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雑誌

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Young Investigator Award Winner's Special Article

Impact of Lifestyle on Overall Cancer Risk among Japanese: The Japan Public Health Center-Based Prospective Study (JPHC Study)

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ABSTRACT

In Japan, cancer has long been recognized as a major component of the overall pattern of disease. Currently, there is a need to implement practical control measures with specific numerical targets appropriate for the Japanese population. Using data from the Japan Public Health Center-based Prospective Study, the author estimated the impact of major risk factors on overall cancer risk among a Japanese population. These risk factors included tobacco smoking, alcohol drinking, body mass index, history of diabetes, physical activity, and metabolic factors and their aggregates. The results show that tobacco smoking and heavy alcohol drinking were significantly positively associated with overall cancer risk, and that total physical activity was significantly inversely associated with the risk of cancer. Although people with a history of diabetes may be at increased risk of cancer, extreme body mass index and metabolic factors in the aggregate had little impact on overall cancer risk in the Japanese population.

Key words: cancer; risk factor; attributable fraction; Japanese; cohort study

INTRODUCTION

In Japan, cancer has been recognized as a major component of the overall pattern of disease for decades. Thus, the importance of cancer prevention through lifestyle modification is now widely acknowledged. Internationally, several studies have used epidemiologic evidence to estimate the proportion of all cancers attributable to a number of risk factors, and various international guidelines and recommendations derived from these have been promulgated.[1,2] Not surprisingly, Japanese domestic guidelines and recommendations for cancer prevention have been significantly influenced by these reports. The current need is to implement practical control measures with specific numerical targets appropriate for the Japanese population. Sufficient and reliable data derived from the Japanese population are therefore needed. Estimation of the expected effectiveness of primary prevention requires calculation of the fraction of the population incidence rate of a cancer that can be attributed to major risk factor. However, there are limited data on major risk factors and subsequent cancer risk in Japan.

We launched a large-scale, population-based, prospective study in 1990 in 11 public health center-based areas throughout Japan. The subjects were 140 420 middle-aged residents, and information was collected by using questionnaire surveys, blood samples, health screening data, and a thorough follow-up system.[3] The follow-up period is currently 10 to 15 years and a sufficient number of incident cancers has accumulated. Here, to develop a relevant epidemiological index of the impact of major risk factors—tobacco smoking, alcohol drinking, body mass index (BMI), history of diabetes mellitus (DM), physical activity, and metabolic factors and their aggregates—on overall cancer risk among the Japanese general population, we conducted cohort analyses using data from the Japan Public Health Center-based Prospective Study (JPHC study).

THE JPHC STUDY

The JPHC Study was launched in 1990 for Cohort I and in 1993 for Cohort II. Cohort I comprised 5 prefectural public health center (PHC) areas: Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo). Cohort II comprised 6 PHC areas: Mito (Ibaraki Prefecture), Nagaoka (Niigata Prefecture), Chuo-higashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture), and Suita (Osaka Prefecture). Details

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*The members of the study group are listed in the Appendix.

of the study design are described elsewhere.[3,4] The study population was defined as all registered Japanese inhabitants aged 40 to 59 years (for Cohort I) or 40 to 69 years (for Cohort II) at baseline. Participants were identified by resident registries maintained by local municipalities. This study was approved by the institutional review board of the National Cancer Center of Japan. In the present series of analyses, the Katsushika PHC area was excluded because data on cancer incidence were not available.

A baseline self-administered questionnaire survey was conducted in 1990 to 1994, and a 5-year follow-up questionnaire in 1995 to 1999, with a response rate of around 80%. Subjects with a history of cancer at any site were excluded from the analysis.

