Table 3 Pooled HRs for all-cause and major causes of mortality according to alcohol consumption category (women)*

	Non-drinkers (Never- and ex-drinkers)		Occasional drinkers (<once/week)	Current drinkers (≥once/week)			Trend (per 15 g-increase)		Heterogeneity p Value and I^2 (%)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	<23 g/day HR (95% CI)	23 to <46 g/day HR (95% CI)	≥46 g/day HR (95% CI)	HR (95% CI)	p Value for trend	For trend	For the highest category
Number of subjects (n=165070)	120885		18468	20569	3559	1589				
All causes										
Person-years (n=2092057)	1574957		218893	240869	40144	17195				
Number of cases (n=13541)	11258		932	1041	220	90				
HR, age- and area-adjusted‡	1.00 (Reference)		**0.87 (0.80 to 0.95)**	**0.87 (0.80 to 0.95)**	1.16 (0.90 to 1.50)	**1.38 (1.12 to 1.70)**	**1.02 (1.01 to 1.02)**	**<0.001**	0.397 3.0%	0.559 0.0%
HR, multivariate-adjusted§	1.00 (Reference)		**0.87 (0.80 to 0.95)**	**0.85 (0.79 to 0.92)**	1.01 (0.80 to 1.28)	1.15 (0.93 to 1.42)	**1.01 (1.00 to 1.02)**	**0.010**	0.616 0.0%	0.696 0.0%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.38 (1.24 to 1.53)**	0.88 (0.77 to 1.00)	**0.88 (0.79 to 0.99)**	1.19 (0.86 to 1.63)	1.27 (0.97 to 1.66)				
HR, excluding early deaths§	1.00 (Reference)		**0.90 (0.81 to 0.998)**	**0.91 (0.85 to 0.98)**	1.06 (0.71 to 1.48)	1.21 (0.96 to 1.53)	1.01 (0.999 to 1.02)	0.097	0.819 0.0%	0.867 0.0%
Cause-specific mortality										
Person-years (n=2031281)	1529797		212405	232360	39598	17122				
Cancer										
Number of cases (n=4690)	3787		376	402	93	32				
HR, age- and area-adjusted‡	1.00 (Reference)		0.95 (0.81 to 1.11)	0.89 (0.75 to 1.06)	0.98 (0.70 to 1.38)	1.20 (0.84 to 1.70)	0.996 (0.98 to 1.01)	0.587	0.339 11.9%	0.890 0.0%
HR, multivariate-adjusted§	1.00 (Reference)		0.94 (0.81 to 1.09)	0.88 (0.73 to 1.05)	1.02 (0.81 to 1.29)	1.05 (0.73 to 1.50)	0.995 (0.98 to 1.01)	0.545	0.790 0.0%	0.746 0.0%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.36 (1.12 to 1.67)**	0.95 (0.76 to 1.19)	0.90 (0.70 to 1.17)	1.00 (0.72 to 1.40)	1.06 (0.65 to 1.71)				
HR, excluding early deaths§	1.00 (Reference)		1.00 (0.87 to 1.15)	0.98 (0.82 to 1.18)	1.04 (0.72 to 1.50)	0.92 (0.57 to 1.47)	0.99 (0.96 to 1.03)	0.744	0.100 45.8%	0.502 0.0%
Heart disease										
Number of cases (n=1978)	1678		115	139	30	16				
HR, age- and area-adjusted‡	1.00 (Reference)		0.86 (0.70 to 1.05)	0.86 (0.72 to 1.04)	1.21 (0.81 to 1.82)	**2.11 (1.28 to 3.48)**	1.05 (0.98 to 1.12)	0.171	0.010 66.7%	0.789 0.0%
HR, multivariate-adjusted§	1.00 (Reference)		0.86 (0.70 to 1.06)	0.84 (0.69 to 1.01)	1.02 (0.70 to 1.49)	**1.73 (1.04 to 2.86)**	1.03 (0.96 to 1.10)	0.400	0.048 55.2%	0.584 0.0%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	1.02 (0.76 to 1.36)	0.78 (0.58 to 1.04)	0.77 (0.62 to 0.95)	1.01 (0.65 to 1.56)	1.57 (0.81 to 3.06)				
HR, excluding early deaths§	1.00 (Reference)		0.92 (0.66 to 1.27)	0.89 (0.64 to 1.24)	1.02 (0.64 to 1.60)	1.70 (0.93 to 3.11)	1.04 (0.99 to 1.08)	0.096	0.841 0.0%	0.813 0.0%
Cerebrovascular disease										
Number of cases (n=1899)	1592		117	145	27	18				
HR, age- and area-adjusted‡	1.00 (Reference)		0.86 (0.71 to 1.05)	0.94 (0.75 to 1.18)	0.92 (0.47 to 1.80)	**1.99 (1.24 to 3.18)**	1.02 (0.99 to 1.05)	0.315	0.062 52.4%	0.418 0.0%

