1990 US Dietary Guidelines and the 1992 US Department of Agriculture Food Guide Pyramid (12). Half components of HEI were calculated based on conformity to the recommended serving of five food groups: grains, vegetables, fruits, milk, and meat. These food groups showed a resemblance to the components of the Japanese Food Guide Spinning Top. Although MyPyramid food guide was released later in United States, its similarity with the Japanese Food Guide Spinning Top was still noted (13). HEI was associated with a small reduction in cardiovascular disease risk among men but was not associated with cancer risk among either men or women (14,15). HEI score was updated later as a nine-component Alternate Healthy Eating Index (AHEI) and better predicted chronic disease risk than the HEI (16). AHEI

Table 4. Hazard ratio (HR) of mortality by quartile of the scores on adherence to the Japanese Food Guide Spinning Top among 13,355 men and 15,724 women in the Takayama Study, Japan

Mortality	Quartile of Score Based on the Food Guide				*P* for trend[a]
	1	2	3	4	
Men					
All causes					
No. of deaths	287	257	274	345	
Age-adjusted HR (95% confidence interval)	1	0.91 (0.77-1.08)	0.88 (0.75-1.04)	1.00 (0.85-1.17)	0.98
Multivariate HR (95% confidence interval)[b]	1	0.90 (0.76-1.06)	0.87 (0.73-1.02)	1.01 (0.86-1.19)	0.91
Cardiovascular disease					
No. of deaths	75	66	72	95	
Age-adjusted HR (95% confidence interval)	1	0.90 (0.64-1.25)	0.89 (0.64-1.22)	1.05 (0.77-1.42)	0.75
Multivariate HR (95% confidence interval)[b]	1	0.90 (0.64-1.25)	0.86 (0.62-1.20)	1.06 (0.78-1.45)	0.70
Cancer					
No. of deaths	95	93	97	115	
Age-adjusted HR (95% confidence interval)	1	0.99 (0.74-1.32)	0.95 (0.72-1.26)	1.02 (0.78-1.34)	0.94
Multivariate HR (95% confidence interval)[b]	1	0.98 (0.73-1.30)	0.95 (0.71-1.26)	1.05 (0.80-1.39)	0.76
Other (noncardiovascular, noncancer)					
No. of deaths	117	98	105	135	
Age-adjusted HR (95% confidence interval)	1	0.85 (0.65-1.11)	0.83 (0.64-1.08)	0.95 (0.74-1.22)	0.71
Multivariate HR (95% confidence interval)[b]	1	0.83 (0.63-1.08)	0.80 (0.61-1.04)	0.94 (0.73-1.21)	0.24
Women					
All causes					
No. of deaths	240	227	221	211	
Age-adjusted HR (95% confidence interval)	1	0.91 (0.76-1.09)	0.86 (0.72-1.03)	0.79 (0.66-0.95)	0.01
Multivariate HR (95% confidence interval)[b]	1	0.87 (0.73-1.05)	0.86 (0.72-1.04)	0.78 (0.65-0.94)	0.01
Cardiovascular disease					
No. of deaths	88	92	73	74	
Age-adjusted HR (95% confidence interval)	1	0.99 (0.74-1.33)	0.77 (0.57-1.06)	0.77 (0.56-1.04)	0.04
Multivariate HR (95% confidence interval)[b]	1	0.95 (0.71-1.28)	0.79 (0.58-1.08)	0.76 (0.56-1.04)	0.05
Cancer					
No. of deaths	69	49	66	70	
Age-adjusted HR (95% confidence interval)	1	0.69 (0.48-0.99)	0.90 (0.64-1.26)	0.92 (0.66-1.28)	0.82
Multivariate HR (95% confidence interval)[b]	1	0.68 (0.47-0.98)	0.89 (0.64-1.26)	0.92 (0.66-1.29)	0.84
Other (noncardiovascular, noncancer)					
No. of deaths	83	86	83	67	
Age-adjusted HR (95% confidence interval)	1	0.99 (0.73-1.34)	0.93 (0.69-1.26)	0.73 (0.53-1.00)	0.06
Multivariate HR (95% confidence interval)[b]	1	0.94 (0.69-1.27)	0.93 (0.68-1.26)	0.69 (0.50-0.96)	0.04

[a]To test for the linear trend with mortality, the median value of the score based on the food guide per quartile was used.

[b]Adjusted for age, body mass index, smoking status (current, past, never smoker, or status missing), physical activity (metabolic equivalents-h/wk), education (12 years or longer or not), history of hypertension and diabetes, and women's menopausal status.