Subjects were followed from the starting point until the end of follow-up, which depended on the particular analysis. Residence status, including survival, was confirmed through the residential registry. Access to the resident registry is available to anyone, as mandated by the resident registration law. Among the study subjects, approximately 0.5% were lost to follow-up during the follow-up period. Information on the cause of death for deceased subjects was obtained from death certificates (provided by the Ministry of Health, Labour, and Welfare, with the permission of the Ministry of Internal Affairs and Communications), on which cause of death is classified according to the International Classification of Diseases, Tenth Revision.[5] Resident registration and death registration are required by law in Japan, and the registries are believed to be complete. Incident cancers were identified via notification from the major hospitals in the study area and by data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. The site and histology of each cancer were coded using the International Classification of Diseases for Oncology, Third Edition.[6] In our cancer registry system, the proportion of cases for which information was available from death certificates only (DCO) was around 4%.

Hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were used to describe the relative risk of overall cancer occurrence associated with the presence of major risk factors at the start of each study. The Cox proportional hazards model was used for the analysis, after controlling for potential confounding factors in addition to age and study area.

To express the impact of major risk factors on overall cancer occurrence in this population, the population attributable fraction (PAF) was estimated. This is the fraction of the population incidence rate of cancer that can be attributed to a particular cause—in other words, the reduction in incidence that would be expected had the population been entirely unexposed.[7] PAF was estimated as:

$$\mathrm{pd} \times \left(\mathrm{HR} - \frac{1}{\mathrm{HR}}\right)$$

where **pd** is the proportion of cases exposed to a particular risk factor. This formula is believed to have greater validity, when confounding variables are present, than the more common formula:

$$\frac{\mathrm{Pe}(\mathrm{HR} - 1)}{\mathrm{Pe}(\mathrm{HR} - 1) + 1}$$

where **Pe** is the proportion of the source population exposed to a particular risk factor.[8] We used the formula of Greenland to estimate the 95% CIs of adjusted PAFs.[9]

Impact of tobacco smoking on subsequent cancer risk (Figure 1)[10]

Although the relations between tobacco smoking and cancers at various sites are unequivocal, few studies have examined the subsequent risk and PAF of overall cancer incidence in relation to tobacco smoking. This study aimed to develop a relevant epidemiological index of the impact of tobacco smoking on the subsequent risk of cancer in Japan. We conducted a cohort analysis of the possible association between tobacco smoking habits and overall cancer risk among 92 792 subjects (44 521 men and 48 271 women), with a follow-up period of 9.6 years. From 1990 through 2001, there were 4922 incident cases of cancer (2969 men and 1953 women). Responses to the baseline questionnaire indicated that 52.2% of men and 5.6% of women were current smokers, among whom the HR for subsequent cancer occurrence, as compared with never smokers, was 1.64 (95% CI, 1.48–1.82) and 1.46 (1.21–1.75), respectively. The corresponding PAF of overall cancer incidence in men was 22.4% (15.7%–28.5%) and 7.0% (3.7%–10.3%) in relation to current and past exposures to tobacco smoke. In women, the respective PAFs were only 2.2% and 0.6%, due to the low prevalence of current and former smokers. Our results suggest that avoidance of tobacco smoking would prevent 29% of cancers in men and 3% of cancers in women.

Impact of alcohol drinking on overall cancer risk (Figure 2)[11]

In Japan, both alcohol consumption and the proportion of heavy drinkers have been increasing for decades, and alcohol drinking has been recognized as an important and preventable public health problem. The epidemiological background, types of beverages regularly consumed, and genetic polymorphisms for alcohol-related enzymes in Japanese differ from those in Western populations. We conducted a cohort study of alcohol consumption and overall cancer incidence in 73 281 subjects (35 007 men and 38 274 women) aged 40 to 59 years at baseline over a 9.8-year follow-up period. During the period from 1990 through 2001, we identified a total of 3403 cases of newly diagnosed cancer and 1208 cancer deaths. In men, occasional drinkers had the lowest risk of developing cancer, and a positive linear association with ethanol intake was noted: the HRs

