

## GREEN TEA AND THE RISK OF GASTRIC CANCER IN JAPAN

YOSHITAKA TSUBONO, M.D., YOSHIKAZU NISHINO, M.D., SHOKO KOMATSU, M.D., CHUNG-CHENG HSIEH, Sc.D., SEIKI KANEMURA, M.D., ICHIRO TSUJI, M.D., HARUO NAKATSUKA, Ph.D., AKIRA FUKAO, M.D., HIROSHI SATOH, M.D., AND SHIGERU HISAMICHI, M.D.

**ABSTRACT**

**Background** Although laboratory experiments and case-control studies have suggested that the consumption of green tea provides protection against gastric cancer, few prospective studies have been performed.

**Methods** In January 1984, a total of 26,311 residents in three municipalities of Miyagi Prefecture, in northern Japan (11,902 men and 14,409 women 40 years of age or older), completed a self-administered questionnaire that included questions about the frequency of consumption of green tea. During 199,748 person-years of follow-up, through December 1992, we identified 419 cases of gastric cancer (in 296 men and 123 women). We used Cox regression to estimate the relative risk of gastric cancer according to the consumption of green tea.

**Results** Green-tea consumption was not associated with the risk of gastric cancer. After adjustment for sex, age, presence or absence of a history of peptic ulcer, smoking status, alcohol consumption, other dietary elements, and type of health insurance, the relative risks associated with drinking one or two, three or four, and five or more cups of green tea per day, as compared with less than one cup per day, were 1.1 (95 percent confidence interval, 0.8 to 1.6), 1.0 (95 percent confidence interval, 0.7 to 1.4), and 1.2 (95 percent confidence interval, 0.9 to 1.6), respectively (P for trend=0.13). The results were similar after the 117 cases of gastric cancer that were diagnosed in the first three years of follow-up had been excluded, with respective relative risks of 1.2 (95 percent confidence interval, 0.8 to 1.8), 1.0 (95 percent confidence interval, 0.7 to 1.5), and 1.4 (95 percent confidence interval, 1.0 to 1.9) (P for trend=0.07).

**Conclusions** In a population-based, prospective cohort study in Japan, we found no association between green-tea consumption and the risk of gastric cancer. (N Engl J Med 2001;344:632-6.)

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**G**REEN tea is widely consumed in Asian countries. It has been hypothesized to have a protective effect against the development of gastric cancer, the second leading cause of death from cancer throughout the world.<sup>1</sup> In a variety of animal models, the administration of green-tea extracts or polyphenols inhibits tumorigenesis in several organs, including the stomach.<sup>2,3</sup> Green-tea polyphenols have various anticarcinogenic effects, such as strong antioxidant activity, inhibition of nitrosation and cell proliferation, and induction of apoptosis among carcinoma cells.<sup>2-4</sup>

Case-control studies have found a reduced risk of

gastric cancer in association with the consumption of green tea. Of seven studies reported to date,<sup>5-11</sup> two studies in China<sup>5,6</sup> and two in Japan<sup>7,8</sup> found a significant inverse association between the consumption of green tea and the risk of gastric cancer, and one study in China<sup>9</sup> and one in Japan<sup>10</sup> found a nonsignificant inverse association. One study in Taiwan<sup>11</sup> reported a nonsignificant increase in the risk of gastric cancer among subjects who drank green tea habitually, as compared with those who did not.

Little evidence is available from prospective studies. In a study of Japanese persons in Hawaii,<sup>12</sup> the consumption of green tea was associated with a nonsignificant increase in the risk of gastric cancer — a result that is inconsistent with the findings of most case-control studies. To examine further the association between green tea and the risk of gastric cancer, we conducted a population-based, prospective cohort study in Miyagi Prefecture, a region in northern Japan with a high incidence of gastric cancer (age-adjusted rate per 100,000 world population, 82.7 for men and 32.8 for women<sup>13</sup>) and substantial variation in the consumption of green tea.