NOTE: Information from this table is available online at www.adajournal.org as part of a PowerPoint presentation.

added several new components. One such component is that if appropriate serving of alcohol consumption was maintained, which was similarly considered in the Japanese Food Guide Spinning Top. In a prospective cohort study among women in the United States (age range 40 to 93 years, 87% white), the association of the risk of mortality with a Recommended Food Score based on dietary guidelines was evaluated, and the Recommended Food Score was inversely associated with all causes of mortality (17). The National Health Interview Surveys in the United States (18) showed that the recommended Foods and Behavior score, which reflects the recommended foods and dietary behaviors, modestly reduced the risk of future mortality among men and women. In the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study in the United States, dietary diversity based on five food groups similar to those in our study was measured, and its inverse association with all-cause mortality (19) and with mortality from cardiovascular disease, cancer (except in women), and noncardiovascular, noncancer causes (20) were reported. Considering the similarity in some of the patterns of recommended food groups, the results of our study were comparable to these studies. The measures used in these studies did not thoroughly consider the overconsumption of each component of a food group. The results of our study suggest that, to reduce the risk of mortality, the appropriate consumption of food in each category is important. One previous study using a healthful diet indicator defined by the World Health Organization dietary guidelines analyzed overconsumption by defining an indicator for a healthful diet as consumption of each nutri-

ent or food group within the recommended range. The results showed that the indicator was inversely associated with mortality (21).

The results of our study indicate that diets based on the food guide are not associated with a risk of mortality from cancer. It was previously reported that diets in accordance with the food guidelines or food patterns based on recommended consumption from food groups were associated with a lowered risk of esophageal cancer (22,23) and estrogen receptor-negative breast cancer (24). Similarly, in terms of cancer risk, the benefit of diets based on the Japanese Food Guide Spinning Top might be limited to cancer at specific sites. Using some of the diet recommendations published by the American Institute for Cancer Research, the authors of one study suggested that adherence to the recommendations reduced the risk of cancer incidence but reduced the risk of cancer mortality to a lesser degree (25). Likewise, the benefit in terms of cancer risk of diets based on the Japanese food guide may be limited to the incidence of cancer. A further assessment of this issue was not conducted due to the unavailability of data on the incidence of cancer in all sites.

No benefit of dietary adherence was observed among men in our study considering that the overall mean adherence score was lower among men than that among women. The scores might not have been high enough to derive benefits from diets based on the food guide among men in our study. Alternatively, men with high levels of physical activity may need a higher allowance of energy intake than that recommended in the food guide. The level of physical activity was higher among men than among women and was positively associated with an increased amount of total energy intake. Such an excess intake of energy lowered the adherence score. Two levels of physical activity (low level and moderate or higher level) were defined in the food guide in association with the levels of energy intake, but additional categories for people with higher levels of physical activity may be needed. Moreover, the score on the food guide was positively correlated with the consumption of saturated fat, and the association was stronger among men than among women. In the Japanese Food Guide Spinning Top, there is no recommendation for restricting dietary fat, whereas the HEI and AHEI based on US guidelines considers fat intake. The intake of saturated fat is a major risk factor for cardiovascular disease (26,27), which could explain the less-pronounced association between the adherence score and mortality in our study. Nevertheless, fat is one of the major sources of energy (11), and the consideration of total energy intake in the Japanese food guide might substitute for the need to consider fat intake to a certain degree. Further reasons for the observed differences between men and women may be biological or sex-based in regard to some uncontrolled confounders.

The adherence scores in this study were positively correlated with the intake of some micronutrients estimated from the FFQ after adjustment for total energy intake. Therefore, diets based on the food guide are likely to meet micronutrients requirements, which could explain the reduced mortality found in our study. As in this study, a study based on the third National Health and Nutrition Examination Survey showed that HEI scores were positively correlated with a wide range of blood nutrients that were biomarkers of fruit and vegetable intake, such as serum folate, vitamins C and E, and carotenoids (28).

Limitations of this study include the fact that the FFQ was not specifically designed to measure adherence to this specific food guide. Although the FFQ was validated for major food and nutrient intakes, it is uncertain whether using the FFQ to measure adherence to the food guide was appropriate. The Japanese Food Guide Spinning Top was originally developed for easy use in the actual diets of the general Japanese public (5), not for academic research. The score on the food guide was retrospectively assigned after the follow-up of the study. However, this may not give the prominent influence to the study result because each component of the score was derived from the information in the FFQ, administered at the baseline of the study with using the provided definitions. In addition, the information in deaths occurred was not updated after 1999, and the data may have limited power to detect the association with the mortality.

CONCLUSIONS

This study examined the quality and quantity of total dietary intake and its relationship to health by measuring adherence to the Japanese Food Guide Spinning Top. The results are suggestive of a reduced risk of mortality from cardiovascular disease, noncardiovascular, noncancer causes, and all causes among women. The associations for men and the effects on the risk of cancer for men or women remain unclear. A further assessment of the benefit of the diets based on the food guide in relation to biomarkers or risk factors in major chronic disease would be interesting.

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Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies

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ABSTRACT

Background: Previous experimental studies have suggested many possible anti-cancer mechanisms for green tea, but epidemiological evidence for the effect of green tea consumption on gastric cancer risk is conflicting.

Objective: To examine the association between green tea consumption and gastric cancer.

Methods: We analysed original data from six cohort studies that measured green tea consumption using validated questionnaires at baseline. Hazard ratios (HRs) in the individual studies were calculated, with adjustment for a common set of variables, and combined using a random-effects model.

