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A prospective study of stomach cancer death in relation to green tea consumption in Japan

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To evaluate whether green tea consumption provides protection against stomach cancer death, relative risks were calculated using Cox proportional hazards regression analysis in the Japan Collaborative Study for Evaluation of Cancer Risk, sponsored by the Ministry of Health and Welfare (JACC Study). The study was based on 30 370 men and 42 481 women aged 40 – 79. After adjustment for age, smoking status, history of peptic ulcer, family history of stomach cancer along with certain dietary items, the risks associated with drinking one or two, three or four, five to nine, and 10 or more cups of green tea per day, relative to those of drinking less than one cup per day, were 1.6 (95% CI: 0.9 – 2.9), 1.1 (95% CI: 0.6 – 1.9), 1.0 (95% CI: 0.5 – 2.0), and 1.0 (95% CI: 0.5 – 2.0), respectively, in men (*P* for trend=0.669), and 1.1 (95% CI: 0.5 – 2.5), 1.0 (95% CI: 0.5 – 2.5), 0.8 (95% CI: 0.4 – 1.6), and 0.8 (95% CI: 0.3 – 2.1), respectively, in women (*P* for trend=0.488). We found no inverse association between green tea consumption and the risk of stomach cancer death.
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Epidemiology

Stomach cancer is still the leading cause of cancer death among women and the second among men in Japan (Ministry of Health and Welfare Japan, 2000). It has recently been reported (Setiawan *et al*, 2001; Inoue *et al*, 1998) that the consumption of green tea is inversely associated with the risk of stomach cancer, that is a protective effect. Green tea polyphenols have various anticarcinogenic effects, such as strong antioxidant activity, inhibition of nitrosation and cell proliferation.

Although case-control studies (Setiawan *et al*, 2001; Inoue *et al*, 1998; Ji *et al*, 1996; Yu *et al*, 1995; Kono *et al*, 1988) have found a reduced risk of stomach cancer in association with the consumption of green tea, prospective studies (Tsubono *et al*, 2001; Galanis *et al*, 1998) have not. In two Japanese studies, a decreased risk of stomach cancer was associated with the highest level of consumption of green tea (10 or more cups per day in one study (Kono *et al*, 1988) and seven or more cups per day in the other (Inoue *et al*, 1998)) but not with intermediate levels of consumption. The present study aimed to examine prospectively the association between the consumption of green tea and the risk of stomach cancer death, while controlling potential confounders, using data from the Japan Collaborative Cohort (JACC) Study, a Japan-wide population-based prospective study. This is the first study to analyse prospectively the effects of the consumption of 10 or more cups of green tea per day.

MATERIALS AND METHODS

JACC study

The JACC Study, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (sponsored by the Ministry of Education, Science, Sports and Culture of Japan), is a nation-wide multicentre prospective study to evaluate various risks on cancer incidence and mortality. Study methods and ethical issues have been described in detail elsewhere (Ohno *et al*, 2001; Aoki, 1996; Subcommittee of ethical issues, 1996). Briefly, our study was initiated in 1988 and enrollment continued until the end of 1990. Subjects were followed until the end of 1997 unless they had moved or developed one of the prospectively defined endpoints. Forty-five municipalities were involved in this prospective study. They included six cities, 34 towns and five villages, which covered most of Japan. Enrollment was drawn from participants in the general health checkups that are periodically provided by Japanese municipalities. Because we estimated 1 000 000 person-years of follow-up was necessary for the detection of an association between mortality for cancer of several sites common in Japan and various risk factors, we enrolled 127 477 (54 032 men and 73 445 women) apparently healthy inhabitants after completion of a questionnaire. Two strategies were

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applied to obtain informed consent for participation; in the majority of study areas, it was obtained with a signature on the cover page of the questionnaire. In some study areas, it was obtained at group level by explaining the aim of the study and confidentiality of the data to the leader of the community (Yatsuya *et al*, 2002). The questionnaire was filled in by the participants at home and checked by interviewers. Missing and unclear answers were confirmed or corrected by telephone.

The research protocol of the present study was approved by the Ethics Committee of Medical Care and Research, University of Occupational and Environmental Health, Kitakyushu, Japan.

Follow-up and identification of stomach cancer cases

Our primary endpoints were death from any causes on December 31, 1997 (censored). Those who had moved address were also treated as censored. The mean follow-up period was 8.0 years for men and 8.2 years for women.

