one study (11). Alcohol consumption has increased in Asian populations, especially Japanese, so as to now reach the levels of Western populations (12). At the same time, half of all Japanese people have an atypical allele of the aldehyde dehydrogenase 2 gene (*ALDH2*; Ref. 13), which catalyzes the acetaldehyde metabolism less (14), resulting in a high blood level of acetaldehyde after drinking (15). Because of this genetic polymorphism, Japanese may have a susceptibility to alcohol consumption different from that in Western populations. Therefore, a study using a Japanese population would be expected to detect a stronger effect of alcohol consumption in relation to colorectal cancer than in Western populations.

Studies over the past decade have consistently reported a positive association between smoking and colorectal cancer (16–20). In addition, it has been revealed that smoking requires a long induction period to lead to colorectal carcinogenesis (19, 20). However, evidences of the association and the public health impact of smoking are only available for Western populations (19, 21). It is important to clarify the public health impact of smoking in populations with a high prevalence of smoking like Japanese men (53.5% of males ≥20 years of age in 2000; Ref. 22).

Therefore, we investigated the association of alcohol consumption, smoking, and their joint effect with colorectal cancer and estimated the population-attributable fraction (PAF) to clarify their public health impact, based on a population-based prospective cohort study.

Materials and Methods

Study Population. The Japan Public Health Center-based prospective study on cancer and cardiovascular disease (JPHC study) started in 1990 for the first group (cohort I) and in 1993 for the second group (cohort II). Cohort I covered 5 areas administered by the Public Health Centers (PHC) in 5 prefectures (Iwate, Akita, Nagano, Okinawa, and Tokyo). Cohort II included 6 PHC areas in 6 prefectures (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). Cohort I comprised all residents aged 40–59 as of January 1, 1990 except for Tokyo, and cohort II comprised all residents aged 40–69 as of January 1, 1993 except for Osaka. The study subjects were identified by population registries maintained by local municipalities. When analyzing the present data, we excluded the subjects in Tokyo whose incidence data were not available, and those in Osaka who were not all within the specific age range. Thus, we defined a population-based cohort of 57,714 men (27,063 in cohort I and 30,651 in cohort II) and 59,182 women (27,435 in cohort I and 31,747 in cohort II). Those deemed ineligible during this study period were excluded, such as non-Japanese (29 men and 20 women), those who had already moved away at baseline (94 men and 57 women), and those outside of the 40–59 age parameters in cohort I (2 women). This left 57,591 men and 59,103 women eligible subjects. This study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. The study design is described in detail elsewhere (23).

Baseline Survey. A self-administered questionnaire was distributed mostly by hand and partly by mail to the JPHC study subjects in 1990 for cohort I and in 1993–1994 for cohort II. They were asked about their personal and familial medical histories, smoking, alcohol consumption, dietary habits, and other lifestyle factors (24–26). Among the eligible subjects, 45,452 men (79%) and 49,924 women (84%) returned the questionnaire. From them, we excluded subjects with a self-reported medical history of cancer and with a diagnosis of colorectal cancer before the survey began (687 men and 1,363 women). This additionally reduced the number of eligible subjects to 44,765 men and 48,561 women. Finally, we excluded subjects with incomplete alcohol and/or smoking items (2,225 men and 1,097 women), leaving 42,540 men and 47,464 women as study subjects.

Assessment of Exposure. The average frequency of alcohol consumption was reported in six categories by cohort I: "less than 1 day/month," "1–3 days/month," "1–2 days/week," "3–4 days/week," "5–6 days/week," and "everyday." Subjects consuming alcoholic beverages at least once a week were also asked about types of drinks and average consumption. Subjects in cohort II were asked about drinking status, *i.e.*, never-, ex-, or current drinkers. Ex- and current drinkers provided information on average frequency, types of drinks, and average consumption per day. The average frequency was divided into four categories: "1–3 days/month," "1–2 days/week," "3–4 days/week," and "almost everyday." We assigned a score to each category of frequency as follows: 1.5 for "1–2/week," 3.5 for "3–4/week," 6 for "5–6/week," and "everyday" in the cohort I questionnaire, and 1.5 for "1–2/week," 3.5 for "3–4/week," and 6 for "almost everyday" in the cohort II questionnaire. The amount of ethanol in each type of alcoholic beverages was calculated as follows: 180 ml sake (rice wine) as 23 g ethanol, 180 ml shochu or awamori (white spirits) as 36 g, 633 ml beer as 23 g, 30 ml whiskey or brandy as 10 g, and 60 ml wine as 6 g. Finally, weekly ethanol intake was estimated by multiplying the amount by the score.

Alcohol consumption was classified into five groups in cohort I: nondrinkers (<1 day/month), occasional drinkers (1–3 days/month), and three groups of regular drinkers (1–149 g/week ethanol, 150–299 g/week, and 300 g/week or more; Table 1). Cohort II was categorized into six groups, because nondrinkers were divided into two groups, ex- and never-drinkers. When analyzing the two cohorts together, we combined ex- and never-drinkers into nondrinkers. Three groups of regular drinkers were combined in the analyses of women (Table 2).

To evaluate the validity of alcohol consumption, we compared the estimates from the questionnaires with the 28-day dietary records (7 days in 4 seasons) provided by volunteers in each cohort. Spearman's rank correlations were 0.79 in 94 men and 0.44 in 107 women of cohort I (27), and 0.59 in 176 men and 0.40 in 178 women of cohort II. The reproducibility of the responses on alcohol intake was 0.78 in men and 0.66 in women of cohort I between 1990 and 1995 (5-year interval; Ref. 27), and 0.72 in men and 0.63 in women of cohort II between 1993 and 1997 (4-year interval). Because we also confirmed that assigning a score of 6 to "5–6/week" and "everyday" was as valid as 5.5 to "5–6/week" and 7 to "everyday" in the comparison with the dietary records in cohort I, we used the score 6 in cohort I as well as in cohort II.[3]

The questions on smoking habits included current and former smoking status, age at initiation of smoking, and average number of cigarettes smoked per day. Smoking intensity for current smokers was evaluated by pack-year defined by multiplying the years of smoking times the average number of cigarettes divided by 20 (28). We classified current smokers by the following categories of smoking intensity: <20 pack-years, 20–29 pack-years, 30–39 pack-years, and ≥40 pack-years.

A high prevalence of current smokers was found in both

[3] Unpublished observations.

Table 1 Baseline characteristics by categories on alcohol consumption and smoking status in men

	Alcohol consumption						Smoking status		
	Ex (Non)	Never (Non)	Occasional	Regular (g/week ethanol) 1–149	Regular (g/week ethanol) 150–299	Regular (g/week ethanol) 300+	Never	Ex	Current
Cohort I *n* (%)	4,191 (21.1)		2,162 (10.9)	4,578 (23.1)	4,501 (22.7)	4,426 (22.3)	4,788 (24.1)	4,543 (22.9)	10,527 (53.0)
Age (years) Mean (SD)	50.0 (6.0)		48.8 (5.9)	49.1 (5.9)	49.4 (5.9)	49.1 (5.8)	49.5 (5.6)	50.2 (6.0)	48.9 (6.0)
Family history of colorectal cancer (%)	1.0		0.9	0.8	1.3	0.9	0.9	1.1	1.0
Body mass index (kg/m^2) Mean (SD)	23.6 (3.0)		24.0 (3.2)	23.6 (2.8)	23.5 (2.7)	23.6 (2.9)	24.0 (2.9)	24.0 (2.9)	23.2 (2.8)
Current smokers (%)	47.6		46.2	45.9	57.9	63.9	–	–	–
Regular drinkers (%)	–		–	–	–	–	59.0	69.4	71.6
Physical exercise (% of 1/week or more)	15.5		19.3	21.0	16.8	16.6	19.6	21.5	15.3
Green vegetables (%)[a]	69.0		69.9	71.8	70.9	67.2	72.7	71.8	67.5
Yellow vegetables (%)[a]	49.2		48.7	49.4	44.2	42.3	51.5	50.0	42.8
Fruits (%)[a]	57.2		55.7	58.7	52.8	47.0	62.4	57.6	48.8
Beef (%)[a]	12.5		11.7	11.3	10.9	12.3	11.1	11.9	12.0
Pork (%)[a]	30.4		25.2	29.9	33.1	32.3	30.3	29.4	31.6
Chicken (%)[a]	24.1		20.2	21.5	23.0	24.1	24.3	22.3	22.4
Fish (%)[a]	44.0		37.4	49.2	54.2	56.3	49.1	49.7	49.7
Cohort II *n* (%)	952 (4.2)	4,886 (21.5)	1,936 (8.5)	5,263 (23.2)	4,785 (21.1)	4,860 (21.4)	5,461 (24.1)	5,532 (24.4)	11,689 (51.5)
Age (years) Mean (SD)	58.2 (8.3)	55.5 (8.9)	51.3 (8.3)	52.2 (8.7)	53.1 (8.6)	52.3 (8.2)	53.4 (8.3)	55.7 (8.9)	52.1 (8.6)
Family history of colorectal cancer (%)	1.8	1.5	2.2	1.6	1.4	1.4	1.1	1.7	1.7
Body mass index (kg/m^2) Mean (SD)	23.1 (3.0)	23.3 (3.6)	24.1 (3.1)	23.3 (2.8)	23.5 (2.8)	23.8 (3.1)	24.0 (2.9)	23.8 (2.9)	23.2 (3.2)
Current smokers (%)	44.4	47.6	47.6	45.8	56.7	60.5	–	–	–
Regular drinkers (%)	–	–	–	–	–	–	59.9	66.0	69.1
Physical exercise (% of 1/week or more)	20.0	17.4	18.8	21.7	19.8	19.0	22.3	24.0	16.1
Green vegetables (%)[a]	56.2	48.4	45.3	50.1	50.8	47.2	54.0	53.5	44.8
Carrot (%)[a]	41.1	33.3	31.7	32.5	30.5	29.0	37.7	35.1	27.4
Apple (%)[a]	25.0	22.0	17.8	19.8	16.2	11.9	21.3	23.5	13.6
Citrus fruits (%)[a]	42.4	44.5	38.0	40.1	34.1	27.2	42.8	43.3	31.2
Beef (%)[a]	3.9	5.2	3.5	4.1	4.1	4.8	4.5	3.5	4.8
Pork (%)[a]	16.1	16.0	14.5	14.0	16.3	18.2	16.4	14.6	16.4
Chicken (%)[a]	11.9	9.0	7.2	7.9	8.1	9.0	8.5	9.3	8.1
Fish (%)[a]	52.7	42.7	41.5	47.4	52.8	57.9	48.7	53.0	48.2

[a] Percentage of 3 days/week or more intake.

male and female regular drinkers (Tables 1 and 2). As the level of weekly regular consumption was higher, the percentage of current smokers was higher in males. As for potential confounding factors, we examined age at baseline, body mass index (kg/m^2; Ref. 29), subjects with a family history of colorectal cancer, those exercising once a week or more, and intake frequency of foods such as vegetables, fruits, meats, and fish. However, the impact of these factors showed no positive or negative trend by categories on alcohol consumption and smoking status (Tables 1 and 2). Baseline characteristics by categories on alcohol consumption have also been shown elsewhere (30).