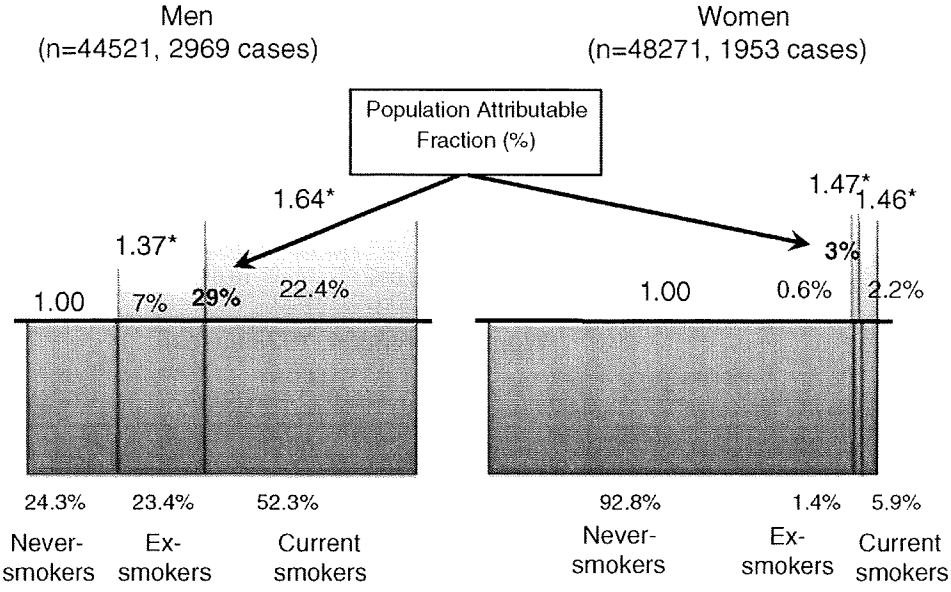

Figure 1. Impact of tobacco smoking on subsequent cancer risk in men and women[10]

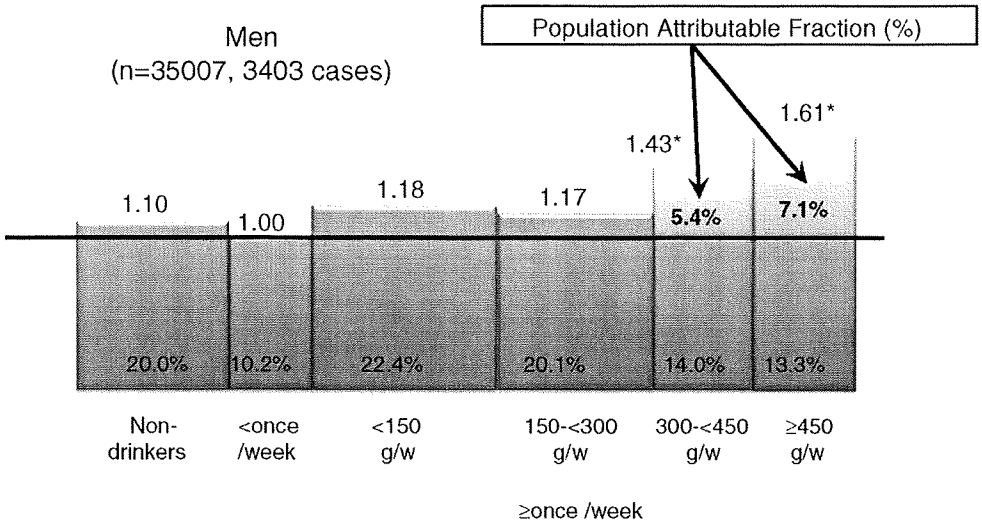

Figure 2. Impact of alcohol drinking on overall cancer risk in men[11]

were 1.18 (95% CI, 0.96–1.44) for 1 g to <150 g per week, 1.17 (0.96–1.44) for 150 g to <300 g per week, 1.43 (1.17–1.75) for 300 g to <450 g per week, and 1.61 (1.32–1.97) for 450 g or more per week (*P* for trend, <0.001). The positive association was more striking among current smokers and for alcohol-related cancers. Relatively few women were regular drinkers. Our results suggest that ethanol intake elevates the risk of cancer in a dose-dependent manner, and that nearly 13% of cancers among men in this study were due to heavy drinking (≥300 g per week of ethanol), to which smoking substantially contributed. Reduction of smoking is therefore important in decreasing the effect of alcohol on cancer risk.