A follow-up survey was conducted annually to verify the vital status of participants. For deceased subjects, the cause of death was obtained from the death certificate at the regional health center, with the permission of the Ministry of Public Management, Home Affairs, Post and Telecommunications. These data were collected at the central office of the Research Committee. Underlying causes of death were determined by the Ministry of Health, Labour and Welfare and coded according to the International Classification of Disease (9th revision: ICD-9) by the end of 1994 and to ICD-10 from 1995. The stomach cancer codes were 151.0 to 151.9 of ICD-9 or C16.0 to c16.9 of ICD-10.

Subjects

Since questions on the daily consumption of green tea were not included in the questionnaire in seven areas (four rural areas and three urban/rural areas), we excluded those data (15 609 men and 19 894 women). Of the 91 974 remaining, the 6469 who were under 40, and the 3115 who were 80 or over were excluded from the analysis. Of the 82 390 participants who were aged 40 – 79 years (34 173 men and 48 217 women) at the time of enrollment, we excluded those with a history of stomach cancer (n=216) and those who were followed-up for 12 months or less (n=800). Of the remaining 33 612 men and 47 762 women aged 40 to 79, 3242 men (9.6%) and 5281 women (11.1%) had green tea consumption data missing from the questionnaire so these too were excluded. The remaining 30 370 men and 42 481 women were included in the present analysis (see Appendix I).

Questionnaire

The self-administered questionnaire on baseline characteristics covered medical history and included lifestyle-related questions such as diet, physical activity, drinking and smoking, occupation, level of education, reproductive history (women only) and the family history of several medical conditions including cancer. Mean time spent filling out the questionnaire was 26.0 and 27.7 min for men and women, respectively.

Questions on dietary habits included the consumption frequency of food items/groups. Five frequency categories were determined for consumption of most dietary products. In addition, the questionnaire asked for an individual's preference for salty foods, consumption of nonalcoholic beverages, smoking, and alcohol. Information on the intake of energy and other nutrients was not available in this study. The frequency of green tea consumption was initially assessed from five possible answers, i.e., every day (more than one cup per day), three to four cups per week, one to two cups per week, one to two cups per month and seldom, to the question: 'Do you drink Japanese tea (green tea)?' For those who consumed tea every day, the number of cups a day was further identified. We created five categories based on the answers to these questions: less than one cup per day, one or two cups per day, three or four cups per day, five to nine cups per day, and 10 or more cups per day according to a previous prospective study (Tsubono *et al*, 2001) for the purpose of compatibility. In Japan the volume of a typical cup of green tea is 100 – 120 ml.

The validity of this food frequency questionnaire was evaluated by comparing it with four 3-day dietary records (total weight) for eight men and 77 women selected from the study areas. Spearman's correlation coefficients for the frequencies were 0.41 for spinach and other coloured vegetables, 0.45 for tomatoes and white vegetables, 0.35 for fruits, and 0.29 for green tea, while other foods ranged between 0.1 and 0.8 (unpublished data).

Data processing

Cox proportional hazard regression analysis was used. The relative risk (RR) and its 95% confidence interval (CI) were calculated based on the regression coefficient and its standard error (Cox, 1972) for an indicator term corresponding to a level of independent variable. For multivariate analysis, several factors were listed as potential confounders according to epidemiological studies (World Cancer Research Fund, 1997; Yatsuya *et al*, 2002; Hoshiyama and Sasaba, 1992). The model always included age (four categories: 40 – 49, 50 – 59, 60 – 69, 70 – 79). Trends of association were assessed by the regression model assigning scores (0 – 4) to the levels of the independent variable. Statistical significance (two sided) was based on the ratio of the regression coefficient and its standard error. Statistical analysis (PHREG procedure) was performed by the Statistical Analysis System (SAS Institute, 1983).

RESULTS

Table 1 compares the characteristics of subjects according to green tea consumption, which showed a similar pattern in men and women. A history of peptic ulcer differed by green tea consumption in both men and women as examined by the Mantel-Haenszel chi-square test for trends ($P<0.01$), being higher among those who consumed less green tea. The proportions of smokers were higher among those who consumed more green tea for both men ($P<0.01$) and women ($P<0.05$). Men and women with a higher intake of green tea also tended to consume rice, miso soup, green-yellow vegetables, white vegetables and fruit more frequently.

Table 2 shows relative risk (RR) of stomach cancer and its 95% confidence interval (CI) according to green tea consumption, and P-value for trends. The age-adjusted relative risk of male subjects drinking one or two cups per day and 10 or more cups per day showed 2.3 (95% CI: 1.4 – 3.8) and 1.8 (95% CI: 1.0 – 3.0); however, after adjustment for certain dietary elements, history of peptic ulcer and family history of stomach cancer as potential confounders; this association was not statistically significant. No dose-response effect from heavier green tea consumption was observed (P for trend >0.05). Multivariate RRs were closer to age-adjusted and age- and smoking adjusted RRs in women. The exclusion of deaths from stomach cancer identified in the first 35 months of follow-up did not alter the findings (data not shown).