Results: During 2 285 968 person-years of follow-up for a total of 219 080 subjects, 3577 cases of gastric cancer were identified. Compared with those drinking <1 cup/day, no significant risk reduction for gastric cancer was observed with increased green tea consumption in men, even in stratified analyses by smoking status and subsite. In women, however, a significantly decreased risk was observed for those with consumption of ≥5 cups/day (multivariate-adjusted pooled HR = 0.79, 95% confidence interval (CI) = 0.65 to 0.96). This decrease was also significant for the distal subsite (HR = 0.70, 95% CI = 0.50 to 0.96). In contrast, a lack of association for proximal gastric cancer was consistently seen in both men and women.

Conclusions: Green tea may decrease the risk of distal gastric cancer in women.

Green tea is one of the most popular beverages in the world and is widely consumed in Japan.[1] Green tea contains polyphenolic antioxidants, such as epigallocatechin gallate, which are thought to contribute to cancer prevention.[2] Early case–control studies found a reduced risk of gastric cancer in association with the consumption of green tea,[3–7] while previous in vitro and in vivo studies suggested many possible anti-cancer mechanisms for green tea. Together, these findings suggest that the consumption of green tea is associated with a decreased risk of gastric cancer.[2]

To date, however, epidemiological evidence for the effect of green tea consumption on cancer risk is conflicting. The recent review of the World Cancer Research Fund in 2007 did not support a possible protective effect of green tea against cancer,[8] and, presently, there is no convincing evidence to support a role for green tea in cancer prevention. In particular, several recent large-scale population-based cohort studies in Japan, established before the mid-1990s and with long-term follow-up, have actively examined the association between green tea consumption and the risk of gastric cancer.[9–14] As to results, however, these studies, which were prospective in design and thus free from recall and selection biases, provide no overall support for the idea that increased consumption of green tea protects against gastric cancer.[15]

Although Japanese tend to consume green tea in a similar manner and the studies estimated consumption dose using similar questions, the studies nevertheless varied in the factors used to adjust for potential confounders and in stratification. One finding was a difference in effect by sex. This may be noteworthy but is yet to be clarified, with some studies showing a decreasing risk tendency in women,[9 12 13] albeit that the strength of the effect appeared to be modest, if it exists at all. The null association in men may, in part, reflect insufficient adjustment for confounding factors such as cigarette smoking. Likewise, differences in the effect of green tea by subsite[12] may point to an inconsistent effect on gastric cancer overall. However, evidence for such specific issues is sparse, probably due to the relatively small number of gastric cancer cases occurring in the upper subsite among cohorts, particularly in women.

To better understand these issues, we conducted a pooled analysis of several large-scale population-based cohort studies in Japan on the association between green tea consumption and gastric cancer risk.

METHODS

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer in Japanese. Topics for the pooled analysis were determined on the basis of discussion among all authors from the viewpoint of both scientific and public health importance. To maintain the quality and comparability of data, we set inclusion criteria for the present purpose a priori, namely population-based cohort studies conducted in Japan; started in the mid-1980s to mid-1990s; included more than 30 000 participants; obtained information on diet, including green tea consumption, using a validated questionnaire at baseline; and collected incidence data for gastric cancer during the follow-up period. Six ongoing studies that met

Table 1 Characteristics of the six cohort studies included in a pooled analysis of green tea consumption and gastric cancer risk, 1988–2004

Study	Population	Age (years) at baseline survey	Year(s) of baseline survey	Population size	Rate of response (%) to baseline questionnaire	Method of follow-up	For the present pooled analysis						
							Age (years)	Last follow-up time	Mean duration of follow-up (years)	Size of cohort		No of gastric cancer cases	
										Men	Women	Men	Women
JPHC-I	Japanese residents of five public health centre areas in Japan	40–59	1990	61595	82	Cancer registry and death certificates	40–59	2001	11.3	15111	16498	379	135
JPHC-II	Japanese residents of 6 public health centre areas in Japan	40–69	1993–1994	78825	80	Cancer registry and death certificates	40–69	2003–2004	10.6	19301	21108	565	206
JACC	Residents from 45 areas throughout Japan	40–79	1988–1990	110792	83	Cancer registry (24 selected areas) and death certificates	40–79	2001	10.2	21113	30017	639	346
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47605	92	Cancer registry and death certificates	40–64	2001	11.0	19007	20596	388	173
3-pref MIYAGI	Residents of three municipalities in Miyagi Prefecture, Japan	40–98	1984	31345	94	Cancer registry and death certificates	40–98	1992	7.6	11902	14409	296	123
3-pref AICHI	Residents of two municipalities in Aichi Prefecture, Japan	40–103	1985	33529	90	Cancer registry and death certificates	40–103	2000	11.5	14045	15973	228	99
Total										100479	118601	2495	1082

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

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these criteria were identified: (1) the Japan Public Health Center-based Prospective Study (JPHC)-I;[16] (2) JPHC-II;[16] (3) the Japan Collaborative Cohort Study (JACC);[17] (4) the Miyagi Cohort Study (MIYAGI);[18] (5) the Three Prefecture Study – Miyagi portion (3-pref MIYAGI);[19] and (6) the Three Prefecture Study – Aichi portion (3-pref AICHI).[19] JPHC was treated as two independent studies (JPHC-I and JPHC-II) because of the different questionnaire used at baseline. One area in JPHC-I and one in JPHC-II, both in Okinawa Prefecture, were excluded from the analysis since tea drinking habits in these areas differed from the rest of Japan and were not comparable with other areas. Further, with regard to JACC, since information on cancer incidence was collected in only 24 of 45 study areas, data from only those 24 areas were used.