Continued

Table 3 Continued

	Non-drinkers (Never- and ex-drinkers)		Occasional drinkers (<once/week)	Current drinkers (≥once/week)			Trend (per 15 g-increase)		Heterogeneity p Value and I^2 (%)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	<23 g/day HR (95% CI)	23 to <46 g/day HR (95% CI)	≥46 g/day HR (95% CI)	HR (95% CI)	p Value for trend	For trend	For the highest category
HR, multivariate-adjusted§	1.00 (Reference)		0.85 (0.70 to 1.03)	0.87 (0.72 to 1.04)	0.78 (0.43 to 1.44)	1.42 (0.81 to 2.49)	1.00 (0.96 to 1.04)	0.985	0.038 57.6%	0.277 20.8%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	1.00 (0.52 to 1.94)	0.85 (0.67 to 1.09)	0.90 (0.74 to 1.10)	1.03 (0.52 to 2.01)	1.24 (0.36 to 4.34)				
HR, excluding early deaths§	1.00 (Reference)		0.80 (0.62 to 1.02)	0.88 (0.71 to 1.09)	0.90 (0.56 to 1.45)	1.48 (0.72 to 3.07)	1.08 (0.89 to 1.30)	0.435	<0.001 97.4%	0.229 28.9%

Numbers in boldface indicate $p<0.05$.
*The pooled analyses included the JPHC-I, JPHC-II, JACC, MIYAGI, OHSAKI and TAKAYAMA studies.
†The pooled analyses included the JPHC-II, JACC, MIYAGI and OHSAKI studies.
‡Adjusted for age (years, continuous) and area (JPHC-I, JPHC-II and JACC).
§Adjusted for smoking (never smoker, past smoker, or current smoker), body mass index (<18.5, 18.5–<25, ≥25), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (<almost daily, almost daily), in addition to adjustment in ‡.

estimates, we assumed that non-drinkers (never- and ex-drinkers) and occasional drinkers (<once/week) did not change their amount of alcohol consumption. The results indicate that, in men, 4.8% of total mortality, 3.1% of cancer mortality, 1.9% of heart disease mortality and 8.6% of cerebrovascular disease mortality could be prevented if current drinkers reduced their alcohol consumption to <23 g/day, and that 4.6% of total mortality, 2.9% of cancer mortality, 1.8% of heart disease mortality and 8.8% of cerebrovascular disease mortality could be prevented if current drinkers reduced their alcohol consumption to <46 g/day. In women, the PAFs were much lower than in men: 0% of total mortality, 0% of cancer mortality, 0.6% of heart disease mortality and 0.7% of cerebrovascular disease mortality could be prevented if female current drinkers reduced their alcohol consumption to <23 g/day, and 0.1% of total mortality, 0% of cancer mortality, 0.6% of heart disease mortality and 0.8% of cerebrovascular disease mortality could be prevented if current drinkers reduced their alcohol consumption to <46 g/day.