**METHODS****Study Cohort**

This prospective cohort study started in January 1984, when we delivered a self-administered questionnaire on various health habits to 33,453 residents, 40 years of age or older, in three municipalities of Miyagi Prefecture. The questionnaires were delivered to and collected at the subjects' residences by members of health-promotion committees appointed by the municipal governments. This procedure yielded a high response rate (94 percent). Usable questionnaires were returned from 31,345 subjects (13,992 men and 17,353 women). The study protocol was approved by the institutional review board of the Tohoku University Graduate School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

**Exposure Data**

The questionnaire included items about the frequency of recent consumption of three beverages (green tea, black tea, and coffee) and 11 items about food, as well as items on the consump-

From the Divisions of Epidemiology (Y.T., Y.N., S. Kanemura, I.T., S.H.) and Environmental Health Sciences (H.S.), Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; the Department of Nutrition, Harvard School of Public Health, Boston (Y.T.); the Faculty of Physical Education, Sendai College, Miyagi, Japan (S. Komatsu); the Division of Biostatistics and Epidemiology, Cancer Center, University of Massachusetts Medical Center, Worcester (C.-C.H.); Miyagi University School of Nursing, Sendai, Japan (H.N.); and the Department of Public Health, Yamagata University School of Medicine, Yamagata, Japan (A.F.). Address reprint requests to Dr. Tsubono at the Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan, or at ytsubono@metamedica.com.

tion of alcohol, smoking, personal and family history of disease, and type of health insurance. The frequency of consumption of green tea was divided into five categories: never, occasionally, one or two cups per day, three or four cups per day, and five or more cups per day. The volume of a typical cup of green tea is 100 ml in the study region. We conducted a validation study of the food-frequency questionnaire in which 119 subjects provided four three-day food records in one year and then responded to the questionnaire. Preliminary results showed that Spearman's coefficient for the correlation between the amounts of green tea consumed according to the questionnaire and the amounts consumed according to the food records was 0.66, and the correlation between consumption measured by the two questionnaires administered six months apart was also 0.66. Because only 5 percent of the subjects said they never drank green tea and only 14 percent said they drank it only occasionally, data from these respondents were collapsed into the single category "less than one cup per day" for the purpose of this analysis.

#### Follow-up

We used population registries in the three municipalities to obtain data on the vital and residential status of the subjects from January 1, 1984, through December 31, 1992. We ascertained the incidence of cancer by means of computerized linkage with the records of the Miyagi Prefectural Cancer Registry, one of the earliest and most accurate population-based cancer registries in Japan.<sup>13</sup> We documented a total of 2646 cases of cancer among the subjects (1490 in men and 1156 in women), of which 663 were cases of gastric cancer (461 in men and 202 in women).

Of the 2646 cases of cancer, we excluded the 541 cases (in 258 men and 283 women) that were diagnosed before the base-line survey. We did not inquire about a history of cancer in the questionnaire, because in Japan at the time of the survey, the majority of patients with cancer were not told the true diagnosis, and hence the accuracy of self-reports was thought to be low. We then excluded 4493 subjects (1832 men and 2661 women) who did not answer the question about consumption of green tea. Consequently, our analysis included 26,311 subjects (11,902 men and 14,409 women), 419 of whom had gastric cancer (296 men and 123 women). The diagnosis of adenocarcinoma had been histologically confirmed in 80 percent of the cases. Among the 287 patients for whom the location of the tumor was known, 40 percent had a tumor in the body of the stomach, 33 percent in the antrum or pylorus, 21 percent in the cardia, and 5 percent in overlapping regions.

#### Statistical Analysis

We counted person-years of follow-up for each subject from January 1, 1984, until the date of diagnosis of gastric cancer, the date of emigration outside the study districts, the date of death, or the end of the study period (December 31, 1992), whichever occurred first. A total of 199,748 person-years accrued. We computed the incidence rates for each category of green-tea consumption by dividing the number of cases of gastric cancer by the number of person-years in that category. Relative risk was computed as the incidence rate among subjects in each category of green-tea consumption divided by the rate among subjects who consumed less than one cup per day. We used Cox proportional-hazards regression to adjust for sex, age, and other potentially confounding variables<sup>14</sup> according to the SAS PHREG procedure.<sup>15</sup>

Apart from sex and age, we considered the following variables as potential confounders a priori: history of peptic ulcer; cigarette-smoking status (never smoked, smoked in the past, currently smoking 1 to 19 cigarettes per day, or currently smoking at least 20 cigarettes per day); alcohol consumption (never drank alcohol, drank in the past, currently drinking less often than daily, or currently drinking daily); daily consumption of rice (two or fewer, three, four, or five or more bowls); consumption of black tea and consumption of coffee (for each beverage: never, occasionally, one or two cups per day, or three or more cups per day); consumption of meat, green or yellow vegetables, pickled vegetables, other veg-

etables, fruits, and bean-paste soup (less than one day per week, one or two days per week, three or four days per week, or daily); and type of health insurance (four main types, covering government employees, employees of medium-sized and large companies, employees of small companies, and persons who were self-employed or retired; and other, minor plans). The type of health insurance was used as a measure of socioeconomic status (occupation), since all people in Japan are covered by public health insurance plans according to their occupation or that of the head of the household, and most people (98 percent of the study subjects) are enrolled in one of the four major insurance plans.