We excluded data for subjects with missing information on green tea consumption or a history of cancer at baseline. Selected characteristics of these studies are presented in table 1. Each study was approved by the relevant institutional review board. Results on the association between green tea intake and gastric cancer risk in these cohorts have been reported.[9 10 12 13] For the present analysis, we used updated data sets with an extended follow-up period.

Follow-up

Subjects were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993–1994; JACC, 1988–1990; MIYAGI, 1990; 3-pref MIYAGI, 1984; 3-pref AICHI, 1985) to the last date of follow-up for incidence of gastric cancer in each study (JPHC-I, 2001; JPHC-II, 2003–2004; JACC, 2001; MIYAGI, 2001; 3-pref MIYAGI, 1992; 3-pref AICHI, 2000). Residence status in each study, including survival, was confirmed through the residential registry.

Case ascertainment

In all cohorts included in the present study, cancer diagnoses were identified through population-based cancer registries and active patient notification from major local hospitals. Although the quality and completeness of the case ascertainment varied by cohort, the overall percentage of cases registered from a death certificate only was 8.7% and the estimated ascertainment of cancer diagnoses was nearly 90%. Cases were coded using the International Classification of Disease, Tenth Revision,[20] or the International Classification of Diseases for Oncology, Third Edition.[21] Study outcome was defined as incident gastric cancer (code: C16) diagnosed during the follow-up period of each study. In JPHC-I, JPHC-II, MIYAGI, and 3-pref MIYAGI, in which subsite information was routinely collected, gastric cancers were also classified into proximal (C16.0–C16.1) and distal subsite (C16.2–C16.6). In epidemiological studies using Japanese populations, it is not practical to restrict "cardia (C16.0)" in the analysis because clinical site in gastric cancer diagnosis in Japan is based on the Japanese Classification of Gastric Carcinoma,[22] in which tumour location is usually described anatomically in three parts, namely upper third, middle third, and lower third. In most cases this hampers the clear division of the upper third into "cardia" and "fundus," unless the medical record provided extra information. For this reason, we used the proximal subsite and distal subsite to perform subsite-specific analysis.

Assessment of green tea consumption

In each study except JACC, the frequency and daily amounts of green tea consumption were asked about in the self-administered questionnaire in the same categories of almost none, 1–2 days/week, 3–4 days/week, and almost daily (1–2 cups/day, 3–4 cups/day, and ≥5 cups/day). In JACC, in contrast, daily consumption was asked about in terms of the actual number of cups of green tea consumed each day so these data were re-categorised into the same categories as the other studies. Spearman correlation coefficients for the correlation between green tea consumption (g/day) estimated from the questionnaire and that from the dietary record were JPHC-I, 0.57 in men and 0.63 in women;[23] JPHC-II, 0.39 in men and 0.48 in women;[12] JACC, 0.47;[24] and MIYAGI and 3-pref MIYAGI, 0.71 in men and 0.53 in women.[25] 3-Pref AICHI, for which information on the validation of green tea consumption was not available, utilised the same questionnaire as 3-pref MIYAGI.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of gastric cancer, migration from the study area, death, or the end of follow-up, whichever came first. In each individual study, sex- and area-(JPHC-I, JPHC-II, and JACC) adjusted hazard ratios (HRs) (model 1) and 95% confidence intervals (95% CIs) for gastric cancer were estimated for each green tea intake category using a Cox proportional hazards model. Green tea consumption of <1 cup/day was used as reference category in consideration of the fact that green tea is a common beverage in Japan and very few people are non-consumers. Further multivariate adjustments were made by including covariates in the regression model which were either known or suspected risk factors for cancer or had previously been found to be associated with the risk of gastric cancer.[8 26] The adjustments were made in two ways: first for smoking (for men: never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day; for women: never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (≥once/week): for men: <23 g/day, 23 to <46 g/day, ≥46 g/day; for women: <23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day) in addition to adjustment in model 1 (model 2); second for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to adjustment in model 2 (model 3). In estimation of HR by model 3, each cohort used different food items for pickled vegetables and green–yellow vegetables due to the different food items asked about in each questionnaire. We further conducted stratified analysis by smoking status, namely among never smokers and among current smokers. Also, analyses confining the outcome to the proximal or distal subsite were conducted using JPHC-I, JPHC-II, MIYAGI and 3-pref MIYAGI, for which subsite information was available. An indicator term for missing data was created for each covariate. SAS (version 9.1) or Stata (version 10) statistical software was used for these estimations.

