A potential anti-carcinogenic effect of green tea has drawn much interest in experimental and epidemiologic studies.\(^1\) A fairly large number of epidemiologic studies have investigated the protective association between green tea and gastric cancer,\(^2,3\) but a few studies have shown an inhibitory effect of green tea or tea catechin in the development of chemically-induced carcinoma of the colorectum as well as of the stomach. Specifically, in vitro experiments suggest that green tea polyphenols inhibit the formation of heterocyclic amines, which is formed during the cooking of meats and fish and is implicated in the development of colorectal cancer.\(^7\) Animal experiments also suggest that green tea polyphenols suppress colon-carcinogenesis induced by heterocyclic amines.\(^4\)

Epidemiologically, five case-control studies and one prospective cohort study have examined the association between consumption of green tea and the risk of colorectal cancer.\(^5,9-13\) For colon cancer, a case-control study in Japan found a significant inverse association,\(^10\) while the other five studies found no significant relation.\(^5,9,11-13\) For rectal cancer, a case-control study in China found a significant inverse association,\(^12\) while the other five studies found no significant relation.\(^5,9,11,13\) The only prospective cohort study conducted among atomic bomb survivors of Hiroshima and Nagasaki, Japan, found no association between...
consumption of green tea and risk of colon or rectal cancer.15
To further examine the association between consumption of
green tea and the risk of colorectal cancer, we conducted a pooled
analysis of two population-based prospective cohort studies in
Miyagi Prefecture in rural northern Japan.

Study Cohort
Study designs of the two cohort studies have been described in
detail elsewhere.14,15 Briefly, Cohort 1 started in January 1984,
when we delivered a self-administered questionnaire to 33,453
men and women (40 years of age or older) in three municipalities
of Miyagi Prefecture. Usable questionnaire were returned from
31,345 subjects (93.7%).14 For Cohort 2, we delivered a self-
administered questionnaire from June through August 1990 to
51,921 men and women (40-64 years of age) in 14 municipalities
of the Prefecture. Usable questionnaires were returned from
47,605 subjects (91.7%).14 Protocols for the two cohort studies
were approved by the institutional review board of Tohoku
University Graduate School of Medicine. We considered the
return of the self-administered questionnaires signed by the sub-
jects to imply their consent to participate in the studies.

Exposure Data
The questionnaires asked about "recent" (Cohort 1) or "usual"
(Cohort 2) consumption of green tea. The two questionnaires used
the same five categories: never, occasionally, 1-2 cups per day, 3-
4 cups per day, 5 or more cups per day. "Never" and "occasional-
ly" categories were collapsed into the single category "less than
one cup per day" for the purpose of this analysis.
To examine the reproducibility and validity of the questionnaire
measurements of green tea intake, we collected 12-day diet
records from 56 men and 60 women who lived in the two municipali-
ities in the study district.16 Spearman correlation coefficients
between green tea consumption assessed by the Cohort 2 ques-
tionnaire and that measured by the diet records were 0.71 in men
and 0.53 in women. Spearman correlation coefficients between
green tea intake measured by the two questionnaires administered
12 month apart were 0.63 in men and 0.64 in women.

Follow-up
For both Cohorts, we used population registries of the municipali-
ties to obtain information on the vital and residential status of the
subjects. We ascertained the incidence of cancer using the Miyagi
Prefectural Cancer Registry covering the study areas.7 In this can-
cer registry, the proportion of colon cancer cases for which inform-
ation was available only from death certificates was 3% in men
and 7% in women, the proportion of rectal cancer cases for which
information was available only from death certificates was 2% in
men and 4% in women.7 Follow-up was conducted from January
1, 1984, through December 31, 1992, for Cohort 1, and from
August 1, 1990, through March 31, 1997, for Cohort 2. The pro-
portions of subjects who were lost to follow-up were 18.5% for
Cohort 1, and 3.9% for Cohort 2. We defined subjects who were
lost to follow-up as those who moved out of the study areas dur-
ing follow-up period, and we assumed that subjects who had not
die or lost to follow-up remain alive in the study areas. In
analysis, lost to follow-up was treated as censoring case.
We excluded cancer cases prevalent at baseline (541 in Cohort
1, and 1,110 in Cohort 2). We also excluded the subjects who did
not respond to the question on green tea (4,493 in Cohort 1, and
6,891 in Cohort 2). Consequently, our analysis included 26,311
subjects with 269 colorectal cancer cases (158 colon and 111 rec-
tum) in Cohort 1, and 39,604 subjects with 247 with colorectal
cancer cases (147 colon and 100 rectum) in Cohort 2.