We repeated all analyses after excluding the 117 patients with gastric cancer diagnosed in the first three years of follow-up (88 men and 29 women). The P values for the test of linear trend were calculated by treating the green-tea consumption category as an ordinal variable. All reported P values are two-tailed.

#### RESULTS

The consumption of green tea varied substantially among the study subjects; the proportions of subjects drinking less than one, one or two, three or four, and five or more cups per day were 19 percent, 17 percent, 22 percent, and 42 percent, respectively. Table 1 compares the characteristics of subjects according to green-tea consumption. Men and women with higher intake tended to be slightly older and to consume rice, green or yellow vegetables, pickled vegetables, other vegetables, fruits, and bean-paste soup more frequently. By contrast, the prevalence of a history of peptic ulcer and consumption of alcohol, meat, and coffee did not vary according to the consumption of green tea. Heavy smoking (20 or more cigarettes per day) was associated with a high intake of green tea among men but not among women.

Because of logistical limitations, we discontinued the follow-up of subjects who moved out of the study districts. Consequently, 16 percent of the participants (4289 subjects) were lost to follow-up. However, the proportions of subjects who moved did not differ according to the category of green-tea intake (16 percent, 17 percent, 17 percent, and 16 percent for subjects consuming less than one, one or two, three or four, and five or more cups per day, respectively).

We found no inverse association between green-tea intake and the risk of gastric cancer, regardless of whether the data for men and women were combined or separated (Table 2). Exclusion of the cases of gastric cancer diagnosed in the first three years of follow-up did not substantially change the results. When we performed a stratified analysis according to three-year follow-up periods, the relative risk for consumption of five or more cups of green tea per day was 1.0 (95 percent confidence interval, 0.6 to 1.6) in the first three years (117 cases of gastric cancer), 1.2 (95 percent confidence interval, 0.8 to 2.0) in the second three years (144 cases), and 1.5 (95 percent confidence interval, 0.9 to 2.5) in the last three years (158 cases). The results were similar when we replaced the categorical variable for smoking with the number of pack-years of smoking or the number of cigarettes currently smoked per day (data not shown).

**TABLE 1.** CHARACTERISTICS OF THE SUBJECTS ACCORDING TO GREEN-TEA CONSUMPTION.\*

CHARACTERISTIC	GREEN-TEA CONSUMPTION (CUPS/DAY)			
	<1	1 OR 2	3 OR 4	≥5
<b>Men</b>				
No.	2253	2194	2585	4870
Age (yr)	56.3±11.3	55.6±11.4	56.4±11.4	57.6±10.8
History of peptic ulcer (%)	14.2	13.8	12.7	13.7
Smoking (%)†				
Never	27.9	23.8	24.8	18.8
Past	23.8	24.0	24.7	23.2
Current (1–19 cigarettes/day)	18.9	16.3	17.5	17.2
Current (≥20 cigarettes/day)	29.4	35.9	33.1	40.9
Current use of alcohol (%)	73.1	79.0	79.1	76.4
Daily dietary consumption (%)				
Rice (≥4 bowls)	46.7	42.1	45.0	50.1
Meat	18.5	19.8	19.1	20.3
Green or yellow vegetables	47.3	49.6	48.0	54.1
Pickled vegetables	60.1	62.1	68.2	73.2
Other vegetables	59.8	61.1	64.9	69.8
Fruits	47.1	48.8	52.7	58.1
Bean-paste soup	83.0	84.5	87.2	89.9
Black tea (≥3 cups)	0.8	0.4	1.9	1.9
Coffee (≥3 cups)	10.6	12.7	10.4	10.4
<b>Women</b>				
No.	2614	2375	3235	6185
Age (yr)	57.4±12.1	56.9±12.0	57.5±11.6	58.2±10.7
History of peptic ulcer (%)	7.7	6.8	5.8	5.7
Smoking (%)				
Never	88.5	90.7	91.2	85.2
Past	3.5	3.3	2.7	3.3
Current (1–19 cigarettes/day)	5.5	4.1	4.8	7.6
Current (≥20 cigarettes/day)	2.4	1.9	1.3	4.0
Current use of alcohol (%)	27.7	32.1	31.0	34.3
Daily dietary consumption (%)				
Rice (≥4 bowls)	19.9	20.1	20.3	23.7
Meat	18.9	20.5	19.7	20.4
Green or yellow vegetables	54.1	56.8	58.0	61.9
Pickled vegetables	62.9	66.8	72.6	80.0
Other vegetables	68.6	71.3	73.4	76.7
Fruits	68.8	71.0	74.5	76.8
Bean-paste soup	81.5	84.5	86.8	87.8
Black tea (≥3 cups)	1.2	0.9	1.2	2.1
Coffee (≥3 cups)	6.9	6.5	5.2	6.5