A random-effects model was used to obtain a single pooled estimate of the hazard ratios from the individual studies for each category. The study-specific hazard ratios were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. The trend association was assessed in a similar manner: investigators from each study calculated the regression coefficient and its standard error of linear trend for green tea consumption category treated as an ordinal variable. These values from the

Table 2 Study-specific multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of gastric cancer incidence by green tea consumption

	Green tea consumption			
	<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day
Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men				
JPHC-I				
Model 2	1.00 (Reference)	0.85 (0.62 to 1.16)	0.86 (0.64 to 1.15)	0.95 (0.72 to 1.25)
Model 3	1.00 (Reference)	0.85 (0.62 to 1.17)	0.87 (0.65 to 1.16)	0.97 (0.73 to 1.28)
JPHC-II				
Model 2	1.00 (Reference)	1.11 (0.81 to 1.51)	1.08 (0.80 to 1.45)	1.06 (0.79 to 1.43)
Model 3	1.00 (Reference)	1.11 (0.82 to 1.52)	1.08 (0.80 to 1.45)	1.06 (0.78 to 1.43)
JACC				
Model 2	1.00 (Reference)	0.81 (0.60 to 1.09)	0.76 (0.58 to 1.00)	0.82 (0.64 to 1.05)
Model 3	1.00 (Reference)	0.80 (0.59 to 1.08)	0.75 (0.57 to 1.00)	0.81 (0.63 to 1.05)
MIYAGI				
Model 2	1.00 (Reference)	0.92 (0.69 to 1.22)	0.88 (0.66 to 1.18)	0.89 (0.68 to 1.16)
Model 3	1.00 (Reference)	0.90 (0.67 to 1.20)	0.87 (0.65 to 1.17)	0.88 (0.67 to 1.15)
3-pref MIYAGI				
Model 2	1.00 (Reference)	1.24 (0.82 to 1.88)	1.15 (0.76 to 1.73)	1.50 (1.06 to 2.13)
Model 3	1.00 (Reference)	1.28 (0.84 to 1.94)	1.20 (0.79 to 1.80)	1.55 (1.09 to 2.20)
3-pref AICHI				
Model 2	1.00 (Reference)	1.31 (0.76 to 2.27)	1.28 (0.77 to 2.13)	1.69 (1.03 to 2.77)
Model 3	1.00 (Reference)	1.27 (0.74 to 2.21)	1.22 (0.73 to 2.03)	1.60 (0.97 to 2.63)
Women				
JPHC-I				
Model 2	1.00 (Reference)	0.74 (0.44 to 1.23)	0.90 (0.57 to 1.41)	0.58 (0.36 to 0.95)
Model 3	1.00 (Reference)	0.75 (0.45 to 1.25)	0.90 (0.58 to 1.42)	0.58 (0.36 to 0.95)
JPHC-II				
Model 2	1.00 (Reference)	0.92 (0.55 to 1.54)	1.14 (0.72 to 1.80)	0.72 (0.45 to 1.17)
Model 3	1.00 (Reference)	0.93 (0.56 to 1.56)	1.18 (0.74 to 1.86)	0.74 (0.45 to 1.20)
JACC				
Model 2	1.00 (Reference)	1.04 (0.71 to 1.54)	0.85 (0.60 to 1.20)	0.88 (0.64 to 1.21)
Model 3	1.00 (Reference)	1.04 (0.71 to 1.53)	0.85 (0.60 to 1.19)	0.88 (0.64 to 1.21)
MIYAGI				
Model 2	1.00 (Reference)	0.83 (0.54 to 1.28)	0.95 (0.63 to 1.43)	0.73 (0.49 to 1.10)
Model 3	1.00 (Reference)	0.81 (0.53 to 1.26)	0.89 (0.59 to 1.35)	0.67 (0.44 to 1.02)
3-pref MIYAGI				
Model 2	1.00 (Reference)	0.81 (0.44 to 1.47)	0.72 (0.41 to 1.26)	0.82 (0.51 to 1.32)
Model 3	1.00 (Reference)	0.82 (0.45 to 1.49)	0.72 (0.41 to 1.27)	0.83 (0.51 to 1.35)
3-pref AICHI				
Model 2	1.00 (Reference)	1.19 (0.48 to 2.92)	1.28 (0.59 to 2.78)	1.52 (0.71 to 3.21)
Model 3	1.00 (Reference)	1.20 (0.49 to 2.95)	1.29 (0.59 to 2.80)	1.54 (0.72 to 3.28)

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (<23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.
JACC, The Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; MIYAGI, The Miyagi Cohort Study; 3-pref AICHI, The Three Prefecture Study – Aichi portion; 3-pref MIYAGI, The Three Prefecture Study – Miyagi portion.

individual studies were then combined using a random-effects model. We tested for and quantified the heterogeneity of the HRs for the highest category and the trend association of green tea consumption association among studies using the Q and I^2 statistics. Stata 10 was used for meta-analysis.

RESULTS

The present study included 219 080 subjects (100 479 men and 118 601 women) and 3577 cases of gastric cancer (2495 men and 1082 women) accumulated during 2 285 968 person-years of follow-up (table 1). Among both men and women, 80% of subjects consumed green tea every day, with 35% of men and 33% of women consuming ≥5 cups per day. Distribution of intake frequency was similar between men and women. In most cohorts, men and women with higher intake also tended to consume more rice, green–yellow vegetables, soy bean paste soup or pickled vegetables. The proportion of current smokers was also higher among men with higher green tea intake, but this characteristic was less clear among women.[9 10 12 13] The study-specific HRs and 95% CIs of total gastric cancer incidence by green tea consumption are presented in table 2.