Statistical Analysis
We counted person-year of follow-up for each subject from the
beginning of follow-up until the date of diagnosis of colorectal
cancer, the date of death, or the end of the follow-up period,
whichever occurred first. Total person-years accrued were
200,039 for Cohort 1 and 290,836 for Cohort 2.
We estimated hazard ratios (HRs) and their 95% confidence
intervals (CIs) of colon and rectal cancer according to the level of
green tea consumption. We used Cox proportional-hazards regres-
sion to adjust for potentially confounding variables. For the two
Cohorts, we considered the following variables as potential con-
founders: sex, age, family history of colorectal cancer, smoking
status, body mass index (kg/m2), alcohol consumption, and con-
sumption frequencies of black tea and coffee. For Cohort 1, we
further adjusted for consumption frequencies of meat, green or
yellow vegetables, other vegetables and fruits. For Cohort 2, we
further adjusted for consumption frequencies of beef, pork, ham,
liver, spinach, carrot and pumpkin, tomato, orange, other fruits,
and juice.
To obtain a summary measure of results from Cohort 1 and
Cohort 2, the general variance-based method was used to combine
each HR and 95% CI.14 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.

Table 1 compares the characteristics between subjects who con-
sumed less than one cup per day and those who consumed five or
more cups of green tea per day. For both Cohorts, men who con-
sumed five or more cups per day were older, more likely to be
current smokers and to consume black tea, less likely to consume
coffee, as compared with the men who consumed less than one
cup per day.
In Cohort 1, women who consumed five or more cups per day
were older, more likely to be current smokers, drinkers and to
consume black tea, less likely to consume coffee, as compared
with the women who consumed less than one cup per day. In
Cohort 2, women who consumed five or more cups per day were
| Characteristics                  | Men | Women |
|----------------------------------|-----|-------|
| No.                              |     |       |
| Age (yr), mean ± standard deviation | 56.3 ± 11.3 | 57.6 ± 10.8 |
| Smoking (%)                      |     |       |
| Never                            | 27.9 | 17.1 |
| Past                             | 23.8 | 20.8 |
| Current (1-19 cigarettes / day)  | 18.9 | 13.5 |
| Current (20+ cigarettes / day)   | 29.4 | 48.7 |
| Alcohol drinking (%)             |     |       |
| Never                            | 16.3 | 17.7 |
| Past                             | 10.6 | 8.0  |
| Current                          | 73.1 | 74.4 |
| Body mass index (%)              |     |       |
| <18.5                            | 5.2  | 2.2  |
| 18.5-24.9                        | 72.3 | 68.5 |
| 25.0+                            | 22.5 | 29.3 |
| Daily beverage consumption (%)   |     |       |
| Black tea (cups / day)           |     |       |
| Never                            | 65.0 | 59.8 |
| Occasionally                     | 31.3 | 36.8 |
| 1-2                              | 2.9  | 2.3  |
| 3+                               | 0.8  | 1.1  |
| Coffee (cups / day)              |     |       |
| Never                            | 34.7 | 19.8 |
| Occasionally                     | 35.2 | 41.7 |
| 1-2                              | 19.5 | 24.6 |
| 3+                               | 10.6 | 13.9 |
Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of colon and rectum cancer according to green-tea consumption.\(^*\)