Follow-Up. We followed study subjects until December 31, 1999. When subjects died, we used mortality data from the Ministry of Health, Labor, and Welfare. Subjects moving to other municipalities were also annually identified through residential registers in PHC areas. Among study subjects, 5.0% moved away and 0.04% were lost to follow-up during the study period.

Identification of Colorectal Cancer Incidence. After January 1, 1990 in cohort I and January 1, 1993–1994 in cohort II, incidence data on colorectal cancer were collected for the JPHC cancer registry through two data sources, local major hospitals and population-based cancer registries. Death certificates were used to supplement the information on cancer incidence.

Cases of colorectal cancer were extracted from the JPHC cancer registry based on site codes [International Classification of Diseases for Oncology, second edition (ICD-O-2) code: C180–189 (colon) and C199, 209 (rectum); Ref. 31]. Up to December 31, 1999, 772 incident cases of colorectal cancer were identified. For multiple primary cancers in colon or rectum at different times, the earliest diagnosis was applied. For those occurring simultaneously, the most advanced and most invasive diagnosis was applied. Among these incident cases, 716 were pathologically confirmed as adenocarcinoma (M: 8140, 8210, 8211, 8240, 8243, 8260, 8261, 8262, and 8263 for ICD-O-2). Such cases were additionally classified into two groups according to the depth of tumor invasion, *i.e.*, invasive cancer over a mucosal layer corresponding to code 3 (malignant, primary site) in "behavior code for neoplasms" (298 colon cases and 206 rectal cases), and noninvasive cancer within a mucosal layer corresponding to code 2 (carcinoma *in situ*; 165 colon and 38 rectum) in ICD-O-2 (the depth in 5 colon and 4 rectal tumors were unknown).

In our cancer registry system, the proportion of cases for which information was available only from death certificates was 1.0% for colorectal cancer and 3.1% for all of the cancers during the study period. These figures were considered of satisfactory quality for the present study based on the international standard (1).

Table 2 Baseline characteristics by categories on alcohol consumption and smoking status in women

	Alcohol consumption				Smoking status		
	Ex	Never (Non)	Occasional	Regular	Never	Ex	Current
Cohort I *n* (%)	16,668 (77.5)		2,567 (11.9)	2,281 (10.6)	19,934 (92.6)	369 (1.7)	1,213 (5.6)
Age (years) Mean (SD)	49.9 (5.8)		48.3 (5.8)	48.2 (5.8)	49.5 (5.8)	49.2 (6.4)	48.5 (5.9)
Family history of colorectal cancer (%)	0.8		1.5	1.1	0.9	0.6	0.8
Body mass index (kg m^{-2}) Mean (SD)	23.7 (3.3)		23.5 (2.9)	23.2 (2.9)	23.6 (3.2)	24.2 (3.4)	23.4 (3.8)
Current smokers (%)	4.1		6.6	16.2	–	–	–
Regular drinkers (%)	–		–	–	9.2	24.4	30.3
Physical exercise (% 1/week or more)	13.4		17.6	17.4	14.3	17.2	13.7
Green vegetables (%)[a]	78.4		75.3	78.3	78.5	71.3	72.4
Yellow vegetables (%)[a]	65.5		63.6	61.5	65.5	61.0	55.0
Fruits (%)[a]	73.7		79.1	73.0	75.4	67.0	59.2
Beef (%)[a]	10.0		9.1	11.2	9.7	13.2	14.0
Pork (%)[a]	32.4		35.6	34.6	33.1	32.7	31.4
Chicken (%)[a]	29.9		29.3	28.1	30.0	27.5	25.2
Fish (%)[a]	53.8		55.2	59.9	55.2	47.9	48.4
Cohort II *n* (%)	223 (0.9)	21,112 (81.4)	2,112 (8.1)	2,501 (9.6)	24,133 (93.0)	278 (1.1)	1,537 (5.9)
Age (years) Mean (SD)	53.7 (8.4)	54.9 (8.7)	49.1 (7.5)	50.1 (8.0)	54.0 (8.8)	53.9 (9.6)	51.4 (8.6)
Family history of colorectal cancer (%)	–	1.3	1.4	1.6	1.4	1.3	0.8
Body mass index (kg/m^2) Mean (SD)	23.6 (3.8)	23.6 (3.3)	23.5 (3.1)	23.1 (3.2)	23.5 (3.2)	23.8 (3.4)	23.2 (3.8)
Current smokers (%)	28.1	3.9	9.0	18.6	–	–	–
Regular drinkers (%)	–	–	–	–	8.5	26.7	31.2
Physical exercise (% 1/week or more)	20.2	18.5	19.6	21.5	19.1	17.9	16.0
Green vegetables (%)[a]	61.6	61.2	56.4	60.8	61.5	59.6	49.9
Carrot (%)[a]	52.2	53.0	49.2	45.9	52.9	45.8	38.4
Apple (%)[a]	29.6	33.6	31.2	30.7	33.9	26.3	21.7
Citrus fruits (%)[a]	55.2	60.9	60.9	57.6	61.6	51.3	44.8
Beef (%)[a]	6.9	4.2	5.1	5.3	4.4	5.0	5.4
Pork (%)[a]	15.8	18.8	18.8	17.3	18.8	13.8	16.2
Chicken (%)[a]	8.4	10.2	9.6	9.4	10.2	11.3	8.5
Fish (%)[a]	52.7	49.1	45.9	52.9	49.7	51.7	42.5

[a] Percentage of 3 days/week or more intake.

Statistical Analysis. Person-years of follow-up were determined from January 1, 1990 (cohort I) or 1993–1994 (cohort II) until the date of diagnosis of colorectal cancer, the date of a subject's death, the date of moving from a PHC area, or December 31, 1999, whichever occurred first. Incidence rates of colorectal cancer were calculated using person-years as the denominators and standardized with a 5-year age distribution at baseline in each cohort (40–44, 45–49, 50–54, and 55–59 in cohort I, and 40–44, 45–49, 50–54, 55–59, 60–64, and 65–69 in cohort II; Ref. 32).

Relative risks (RRs) and 95% confidence intervals (CIs) for alcohol consumption and smoking were estimated by the Cox proportional hazards model, according to the SAS PHREG procedure (33). The estimates were adjusted for the following potential confounding factors incorporated into the model: age (5-year groups), family history of colorectal cancer (anyone or none), body mass index (quartiles in each cohort), physical exercise (less than once a week and once a week or more), smoking status (when calculating RR for alcohol consumption; never-, ex-, and current smokers), alcohol consumption (when calculating RR for smoking status and intensity; nondrinkers, occasional drinkers, 1–149 g/week, 150–299 g/week, and ≥300 g/week), and PHC area. The factors relating to dietary habits, which were slightly different between both cohorts, were not considered as confounding factors, because they hardly affected the RR of alcohol consumption and smoking status. The linear trend of alcohol consumption or smoking intensity was assessed by assignment of ordinal values to categories among drinkers or current smokers, respectively. *P*s for those trends were evaluated using the two-sided test with 0.05 as the significance level.

First, we estimated the RR of all cases of colorectal cancer in each cohort, because slightly different questionnaires were used. Second, in addition to all of the cases, we combined two cohorts and calculated the RRs and the linear trends of invasive colorectal, colon, and rectal cancer to obtain more power to detect the association after confirming the same risk trend in the two cohorts. When we estimated the RR of the invasive, we defined the noninvasive as a censored case. Similarly, we considered rectal cancer as a censored case in colon cancer end point and colon cancer as a censored case in rectal cancer end point.

We also calculated the RRs of colorectal cancer for combined categories of alcohol consumption and smoking status, and tested statistical interactions, using the differences between two likelihood ratios of the models with and without the interaction terms between alcohol consumption and smoking status (34).

Table 3 Age-standardized incidence rate, multivariate-adjusted relative risk (RR), and 95% confidence interval (CI) of colorectal cancer by categories on alcohol consumption in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999)

	Ex-drinkers	Never-drinkers (Nondrinkers)	Occasional drinkers	Regular drinkers (g/week ethanol)			*P* for trend among drinkers
				1–149	150–299	300+	
Cohort I (aged 40–59)							
No. of cases (n = 244)	42		15	39	58	90	
Person-years	39,165		20,305	42,812	42,470	41,134	
Incidence rates[a]	104.7		78.7	91.8	135.2	226.4	
RR[b] (95% CI) (n = 240)	1.0 (reference)		0.8 (0.4–1.4)	0.9 (0.6–1.4)	1.2 (0.8–1.8)	2.0 (1.4–3.0)	<0.001
Cohort II (aged 40–69)							
No. of cases (n = 213)	8	40	10	46	50	59	
Person-years	5,817	30,939	12,483	33,277	30,500	31,196	
Incidence rates[a]	99.0	109.8	92.2	149.6	166.0	207.7	
RR[b] (95% CI) (n = 207)	0.9 (0.4–2.0)	1.0 (reference)	0.9 (0.4–1.9)	1.5 (0.9–2.3)	1.6 (1.1–2.5)	2.0 (1.3–3.0)	0.024

[a] Incidence rate (per 100,000 person-years) standardized by distribution of 5-year age groups at baseline in each cohort.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), smoking status (never-, ex-, and current smokers), physical exercise (less than once a week and once a week or more), and 4 Public Health Center (PHC) areas in Cohort I or 5 PHC areas in Cohort II

The PAF was estimated by $P_c(RR_a - 1)/RR_a$, where P_c was the prevalence of exposure among incident cases and RR_a was the adjusted RR. The 95% CI of the PAFs were estimated by the formula of Greenland (35). We estimated the PAFs of drinkers to nondrinkers, current and ex-smokers to never-smokers, and drinkers currently and formerly smoked to non-drinkers never smoked.

