A nested case–control study of stomach cancer in relation to green tea consumption in Japan

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To evaluate whether green tea consumption provides protection against stomach cancer, the relative risks (RRs) were calculated 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 157 incident cases and 285 controls aged 40–79 years. Cox proportional hazards regression analysis was used to estimate the RRs for stomach cancer. It was found that green tea consumption had no protective effect against stomach cancer. After adjustment for age, smoking status, H. pylori infection, history of peptic ulcer, and family history of stomach cancer along with certain dietary elements, 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 1.3 (95% confidence interval (CI): 0.6–2.8), 1.0 (95% CI: 0.5–1.9), 0.8 (95% CI: 0.4–1.6), and 1.2 (95% CI: 0.6–2.5), respectively (P for trend = 0.899). We found no inverse association between green tea consumption and the risk of stomach cancer.

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Stomach cancer is the second most common cancer worldwide (Parkin et al, 1999). In Japan, this cancer is the leading cause of cancer death among women and the second among men (Statistics and Information Department, Minister’s secretariat, Ministry of Health and Welfare Japan, 2000). It has recently been reported that green tea consumption is inversely associated with the risk of stomach cancer; in other words, it has a protective effect. Green tea polyphenols have various anticarcinogenic effects, such as strong antioxidant activity, and inhibition of nitrosation and cell proliferation.

Although case–control studies (Kono et al, 1988; Yu and Hsieh, 1991; Yu et al, 1995; Ji et al, 1996; Inoue et al, 1998; Setiawan et al, 2001) have found a reduced risk of stomach cancer in association with green tea consumption, prospective studies (Galanis et al, 1998; Nakachi et al, 2000; Nagao et al, 2001; Tsubono et al, 2001) have not. A recent prospective study found that green tea had a protective effect against stomach cancer. Urinary tea polyphenols have been associated with protection from the risk of stomach cancer, while controlling Helicobacter pylori infection. Past studies did not consider the presence or absence of a history of infection with H. pylori, a strong risk factor for stomach cancer (Asaka et al, 1997). Assuming that green tea consumption is related to H. pylori infection, when a subject has a history of infection with H. pylori and consumes a large quantity of green tea, the protective effect, if any, would be masked. The present nested case–control study aimed to examine the association between green tea consumption and the risk of stomach cancer, while controlling H. pylori infection and other 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 the effects of green tea consumption while controlling H. pylori infection.

MATERIAL AND METHODS

JACC Study

This study was part of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (the JACC Study), a nation-wide multicentre collaborative study to prospectively evaluate various risk or protective factors for cancer mortality and
incidence. Details of the study design were reported previously. Briefly, the cohort included 110792 men and women (46465 and 64327, respectively), aged 40–79 years at recruitment, who were enrolled from 1988 to 1990. Enrollment was based on the participants of a general health checkup periodically provided by the 45 municipalities involved. The informed consent procedures were approved by the Ethics Committee of Medical Care and Research, University of Occupational and Environmental Health, Kitakyushu, and the Ethical Board of the Nagoya University School of Medicine, Japan.

At the time of recruitment, baseline characteristics were gathered by a self-administered questionnaire, which covered the medical history and included items such as drinking and smoking, level of education, and family history of several medical conditions including cancer. About one-third of the cohort members (n = 39293) also donated a residual serum sample (about 2 ml) to be used for the general health checkup. This sample was partitioned into 0.3 – 0.5 ml aliquots and stored at –80°C until laboratory analyses were performed. The H. pylori antibody level was measured in the serum using HM-CAPTM (Enteric Products, Westbury, NY, USA) with an antigen from Japanese (J-HM-CAP). The cutoff value was determined at 2.3, which was recommended in the manufacturer’s instructions.

Follow-up and identification of stomach cancer cases, and selection of control subjects

The vital status of each participant was checked annually by each regional research centre, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications to review their population register sheets. The incidence of Public Management, Home Affairs, Post and Telecommunications of Medicine, Japan.