In men (table 3), no notable association was found as a whole. No change in results was seen when subjects were stratified as never smokers and current smokers, and when outcome was confined to proximal or distal subsite. The results

Table 3 Results from a pooled analysis (random-effects model) of gastric cancer incidence by green tea consumption in Japanese men, 1984–2004

		Green tea consumption						
		<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day	p For trend	p For heterogeneity (for the highest category)	p For heterogeneity (for trend)
	Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			
Total								
No of subjects	100479	19877	21355	26369	32878			
Person-years	1035158	205165	219427	271469	339097			
No of cases	2495	420	452	610	1013			
Age-standardised rate (per 100 000)	241.12	236.20	236.06	222.44	257.18			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	0.98 (0.85 to 1.14)	0.95 (0.82 to 1.09)	1.10 (0.90 to 1.34)	*0.394*	0.026	0.110
Multivariate-adjusted (model 2)		1.00 (Reference)	0.97 (0.84 to 1.12)	0.94 (0.81 to 1.08)	1.06 (0.86 to 1.29)	*0.792*	0.024	0.132
Multivariate-adjusted (model 3)		1.00 (Reference)	0.97 (0.83 to 1.12)	0.93 (0.81 to 1.08)	1.06 (0.86 to 1.30)	*0.739*	0.025	0.104
Smoking status								
Never smokers								
No of subjects	19334	4257	4176	5229	5672			
Person-years	204380	45197	44025	54939	60219			
No of cases	312	56	60	73	123			
Age-standardised rate (per 100 000)	157.74	142.01	162.62	135.76	177.75			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	1.12 (0.73 to 1.72)	0.97 (0.67 to 1.41)	1.28 (0.90 to 1.82)	*0.063*	0.518	0.535
Multivariate-adjusted (model 2)		1.00 (Reference)	1.10 (0.74 to 1.64)	0.96 (0.66 to 1.39)	1.27 (0.89 to 1.81)	*0.337*	0.581	0.730
Multivariate-adjusted (model 3)		1.00 (Reference)	1.15 (0.75 to 1.76)	0.99 (0.68 to 1.45)	1.34 (0.93 to 1.92)	*0.221*	0.552	0.671
Current smokers								
No of subjects	53438	10510	11540	13724	17664			
Person-years	555136	109862	119803	142719	182752			
No of cases	1366	227	254	342	543			
Age-standardised rate (per 100 000)	265.29	252.94	272.87	256.63	272.79			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	0.99 (0.83 to 1.19)	1.00 (0.82 to 1.22)	1.05 (0.82 to 1.35)	*0.564*	0.064	0.050
Multivariate-adjusted (model 2)		1.00 (Reference)	0.99 (0.82 to 1.19)	0.99 (0.81 to 1.20)	1.03 (0.81 to 1.31)	*0.817*	0.090	0.107
Multivariate-adjusted (model 3)		1.00 (Reference)	0.98 (0.81 to 1.18)	0.97 (0.80 to 1.19)	1.01 (0.79 to 1.29)	*0.727*	0.086	0.053
Subsite								
Proximal (upper third)								
No of subjects	65321	15019	14943	16517	18842			
Person-years	662495	155665	152476	168202	186152			
No of cases	217	38	41	42	96			
Age-standardised rate (per 100 000)	36.82	30.61	31.60	26.53	49.10			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	1.11 (0.71 to 1.74)	0.76 (0.46 to 1.26)	1.43 (0.97 to 2.12)	*0.069*	0.973	0.847
Multivariate-adjusted (model 2)		1.00 (Reference)	1.09 (0.70 to 1.72)	0.77 (0.46 to 1.29)	1.42 (0.96 to 2.11)	*0.080*	0.994	0.785
Multivariate-adjusted (model 3)		1.00 (Reference)	1.10 (0.70 to 1.73)	0.79 (0.46 to 1.35)	1.43 (0.96 to 2.14)	*0.081*	0.919	0.737

Continued

Table 3 Continued

	Total	Green tea consumption: <1 cup/day HR (95% CI)	1–2 cups/day HR (95% CI)	3–4 cups/day HR (95% CI)	⩾5 cups/day HR (95% CI)	p For trend	p For heterogeneity (for the highest category)	p For heterogeneity (for trend)
Distal (lower two thirds)								
No of subjects	65321	15019	14943	16517	18842			
Person-years	662495	155665	152476	168202	186152			
No of cases	947	185	185	249	328			
Age-standardised rate (per 100 000) (Random effect model)	151.35	136.73	144.95	154.07	160.99			
Age- and area-adjusted (model 1)		1.00 (Reference)	0.92 (0.74 to 1.13)	0.97 (0.80 to 1.18)	1.02 (0.84 to 1.24)	*0.690*	0.370	0.270
Multivariate-adjusted (model 2)		1.00 (Reference)	0.89 (0.72 to 1.11)	0.93 (0.77 to 1.14)	0.95 (0.78 to 1.15)	*0.746*	0.469	0.299
Multivariate-adjusted (model 3)		1.00 (Reference)	0.91 (0.73 to 1.12)	0.95 (0.77 to 1.16)	0.96 (0.79 to 1.17)	*0.856*	0.481	0.316

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ⩾20 cigarettes/day), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (⩾once/week: <23 g/day, 23–<46 g/day, ⩾46 g/day), rice intake (<4 bowls/day, ⩾4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ⩾3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.

between studies for the highest category of green tea consumption for male total gastric cancer risk showed significant heterogeneity (p = 0.025), and the I^2 statistic suggested that 61% of between-study heterogeneity among the highest category was attributable to variability in the true effect of green tea.