In women, RRs were estimated only in both cohorts combined, because of the few cases and noncases in drinkers and/or smokers, and the insufficient statistical power by each cohort.

Results

Age-standardized incidence rates increased among drinkers in both cohorts (Table 3). Drinkers consuming ≥300 g/week had a higher risk of colorectal cancer compared with nondrinkers in both cohort I (RR, 2.0; 95% CI, 1.4–3.0) and cohort II (RR, 2.0; 95% CI, 1.3–3.0). We observed linear positive trends of RR according to the level of alcohol consumption ($P < 0.001$ in cohort I and $P = 0.024$ in cohort II). The risk of ex-drinkers did not substantially differ from those of nondrinkers in cohort II.

The RR of invasive cancer for alcohol consumption showed the same trend as all of the cases of colorectal cancer (RR, 2.1 in all cases and 1.7 in invasive cancer for those consuming ≥300 g/week to nondrinkers; Table 4). The association with alcohol consumption was also shown in both colon and rectal cancer, as well as in all of the cases. Statistical significance in linear trends was consistent among all endpoints. The PAF% for alcohol consumption at least occasional drinking to nondrinking was 24% (95% CI, 8–38%) in all colorectal cancer (7% to 150–299 g/week and 17% to ≥300 g/week).

Meanwhile, the RRs of current smokers for colorectal cancer were 1.5 (95% CI, 0.9–2.1) in cohort I, 1.2 (95% CI, 0.8–1.8) in cohort II, and 1.4 (95% CI, 1.1–1.8) in two cohorts combined, compared with never-smokers (Table 5 shows only the combined results). The association did not change after exclusion of noninvasive cases and did not depend on the subsite. The nonsignificant linear trend was obtained according to smoking intensity except for rectal cancer. Furthermore, long-term smoking significantly elevated the risk compared with never-smoking: RR, 1.3 (95% CI, 0.7–2.2) for ≤25 years, 1.4 (0.9–2.2) for 25–29 years, 1.4 (0.99–2.1) for 30–34 years, and 1.5 (1.1–2.0) for ≥35 years. Smoking intensity in the remote past (before age 30 years) showed no dose-response relationship (data not shown). The PAF% for currently and formerly smoking to never-smoking was 22% (95% CI, 9–36%).

Next, we assessed the joint effect of alcohol consumption and smoking status in men (Table 6). Colorectal cancer risk for drinkers of ≥300 g/week of ethanol who smoked was estimated at 3.0 (95% CI, 1.8–5.1), compared with nondrinkers who never smoked. The association did not differ between colon and

Table 4 Relative risk (RR) and 95% confidence interval (CI) of colorectal cancer by the depth of tumor invasion and the site in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999) combined

	Nondrinkers	Occasional drinkers	Regular drinkers (g/week ethanol)			*P* for trend among drinkers
			1–149	150–299	300+	
Person-years	74,123	32,273	75,001	71,933	71,194	
Colorectal cancer[a] (n = 447)	87	24	83	107	146	
RR[b] (95% CI)	1.0 (reference)	0.8 (0.5–1.3)	1.1 (0.8–1.5)	1.4 (1.1–1.9)	2.1 (1.6–2.7)	<0.001
Invasive colorectal cancer (n = 298)	65	18	53	72	90	
RR[b] (95% CI)	1.0 (reference)	0.9 (0.5–1.5)	1.0 (0.7–1.5)	1.3 (0.9–1.9)	1.7 (1.2–2.4)	<0.001
Colon cancer[a] (n = 299)	62	16	51	71	99	
RR[b] (95% CI)	1.0 (reference)	0.8 (0.4–1.3)	1.0 (0.7–1.4)	1.3 (0.9–1.8)	1.9 (1.4–2.7)	<0.001
Rectal cancer[a] (n = 148)	25	8	32	36	47	
RR[b] (95% CI)	1.0 (reference)	1.0 (0.5–2.3)	1.6 (0.9–2.6)	1.7 (1.01–2.8)	2.4 (1.5–4.0)	0.015

[a] Including noninvasive and invasive cancers.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), smoking status (never-, ex-, and current smokers), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

Table 5 Relative risk (RR) and 95% confidence interval (CI) for smoking status and intensity in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999) combined

	Never-smokers	Ex-smokers	Current smokers	(Pack-years)				*P* for trend among current smokers
			All	<20	20–29	30–39	40+	
Person-years	78,706	76,424	169,394	32,566	45,323	41,855	46,080	
Colorectal cancer[a] (*n* = 447)	78	124	245	33	50	73	83	
RR[b] (95% CI)	1.0 (reference)	1.3 (0.98–1.7)	1.4 (1.1–1.8)	1.1 (0.8–1.7)	1.3 (0.9–1.9)	1.4 (1.05–2.0)	1.4 (0.99–1.8)	0.47
Invasive colorectal cancer (*n* = 298)	50	85	163	23	32	43	60	
RR[b] (95% CI)	1.0 (reference)	1.5 (1.02–2.1)	1.6 (1.1–2.1)	1.3 (0.8–2.2)	1.4 (0.9–2.2)	1.4 (0.9–2.1)	1.6 (1.1–2.3)	0.64
Colon cancer[a] (*n* = 299)	53	86	160	17	31	55	54	
RR[b] (95% CI)	1.0 (reference)	1.4 (0.96–1.9)	1.4 (0.99–1.9)	0.9 (0.5–1.5)	1.2 (0.8–2.0)	1.7 (1.1–2.4)	1.3 (0.9–2.0)	0.16
Rectal cancer[a] (*n* = 148)	25	38	85	16	19	18	29	
RR[b] (95% CI)	1.0 (reference)	1.2 (0.7–2.0)	1.4 (0.9–2.3)	1.6 (0.9–3.0)	1.5 (0.8–2.7)	1.0 (0.6–1.9)	1.4 (0.8–2.3)	0.48

[a] Including noninvasive and invasive cancers.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), alcohol consumption (nondrinkers, occasional, 1–149 g, 150–299 g, and 300 g+), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

rectum. We detected no interaction between alcohol consumption and smoking status (*P* for interaction = 0.88 in colorectum, 0.75 in colon, and 0.44 in rectum). The PAF% for alcohol consumption and/or currently or formerly smoking was estimated at 46% (95% CI, 14–66%), compared with nondrinking and never-smoking.

Female regular drinkers had no elevated risk of colorectal cancer compared with nondrinkers (RR, 0.7; 95% CI, 0.4–1.1; Table 7). Occasional drinkers to nondrinkers were inversely associated with colorectal cancer (RR, 0.5; 95% CI, 0.3–0.9). Female ex- and current smokers had a nonsignificant increased risk of colorectal cancer, as well as male ex- and current smokers (RR, 1.3; 95% CI, 0.5–3.6 for ex-smokers; RR, 1.4; 95% CI, 0.8–2.4 for current smokers).

Discussion

Our results confirmed that alcohol consumption was positively associated with colorectal cancer in a Japanese population of middle-aged and elderly men. A clear linear trend of RR was observed among drinkers. However, the RR for 24 g/day increment of alcohol consumption did not substantially differ from the result of a previous meta-analysis (36), which estimated the pooled RR at 1.32 (against 1.11, 95% CI, 1.06–1.17 in the present study; data not shown in tables).

Female regular drinkers showed no increased risk of colorectal cancer. Eighty percent of them were categorized into the lowest group (1–149 g/week ethanol). In men, the lowest group of regular drinkers showed no significant risk of colorectal

Table 6 Relative risk (RR) and 95% confidence interval (CI) for alcohol consumption and smoking status in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999) combined

	Nondrinkers	Occasional drinkers	Regular drinkers (g/week ethanol)			*P* for interaction
			1–149	150–299	300+	
Colorectal cancer[a] (*n* = 447)						
Never-smokers (*n* = 78)	17	8	20	15	18	0.88
RR[b] (95% CI)	1.0 (reference)	1.2 (0.5–2.8)	1.3 (0.7–2.5)	1.4 (0.7–2.9)	2.2 (1.1–4.3)	
Ex-smokers (*n* = 124)	30	6	20	28	40	
RR[b] (95% CI)	1.6 (0.9–3.0)	1.2 (0.5–3.1)	1.3 (0.7–2.5)	1.9 (1.04–3.5)	3.2 (1.8–5.7)	
Current smokers (*n* = 245)	40	10	43	64	88	
RR[b] (95% CI)	1.5 (0.8–2.6)	1.1 (0.5–2.4)	1.9 (1.1–3.4)	2.2 (1.3–3.8)	3.0 (1.8–5.1)	
Colon cancer[a] (*n* = 299)						
Never-smokers (*n* = 53)	11	5	12	13	12	0.75
RR[b] (95% CI)	1.0 (reference)	1.1 (0.4–3.3)	1.2 (0.5–2.7)	1.9 (0.8–4.2)	2.2 (0.97–5.0)	
Ex-smokers (*n* = 86)	21	3	11	21	30	
RR[b] (95% CI)	1.8 (0.9–3.7)	0.9 (0.3–3.3)	1.1 (0.5–2.6)	2.2 (1.04–4.5)	3.6 (1.8–7.3)	
Current smokers (*n* = 160)	30	8	28	37	57	
RR[b] (95% CI)	1.7 (0.9–3.4)	1.3 (0.5–3.3)	1.9 (0.96–3.9)	2.0 (1.01–3.9)	3.0 (1.6–5.7)	
Rectal cancer[a] (*n* = 148)						
Never-smokers (*n* = 25)	6	3	8	2	6	0.44
RR[b] (95% CI)	1.0 (reference)	1.3 (0.3–5.4)	1.6 (0.5–4.6)	0.6 (0.1–2.9)	2.3 (0.7–7.1)	
Ex-smokers (*n* = 38)	9	3	9	7	10	
RR[b] (95% CI)	1.4 (0.5–3.8)	1.8 (0.4–7.2)	1.7 (0.5–4.7)	1.4 (0.5–4.2)	2.4 (0.9–6.6)	
Current smokers (*n* = 85)	10	2	15	27	31	
RR[b] (95% CI)	1.0 (0.4–2.8)	0.6 (0.1–3.1)	1.9 (0.7–4.8)	2.7 (1.1–6.5)	3.1 (1.3–7.5)	