| Green-tea consumption (cups/day) | <1 | 1 or 2 | 3 or 4 | 5+ | P for trend |
|---------------------------------|----|--------|--------|----|------------|
| Colon                           |    |        |        |    |            |
| No. of cases / person-year of follow-up |      |        |        |    |            |
| Cohort 1                        | 26/36,642 | 30/34,157 | 36/43,780 | 66/85,460 |          |
| Cohort 2                        | 39/84,398 | 29/68,774 | 36/62,753 | 43/74,911 |          |
| Sex- and age-adjusted HR        |      |        |        |    |            |
| Cohort 1                        | 1.0 | 1.25 (0.74-2.11) | 1.13 (0.68-1.86) | 1.02 (0.65-1.61) | 0.79 |
| Cohort 2                        | 1.0 | 0.93 (0.58-1.51) | 1.11 (0.71-1.75) | 0.94 (0.61-1.45) | 0.93 |
| Pooled                          | 1.0 | 1.06 (0.75-1.52) | 1.12 (0.80-1.56) | 0.98 (0.71-1.34) | 0.80 |
| Multivariate HR1                |      |        |        |    |            |
| Cohort 1                        | 1.0 | 1.19 (0.70-2.03) | 1.08 (0.65-1.80) | 1.03 (0.65-1.64) | 0.87 |
| Cohort 2                        | 1.0 | 0.96 (0.59-1.57) | 1.12 (0.70-1.77) | 0.93 (0.59-1.46) | 0.85 |
| Pooled                          | 1.0 | 1.06 (0.74-1.52) | 1.10 (0.78-1.55) | 0.97 (0.70-1.35) | 0.81 |
| Multivariate HR2                |      |        |        |    |            |
| Cohort 1                        | 1.0 | 1.16 (0.65-2.08) | 0.88 (0.49-1.58) | 0.82 (0.49-1.39) | 0.27 |
| Cohort 2                        | 1.0 | 1.01 (0.57-1.78) | 1.23 (0.72-2.11) | 0.84 (0.48-1.45) | 0.67 |
| Pooled                          | 1.0 | 1.08 (0.72-1.62) | 1.05 (0.71-1.57) | 0.83 (0.57-1.21) | 0.27 |
| Rectum                          |      |        |        |    |            |
| No. of cases / person-year of follow-up |      |        |        |    |            |
| Cohort 1                        | 18/36,642 | 20/34,157 | 22/43,780 | 51/85,460 |          |
| Cohort 2                        | 38/84,398 | 20/68,774 | 15/62,753 | 27/74,911 |          |
| Sex- and age-adjusted HR        |      |        |        |    |            |
| Cohort 1                        | 1.0 | 1.20 (0.63-2.27) | 1.01 (0.54-1.88) | 1.17 (0.68-2.00) | 0.68 |
| Cohort 2                        | 1.0 | 0.65 (0.38-1.12) | 0.48 (0.27-0.88) | 0.64 (0.39-1.05) | 0.05 |
| Pooled                          | 1.0 | 0.84 (0.56-1.29) | 0.69 (0.45-1.06) | 0.84 (0.58-1.21) | 0.27 |
| Multivariate HR1                |      |        |        |    |            |
| Cohort 1                        | 1.0 | 1.34 (0.70-2.56) | 1.14 (0.60-2.15) | 1.34 (0.77-2.33) | 0.40 |
| Cohort 2                        | 1.0 | 0.62 (0.36-1.06) | 0.44 (0.24-0.82) | 0.57 (0.34-0.95) | 0.02 |
| Pooled                          | 1.0 | 0.85 (0.56-1.29) | 0.70 (0.45-1.08) | 0.85 (0.58-1.23) | 0.31 |
| Multivariate HR2                |      |        |        |    |            |
| Cohort 1                        | 1.0 | 1.09 (0.49-2.41) | 1.00 (0.46-2.15) | 1.31 (0.68-2.51) | 0.39 |
| Cohort 2                        | 1.0 | 0.54 (0.27-1.07) | 0.39 (0.18-0.84) | 0.66 (0.37-1.20) | 0.14 |
| Pooled                          | 1.0 | 0.73 (0.43-1.22) | 0.62 (0.36-1.07) | 0.90 (0.58-1.40) | 0.67 |