The association in the multivariate models between these potential confounders and stomach cancer was not statistically significant except for a family history of stomach cancer (RRs were 1.5 (95% CI: 1.0 – 2.3) for men and 2.6 (95% CI: 2.6 – 4.3) for women).

DISCUSSION

This study is the largest prospective study to investigate green tea consumption and the risk of stomach cancer death. Among possible limitations of the present study was incomplete data. About

Table 1 Characteristics of the subjects according to green-tea consumption

	Green tea consumption (cups per day)						
	<1	**1 or 2**	**3 or 4**	**5 to 9**	**≥10**	**Total**	***P* for trend***
Men							
Age class							
40–49 *n*=7807	19.6	19.8	25.2	27.0	8.4	100.0	–
50–59 *n*=8923	16.5	14.3	22.9	32.7	13.6	100.0	–
60–69 *n*=9396	14.8	13.0	23.9	34.2	14.2	100.0	–
70–79 *n*=4244	14.9	14.3	25.0	33.4	12.5	100.0	–
History of peptic ulcer (%)	23.9	22.2	22.5	21.2	23.0	22.3	0.004
Family history of stomach cancer (%)#	11.5	10.9	11.6	12.4	13.3	11.9	0.001
Smoking (%)							
Current	50.8	54.8	51.8	53.1	56.3	53.1	0.000
Past	26.0	25.6	27.5	26.7	25.7	26.5	0.617
Daily dietary consumption (%)							
Rice (≥4 bowls/day)	40.5	38.8	40.4	48.0	51.4	43.9	0.000
Miso soup (≥1 cup/day)	71.0	67.5	69.9	74.6	77.5	72.1	0.000
Preference for salty foods (yes)	40.9	41.9	41.8	42.5	44.5	42.2	0.002
Green-yellow vegetables (≥1/day)	30.4	32.2	32.5	35.9	39.7	34.0	0.000
White vegetables (≥1/day)	25.3	27.9	27.6	28.7	31.2	28.0	0.000
Fruits (≥3/week)	23.1	28.3	28.2	29.2	31.7	28.1	0.000
Women							
Age class							
40–49 *n*=10243	22.7	17.2	25.7	27.5	6.9	100.0	–
50–59 *n*=12964	19.5	12.2	25.6	33.6	9.1	100.0	–
60–69 *n*=13466	18.8	11.4	25.6	34.8	9.3	100.0	–
70–79 *n*=5808	16.7	12.0	29.0	33.5	8.8	100.0	–
History of peptic ulcer (%)	13.5	11.7	12.0	10.6	10.2	11.6	0.000
Family history of stomach cancer (%)	12.9	13.1	12.7	13.0	14.4	13.0	0.216
Smoking (%)							
Current	6.2	6.3	4.8	4.8	7.0	5.5	0.023
Past	1.7	1.5	1.5	1.5	1.9	1.6	0.887
Daily dietary consumption (%)							
Rice (≥4 bowls/day)	18.1	16.3	19.1	20.9	20.5	19.2	0.000
Miso soup (≥1 cup/day)	64.5	62.4	63.3	67.9	72.5	65.7	0.000
Preference for salty foods (yes)	25.8	25.5	25.5	26.9	32.4	26.6	0.000
Green-yellow vegetables (≥1/day)	38.9	40.7	41.6	44.4	48.5	42.4	0.000
White vegetables (≥1/day)	38.6	37.0	36.9	38.6	42.1	38.2	0.013
Fruits (≥3/week)	37.9	45.2	43.8	45.6	52.4	44.2	0.000

*Mantel-Haenszel chi-square test; #We defined a positive family history of stomach cancer as when the subject had at least one first-degree relative (parents or siblings) with a history of stomach cancer.