[a] Including noninvasive and invasive cancers.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

Table 7 Age-standardized incidence rate, multivariate-adjusted relative risk (RR) and 95% confidence interval (CI) of colorectal cancer by categories on alcohol consumption and smoking status in Cohort I women (1990–1999) and Cohort II (1993–1999) women combined

	Alcohol consumption			Smoking status		
	Nondrinkers	Occasional drinkers	Regular drinkers	Never-smokers	Ex-smokers	Current smokers
No. of cases (n = 259)	230	12	17	239	4	16
Person-years	300,634	38,181	37,706	350,470	5,209	20,841
Incidence rate[a]	76.3	40.2	52.9	69.9	78.4	91.0
RR[b] (95% CI) (n = 253)	1.0 (reference)	0.5 (0.3–0.9)	0.7 (0.4–1.1)	1.0 (reference)	1.3 (0.5–3.6)	1.4 (0.8–2.4)

[a] Incidence rate (per 100,000 person-years) standardized by distribution of 5-year age group at baseline in both cohorts.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), smoking status (when calculating RR for alcohol consumption; never-, ex-, and current smokers), alcohol consumption (when calculating RR for smoking status; non-, occasional, regular drinkers), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

cancer. Thus, female regular drinkers may not be associated with colorectal cancer because of the small proportion of heavy drinkers.

On the basis of our estimate, 24% of colorectal cancer was attributable to alcohol consumption in men. Because relatively heavy drinkers (≥150 g/week = ≥1.5 drinks/day) contribute to a large part of the PAF, a reduction in the number of such drinkers may lead to a decrease in colorectal cancer. To our knowledge, no reported prospective studies estimated the PAF of alcohol consumption in colorectal cancer. One case-control study evaluated the PAF as 19% (37).

One reason for the high PAF may be the high prevalence of heavy drinkers. Men in the highest categories who weekly consumed ≥300 g/week of ethanol (≥3 drinks/day) accounted for 22% in our study. In the case-control study estimating the PAF (37), drinkers consuming only ≥0.7 drinks/day accounted for 33% of male controls. Moreover, based on calculation of the published numbers, in other cohort studies, the highest consumers either took at most "2 drinks/day or more" or accounted for a smaller percentage: 14% of subjects consumed ≥2.5 drinks/day in a Netherlands study (5); men accounted for 14% of person-years consuming ≥2 drinks/day in a Health Professionals Follow-up Study (6); 21% of subjects consumed ≥2 drinks/day in a Hawaiian-Japanese study (8); and only 8.7% of subjects consumed ≥3 drinks/day in a United States study (38).

Another reason may be the different distribution of the genetic polymorphisms on alcohol-related enzymes including *ALDH2* in Japanese, although we have not investigated the genetic polymorphisms in our subjects. The *ALDH2* genotypes with the atypical allele (Glu487Lys) [frequency: 0.28 in Japanese (13) *versus* <0.03 in Caucasian (39)] exert little ALDH2 activity (40) and cause a high acetaldehyde levels in blood (15). Although acetaldehyde has not been concluded to be a human colorectal carcinogen, some *in vitro* and animal studies suggest that acetaldehyde triggers carcinogenesis in the colorectum (41–43) via folate deficiency (44, 45). However, because the magnitude of RR in our study population was not higher than that of a pooled one as mentioned above (36), the effect of such genetic susceptibility may be limited.

Current and ex-smokers had an increased risk of colorectal cancer in men and women. The risk showed a nonsignificant linear trend according to smoking intensity in men. We also confirmed that the long-term smoking elevated the risk in men. Smoking intensity before age 30 years, however, failed to show the dose-response relationship seen in a previous study (19), possibly due to estimating the remote past pack-years using current numbers of cigarettes smoked per day.

Recent prospective studies consistently reported a positive association of smoking adjusted for potential confounding factors (17, 18), especially when accounting for the long induction period (19, 20). In addition, tobacco smoke includes various carcinogens such as polynuclear aromatic hydrocarbons and *N*-nitrosamines. These carcinogens in tobacco smoke are reasonable risks for colorectal carcinogenesis (46, 47). As mentioned in a recent review regarding the causality (16), evidence has been sufficiently accumulated to add colorectal cancer to the list of tobacco-associated malignancies. In the present study of a Japanese population, we could attribute 22% of colorectal cancer to currently and formerly smoking. In the Health Professionals Follow-up Study, smoking was responsible for 21% of the incidence of this cancer (19). The Cancer Prevention Study II reported that 12% of colorectal cancer deaths were attributable to smoking (21). Therefore, we can expect to reduce a large part of colorectal cancer by eliminating tobacco consumption, especially in the population with the high prevalence of smoking.

Many previous studies have defined invasive adenocarcinoma as "colorectal cancer." However, in our opinion, "colorectal cancer" should be defined as not only invasive adenocarcinoma but also noninvasive adenocarcinoma. Thus, we needed to confirm that our definition is comparable with the Western definition. As a result, the RR of all cases (including the noninvasive type) approximately corresponded to those of only the invasive type. However, 2 case-control studies showed that pack-years as smoking intensity was associated significantly with the noninvasive type rather than the invasive type (48, 49). Additional studies will be needed to determine whether or not the association of some risk factors differs in terms of these two definitions.

The major strengths of our study include its prospective design, a general population with a high response rate (80%), and the relatively low proportion of subjects lost to follow-up (0.04%). Information on alcohol consumption and smoking was collected before any subsequent diagnosis of colorectal cancer, thus avoiding the exposure recall bias inherent in case-control studies. The findings of this study can be generalized to middle-aged and elderly Japanese men, because the study subjects were selected from the general population, and there was a high response rate. Moreover, two cohorts starting at different times produced the same results.

The adjustment for the frequencies of food intake did not change the RR estimates of alcohol consumption and smoking status (data not shown). In addition, recent prospective studies have reported the weak association of fruits and vegetables (50), and meats (51). Thus, no food variables were used in the final multivariate model. However, we could not examine whether or not some nutrients, such as folate and methionine (6), affected the association of alcohol consumption and smoking status because of the inavailability of these nutrients.

In conclusion, alcohol consumption dose-dependently in-

creased the risk of colorectal cancer in men. Smoking was also associated significantly with colorectal cancer in men and not significantly in women. From the risk estimates, 46% of colorectal cancer is attributable to alcohol consumption and smoking in middle-aged and elderly Japanese men.

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Gastric Cancer Surgery: Morbidity and Mortality Results From a Prospective Randomized Controlled Trial Comparing D2 and Extended Para-Aortic Lymphadenectomy—Japan Clinical Oncology Group Study 9501

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
Radical gastrectomy with regional lymphadenectomy is the only curative treatment option for gastric cancer. The extent of lymphadenectomy, however, is controversial. The two European randomized trials only reported an increase in operative morbidity and mortality, but failed to show survival benefit, in the D2 lymphadenectomy group. We conducted a randomized controlled trial to compare the Japanese standard D2 and D2 + para-aortic nodal dissection.

Patients and Methods
Only experienced surgeons in both procedures from 24 Japanese institutions participated in the study. Patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) who were surgically fit were intraoperatively randomized. Postoperative morbidity and hospital mortality were recorded prospectively in a fixed format and were compared between the two groups in this study.

Results
A total of 523 patients were randomized between July 1995 and April 2001. Postoperative complications were reported in 24.5% of all patients. Although the morbidity for the extended surgery group (28.1%) was slightly higher than the standard group (20.9%), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the two groups. Hospital mortality was reported at 0.80%: one patient in each group died of operative complications, while one from each group died of rapid progressive cancer while inpatient.

Conclusion
Specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Para-aortic lymphadenectomy could be added without increasing major surgical complications in this setting.

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Gastric cancer is the second most common malignancy in the world, and surgical resection remains the only curative treatment option. Lymph node metastases occur during the early stages of this disease, and regional lymphadenectomy is recommended as part of radical gastrectomy. However, the extent of lymphadenectomy to achieve the optimal result is controversial, and there is no worldwide consensus.

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s.[1] This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches). Early studies have reported that between 30% to 40% of patients

Table 1. Eligibility Criteria of the Study

Before operation
Entry criteria
Histologically proven adenocarcinoma
75 years or younger
Forced expiratory volume in 1 second ≥ 50%
Arterial oxygen pressure in room air ≥ 70 mm Hg
Creatinine clearance ≥ 50 mL/min
Written consent
Exclusion criteria
Carcinoma in the remnant stomach
Borrmann type 4 (linitis plastica)
Synchronous or metachronous malignancy in other organs except for cervical carcinoma in situ and colorectal focal cancer in adenoma
Past history of myocardial infarction or positive results of exercise ECG
Liver cirrhosis or chronic liver disease with indocyanine green test 10%
During operation
Macroscopic T staging is T2-subserosa, T3, or T4
Potentially curative operation is possible
No gross metastasis in para-aortic nodes (frozen section diagnosis not allowed)
Peritoneal lavage cytology is negative for cancer cells

with positive lymph node metastases including the second tier lymph nodes, have survived longer than 5 years with D2 lymphadenectomy.[2] However, D2 gastrectomy has a steep learning curve,[3] and may be associated with a higher-than-expected operative morbidity and mortality.

Two European randomized controlled trials comparing D1 and D2 gastrectomy revealed a high operative mortality exceeding 10% in the D2 group.[4,5] Based on these reports, the British National Health Service Cancer Guidance discourages the use of D2 technique in routine clinical practice.[6] In contrast, D2 gastrectomy is considered a standard and safe procedure in Japan, where 100,000 cases of gastric cancers are diagnosed every year. General surgeons are taught this technique early during their surgical training.[7] The Japanese nationwide registry reported an operative mortality of less than 2%, and in specialized institutions, less than 1% for D2 gastrectomy.[8,9]

Since the eighties, even more radical extended lymphadenectomy procedures had been practiced in many Japanese specialized centers. It was reported that 20% to 30% of patients with nonearly gastric cancer had microscopic metastasis present in the para-aortic nodes.[10-13] The 5-year survival for these patients has reached 14% to 30% after extended systematic dissection. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected, primarily for ultimate local tumor control. However, this extended dissection may not only increase operative morbidity but also may effect the function of other abdominal organs.