\*Plus-minus values are means ±SD.

†Because of rounding, not all percentages add to 100.

When the data were stratified according to smoking status, there was a trend toward a positive association between green-tea consumption and the risk of gastric cancer in subjects currently smoking 20 or more cigarettes per day ( $P$  for trend = 0.06), but not in those currently smoking 1 to 19 cigarettes per day, former smokers, or those who had never smoked. However, in a multivariate model that included green-tea intake (number of cups consumed per day), current smoking (number of cigarettes smoked per day), and the product of these two variables, the interaction between them was not significant ( $P$  for the product term = 0.17). The association between the consumption of green tea and the risk of gastric cancer was not substantially modified by the other variables

we examined, including type of health insurance (data not shown).

We examined the relation between the risk of gastric cancer and the consumption of black tea and coffee but found no associations. After adjustment for sex, age, green-tea consumption, and the same covariates as those used for analysis of green-tea consumption, the relative risk of gastric cancer for men and women who drank black tea, in comparison with those who never drank black tea, was 1.1 (95 percent confidence interval, 0.8 to 1.5) for those drinking black tea occasionally, 1.0 (95 percent confidence interval, 0.6 to 1.8) for those drinking one or two cups per day, and 1.1 (95 percent confidence interval, 0.4 to 2.8) for those drinking three or more cups per day

TABLE 2. RELATIVE RISK OF GASTRIC CANCER ACCORDING TO GREEN-TEA CONSUMPTION.\*

VARIABLE	GREEN-TEA CONSUMPTION (CUPS/DAY)				P FOR TREND
	<1	1 OR 2	3 OR 4	≥5	
<b>Men and women</b>					
No. of cases of gastric cancer	66	68	79	206	
Person-years of follow-up	36,572	34,129	43,748	85,299	
Sex- and age-adjusted RR	1.0	1.1 (0.8–1.6)	1.0 (0.7–1.4)	1.3 (1.0–1.7)	0.05
Multivariate RR1	1.0	1.1 (0.8–1.6)	1.0 (0.7–1.4)	1.2 (0.9–1.6)	0.13
Multivariate RR2	1.0	1.2 (0.8–1.8)	1.0 (0.7–1.5)	1.4 (1.0–1.9)	0.07
<b>Men</b>					
No. of cases of gastric cancer	41	49	55	151	
Person-years of follow-up	16,979	15,927	18,915	36,541	
Age-adjusted RR	1.0	1.3 (0.8–1.9)	1.2 (0.8–1.7)	1.6 (1.1–2.2)	0.007
Multivariate RR1	1.0	1.3 (0.8–1.9)	1.2 (0.8–1.8)	1.5 (1.0–2.1)	0.03
Multivariate RR2	1.0	1.2 (0.7–1.9)	1.2 (0.7–1.9)	1.5 (1.0–2.3)	0.05
<b>Women</b>					
No. of cases of gastric cancer	25	19	24	55	
Person-years of follow-up	19,593	18,202	24,833	48,758	
Age-adjusted RR	1.0	0.8 (0.5–1.5)	0.7 (0.4–1.3)	0.8 (0.5–1.3)	0.53
Multivariate RR1	1.0	0.8 (0.5–1.5)	0.7 (0.4–1.3)	0.8 (0.5–1.3)	0.46
Multivariate RR2	1.0	1.2 (0.6–2.3)	0.7 (0.4–1.5)	1.1 (0.6–2.0)	0.86