Impact of BMI on overall cancer risk (Figure 3)[12]

To determine whether BMI extremes in otherwise healthy individuals affect the likelihood that cancer will occur, we conducted a cohort analysis of the possible association between BMI and the risk of overall cancer incidence among 88 927 subjects (42 093 men and 46 834 women), with a 9.5-year follow-up. In men, there was a U-shaped association between BMI and cancer occurrence: men with a BMI of 23 to less than 25 had the lowest risk of cancer occurrence (BMI 14–<19: HR = 1.29, 95% CI = 1.08–1.54; BMI 30–<40: 1.22, 0.92–1.61). This tendency did not change substantially after excluding cases diagnosed early during the follow-up period; cancer mortality showed a similar trend, but with higher risk values. When analyzed according to smoking category, a low BMI had a stronger effect on cancer occurrence in current smokers than in never smokers. There was no marked fluctuation in risk in women. A very low BMI seems to have a greater impact on overall cancer risk in populations with a lower average BMI. Therefore, although

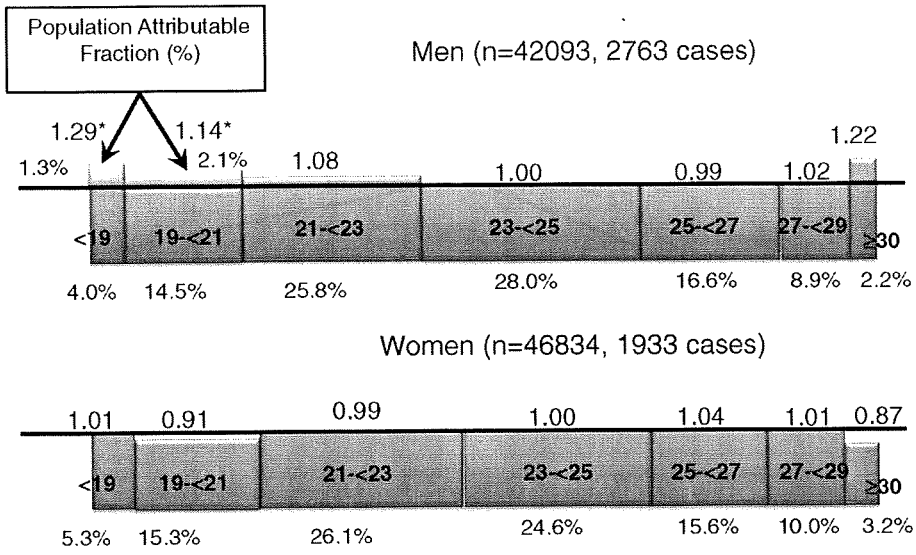

Figure 3. Impact of body mass index (BMI) on overall cancer risk[12]

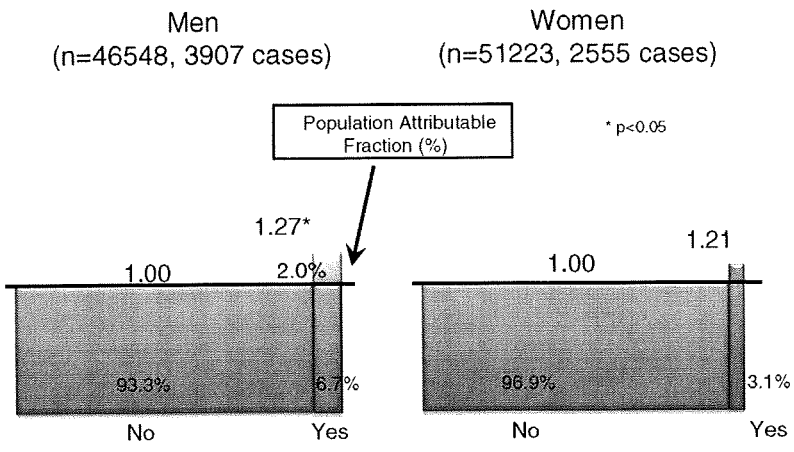

Figure 4. Diabetes mellitus and overall cancer risk[13]

much attention has been paid to the effects of obesity, the health effects at both BMI extremes should be considered in populations with a low average BMI.