There has never been a prospective study to assess the perioperative morbidity and mortality in Japanese patients after D2 gastrectomy or more extended surgery. To evaluate the survival benefit and operative complications of D2 gastrectomy and extended para-aortic dissection in gastric cancer surgery, a multi-institutional randomized controlled trial was conducted on behalf of the Japan Clinical Oncology Group (JCOG). The accrual closed with 523 patients. We hereby present the data on the operative morbidity and mortality, which are the secondary end points of this trial. Survival analysis is scheduled to take place in August 2006.

Objectives and End Points of the Study

A prospective randomized controlled trial was designed to compare the two surgical techniques: the standard lymphadenectomy and the standard lymphadenectomy with the addition of para-aortic node dissection for gastric cancer. Only surgeons with sufficient experience of para-aortic dissection for gastric cancer participated in the trial. Since the role of neoadjuvant and adjuvant chemotherapy was not established, no patients received chemotherapy until recurrent disease was diagnosed.

The primary end point was the overall survival, while the secondary end points were the relapse-free survival, operative morbidity, hospital mortality, and quality of life. Randomization and data handling for this study was performed by the Data Centre of the JCOG, a government-sponsored organization for multi-institutional clinical trials.[14]

Eligibility Criteria

Eligibility criteria for this study are shown in Table 1. Patients with advanced gastric cancer deemed curable and fit for surgery were recruited into the trial following informed consent. Borrmann type 4 tumors (linitis plastica) were excluded because of their very poor prognosis after surgery. Liver cirrhosis and ischemic heart disease were important risk factors for mortality after surgery and hence were excluded from the study. Para-aortic lymph node metastasis is extremely rare in T1 (invasion confined

to the mucosa or submucosa) and T2-MP tumors (invasion confined to the muscularis propria); hence, these patients were not eligible for randomization. Only patients diagnosed with T2-SS (subserosal invasion) or deeper tumors at the time of laparotomy were included in the study. T2-SS is clinically recognized as a white discoloration on the serosal surface, without overt tumor serosal exposure.

During the operation, the para-aortic nodes were inspected to exclude patients with gross metastasis (enlarged and/or hard nodes) in this region. Frozen section diagnosis of the para-aortic nodes was forbidden to avoid technical contamination between the two groups of patients. Peritoneal lavage cytology was performed immediately after initial laparotomy, and absence of free cancer cells was confirmed before enrollment.

Random Assignment

While waiting for the result of lavage cytology, the surgeon examined the above eligibility criteria and started the D2 procedure. When the negative cytology result was obtained 30 to 60 minutes later, he informed the JCOG Data Centre for enrollment. Patients were then randomly assigned either to receive standard lymphadenectomy (group A) or extended lymphadenectomy (group B). The sizes of the groups were balanced according to T stage (T2 *v* T3/T4), tumor growth pattern (expansive *v* infiltrative growth), and institution. The randomization arm was notified to the surgeon immediately, who then completed the operation according to the allocated protocol.

Surgical Methods

Group A: Standard D2 gastrectomy. Patients were treated with gastrectomy and D2 lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total, proximal subtotal, or distal subtotal gastrectomy. D2 lymphadenectomy was a standard procedure for dissection of tumors located in the upper two thirds of the stomach as defined in the 12th edition of the Japanese Classification (1993)[15] when the study was initially designed. An extended D2 lymphadenectomy was performed for tumors located in the lower third of the stomach, which involves further dissecting the hepatoduodenal nodes (No.12a), retropancreatic nodes (No.13) and nodes along the superior mesenteric vein (No.14v). This technique was frequently performed as a standard procedure in the specialized centers, and thus adopted in this study (all except No.13 have been integrated as "D2" in the 13th edition of Japanese classification[16]).

In total or proximal subtotal gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy, while it was preserved in distal subtotal gastrectomy for distal tumors.

Group B: D2 gastrectomy combined with para-aortic lymphadenectomy. Patients in this group had similar procedure to group A, but with additional para-aortic lymph node dissection. The area to be dissected was defined in the Japanese classification (Fig 1). Proximal tumors were treated with the standard D2 lymphadenectomy, and also all "No.16-a2" (para-aortic nodes between the level of the celiac axis and the left renal vein) and "No.16-b1" (para-aortic nodes between the left renal vein and the inferior mesenteric artery) were removed. Standard distal subtotal gastrectomy was performed for the distal tumors including the "No.16-a2" and "No.16-b1" nodes; however, dissection of the left upper lateral nodes ("No.16-a2-lat") was optional.

Both group A and group B patients were followed up according to a fixed schedule, without receiving adjuvant chemotherapy.

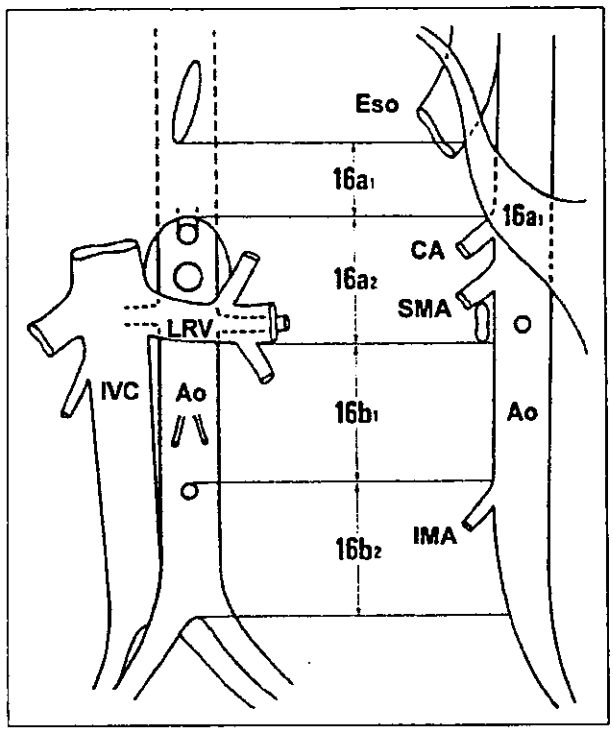

Fig 1. Anatomic definitions of para-aortic lymph nodes.[15] The nodes No.16a2 and No.16b1 are defined as "regional nodes" and were dissected in the extended surgery group. Ao, aorta; CA, celiac artery; Eso, esophagus; IMA, inferior mesenteric artery; IVC, inferior vena cava; LRV, left renal vein; SMA, superior mesenteric artery.

Evaluation of Operative Morbidity and Mortality

Operative methods and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma.[15] The following information was included on the case report form for prospective data collection concerning the four major groups of operative morbidity: presence or absence of anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia. Anastomotic leak was diagnosed radiologically either on routine postoperative contrast swallow or based on clinical suspicion, and was recorded regardless of its clinical significance. Pancreatic fistula was usually diagnosed when fluid with a high amylase concentration drained from the peripancreatic area for more than 7 days.

Other complications were recorded on a free format. The duration of surgery, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization.

Sample Size

The projected 5-year survival rates for groups A and B patients were 50% and 62%, respectively, and we initially planned to recruit 412 patients (206 each group) to detect this difference with one-sided α error of .05 and statistical power of 80%. At first, the recruitment was slow, but it improved as the study progressed. When the planned recruitment was almost achieved, the JCOG Clinical Trial Review Committee approved the amendment to increase the number of patients to 520 (260 each group) to

Table 2. Patients' Demographics and Tumor Characteristics

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)
Male-female ratio	176/87 = 2.02	182/78 = 2.33	358/165 = 2.17
Age, years			
Median	60	61	61
Range	25-75	27-75	25-75
Tumor diameter, cm			
Median	5.5	5.5	5.5
Range	2-17	2-15.2	2-17
T-stage (macroscopic)			
T2-SS	99	93	192
T3	150	159	309
T4	14	8	22
Tumor location			
Upper 1/3	53	47	100
Middle 1/3	103	103	206
Lower 1/3	107	110	217

NOTE. All data are numbers of patients except where otherwise indicated.
Abbreviation: SS, subserosal invasion.

enforce the statistical power to detect 8% difference in the 5-year survival rates, with a 5.5-year accrual period and an additional 5-year follow-up.

Institutions and Quality Control of Surgery

The approval of the institutional review board from all participating institutions was obtained. Initially, the 12 institutions of the Gastric Cancer Surgical Study Group of the JCOG participated in the trial. Twelve institutions were added to increase patient recruitment before February 1999.

All participating surgeons agreed to the technical details for surgery during the planning stages of this trial. Significant experience in gastric cancer surgery, especially experience in extended lymphadenectomy, was a prerequisite for a surgeon's participation in the trial. Surgeons with experience of more than 100 D2 gastrectomies, or institutions with a specialized unit with annual gastrectomy volume of 80 cases or more were selected.

During the recruitment period, participating surgeons and Data Centre representatives met three times per year to monitor the study. In each meeting, videos of para-aortic dissection were presented for critique from four or five institutions, and the technical details were discussed. To assess compliance with lymphadenectomy, dissection, node recovery status in all nodal "stations," and the number of dissected nodes in the para-aortic area were recorded in the case report form, and the results were monitored.

Statistical Methods

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between groups were evaluated using Fisher's exact test. Differences in length of hospital stay and blood loss were compared by Wilcoxon test. All P values are two-sided, and statistical analysis was done using SAS (SAS Institute, Cary, NC) version 8.12.

Recruitment

Recruitment commenced in July 1995, and closed in April 2001. A total of 523 patients were enrolled: 263 in group A and 260 in group B. A large variance was observed for the number of patients recruited between the institutions. Fifty-three percent of all patients were recruited by the five major hospitals.

The JCOG site-visit audit reported that written consent was available for all except nine patients from one institution. In another institution, an additional six patients had informed consent submitted by a family member.

Patients and Surgery

Patient demographics and tumor characteristics are presented in Table 2. The two groups were well balanced, as there were no significant differences in their baseline data.