In women (table 4), in contrast, subjects who consumed ⩾5 cups of green tea every day had a significantly decreased risk of gastric cancer (HR = 0.79, 95% CI = 0.65 to 0.96). We also observed a significant trend of decreased risk with increasing consumption (p for trend = 0.043). Results did not change for never smokers (HR = 0.79, 95% CI = 0.64 to 0.97 for ⩾5 cups of green tea). When outcome was confined to gastric cancer at a distal site, similar decreased risk was observed (HR = 0.70, 95% CI = 0.50 to 0.96 for ⩾5 cups of green tea; p for trend = 0.042). Results between studies for female never smokers showed significant heterogeneity (p for heterogeneity <0.001), and the I^2 statistic suggested 85% of between-study heterogeneity for trend association was attributable to variability in the true effect of green tea.

DISCUSSION

Although many experimental studies have indicated a role for green tea in cancer prevention,[2] epidemiological evidence for the effect of green tea consumption on cancer risk is conflicting. To address this discrepancy, we carried out a pooled analysis of major population-based cohort studies in Japan. Results showed a significant decrease in risk only among women in the highest category of green tea consumption. This decrease in risk was similarly observed among never smokers and for distal gastric cancer. We observed no association between green tea consumption and gastric cancer in men.

For the heterogeneity of results among the highest category of total men, two studies which were started in the mid 1980s, in other words earlier than other studies, tended to show an increased risk while the other later studies showed a decreased risk tendency. This heterogeneity may have resulted from a slight difference in the birth cohort due to the earlier starting point. In women, in contrast, heterogeneity was observed only for the trend association among never-smokers, in which one of the two studies started in the mid 1980s showed different results from the other studies. Therefore, these heterogeneities observed in men and women may not be solely attributable to such differences in birth cohort.

Our results raise several noteworthy issues on the association between green tea consumption and gastric cancer risk. First, we observed a clear sex difference in the association between green tea consumption and gastric cancer risk. Although most previous cohort studies in Japan have reported a null association, those which conducted separate analyses by sex[9 12 13] in fact observed a decreased risk tendency in women, whereas those which only reported combined results tended to observe an overall null association.[10 11]

Several possibilities may explain the null association for men. The first is that the highest category in women may have included more subjects with a higher consumption of green tea than the highest category in men, hampering the detection of an effect in men, if any. One of the cohorts, JACC, in which information was obtained on the number of cups consumed per day, showed no such trend.[9] Further, the null association in men may have been partly due to residual confounding effects, especially cigarette smoking. In our previous systematic review, we concluded that there is convincing evidence that cigarette smoking moderately increases the risk of gastric cancer among

Table 4 Results from a pooled analysis (random-effects model) of gastric cancer incidence by green tea consumption in Japanese women, 1984–2004

		Green tea consumption					p For heterogeneity (for the highest category)	p For heterogeneity (for trend)
		<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day			
	Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p For trend		
Total								
No of subjects	118601	23316	21460	32459	41366			
Person-years	1250810	244097	226618	342038	438057			
No of cases	1082	215	174	303	390			
Age-standardised rate (per 100 000)	86.50	99.89	87.01	87.88	78.96			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	0.98 (0.84 to 1.15)	0.92 (0.77 to 1.11)	0.81 (0.67 to 0.97)	0.031	0.416	0.415
Multivariate-adjusted (model 2)		1.00 (Reference)	0.90 (0.73 to 1.10)	0.93 (0.77 to 1.11)	0.80 (0.66 to 0.96)	0.063	0.402	0.265
Multivariate-adjusted (model 3)		1.00 (Reference)	0.90 (0.73 to 1.10)	0.92 (0.76 to 1.11)	0.79 (0.65 to 0.96)	0.043	0.351	0.283
Smoking status								
Never smokers								
No of subjects	95558	18422	17360	26897	32879			
Person-years	1023763	196333	185652	287616	354163			
No of cases	871	171	144	246	310			
Age-standardised rate (per 100 000)	86.36	100.79	89.07	85.78	78.61			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	0.90 (0.72 to 1.14)	0.90 (0.73 to 1.11)	0.80 (0.66 to 0.98)	0.692	0.574	<0.001
Multivariate-adjusted (model 2)		1.00 (Reference)	0.91 (0.72 to 1.15)	0.91 (0.74 to 1.12)	0.80 (0.65 to 0.98)	0.770	0.548	<0.001
Multivariate-adjusted (model 3)		1.00 (Reference)	0.91 (0.73 to 1.15)	0.90 (0.73 to 1.11)	0.79 (0.64 to 0.97)	0.780	0.531	<0.001
Current smokers			(≥1 cups/day)					
No of subjects	7694	1636	6058					
Person-years	78141	16561	61580					
No of cases	66	12	54					
Age-standardised rate (per 100 000)	88.54	74.54	89.21					
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	0.94 (0.48 to 1.82)			0.744	0.715	0.882
Multivariate-adjusted (model 2)		1.00 (Reference)	0.86 (0.44 to 1.68)			0.690	0.488	0.459
Multivariate-adjusted (model 3)		1.00 (Reference)	0.90 (0.41 to 1.97)			0.799	0.299	0.383
Subsite			(≥1 cups/day)					
Proximal (upper third)								
No of subjects	72611	16271	56340					
Person-years	758865	173390	585474					
No of cases	53	8	45					
Age-standardised rate (per 100 000)	7.60	7.05	7.80					
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	1.23 (0.56 to 2.71)			0.869	0.993	0.828
Multivariate-adjusted (model 2)		1.00 (Reference)	1.17 (0.53 to 2.59)			0.844	0.974	0.834
Multivariate-adjusted (model 3)		1.00 (Reference)	1.17 (0.52 to 2.60)			0.874	0.979	0.850