*: The multivariate hazard ratio (HR) has been adjusted for sex; age; family history of colorectal cancer; cigarette smoking; alcohol consumption; body mass index in kg / m\(^2\) (<18.5, 18.5-24.9, 25.0 + ); consumption of black tea, and coffee. The multivariate HR for cohort1 has also been adjusted for consumption of meat, green-yellow vegetables, other vegetables, and fruits. The multivariate HR for Cohort2 has also been adjusted for consumption of beef, pork, ham, chicken, liver, spinach, carrot or pumpkin, tomato, orange, other fruits, and juice. HR1 denotes the relative risk with all cases of colorectal cancer included in the multivariate analysis, and HR2 the relative risk with cases diagnosed in the first three years of follow-up excluded from the analysis. 95% confidence intervals in parentheses.
### Table 3. Pooled multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) of colorectal cancer according to green tea consumption.

| Green-tea consumption (cups/day) | Colon          | Rectum          |
|---------------------------------|----------------|-----------------|
|                                  | 1 or 2         | 3 or 4          | 5+    | P for trend |
| <1                              |                |                 |       |             |
| **Men**                          |                |                 |       |             |
| Sex*                            |                |                 |       |             |
| No. of cases                    | 36             | 39              | 46    | 64          | 0.69          |
| Pooled multivariate HR          | 1.0            | 1.32 (0.83-2.10)| 1.35 (0.86-2.12)| 1.12 (0.72-1.74) |
| **Women**                       |                |                 |       |             |
| No. of cases                    | 29             | 20              | 26    | 45          | 0.34          |
| Pooled multivariate HR          | 1.0            | 0.78 (0.43-1.40)| 0.78 (0.45-1.35)| 0.79 (0.49-1.29) |
| Alcohol consumption** Current drinkers | No. of cases | 33             | 37    | 38          | 52            | 0.77          |
| Pooled multivariate HR          | 1.0            | 1.30 (0.80-2.10)| 1.16 (0.72-1.87)| 0.98 (0.61-1.57) |
| **Nondrinkers**                 |                |                 |       |             |
| No. of cases                    | 26             | 16              | 23    | 42          | 0.71          |
| Pooled multivariate HR          | 1.0            | 0.73 (0.39-1.37)| 0.82 (0.46-1.46)| 0.86 (0.52-1.44) |
| **Men**                          |                |                 |       |             |
| Sex*                            |                |                 |       |             |
| No. of cases                    | 37             | 27              | 19    | 36          | 0.02          |
| Pooled multivariate HR          | 1.0            | 0.85 (0.50-1.45)| 0.58 (0.32-1.04)| 0.62 (0.38-1.02) |
| **Women**                       |                |                 |       |             |
| No. of cases                    | 19             | 13              | 18    | 42          | 0.23          |
| Pooled multivariate HR          | 1.0            | 0.81 (0.40-1.66)| 0.95 (0.48-1.89)| 1.30 (0.70-2.42) |
| Alcohol consumption** Current drinkers | No. of cases | 32             | 24    | 16          | 34            | 0.05          |
| Pooled multivariate HR          | 1.0            | 0.85 (0.49-1.49)| 0.52 (0.28-0.97)| 0.64 (0.38-1.09) |
| **Nondrinkers**                 |                |                 |       |             |
| No. of cases                    | 15             | 13              | 14    | 30          | 0.54          |
| Pooled multivariate HR          | 1.0            | 0.96 (0.42-2.22)| 0.87 (0.36-2.10)| 1.17 (0.56-2.42) |

*: The pooled multivariate hazard ratio (HR) has been adjusted for age; family history of colorectal cancer; cigarette smoking; alcohol consumption; body mass index in kg / m$^2$ (<18.5, 18.5-24.9, 25.0 + ); consumption of black tea, and coffee.

**: The pooled multivariate hazard ratio (HR) has been adjusted for sex; age; family history of colorectal cancer; cigarette smoking; body mass index in kg / m$^2$ (<18.5, 18.5-24.9, 25.0 + ); consumption of black tea, and coffee.

The multivariate HR for cohort1 has also been adjusted for consumption of meat, green-yellow vegetables, other vegetables, and fruits.

The multivariate HR for cohort2 has also been adjusted for consumption of beef, pork, ham, chicken, liver, spinach, carrot or pumpkin, tomato, orange, other fruits, and juice.

95% confidence intervals in parentheses.
older, more likely to be current smokers and to consume black tea, less likely to be current alcohol drinkers and to consume coffee, as compared with the women who consumed less than one cup per day.