The operative details are shown in Table 3. Total gastrectomy was performed in 38% of all patients, and the vast majority of total gastrectomies (186 of 199 cases) were accompanied by splenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor, accounting for 11% of all total gastrectomies. In four cases, proximal subtotal gastrectomy with splenectomy was performed instead of total gastrectomy. Para-aortic lymphadenectomy required longer operation time (median, 63 minutes) and resulted in greater blood loss (median, 230 mL) than the standard D2. Blood transfusion was required approximately twice as often.

Protocol Violation and Ineligible Cases

There were 10 cases of protocol violation (1.9%). In one case, the para-aortic nodes were examined by frozen

Table 3. Operative Details

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)	P
Gastrectomy, No. of patients				.62
Total	102	97	199	
Distal subtotal	160	160	320	
Proximal subtotal	1	3	4	
Splenectomy, No. of patients	98	93	191	.79
Pancreatectomy, No. of patients	9	13	22	.39
Operation time, minutes				< .001
Median	237	300	270	
Range	127-625	153-600	127-625	
Blood loss, mL				< .001
Median	430	660	530	
Range	32-1,810	60-2,885	32-2,885	
Blood transfusion				< .001
No. of cases	37	78	115	
%	14.1	30.0	22.0	
No. of retrieved nodes				< .001
Median	54	74	61	
Range	14-161	30-235	14-235	

section before registration. In another case, the surgeon performed para-aortic dissection despite the allocation to group A because after randomization, he found a positive node behind the common hepatic artery, believed to be strongly suggestive of metastasis in the para-aortic area. The postoperative course of this patient, who was allocated to group A but treated as group B, was uneventful, and analyzing this patient as either group A or group B had no effect on the results in this study. We left this case in group A based on intention-to-treat analysis. In the other eight patients, nodal stations No.13 and/or No.14v were not dissected in distal third tumors.

In another case, the initial histological diagnosis following endoscopic biopsy was poorly differentiated adenocarcinoma but the final histology of the resected stomach revealed gastric lymphoma. We included this patient in the morbidity/mortality analysis, but will exclude their data from the final survival analyses.

Operative Morbidity

The overall operative morbidity rate was 24.5%. The morbidity for group B patients was higher than group A (28.1% and 20.9%, respectively), but the difference did not reach statistical significance ($P = .067$). The incidence of the four major surgical complications was not different between the two groups (Table 4).

There were various other complications reported, and the incidence was significantly higher in group B than group A patients. Paralytic ileus causing significant delay of recommencement of oral feeding, abdominal and/or left pleural lymphorrhea requiring prolonged drainage for more than 1 week, and severe diarrhea, were specific to the extended para-aortic dissection group (Table 4). Reoperation was needed in 12 patients (2.3%), and there was no difference in the reoperation rate between the two groups. Median hospital stay after surgery was 21 days in group A, and 24 days in group B ($P < .01$).

Hospital Mortality

There were four hospital deaths (0.8%)—two in each group. Each group had one patient who died of postoperative complications, and one died of rapidly progressive cancer. All other patients recovered from surgery and were discharged from hospital.

In this randomized controlled trial, the role of para-aortic dissection will be evaluated in terms of survival benefit,

Table 4. Operative Morbidity and Hospital Mortality

	Group A (n = 263)		Group B (n = 260)		
	No. of Patients	%	No. of Patients	%	P
Any complication	55	20.9	73	28.1	.067
Anastomotic leak	6	2.3	5	1.9	.99
Pancreatic fistula	14	5.3	16	6.2	.71
Abdominal abscess	14	5.3	15	5.8	.85
Pneumonia	12	4.6	4	1.5	.072
Others	24	9.1	52	20.0	< .001
Obstruction or ileus	5		11		
Lymphorrhea	0		10		
Left pleural effusion	1		6		
Severe diarrhea	0		3		
Reoperation	5	1.9	7	2.7	.57
Hospital death	2	0.8	2	0.8	.99

operative morbidity/mortality, and quality of life. The results will provide important information and should guide decision making regarding the choice of operative methods. The quality of life and survival among these patients are still in the follow-up phase, and the analyses will take place in 2004 and 2006, respectively. This report compares the morbidity and mortality rates of D2 plus para-aortic node dissection with standard D2 dissection.

There is a wide variation in operative morbidity and mortality following gastric cancer surgery among countries and institutions. The presence of comorbid disease that affects patient fitness for surgery, surgical experience of the operator, and the workload volume seem to be important factors.[17,18] The mortality for gastrectomy in Western countries often exceeds 5% and approaches 16% in some series.[19-21] Conversely, Japanese studies have consistently reported a mortality rate of lower than 2% in retrospective observations. To date, the present study is the first large-scale prospective randomized controlled trial in Japan to compare surgical techniques under strict quality control and data management. The extremely low hospital death rate after extended para-aortic lymphadenectomy (0.8%) in this multi-institutional setting confirms the findings from previous retrospective reports.

This trial is a striking contrast to the the Dutch[4] and British[5] D1/D2 trials, in which D2 lymphadenectomy was associated with operative mortality rates of 10% and 13%, respectively. One important criticism of the European randomized trials was the issue of learning curve, as many British and Dutch surgeons participating in the trials were new to the D2 procedure. Surgical experience, specific anatomic knowledge, and careful postoperative managements by experienced teams are crucial to the success of this type of surgery. An Italian group appropriately carried out a phase 2 study of D2 lymphadenectomy in selected institutions[22] until an acceptable operative mortality rate was achieved, before conducting a randomized controlled trial comparing D1 and D2 gastrectomies.

The D2 gastrectomy procedure is known as "extended lymphadenectomy" in Western countries, while Japanese surgeons employ D2 as a standard technique, and reserve the term "extended" for para-aortic dissection. Lymphatic drainage from the stomach flows to the perigastric nodes and then to the nodes around the celiac axis and its main branches. From here it enters the para-aortic nodes before joining the systemic circulation via the thoracic duct. Hence, the para-aortic nodes may be regarded as the final station of nodes that can be dissected to remove the threat of systemic metastases originating from the lymphatic system. Many Japanese surgeons in specialized centers who performed para-aortic dissection found microscopic metastases in this region, and believe that this type of surgery may be potentially worthwhile. However, the risk associated with para-aortic dissection dictates advanced operative skills and intensive postoperative care. Therefore, scientific evidence supporting a survival benefit must be obtained before employing this technique in routine gastric cancer surgery.

The very low operative morbidity and mortality achieved in this JCOG trial can be attributed to several factors: (1) we selected a group of fit patients who could tolerate para-aortic dissection in the study. (2) Only specialist surgeons with an established track record of extended lymphadenectomy participated in the trial. (3) High-throughput centers were selected for their operative skills and standardized postoperative management. (4) Pancreatectomy was avoided whenever possible, while splenectomy accompanied total gastrectomy in most cases. We report that there was no significant difference in the overall complications between the two groups; however, the para-aortic dissection group had significantly higher "other" complications (on free format) compared with standard D2. Lymphorrhea and paralytic ileus were more specific to this operation. This observation may be biased because of the surgeon's awareness of the patient's randomization arm of para-aortic dissection.

In the British and Dutch trials, splenectomy with or without distal pancreatectomy was highlighted as a major risk factor for operative morbidity and mortality.[5,23] Total gastrectomy for proximal tumor requires more advanced surgical skill and is associated with a higher morbidity compared to distal gastrectomy. Proximal gastric tumors are rapidly increasing in number in the western countries,[24,25] while the incidence remains stable in Japan,[26] and this may partly explain the superior results obtained in Japanese studies. However, no difference was observed in the distribution of the primary tumor location between the Dutch[4] and the Japanese cohort. The proportion of total to distal gastrectomy was also very similar. Therefore, variation in tumor location and type of gastrectomy could not account for the difference in morbidity/mortality, at least between these trials. JCOG recently launched a randomized controlled trial to evaluate the role of splenectomy combined with total gastrectomy in proximal tumors.[27]

Gastric cancer, though decreasing in incidence worldwide, remains a major health problem in many countries. R0 (no residual disease) resection is the only curative measure; but the more extended the surgery, it is believed the greater is the risk of operative morbidity and mortality. The type of gastrectomy and the extent of lymphadenectomy must be carefully planned for each individual patient with gastric cancer. The Japanese guidelines clearly define D2 gastrectomy as standard surgery[28] based on the excellent results in Japanese studies, while the British cancer guidance[6] discourages D2 based on the poor results of their randomized trial. This contrast should be addressed by surgeons' efforts, such as establishment of specialized standard training systems or production of evidence by high-quality randomized trials in specialized centers.

In conclusion, this study has shown that specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Extending the surgery to para-aortic lymphadenectomy did not increase the major operative complications and hospital deaths. However, compared with the D2 procedure, para-aortic dissection requires a longer operation time, leads to a larger volume of blood loss, and longer hospital stay. Until survival benefits are clarified when the data mature sufficiently, para-aortic lymphadenectomy for gastric cancer should be regarded as experimental surgery[28] and only performed in specialized institutions within the context of a well-designed clinical trial.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Green tea consumption and subsequent risk of gastric cancer by subsite: the JPHC Study☆

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Abstract

Objective: To investigate the relationship between green tea consumption and subsequent risk of gastric cancer at different anatomical subsites in a population-based prospective study.

Methods: The Japan Public Health Center-based prospective study (JPHC Study) was established in 1990 for Cohort I and in 1993 for Cohort II. Among 72,943 subjects (34,832 men and 38,111 women), 892 gastric cancer cases (665 men and 227 women) were identified from 1990 to 2001.

Results: While no association between green tea consumption and gastric cancer was observed among men, a decreased risk of gastric cancer was observed among women after adjustment for potential confounding factors. This result was more remarkable when only the tumors in the distal portion were analyzed; for that subsite, the relative risk was 0.51 (95% confidence interval 0.30–0.86) in the highest category of green tea consumption (5 or more cups per day *versus* less than 1 cup per day) (p for trend = 0.01). The null association for upper-third gastric cancer was consistent for both sexes.

Conclusions: An inverse association between green tea consumption and distal gastric cancer was observed among women. More prospective studies with detailed information are needed to confirm the role of green tea in the occurrence of gastric cancer.

Introduction

Gastric cancer is one of the cancers known to have its risk modified primarily by dietary factors. Accumulated evidence shows that a reduction in salty food intake and an increase in vegetable and fruit intake are important in the primary prevention of gastric cancer [1].