DM and the risk of cancer (Figure 4)[13]

As in many other countries, DM is a serious public health problem in Japan. One global estimate projects an increase in prevalence from 6.5% in 1995 to 8.7% in 2025 among Japanese aged 20 years or older. This increase in DM will likely influence trends in related health conditions, including cancer. Clarification of the association between DM and cancer in populations with an increasing DM prevalence, eg, Japanese, is thus a crucial task, not only with respect to causation but also with regard to the formulation of clinical strategies and public health policies for the target population.

We prospectively examined the association between a history of DM and subsequent risk of cancer. A total of 97 771 subjects (46 548 men and 51 223 women) who responded to the baseline questionnaire from 1990 through 1994 were followed up for cancer incidence through 2003. At baseline, 6.7% of men and 3.1% of women had a history of DM. A total of 6462 cases of newly diagnosed cancer were identified. In men, there was a 27% increase in the risk of overall cancer incidence in those with a history of DM (HR, 1.27; 95% CI, 1.14–1.42). The HRs were especially high for cancers of the liver (2.24, 1.64–3.04), pancreas (1.85, 1.07–3.20), and kidney (1.92, 1.06–3.46). We also observed a moderate increase in the risk of colon cancer (1.36, 1.00–1.85) and a borderline significant increase in stomach cancer (1.23, 0.98–1.54). In women, there were borderline significant increases in overall cancer risk (1.21, 0.99–

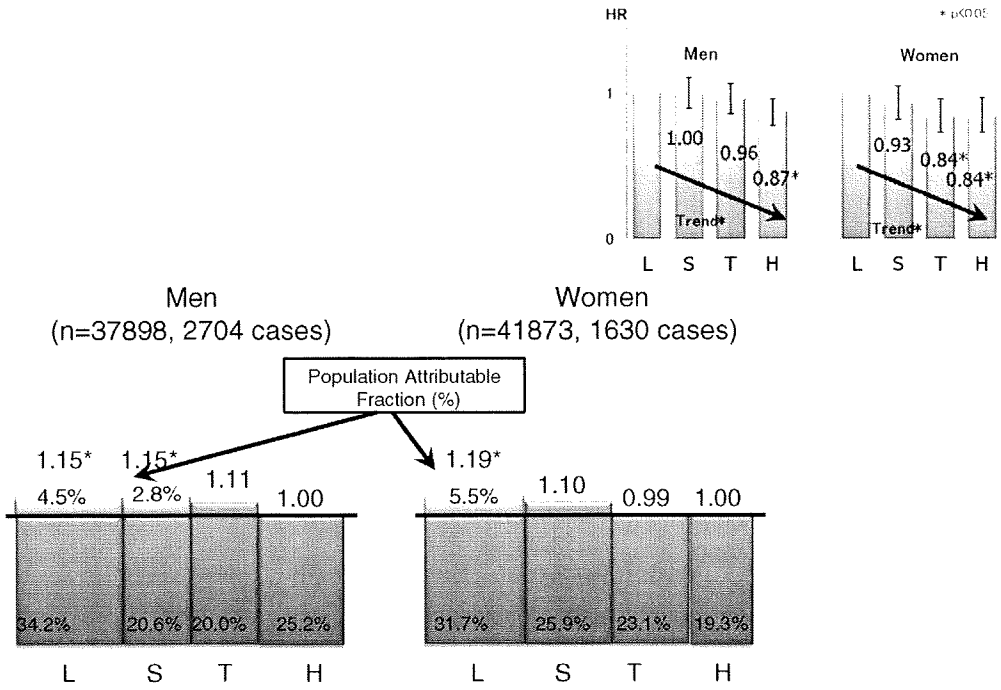

Figure 5. Daily total physical activity level and overall cancer risk[14]

1.47) and ovarian cancer (2.42, 0.96–6.09), and statistically significant increases in the risks for stomach cancer (1.61, 1.02–2.54) and liver cancer (1.94, 1.00–3.73). It appears that, among the general Japanese population, individuals with DM may be at increased risk for overall cancer and for cancer at specific sites.