DISCUSSION

In this pooled analysis, we found J- or U-shaped associations between the amount of alcohol consumed and the risks of total and major causes of mortality in men, and the risks of total and heart disease mortality in women. When ex-drinkers were excluded from the baseline category, the HRs for the low drinkers were reduced and those for the high drinkers were increased. We confirmed that, overall, alcohol consumption of <46 g/day in male and <23 g/day in female Japanese was associated with a lower mortality risk than those for non-drinkers and heavy drinkers. A similar pattern was observed when deaths within 5 years after baseline were excluded from the analysis and when analysis was stratified by smoking status. In addition, mortality risk appeared to increase linearly with rising alcohol dose among drinkers. Using these estimates, we calculated that 5% of total mortality, 3% of cancer mortality, 2% of heart disease mortality and 9% of cerebrovascular disease mortality in men, but only 0–1% of these risks in women, could be prevented by reducing alcohol consumption to <46 g/day in men and <23 g/day in women.

The present study has several strengths. It included most of the ongoing, large-scale, prospective cohorts in Japan. In addition, the birth generation of the study subjects in the cohorts overlapped. Therefore, pooling of these cohorts allows for stable summary quantitative estimates of the effect of alcohol consumption on premature death in middle-aged and elderly Japanese adults. At the same time, because this study was not based on a meta-analysis of published studies, the possibility of publication bias is small. In the studies included in this pooled analysis, alcohol consumption was measured before death, which precludes the possibility of selection and recall bias. In addition, the categories for alcohol intake and the covariates used were identical among studies, which removes a potential source of heterogeneity that can occur when conducting a meta-analysis of published studies.

However, there are several limitations that warrant consideration. As our analyses were conducted using only a baseline questionnaire, we were unable to consider changes over time in alcohol intake. Also, we were unable to assess alcohol consumption by type of beverage. Because questions on alcohol consumption differed among studies, heterogeneity of the distribution of alcohol categories between the studies could not be distinguished from misclassification caused by measurement

error occurring in each study. In this pooled analysis, mortality was defined as an outcome; thus, it is difficult to distinguish whether alcohol consumption was associated with incidence, survival or both.

There is strong and consistent epidemiological evidence of a significant inverse association between low to moderate alcohol consumption and cardiovascular disease.[26] Alcohol consumption is linked to changes in several vascular and biochemical factors that have potential cardioprotective benefits. Alcohol consumption is believed to reduce the risk of cardiovascular events primarily by increasing high-density lipoprotein (HDL) cholesterol levels, decreasing platelet aggregation via inhibition of prostaglandin synthesis and changes in fibrinogen, and lowering levels of tissue-plasminogen activator (t-PA) and PA inhibitor (PAI-1).[27 28] However, the anticoagulant effect of alcohol, despite its beneficial effect on ischaemic stroke, may increase the risk of haemorrhagic stroke.[29–31]

Regarding cancer, the latest evaluation in 2007, by the International Agency for Research on Cancer, confirmed that alcoholic beverages are carcinogenic to humans (group 1) and concluded that the occurrence of certain sites of cancer, such as those of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast, is causally related to alcohol consumption.[32 33] The association between alcohol and cancer may be the result of high acetaldehyde exposure, which is considered carcinogenic.[32] In addition, excessive alcohol intake impairs folate absorption and bioavailability by inhibiting expression of reduced folate carrier and decreasing hepatic uptake and renal conservation of circulating folate.[34] Decreased folate status can contribute to aberrant DNA synthesis and methylation, which may increase the risk of cancer.[35]

Our results suggest that there is a specific level of alcohol consumption with the least risk, which was observed among men consuming <46 g/day and women consuming <23 g/day. Also, in drinkers, the increase in cancer risk appeared to be linear with respect to the amount of alcohol consumed. A previous meta-analysis estimated that 2–4 drinks/day (20–40 g/day) in men and 1–2 drinks/day (10–20 g/day) in women was inversely associated with total mortality[1]; these values roughly accord with the estimates for the present Japanese population. However, approximately half of all Japanese have an ALDH2-deficient phenotype. ALDH2 is a key enzyme in the conversion of acetaldehyde to acetate,[36] and a deficiency in this enzyme results in greater acetaldehyde exposure.[37] The high prevalence of ALDH2 deficiency indicates a need for caution in interpreting the results for non-drinkers, and for never- and ex-drinkers, because some of these subjects were unable to drink because of this deficiency, which would result in risk inflation in this category. ALDH2 deficiency potentially increases not only the risk of alcohol-related diseases, including cancer, but also the fraction of mortality attributable to high alcohol drinking in the population with a high prevalence of this deficiency.