A possible protective effect of green tea on gastric cancer has also been suggested. Antioxidant activities and the ability to inhibit nitrosation of polyphenols have been isolated from green tea in both *in vitro* and *in vivo* studies [2–4]. In contrast with the *in vivo* studies and the majority of case-control studies that have provided evidence for a protective effect of green tea against gastric cancer [5], recent prospective studies have not shown any association between green tea consumption and gastric cancer risk [6–8]. Although not statistically significant, a decreased risk was suggested for women in two of the studies [6, 8] and additional data from prospective studies are strongly needed. To clarify this relationship, we analyzed the data from a population-based prospective cohort study conducted in Japan, where green tea is commonly consumed.

Previous studies have also demonstrated that gastric cancer cannot be explained as a single entity [9]. In

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contrast to the decline in the occurrence of distal gastric cancers [10], recent reports have revealed that the incidence of cancer localized to the cardia may be on the rise [11, 12]. The observed differences in clinical and pathologic profiles suggest that these two tumors are distinct diseases with different etiologies [13]. This is the first study to prospectively analyze the relationship considering the anatomical subsites of the tumors.

Materials and methods

Study population

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) was established in 1990 for Cohort I and in 1993 for Cohort II, which has been partially reported on elsewhere [14, 15]. Cohort I, consisting of three Public Health Center (PHC) areas (Ninohe PHC area of Iwate prefecture, Yokote PHC area of Akita prefecture, and Saku PHC area of Nagano prefecture), and Cohort II, consisting of four PHC areas (Mito PHC area of Ibaraki prefecture, Kashiwazaki PHC of Niigata prefecture, Chuo-higashi PHC of Kochi prefecture, and Kamigoto PHC of Nagasaki prefecture) were used in the present analysis. The study population was defined to be all inhabitants in the study areas (23 cities, towns, or villages in 7 PHCs) aged 40–59 years in Cohort I and aged 40–69 years in Cohort II at the baseline of the survey. We did not include the Ishikawa PHC area and the Miyako PHC area in the Okinawa prefecture. According to our previous report [16, 17], the distribution of risk factors including smoking habits and dietary factors in Okinawa were quite different from those of other PHC areas, which in turn made us unable to adjust these factors simultaneously to the other areas. Cohort I and Cohort II also contained subjects from the Katsushika PHC of Tokyo prefecture and Suita PHC of Osaka prefecture, respectively, who took part in a health check-up program at age 40 and 50 during 1990–1994 for Katsushika PHC and 1993–1994 for Suita PHC. We did not include these subjects because the selection of subjects was different from that of other PHC areas and cancer incidence was not monitored in the Katsushika PHC area. Consequently, the background of the study subjects were quite different and there was no overlap with the recent cohort studies in Japan on green tea and gastric cancer whose subjects were drawn from residents in three municipalities of Miyagi Prefecture [6], or bomb survivors who have been under continued surveillance [7], or participants of general health check ups of 45 municipalities [8].

As a whole, a population-based cohort of 43,322 men (19,753 in Cohort I and 23,569 in Cohort II) and 45,258 women (20,539 in Cohort I and 24,719 in Cohort II) was established.

Baseline questionnaire

Subjects were asked to reply to a lifestyle questionnaire, covering sociodemographic characteristics, medical history, and diet, as well as drinking habits for green tea, black tea, and coffee. The survey was conducted in 1990 for Cohort I and in 1993 for Cohort II (with the exception of Tomobe town, with 12,463 subjects, which belongs to Mito PHC in Cohort II, where the survey was conducted in 1994). A total of 74,397 subjects (84%), 35,307 men and 39,090 women, returned their questionnaires. Frequency and daily amounts of consumption were ascertained for beverages including green tea using precoded answers (almost none; 1–2 or 3–4 days per week; 1–2, 3–4, or 5 or more cups per day for those who consume 'almost daily'). 'Almost daily' category included those who consume 5–7 days per week.

Although the style of the questions differed slightly between the two cohorts, questions concerning current or former smoking status, age at initiation of smoking, number of cigarettes consumed per day for smokers, and age at cessation of smoking for past smokers were included in both questionnaires.

Dietary factors included in the questionnaire have been reported elsewhere [17]. Briefly, the weekly intake frequency of 27 food items in four categories was reported in Cohort I and intake of 33 food items in five categories was reported in Cohort II. Food items were also slightly different between Cohort I and Cohort II, and thus for multiple adjustment of these variables, we were not able to simply combine the data sets. The statistical methods used are described below.

The family history of gastric cancer was regarded positive if one of the subject's parents or siblings had gastric cancer.

We excluded subjects with a self-reported cancer at baseline, subjects who were not Japanese, and subjects who had already moved away at the baseline, which we confirmed during the follow-up period. These exclusions left 34,832 eligible men and 38,111 women in the study.

Follow-up and identification of gastric cancer

Death and move out. Subjects were followed from January 1, 1990, to December 31, 2001, for Cohort I and from January 1, 1993 (1994 for Tomobe Town), to December 31, 1999, for Cohort II. In Japan, all death certificates are submitted to a local government office

and forwarded to the PHC in the area of residence. Mortality data are then sent to the Ministry of Health, Labour and Welfare and coded for the National Vital Statistics. The registration of deaths in Japan is required by the Family Registration Law and is believed to be complete. Therefore, all deaths of cohort subjects were based on death certificates from each PHC, whenever the subjects stayed in their original area. Any changes in residency status were identified annually through the residential registry in each area. Among study subjects, 3448 (4.7 %) moved out, 3402 (4.7 %) died, and 53 (0.07 %) were lost to follow-up within the study period.

Cancer registry for JPHC Study. Newly diagnosed cases of cancer were collected through two data sources, one from local major hospitals and the other from population-based registries (usually prefecture-wide). Candidate patients were linked by name, address, and date of birth, and entered in the cancer registry for the JPHC Study when the birth date and residence fulfilled cohort inclusion criteria. The death certificate was used as a supplementary information source for the cancer registry, by which 550 cancers were identified. Of all 6308 entries in the cancer registry as of July 2002 that were diagnosed from 1990 to 2001, 156 of those cases were not confirmed by medical records, and they accounted for 2.5% (death certificate only; DCO) of all entries in the cancer registry.

Identification of gastric cancer. Cases of gastric cancer were extracted from the cancer registry for the JPHC Study, based on site (International Classification of Diseases for Oncology [ICD-O] code: C160–169) [18]. A total of 892 cases of gastric cancer, 665 men and 227 women, were documented with a histologically proven diagnosis at surgery or autopsy (561; 63%), biopsy (294; 33%), or cytology (15; 2%), made from 1990 to 2001 for Cohort I and from 1993 to 1999 for Cohort II, as of July 2002. The diagnosis in 35 cases was based on clinical findings or unspecified evidence and was not regarded as gastric cancer cases. No DCO cases were included because the cases were restricted to subjects with a histological diagnosis.

Gastric cancers were classified into three categories; upper third, distal, and unclassified. Until quite recently in Japan, the upper-third of the stomach has been called the 'cardia', based on the guidelines for gastric cancer classification [19]. Because it seemed difficult to distinguish this from the real cardia, which is located mainly in the esophagogastric junction from the upper-third of the stomach, we combined them into one group for analysis in this study (ICD-O code C160–161). A tumor located toward the lower side of the stomach was classified as distal gastric cancer (ICD-O code C162–167). Those subsites that could not be classified because of a diffuse lesion (ICD-O code C168) or those with no information (ICD-O code C169) were categorized as an unclassified subsite. Histologic classification was based on a review of the record reported by each hospital, conducted by one of the authors [S. Sasazuki] in consultation with a pathologist. The subdivisions were made based on classification derived by Lauren [20].

Statistical analysis

A move from the study area, death of other reasons from gastric cancer, and diagnosis of gastric cancer at another subsite (for subsite analysis) were treated as censoring. Time at risk for each subject was calculated as the duration from the start of the study periods of January 1, 1990, for Cohort I and January 1, 1993, for Cohort II except for Tomobe Town (January 1, 1994) to a histological diagnosis of gastric cancer, move from the PHC area, death, or December 31, 2001, for Cohort I and December 31, 1999, for Cohort II, whichever came first. Cochran–Mantel–Haenszel statistics were used to test the baseline characteristics. Cox's proportional hazards regression model was used to estimate the relative risks (RRs) of gastric cancer according to green tea consumption. When covariates of age, PHC areas, and smoking were used in the model (RR^a in Tables 3 and 4), Cohort I and Cohort II were simply combined, because the questionnaires were essentially the same regarding smoking status for Cohort I and Cohort II, and separate analysis showed similar results. Because there was no strong evidence of heterogeneity between separate estimates when further covariates of fruit, green or yellow vegetables, salted cod roe or fish gut, rice, miso soup, black tea, and coffee were added to the model ($\chi^2 = 0.7644$, $p = 0.38$), combination of estimates of Cohort I and Cohort II data was done by weighting the separate estimates by the inverse of the estimated variance. That is, $\beta_c = (1/v_1 \times \beta_1 + 1/v_2 \times \beta_2)/(1/v_1 + 1/v_2)$, $RR_c = \exp(\beta_c)$; β_c is the combined parameter estimate, v_1 is the variance of Cohort I, β_1 is the parameter estimate of Cohort I, v_2 is the variance of Cohort II, β_2 is the parameter estimate of Cohort II, RR_c is the combined RR (RR^b in Tables 3 and 4) (Woolf's method) [21]. The weighted average procedure was also applied to the test-for-trend statistics by using $\chi^2 = (\log RR_c)^2 \times (1/v_1 + 1/v_2)$.

Age was categorized into one of six groups: 40–44, 45–49, 50–54, 55–59, 60–64, and 65–69 years, based on age at baseline. Fruit consumption was categorized into three groups: less than 2 days per week, 3–4 days per week, and almost daily. The consumption of green or yellow vegetables was the sum of the frequencies of

intake of green vegetables and yellow vegetables, and was classified into three groups: less than 4 times per week, 5–7 times per week, and more than 8 times per week. Salted cod roe or fish gut consumption was expressed as the sum of the frequencies of intake of each and was categorized into three groups: none, 1–2 times per week, and 3 or more times per week. Rice consumption was categorized in two groups: up to 3 bowls, or more than 3 bowls per day. Miso soup consumption was categorized into three groups: rare to 3–4 days per week, 1–2, and 3 or more bowls per day for those who consume almost every day. Black tea consumption was categorized into three categories: rare, 1–2, and more than 3 days per week. Coffee consumption was categorized into four groups: rare, 1–2, 3–4 days per week, and almost daily. Smoking was categorized into four groups: never, past, current smoking of 20 or less cigarettes per day, and current smoking of more than 20 cigarettes per day.