Daily total physical activity level and overall cancer risk (Figure 5)[14]

A number of investigators have reported that physical activity has beneficial effects on the risk of cancer at specific sites. As a result, physical activity is now regarded as an important target for cancer prevention. At present, however, information on the association between physical activity and overall cancer risk is limited. Given that exercise and physical activity probably affect cancer development at different sites via the same or very similar mechanisms, at least to some degree, it is reasonable to assess the preventive effect of physical activity not only on cancer at specific sites but also on all cancers in aggregate. Further, from a public health perspective, a better understanding of the preventive effect of physical activity on overall cancer risk would provide concrete information for estimating the effects of physical activity measures in health policy planning.

We prospectively examined the association between daily total physical activity (using a score for metabolic equivalents per day) and subsequent cancer risk. A total of 79 771 Japanese men and women aged 45 to 74 years who responded to a questionnaire in 1995 through 1999 were followed for overall cancer incidence (4334 cases) through 2004. As compared with subjects in the lowest quartile, increased daily physical activity was associated with a significantly decreased risk of cancer in both sexes. In men, the HRs for the second, third, and highest quartiles were 1.00 (95% CI, 0.90–1.11), 0.96 (0.86–1.07), and 0.87 (0.78–0.96), respectively (P for trend = 0.005); in women, the HRs were 0.93 (0.82–1.05), 0.84 (0.73–0.96), and 0.84 (0.73–0.97), respectively (P for trend = 0.007). The decrease in risk was clearer in women than in men, especially among the elderly and those who regularly engaged in leisure sports or physical exercise. By site, decreased risks were observed for cancers of the colon, liver, and pancreas in men, and for cancer of the stomach in women. On estimation of the PAF from our results, 4.5% of male cases and 5.5% of female cases were considered preventable if the persons in the lowest physical activity category had increased their activity to a higher level. Increased daily physical activity may thus be beneficial in preventing cancer in a relatively lean population.

Impact of metabolic factors on subsequent cancer risk (Figure 6)[15]

As in many countries, metabolic syndrome has recently attracted substantial attention in Japan, and this is reflected in the government's decision to start a nationwide intervention strategy in April 2008. The National Health and Nutrition Survey in Japan reported that the prevalence of metabolic syndrome in the Japanese population aged 40 to 74 years in 2005 was 25.5% in men and 10.3% in women. Given the expectation that this would likely influence related health conditions, including cancer, clarification of the association between metabolic factors and cancer is a crucial task, not only with respect to causation, but also with regard to the