Each of these subjects was matched with two control subjects with respect to sex, age at recruitment (as near as possible), and case – control study nested within the cohort and those who were not selected in terms of the variables included in the multivariate model. The lag time between blood sampling and stomach cancer diagnosis varied between 12 and 113 months (median, 50 months). Each of these subjects was matched with two control subjects with respect to sex, age at recruitment (as near as possible), and study area, who had also provided an adequate baseline blood sample, and who were alive and free of confirmed cancer by the end of 1997. Owing to a lack of eligible subjects, a few sets (n = 10) contained only one control, and thus there was a total of 410 controls.

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 these data (49 cases and 88 controls). Of the 161 cases and 322 controls remaining, eight cases (5.0%) and 38 controls (11.8%) had green tea consumption data missing from the questionnaire; so these too were excluded. Owing to a lack of eligible subjects, 16 sets were further excluded. The remaining 151 cases and 265 controls were included in the present analysis.

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 the level of an independent variable. For multivariate analysis, several factors were listed as potential confounders according to epidemiological studies (Boeing, 1991; Hoshiyama and Sasaba, 1992; World Cancer Research Fund, 1997; Hoshiyama et al, 2002; Yatsuya et al, 2002). Trends of association were assessed by the regression model assigning scores (0–4) to the levels of the independent variables. Statistical significance (two-sided) was based on the ratio of the regression coefficient and its standard error. Statistical analysis (PHREG procedure) was performed using the Statistical Analysis System (SAS Institute, 1983).

RESULTS

Table 1 compares the characteristics of the cases and the controls. The consumption of green tea varied substantially. The proportion with a history of H. pylori infection was higher for the cases than for the controls. The proportion with a family history of stomach cancer was also higher for the cases than for the controls. The proportion of current smokers was also higher than for the cases for the controls. The proportion of current smokers was also higher for the cases than for the controls. The proportion of current smokers was also higher than for the controls. The proportion of current smokers was also higher than for the controls.

Table 2 shows the RR and its CI for stomach cancer according to green tea consumption. The age/sex-adjusted RRs 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 1.2 (95% CI: 0.5 – 2.9), 0.9 (95% CI: 0.4 – 1.9), 0.7 (95% CI: 0.3 – 1.5), and 1.0 (95% CI: 0.4 – 2.4), respectively. Multivariate RRs were similar to age/sex-adjusted and age/sex- and H. pylori infection-adjusted RRs.

Table 1 Characteristics of cases and controls

| No          | Case 151 | Control 265 |
|-------------|----------|-------------|
| Age (years) | 61.7     | 61.5        |
| Green tea (cups per day) |          |             |
| <1          | 18       | 31          |
| 1 or 2      | 19       | 23          |
| 3 or 4      | 41       | 73          |
| 5–9         | 50       | 105         |
| ≥10         | 23       | 33          |
| H. pylori infection (%) | 88.7 | 77.7        |
| History of peptic ulcer (%) | 19.7  | 18.2        |
| Family history of stomach cancer (%)* | 20.5 | 16.2        |
| ≤6 years of schooling (%) | 37.1 | 32.0        |
| Smoking (%)  |          |             |
| Current     | 32.2     | 28.7        |
| Past        | 18.5     | 18.0        |
| Daily dietary consumption (%) |          |             |
| Rice (≥4 bowls day−1) | 36.5 | 31.8        |
| Miso soup (≥1 cup day−1) | 83.7 | 77.9        |
| Preference for salty foods (yes) | 32.8 | 29.6        |
| Green-yellow vegetables (≥1 day−1) | 46.7 | 42.3        |
| White vegetables (≥1 day−1) | 38.6 | 40.5        |
| Fruits (≥3 week−1) | 44.4 | 39.3        |

*We defined a positive family history of stomach cancer as when the subject had at least one first-degree relative (parent or siblings) with a history of stomach cancer.
*Information on educational level was measured as the age of formal schooling completed and was classified into two categories: ≤15 years old (corresponds to ≤9 years of schooling) and >16 years old (corresponds to >10 years of schooling).
H. pylori infection. Subjects with chronic gastritis caused by Tsubono et al. evidence is available from prospective studies (Galanis consistent with the finding of this prospective study. Little other prevention. Tsubono et al. it would be an inexpensive and convenient method of primary countries. If drinking green tea protects against stomach cancer, idiosyncracy of our questionnaire pertaining to Japanese tea that a slight misclassification could have derived from the Ministry of Agriculture, Forestry, and Fisheries, 1999). We believe one that most often comes to mind. About 89% of the total kinds of Japanese tea, although for Japanese people green tea is the information therefore seemed to occur randomly. The second possible problem with the present study was in the questionnaire. The original words of the question on green tea were: Do you drink Japanese tea (green tea)? There are various kinds of Japanese tea, although for Japanese people green tea is the one that most often comes to mind. About 89% of the total production of Japanese tea in 1999 was ordinary green tea (The Ministry of Agriculture, Forestry, and Fisheries, 1999). We believe that a slight misclassification could have derived from the idiosyncrasy of our questionnaire pertaining to Japanese tea (green tea).