The trend was assessed by assigning ordinal values for categorical variables. Reported p values were two-sided, and all statistical analyses were done using the Statistical Analysis System (SAS) [22].

Results

Among 665 gastric cancer cases in men, 88 (13%) were upper-third gastric cancers, and 461 (69%) were distal cancers. For 227 cases in women, the corresponding numbers were 21 (9.3%) and 170 (75%), respectively. As for histological categorization, differentiated and undifferentiated types were 386 (58%) and 197 (30%), respectively, among men and 85 (37%) and 115 (51%) among women. The results for analysis based on histologic type did not differ materially, and we present the results combining these types.

Baseline characteristics of men and women according to green tea consumption are shown for Cohort I and Cohort II separately (Tables 1 and 2). For Cohort I, all listed variables were differently distributed according to green tea consumption, except for current smoking and heavy alcohol drinking in women. For Cohort II, only heavy smoking in women was not differently distributed according to green tea intake. RRs and 95% confidence intervals (CIs) of gastric cancer by subsite in relation to green tea consumption among men are shown in Table 3. Green tea consumption was not related to gastric cancer at any site.

Table 1. Baseline characteristics according to green tea consumption in men and women: Cohort I

	Men				p for Trend[a]	Women				p for Trend[a]
	Green tea consumption (cups per day)					Green tea consumption (cups per day)				
	< 1	1–2	3–4	5+		< 1	1–2	3–4	5+	
No.	4379	3183	3624	3942		5305	3247	3825	4130	
Age	48.8 (0.1)	48.7 (0.1)	49.6 (0.1)	51.2 (0.1)	< 0.0001	49.2 (0.1)	49.0 (0.1)	48.9 (0.1)	51.0 (0.1)	< 0.0001
Current smoker (%)	54.4	54.4	55.2	58.5	0.0002	5.2	5.0	3.9	6.0	0.48
Heavy smoker (%)[b]	16.4	15.6	17.0	21.8	< 0.0001	0.3	0.4	0.2	0.5	0.26
Heavy smoker (%)[c]	28.1	28.7	32.0	42.4	< 0.0001	0.3	0.4	0.3	0.8	0.005
Alcohol drinking, 1+ per week (%)	70.6	75.1	75.8	73.0	0.006	11.5	12.0	13.5	14.6	< 0.0001
Heavy drinking (%)[d]	38.3	42.2	42.7	40.8	0.01	1.6	0.9	0.8	1.5	0.38
Fruit, daily (%)	24.9	28.5	29.2	35.0	< 0.0001	47.8	53.8	54.5	57.0	< 0.0001
Green or yellow vegetables, daily (%)	25.4	29.3	30.1	34.8	< 0.0001	37.1	43.2	45.0	49.2	< 0.0001
Pickled vegetables, daily (%)	48.2	54.8	58.5	66.7	< 0.0001	59.0	63.8	69.7	77.8	< 0.0001
Salted or dried fish, 3+ per week (%)	33.3	36.4	38.0	41.6	< 0.0001	38.2	42.7	44.2	50.1	< 0.0001
Salted cod roe or fish gut, 3+ per week (%)	50.8	54.1	53.7	54.0	0.006	39.5	43.2	43.1	48.0	< 0.0001
Miso soup, daily (%)	81.6	85.4	86.1	87.5	< 0.0001	78.7	82.2	82.7	82.5	< 0.0001
Rice, 4+ bowls per day (%)	53.8	50.2	54.7	60.8	< 0.0001	24.1	19.1	17.6	21.3	< 0.0001
Coffee, daily (%)	31.4	35.9	31.1	24.2	< 0.0001	32.1	38.5	29.2	21.4	< 0.0001
Black tea, 1+ cups per week (%)	10.6	14.9	15.6	14.4	< 0.0001	12.8	18.1	20.5	17.7	< 0.0001
Family history of gastric cancer (%)	7.0	8.0	8.2	10.7	< 0.0001	6.8	7.4	9.3	11.2	< 0.0001
Body mass index	23.4 (0.04)	23.4 (0.05)	23.3 (0.04)	23.1 (0.04)	< 0.0001	23.4 (0.04)	23.3 (0.05)	23.3 (0.05)	23.5 (0.05)	0.07

Values are means (SE) unless otherwise specified.
[a] Based on Cochran–Mantel–Haenszel statistics.
[b] Current smoker with 21+ cigarettes / day.
[c] Ever smoker with 30+ pack years.
[d] Alcohol drinking of 250+ mg ethanol per week.

Table 2. Baseline characteristics according to green tea consumption in men and women: Cohort II

	Men				*p* for Trend[a]	Women				*p* for Trend[a]
	Green tea consumption (cups per day)					Green tea consumption (cups/d)				
	<1	1–2	3–4	5+		<1	1–2	3–4	5+	
No.	2763	5028	6316	5293		2489	4477	7462	6810	
Age	51.4 (0.2)	52.0 (0.1)	53.8 (0.1)	55.9 (0.1)	<0.0001	52.4 (0.1)	52.9 (0.1)	54.6 (0.1)	56.1 (0.1)	<0.0001
Current smoker (%)	56.5	55.9	53.4	55.0	0.06	9.4	6.5	5.2	6.7	0.0001
Heavy smoker (%)[b]	20.3	20.0	18.2	20.7	0.95	0.9	0.4	0.4	0.7	0.97
Heavy smoker (%)[c]	38.7	38.6	42.9	51.1	<0.0001	1.5	0.7	0.7	1.2	0.88
Alcohol drinking, 1+ per week (%)	63.1	67.5	65.1	58.8	<0.0001	14.0	12.7	10.5	10.3	<0.0001
Heavy drinking (%)[d]	31.1	32.6	31.4	29.0	0.004	2.0	1.1	1.0	1.0	0.0005
Fruit, daily (%)	31.2	37.4	43.7	48.5	<0.0001	56.1	63.5	69.2	70.7	<0.0001
Green or yellow vegetables, daily (%)	41.7	45.8	53.9	58.6	<0.0001	59.7	63.7	70.1	71.8	<0.0001
Pickled vegetables, daily (%)	32.7	40.5	47.5	52.5	<0.0001	39.2	45.0	51.5	57.8	<0.0001
Salted or dried fish, 3+ per week (%)	40.8	45.2	49.5	50.8	<0.0001	42.0	47.1	50.6	52.8	<0.0001
Salted cod roe or fish gut, 3+ per week (%)	14.2	13.7	15.0	17.7	<0.0001	9.7	10.3	9.8	12.9	<0.0001
Miso soup, daily (%)	58.6	69.5	74.0	79.4	<0.0001	57.9	64.2	68.7	71.2	<0.0001
Rice, 4+ bowls per day (%)	32.3	32.2	37.4	41.8	<0.0001	12.1	10.9	11.5	12.7	0.06
Coffee, daily (%)	43.6	45.3	39.2	29.3	<0.0001	41.3	44.6	35.8	24.2	<0.0001
Black tea, 1+ cups per week (%)	14.0	16.4	16.4	16.7	0.008	19.1	22.3	23.4	22.4	0.005
Family history of gastric cancer (%)	5.1	5.8	6.7	6.4	0.007	5.6	5.8	6.7	6.6	0.03
Body mass index	23.4 (0.05)	23.3 (0.04)	23.1 (0.04)	23.2 (0.04)	<0.0001	23.4 (0.07)	23.3 (0.05)	23.3 (0.04)	23.5 (0.04)	0.05

Values are means (SE) unless otherwise specified.
[a] Based on Cochran–Mantel–Haenszel statistics.
[b] Current smoker with 21+ cigarettes per day.
[c] Ever smoker with 30+ pack years.
[d] Alcohol drinking of 250+ mg ethanol per week.

Table 3. RRs and 95% CIs of gastric cancer by anatomical subsite in relation to green tea consumption among men

	Green tea consumption (cups per day)				
	<1	1–2	3–4	5+	*p* for trend
All site					
RR[a] (95% CI), n = 661	1.0	0.95 (0.74–1.21)	0.89 (0.71–1.13)	0.97 (0.77–1.22)	0.81
RR[b] (95% CI), n = 610	1.0	0.94 (0.72–1.22)	0.84 (0.65–1.08)	0.98 (0.77–1.25)	0.65
Upper-third including cardia					
RR[a] (95% CI), n = 88	1.0	1.07 (0.53–2.17)	0.88 (0.44–1.75)	1.24 (0.65–2.35)	0.54
RR[b] (95% CI), n = 80	1.0	1.06 (0.51–2.18)	0.73 (0.34–1.57)	1.17 (0.60–2.30)	0.75
Distal					
RR[a] (95% CI), n = 457	1.0	0.88 (0.65–1.17)	0.85 (0.64–1.12)	0.88 (0.67–1.16)	0.42
RR[b] (95% CI), n = 423	1.0	0.88 (0.64–1.20)	0.79 (0.59–1.07)	0.92 (0.69–1.22)	0.37

[a] Calculated from a proportional hazards regression analyzing the two cohorts together. Adjusted for age, area, and cigarette smoking.
[b] Calculated from weighted average of the results from separate proportional hazards regressions fitted to the individual cohorts. Further adjusted for consumption of fruit, green or yellow vegetables, fishgut, miso soup, rice, black tea, and coffee.

When potential confounding factors were further adjusted based on the method described in the previous section, the overall results did not differ materially.

For women, a decreased risk of gastric cancer in relation to green tea consumption was observed after controlling potential confounding factors; adjusted RRs and 95% CI for 1–2, 3–4, and 5 or more cups per day compared to less than one cup per day were 0.85 (0.53–1.38), 1.04 (0.68–1.58), and 0.67 (0.43–1.04), respectively (p for trend = 0.08) (Table 4). This association was more remarkable when cancer was restricted to the distal portion; RR = 0.51 (95% CI 0.30–0.86) in the highest category (five cups or more) of green tea consumption (p for trend = 0.01).