With regard to sex differences in the protective effect of alcohol, previous studies examined possible mechanisms for this difference.[1 2] Women have a higher blood alcohol concentration when men and women consume the same amount of alcohol.[38] Also, women metabolise ethanol differently and have lower gastric alcohol dehydrogenase activity, resulting in higher blood ethanol levels.[39] Women who consume moderate or high levels of alcohol have a higher risk than men of death from any cause, owing to their increased risk of cancer.[9] We could not assess this association in detail, especially among female heavy drinkers, because the proportion of such women was too small, even in pooled analysis.

What is already known on this subject

- A number of studies have suggested the health benefits of light to moderate alcohol consumption with respect to total and cardiovascular mortality, and the harmful effect of heavy alcohol drinking for certain sites of cancer.
- However, because published studies use different alcohol consumption categories, meta-analysis for the purpose of quantitative assessment is not possible.

What this study adds

This study confirmed that maintaining alcohol consumption below 46 g/day in men and below 23 g/day in women minimises the risks of total mortality and mortality from major diseases in the Japanese population.

Finally, regarding public policy implications, maintaining light to moderate alcohol consumption, specifically <46 g/day in men and <23 g/day in women, may be a feasible public health recommendation for the Japanese population. However, it might not be appropriate to recommend that non-drinkers begin drinking, because of the observed increase in risk with rising alcohol dose among drinkers, the high prevalence of ALDH2 deficiency in Japanese subjects, and the fact that many abstainers have good reasons to refrain from drinking.[40]

In conclusion, our results suggest that maintaining alcohol consumption at <46 g/day (2 *go*) in men and <23 g/day (1 *go*) in women may minimise the risks of total mortality and mortality from major diseases in the Japanese population.

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

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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

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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					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	p 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				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		
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
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						
		<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day		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)	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								
Proximal (upper third)			(≥1 cups/day)					
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				p For trend	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			
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			
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) (Random effect model)	52.10	58.86	45.95	61.30	44.24			
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.

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Our study also had several limitations. First, we used only baseline information on green tea consumption, and thus could not assess the effects of lifetime consumption on risk or changes in consumption during follow-up. Non-consumers of green tea are rare in Japan and it is possible that these subjects are a selection of the population that is at increased risk of gastric cancer. Some subjects with gastric cancer might have decreased their consumption before the diagnosis because of their symptoms. Likewise, it is possible that the observed protective effect of green tea among heavy drinkers only might be that the gastrointestinal symptoms associated with *H pylori* infection might force a person to avoid drinking green tea. Such 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 association. However, analyses of each cohort which excluded the early cases did not substantially change the results.[9 10 13 14] Second, the proportion of missing values for green tea consumption among the study subjects was 4.2% and excluded from the study. The exclusion of these subjects may have distorted the results, although the proportion was low and any influence may not have been substantial. Third, random variation related to exposure measurement might have attenuated the associations. In addition, we used the indicator terms for missing covariates, and this may have introduced bias. The proportion of missing data was 8.6% for smoking, 8.1% for alcohol intake, 2.7% for rice intake, 2.2% for soy bean paste soup intake, 15.7% for coffee intake, 4.1% for pickled vegetable intake and 4.5% green–yellow vegetable intake, showing variation by covariate, some cases of which were not negligible. We conducted analyses which were restricted to subjects with complete information and obtained closely similar values. Fourth, we are unable to exclude the possibility that our estimates were distorted because of residual confounding. Finally, we did not obtain information on *H pylori* infection status for the whole population, a strong risk factor for gastric cancer. Green tea is suggested to have antibacterial effects,[37–39] and green tea may be associated with gastric cancer risk through the effect of green tea on this infection. It is therefore likely that the failure to adjust for this infection may have resulted in the apparent protective effect of green tea on gastric cancer risk.