Continued

Table 4 Continued

	Total	Green tea consumption <1 cup/day HR (95% CI)	1–2 cups/day HR (95% CI)	3–4 cups/day HR (95% CI)	≥5 cups/day HR (95% CI)	p For trend	p For heterogeneity (for the highest category)	p For heterogeneity (for trend)
Distal (lower two thirds)								
No of subjects	72611	16271	14878	18983	22479			
Person-years	758865	173390	157522	199008	228944			
No of cases	370	83	64	117	106			
Age-standardised rate (per 100 000)	52.10	58.86	45.95	61.30	44.24			
(Random effect model)								
Age- and area-adjusted (model 1)		1.00 (Reference)	0.80 (0.57 to 1.12)	0.97 (0.72 to 1.31)	0.74 (0.53 to 1.03)	0.100	0.221	0.314
Multivariate-adjusted (model 2)		1.00 (Reference)	0.80 (0.57 to 1.12)	0.96 (0.71 to 1.30)	0.70 (0.50 to 0.995)	0.051	0.274	0.889
Multivariate-adjusted (model 3)		1.00 (Reference)	0.80 (0.57 to 1.13)	0.96 (0.71 to 1.30)	0.70 (0.50 to 0.96)	0.042	0.358	0.361

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (<23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.

the Japanese population.[27] In the present study, however, adjustment for smoking status did not change the results. Likewise, in stratified analysis by smoking status, we observed no substantial difference in the effect of green tea consumption between never smokers and current smokers. An anti-*Helicobacter pylori* effect by green tea is another possible explanation. A previous nested case–control study in two of the six cohorts[28] reported that *H pylori* did not distribute differentially in relation to tea polyphenol level in men, while positivity of *H pylori* infection was higher among women with lower tea polyphenol levels. This suggests some possibility in the sex difference in relation to the effect of green tea on *H pylori*, although this does not explain directly why green tea is associated with a decreased risk in women only. Further research on this issue is needed.

A difference in the effect of green tea by sex has also been observed for cardiovascular disease,[14 29] for which an oestrogen-related mechanism has been proposed. In support of this, tea flavonoids such as kaempferol have been shown to exhibit oestrogenic activity in vitro.[30] In addition, tea contains lignan polyphenols, such as secoisolaracinol, which are considered phytoestrogenic.[31] The phytoestrogens in tea might also partly account for the stronger protective effect of green tea against cancer in women than in men,[32 33] although an oestrogen-related protective mechanism against gastric cancer, if any, warrants further investigation. The pro-oxidant properties of tea polyphenols[34 35] or other factors related to men may explain the null findings observed in men.[28]

Second, a decreased risk in women was only seen for the distal subsite, and not for the proximal subsite. Only three studies have investigated the association by anatomical subsite,[6 7 12] of which two showed a decreased risk for the distal but not proximal subsite.[7 12] Consumption of tea at scalding temperatures increases the risk of proximal gastric cancer;[7] if present, this practice may have attenuated the risk reduction by green tea itself, confounding the results for the proximal subsite. Although the association with proximal gastric cancer was not clear in women, the risk appeared to be increased in the highest green tea consumption category in men. This may have been partly due to the effect of scalding hot tea. Due to the small number of proximal cancer cases in women, we bundled several frequent consumption categories together, and this may also partly explain the unclear risk trend for proximal cancer in women. Additional factors may include the proposed difference in aetiology between proximal and distal subsites, as well as the influence of *H pylori*. Specifically, *H pylori* may be associated with an increased risk of distal gastric cancer but not of cardia or oesophageal adenocarcinoma, in which eradication of the bacteria rather increases the risk of gastro-oesophageal reflux.[36] Experimental studies support the notion that green tea catechins have an inhibitory effect on *H pylori* infection and suppress *H pylori*-induced gastritis.[37–39] These findings suggest that the protective effect of green tea on gastric cancer may operate by decreasing the effect of this bacterium.

The present study had several strengths. First, we analysed data from cohort studies that used validated questionnaires to collect data on green tea consumption. In particular, the question used to assess green tea consumption was almost identical across the studies. Second, each study controlled for a common set of variables that are known or suggested to cause or prevent gastric cancer. Third, with a large number of habitual consumers of green tea, we were able to examine the effect of green tea with reasonable statistical power, albeit that power appeared insufficient in the sub-analyses in each cohort.