Table 2 presents the HRs for colon and rectal cancer according to green tea consumption. After adjustment for sex and age, green tea consumption was not associated with the risk of rectal cancer in Cohort 1, Cohort 2, and the two Cohorts combined. Multivariate adjustment or the exclusion of cases of colon cancer diagnosed in the first three years of follow-up did not change the findings materially.

After adjustment for sex and age, green tea consumption was not associated with risk of rectal cancer in Cohort 1, but was associated with lower risk of rectal cancer in Cohort 2. When the two Cohorts were pooled, however, green tea consumption was not associated with risk of rectal cancer. Null results in the pooled analysis did not change materially with multivariate adjustment or with the exclusion of cases of rectal cancer diagnosed in the first three years of follow-up.

We conducted stratified analyses according to sex, age, cigarette smoking, alcohol consumption, body mass index, and family history of colorectal cancer. Table 3 presents the pooled HRs stratified by sex and alcohol consumption. For colon cancer, we found no different results by sex and alcohol consumption. For rectal cancer, green tea consumption was associated with a decreased risk among men and current drinkers, but not among women and nondrinkers. We did not observe different findings for other variables.

We observed significantly lower risk of rectal cancer associated with higher green tea intake among Cohort 2, men and alcohol drinkers, but not among Cohort 1, women or nondrinkers. Pooling of the results from the two Cohorts may require caution in interpretation, because a statistical test for the heterogeneity of the two Cohort results was not significant for sex- and age-adjusted HRs (p>0.05) but for multivariate HRs (p<0.05). Although it is possible that green tea is protective against rectal cancer only among these subgroups of subjects, chance may be a more likely explanation for the discrepancies according to the subgroups.

Although all of the six previous studies of green tea and colorectal cancer included both men and women, only one case-control study in China reported sex-specific results: green tea intake was significantly associated with lower risk of rectal cancer in men and women, while it was not significantly associated with risk of colon cancer in men or women. None of the previous studies reported the results of analyses stratified by categories of alcohol consumption. Future studies of green tea and colorectal cancer should report the findings stratified by sex and drinking status. We used self-reports for a measure of green-tea consumption. In a validation study of the food frequency questionnaire in which 119 subjects provided four 3-day food records in one year and then responded to the questionnaire, we observed a reasonably high degree of validity and reproducibility for the questionnaire measurement of green tea intake; Spearman’s correlation coefficient for green-tea intake measured by the questionnaire and by the food records was 0.66, and the correlation between the two questionnaires administered in 6-month interval was 0.66.4

The proportion of subjects who were lost to follow-up was 18.5% for Cohort 1. The subjects who were lost to follow-up were more likely to be young, be current smokers, have family history of colorectal cancer, and less likely to be current alcohol drinkers, obese, as compared with those who could be follow-up.

As a potential limitation of the study, we could not specifically examine the effect of very high consumption of green tea, since the highest category in our questionnaire was five or more cups per day and we could not divide this category into subcategories (such as 5-9 cups and 10 or more cups). However, the validation study of our food frequency questionnaire found that 53% of the subjects who claimed to consume five or more cups per day in the questionnaire actually consumed seven or more cups per day according to 12-day diet records. This result suggests that a substantial proportion of our subjects in the highest consumption category actually consumed very high amounts of green tea. It is therefore unlikely that we failed to detect a large decrease in the risk of colorectal cancer associated with very high consumption of green tea.

We observed lower consumption of green tea in Cohort 2 than in Cohort 1 subjects. The most likely explanation would be the actual difference in green-tea intake between the two cohorts. Different validity of the questionnaire among the two cohorts may be another possibility, but it is unlikely that the different validity...
of the questionnaire lead to the different observations only for rectal cancer (inverse association in Cohort 2 and no association in Cohort 1) but not for colon cancer (no association in both Cohorts).

In conclusion, our pooled analysis of two population-based prospective cohort studies conducted in rural Japan showed no overall association between the consumption of green tea and the risk of colorectal cancer. The inverse association for rectal cancer observed in subgroup analyses (Cohort 1, men, and current drinkers) warrants further investigations.

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