\*The multivariate relative risk (RR) has been adjusted for sex; age (in years); type of health insurance (five categories); history of peptic ulcer; cigarette smoking (never smoked, smoked in the past, currently smoking 1 to 19 cigarettes per day, or currently smoking 20 or more cigarettes per day); alcohol consumption (never drank alcohol, drank in the past, currently drinking less often than daily, or currently drinking daily); daily consumption of rice (two or fewer, three, four, or five or more bowls); consumption of black tea and consumption of coffee (never, occasionally, one or two cups per day, or three or more cups per day); and consumption of meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits, and bean-paste soup (less than one day per week, one or two days per week, three or four days per week, or daily). RR1 denotes the relative risk with all cases of gastric cancer included in the multivariate analysis, and RR2 the relative risk with cases diagnosed in the first three years of follow-up excluded from the analysis. Values in parentheses are 95 percent confidence intervals.

(P for trend=0.53). The corresponding relative risks for coffee were 0.9 (95 percent confidence interval, 0.6 to 1.2), 0.8 (95 percent confidence interval, 0.5 to 1.1), and 1.0 (95 percent confidence interval, 0.6 to 1.6) (P for trend=0.98). The results were similar when we replaced the categorical variable for smoking with the number of pack-years of smoking or the number of cigarettes currently smoked per day. The exclusion of cases of gastric cancer diagnosed in the first three years of follow-up did not change the findings (data not shown).

## DISCUSSION

Our study had several methodologic advantages over prior studies of green tea and the risk of gastric cancer. We recruited subjects from the general population, and there was a large variation in green-tea consumption among our subjects. In addition, we assessed the consumption of green tea and other variables before cases of gastric cancer and other diseases were diagnosed, thus avoiding recall bias. The questionnaire used to measure green-tea consumption had

a reasonably high level of validity and reproducibility. A large number of cases of gastric cancer were identified, because the incidence rate in the study region was high and the period of follow-up was reasonably long.

Our study had some limitations. Our food-frequency questionnaire included only a limited number of items and could not be used to calculate the consumption of total energy and other nutrients. Although we adjusted for the consumption of dietary items other than green tea as much as possible, we could not exclude the possibility of residual confounding by other dietary characteristics.

We did not obtain information on the presence or absence of a history of infection with *Helicobacter pylori*, a strong risk factor for gastric cancer.<sup>16</sup> The prevalence of *H. pylori* seropositivity (determined by the presence of IgG antibodies) among subjects 55 to 64 years of age in the study area was 88 percent in men and 87 percent in women.<sup>17</sup> The subjects with chronic gastritis caused by *H. pylori* infection might have limited their consumption of foods and beverages.

ages, including green tea. Some studies have suggested an antibacterial effect of green tea,<sup>18,19</sup> which may apply to *H. pylori*. In either case, the prevalence of infection would have been lower in the subjects with higher intakes of green tea. Thus, we believe it is unlikely that the failure to account for *H. pylori* infection masked an inverse association between the risk of gastric cancer and the consumption of green tea.

Another concern is that 16 percent of the participants were lost to follow-up. Nevertheless, the proportion did not differ according to the category of green-tea consumption. Therefore, we believe that loss to follow-up did not have a substantial effect on the observed associations between the consumption of green tea and the risk of gastric cancer.

Our findings are in general agreement with those of a prospective study of Japanese persons in Hawaii, which found no inverse association between green-tea consumption and gastric cancer.<sup>12</sup> Although in that study there was a nonsignificant increase in the risk of gastric cancer among subjects with higher levels of green-tea consumption, the number of cases of gastric cancer was relatively small (108).

Our results contradict those of most case-control studies, which show an inverse association between the risk of gastric cancer and the consumption of green tea.<sup>5-10</sup> In these retrospective investigations, some patients with gastric 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. Epidemiologic studies have found that patients with gastric cancer decrease their consumption of tea two years before the diagnosis<sup>20</sup> and that the accuracy of the recall of an earlier diet is strongly influenced by the recent diet.<sup>21</sup> This bias would partly explain the difference in the findings between prospective and case-control studies.

We also found that there was no association between the risk of gastric cancer and the consumption of black tea or coffee. These results are consistent with the findings of a review conducted by the World Cancer Research Fund, which concluded that probably neither beverage is associated with a decreased or increased risk of gastric cancer.<sup>22</sup>

In conclusion, in a prospective cohort study, we found no association — inverse or otherwise — between the consumption of green tea and the risk of gastric cancer in Japan.

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