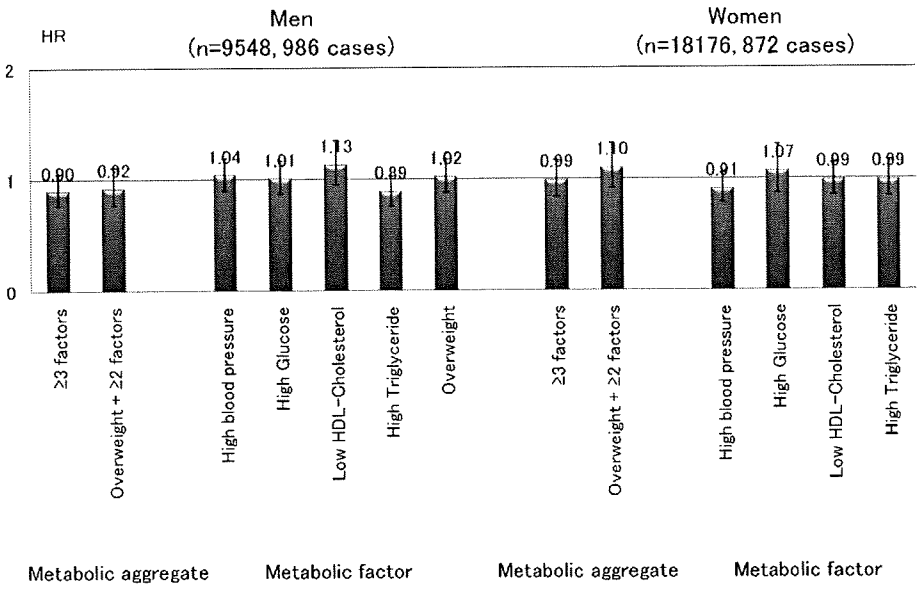

Figure 6. Impact of metabolic factors on subsequent cancer risk[15]

formulation of clinical and public health strategies for the target population. However, the impact of metabolic factors on overall cancer risk has not been clarified.

We prospectively examined whether metabolic factors and their aggregates predict the subsequent occurrence of overall and major sites of cancer. A total of 27 724 participants (9548 men and 18 176 women) aged 40 to 69 years who participated in a questionnaire and health checkup survey in 1993 through 1995 were followed for overall cancer incidence through 2004. HRs and 95% CIs were calculated for metabolic factors (hypertension, high serum glucose, low HDL-cholesterol, hypertriglyceridemia, and overweight) and for 2 aggregates of these criteria (≧3 factors; ≧2 additional factors, plus overweight). In both sexes, the presence of metabolic factors in the aggregate did not predict subsequent occurrence of cancer as a whole. By site, a significant increase in risk was observed for liver cancer in men (≧3 factors: HR, 1.73; 95% CI, 1.03–2.91; and, ≧2 additional factors, plus overweight: 1.99, 1.11–3.58), and pancreatic cancer in women (≧2 additional factors, plus overweight: 1.99, 1.00–3.96). For other sites, positive associations were observed only for specific metabolic factors, namely, hypertriglyceridemia and colon cancer in men (1.71, 1.11–2.62), and obesity and breast cancer in women (1.75, 1.21–2.55). Metabolic factors in the aggregate appear to have little impact on overall cancer risk in the Japanese population, although the association between specific components and specific cancers suggests an etiologic link.

CONCLUSION

We estimated the impact of major risk factors, namely tobacco smoking, alcohol drinking, BMI, history of diabetes, physical activity, and metabolic factors and their aggregates, on overall cancer risk among a Japanese population. Tobacco smoking and heavy alcohol drinking were significantly positively associated with overall cancer risk, and total physical activity was significantly inversely associated with overall cancer risk. In addition, although participants with a history of DM appear to be at increased overall risk of cancer, BMI and metabolic factors in the aggregate had little impact on overall cancer risk in this population.

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APPENDIX

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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

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 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	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.

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.

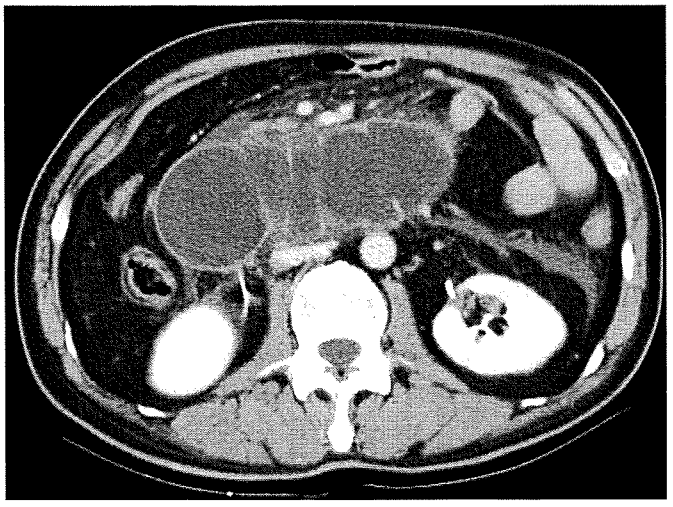

Figure 1 Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline.