Allowing for these methodological issues, this pooled analysis of data from large prospective studies in Japan confirmed a significant decrease in risk of gastric cancer among women with high green tea consumption, especially for the distal subsite. Further investigation of our findings of differences in effect by sex and subsite will help elucidate the mechanism underlying the etiology of gastric cancer.

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Editor's quiz: GI snapshot

Robin Spiller, *editor*

Epigastric pain in a man with previous subtotal gastrectomy

CLINICAL PRESENTATION

A 68-year-old man presented to our hospital with a 2-day history of upper abdominal pain and non-bilious vomiting. Twenty years previously he had undergone a subtotal gastrectomy with Billroth II reconstruction because of a gastric ulcer. He denied alcohol consumption or trauma. Physical examination revealed that his upper abdomen was tender with muscle guarding and rebound tenderness. Laboratory tests showed the following: haemoglobin 11 g/dl (normal, 14–16 g/dl), white blood count 12.9×10^9/l (normal, $4.0–10.0\times10^9$/l), amylase 1744 IU/l (normal, 27–131 IU/l) and lipase 4587 IU/l (normal, 8–58 IU/l). Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline (fig 1). Additionally, a 5×3 cm lesion was identified on CT images showing the target sign in the proximal segment of the afferent loop (fig 2). A diagnosis of afferent loop syndrome (ALS) complicated by acute pancreatitis was made based on symptoms, laboratory studies and CT images. The patient underwent an emergency laparotomy.

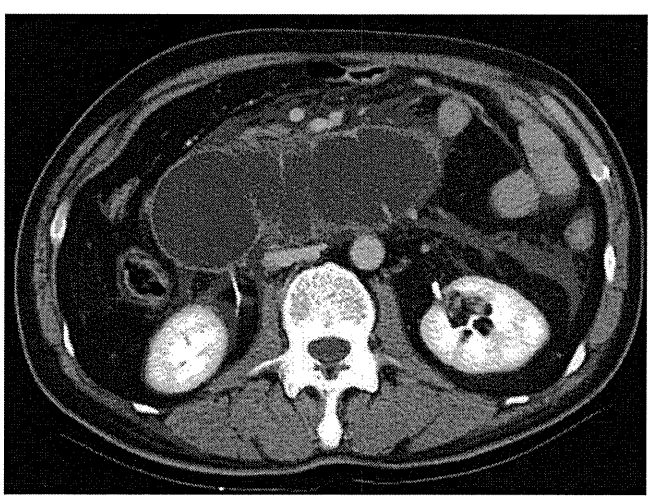

Figure 1 Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline.

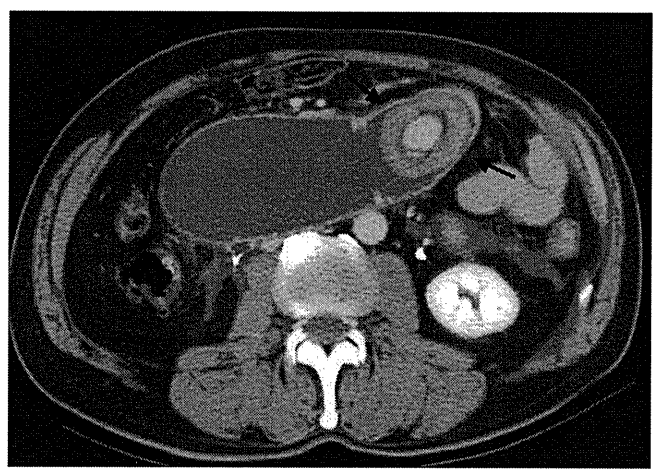

Figure 2 A 5×3 cm lesion with target sign in the proximal segment of afferent loop was identified on CT images (arrows).

QUESTION

What is the cause of afferent loop syndrome?

See page 1436 for the answer.

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