Green tea is widely consumed in Japan and other Asian countries. If drinking green tea protects against stomach cancer, it would be an inexpensive and convenient method of primary prevention. Tsubono et al. reported that there was no association between green tea consumption and the risk of stomach cancer, consistent with the finding of this prospective study. Little other evidence is available from prospective studies (Galanis et al., 1998; Tsubono et al., 2001). Past studies did not consider the influence of H. pylori infection. 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, the prevalence of infection would have been higher among the subjects with higher intakes of green tea. This condition would have masked an inverse association between the risk of stomach cancer and green tea consumption. We examined the association of H. pylori infection and green tea consumption, and found that H. pylori infection did not differ with the consumption of green tea (see Table 3).

Table 3 shows the age/sex-adjusted RR of H. pylori infection positivity according to green tea consumption. H. pylori infection did not differ with the consumption of green tea.

**DISCUSSION**

This nested case–control study is the first study to investigate any association between green tea consumption and the risk of stomach cancer while controlling H. pylori infection. Among the possible limitations of the present study was incomplete data. About 10% of subjects were excluded from the analysis because they had not provided information concerning their daily consumption of green tea. We could not fully evaluate the effects of the exclusion of these data. Nevertheless, there was no difference between the percentages of smokers in the whole data (53.1% of men and 2.9% of women) and those in the included data (51.9% and 3.7%, respectively), as examined by the Cochran–Mantel–Haenszel \( \chi^2 \) test (\( P = 1.000 \) and 0.843, respectively). The missing information therefore seemed to occur randomly.

In summary, we found no inverse association between the consumption of green tea and the risk of stomach cancer in Japan in a nested case–control study.

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

| Green tea consumption (cups day \(^{-1}\)) | \(< 1\) | 1 or 2 | 3 or 4 | 5–9 | \(\geq 10\) | \(P\) for trend |
|---|---|---|---|---|---|---|
| Case/controls | 18/31 | 19/23 | 41/73 | 50/105 | 23/33 | |
| Age/sex-adjusted RR | 1.0 | 1.2 (0.5–2.9) | 0.9 (0.4–1.9) | 0.7 (0.3–1.5) | 1.0 (0.4–2.4) | 0.515 |
| Age/sex- and H. pylori-adjusted RR | 1.0 | 1.1 (0.4–2.9) | 0.9 (0.4–1.9) | 0.7 (0.3–1.5) | 1.1 (0.4–2.5) | 0.628 |
| Multivariate RR* | 1.0 | 1.3 (0.6–2.8) | 1.0 (0.5–1.9) | 0.8 (0.4–1.6) | 1.2 (0.6–2.5) | 0.899 |

*Adjusted for age (four classes), smoking status (never, past, current), sex, H. pylori infection, history of peptic ulcer, family history of stomach cancer, educational level (two levels); consumption of rice, miso soup, green-yellow vegetables, white vegetables, fruits, and preference for salty foods (two categories). Values in parentheses are 95% confidence intervals. RR = relative risk.

**Table 3** Relative risk of H. pylori infection positivity according to green tea consumption among controls

| Green tea (cups day \(^{-1}\)) | Age–sex-adjusted RR of H. pylori infection positive | \(< 1\) | 1 or 2 | 3 or 4 | 5–9 | \(\geq 10\) | \(P\) for trend |
|---|---|---|---|---|---|---|---|
| Age–sex-adjusted RR of H. pylori infection positive | 1.0 | 1.0 (0.2–3.8) | 1.0 (0.3–2.8) | 1.1 (0.4–3.1) | 0.7 (0.2–2.5) | 0.901 |
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Appendix

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