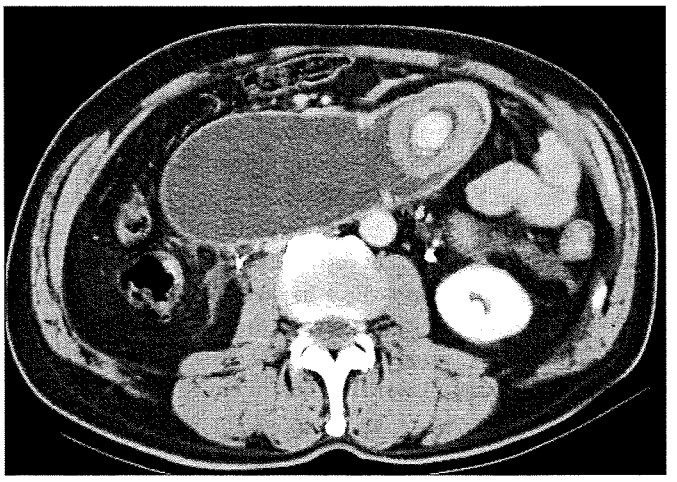

Figure 2 A 5×3 cm lesion with target sign in the proximal segment of afferent loop was identified on CT images (arrows).

QUESTION

What is the cause of afferent loop syndrome?

See page 1436 for the answer.

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REVIEW

Cancer Epidemiology and Control in the Arab World - Past, Present and Future

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Abstract

The Arab world, stretching from Lebanon and Syria in the north, through to Morocco in the west, Yemen in the south and Iraq in the east, is the home of more than 300 million people. Cancer is already a major problem and the lifestyle changes underlying the markedly increasing rates for diabetes suggest that the burden of neoplasia will only become heavier over time, especially with increasing obesity and aging of what are now still youthful populations. The age-distributions of the affected patients in fact might also indicate cohort effects in many cases. There are a number of active registries in the region and population-based data are now available for a considerable number of countries. A body of Arab scientists are also contributing to epidemiological research into the causes of cancer and how to develop effective control programs. The present review covers the relevant PubMed literature and cancer incidence data from various sources, highlighting similarities and variation in the different cancer types, with attempts to explain disparities with reference to possible environmental factors. In males, the predominant cancers vary, with lung, urinary bladder or liver in first place, while for females throughout the region breast cancer is the greatest problem. In both sexes, non-Hodgkins lymphomas and leukemias are relatively frequent, along with thyroid cancer in certain female populations. Adenocarcinomas of the breast, prostate and colorectum appear to be increasing. Coordination of activities within the Arab world could bring major benefits to cancer control in the eastern Mediterranean region.

Asian Pacific J Cancer Prev, **10**, 3-16

Introduction

The countries of the Arab Middle-east share a great deal in terms of culture while markedly differing in their levels of economic development. The variation between and within populations is reflected in different disease profiles, although in all cases the burden of cancer is already appreciable. The available data indicate that incidence rates are rising and with aging as well as continued population growth this means that the problem will loom larger in the future.

Since the literature regarding cancer registration data and associated epidemiological findings are scattered, the present research was undertaken to provide an overview. The countries/populations included are the Lebanon, Syria, Palestine (the West Bank and Gaza and Israeli - Palestinians), Jordan, Egypt, Sudan, Djibouti and Eritrea and the Maghreb countries of North Africa (Libya, Tunisia, Algeria, Morocco and Maruitania) as well as Saudi Arabia, Yemen, the Sultanate of Oman, the United Arab Emirates, Qatar, Bahrain, Kuwait and Iraq. Although population-based cancer incidence rates in Jordan, with and without Egypt, have been published (Freedman et al., 2003; Freedman et al., 2007), a more general coverage has not been hitherto been available. All sources available to the authors were therefore accessed to give as comprehensive a picture as possible regarding the cancer burden, risk factors and preventive approaches. Representative relevant papers in PubMed were cited with the focus on individual organ sites, in an attempt to explain variation in incidence rates in terms of accepted risk and beneficial factors.

Cancer Registration in the Arab World

The established cancer registries within the Arab world are shown in Figure 1. The oldest population-based

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