Table 2 Relative risk of stomach cancer death according to green tea consumption

	Green tea consumption (cups per day)					***P* for trend**
	<1	**1 or 2**	**3 or 4**	**5 to 9**	**≥10**	
Men						
Number of deaths from stomach cancer	24	51	51	76	38	
Person-months of follow-up	472478	437045	683263	904435	352384	
Age-adjusted RR	1.0	2.3 (1.4–3.8)	1.3 (0.8–2.1)	1.4 (0.9–2.3)	1.8 (1.0–3.0)	0.417
Age- and smoking status adjusted RR	1.0	2.2 (1.3–3.7)	1.2 (0.7–2.1)	1.4 (0.9–2.3)	1.7 (1.0–3.1)	0.408
Multivariate RR*	1.0	1.6 (0.9–2.9)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	1.0 (0.5–2.0)	0.634
Women						
Number of deaths from stomach cancer	20	18	40	32	9	
Person-months of follow-up	791277	531587	1046736	1307787	347069	
Age-adjusted RR	1.0	1.3 (0.7–2.5)	1.3 (0.7–2.3)	0.8 (0.4–1.5)	0.9 (0.4–1.9)	0.390
Age and smoking status adjusted RR	1.0	1.2 (0.6–2.4)	1.1 (0.6–1.9)	0.7 (0.4–1.4)	0.8 (0.3–1.6)	0.257
Multivariate RR*	1.0	1.1 (0.5–2.5)	1.0 (0.5–2.1)	0.8 (0.4–1.6)	0.7 (0.3–2.0)	0.476

*Adjusted for age (four classes), smoking status (never, past, current), history of peptic ulcer, family history of stomach cacner, consumption of rice, miso soup, green-yellow vegetables, white vegetables, fruits, and preference for salty foods (two categories: see Table 1). Values in parentheses are 95 per cent confidence intervals.

10% of subjects were excluded from analysis because they had not given information concerning their daily consumption of green tea and the effects of such exclusion are unknown. Nevertheless, there was no difference between the percentages of smokers in the excluded data (51.3% in men and 5.6% in women) and those in the included data (53.1% and 5.4% respectively) examined by

Cochran-Mantel-Haenszel chi-square test (P=0.381 and P=0.068 respectively). The missing information seemed to occur randomly.

If drinking green tea, widely consumed in Japan and other Asian countries, protects against stomach cancer, it would be an inexpensive and convenient method of primary prevention. Another prospective study also found no association between green tea and stomach cancer (Tsubono *et al*, 2001). Little other evidence is available from prospective studies (Galanis *et al*, 1998). In the present study, we showed that high consumption of green tea (>=10 cups per day) was not associated with the risk of stomach cancer death based on multivariate analysis. We also showed that those with a higher intake of green tea also tended to consume rice, miso soup, green-yellow vegetables, white vegetables and fruits more frequently, and that a higher proportion of current smokers also consumed green tea more frequently. Another strong potentially limiting factor is the possibility of general over-reporting since subjects consuming 10 or more cups of green tea per day also reported consuming more of every item asked. If it were so, the effects of high consumption of green tea would be masked by misclassification. However, green tea consumption did not show a dose-response relationship and any preventive effects of green tea might not be substantial after adjustments for several potential confounders.

In general, findings from case-control studies often conflict with those from prospective studies (Bushman, 1998; World Cancer Research Fund, 1997; Blot *et al*, 1996). In these retrospective studies, some patients with stomach cancer might have decreased their consumption of green tea before the diagnosis because of their abdominal symptoms. This change in practice might have biased their recall of past intake in such a way that they underestimated their true consumption, resulting in spurious inverse associations (Tsubono *et al*, 2001). We agree that such bias could partly explain the inconsistent results seen between different study designs.

In Japan, tea is usually made in china pots with hot water (about 80°C) and not only are the first extracts consumed, but also the second and/or the third as well. The effective components of green tea such as polyphenols might be insufficient in the second and/or third extracts. If high consumption of green tea (>=10 cups per day) were protective against stomach cancer, the Japanese custom of drinking second/third extracts would be less effective in the prevention of stomach cancer.

Another possible limitation was that we did not obtain information on the presence or absence of a history of infection with *Helicobacter pylori,* a strong risk factor for stomach cancer (Asaka *et al*, 1997). The subjects with chronic gastritis caused by *H. pylori* infection might have limited their consumption of green tea. If so, the prevalence of infection would have been lower in the subjects with higher intakes of green tea. If not, it is unlikely that the prevalence of infection is higher among the subjects with a high consumption of green tea. Thus, we believe that not considering *H. pylori* infection would not have masked an inverse association between the risk of stomach cancer death and the consumption of green tea.

In summary, we found no inverse association between the consumption of green tea and the risk of stomach cancer death in Japan in a prospective cohort study.

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Appendix I Process to identify subjects in the present study

	Men	Women	Total
At enrolment	54 032	73 445	127 477
No questions	15 609	19 894	35 503
Subtotal	38 423	53 551	91 974
Under 39 years of age	2967	3502	6469
80 or over years of age	1283	1832	3115
Subtotal	34 173	48 217	82 390
History of stomach cancer	144	72	216
Subtotal	34 029	48 145	82 174
Follow-up for less than or equal to 12 months	417	383	800
Subtotal	33 612	47 762	81 374
Missing data	3242	5281	8523
Total	30 370	42 481	72 851