

Tea Consumption and Lung Cancer Risk: A Case-Control Study in Okinawa, Japan

Yoshiyuki Ohno,^{1,8} Kenji Wakai,¹ Keiichiro Genka,² Keisho Ohmine,³ Takashi Kawamura,¹ Akiko Tamakoshi,¹ Rie Aoki,¹ Masayo Senda,¹ Yutaka Hayashi,⁴ Keiichi Nagao,⁵ Seigo Fukuma⁶ and Kunio Aoki⁷

¹Department of Preventive Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, ²National Okinawa Hospital, 3-20-14 Ganeko, Ginowan, Okinawa 901-22, ³Okinawa Prefecture Mental Health Care Center, 212 Miyahira, Haeburu-cho, Okinawa 901-11, ⁴Division of Pathology, Institute of Pulmonary Cancer Research, Chiba University School of Medicine, 1-8-1 Inohana, Chuoh-ku, Chiba 260, ⁵Health Science Center, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, ⁶Chiba Cancer Center, 666-2 Nitona-cho, Chuoh-ku, Chiba 260 and ⁷Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya 464

To disclose the relationship between tea consumption and lung cancer risk, we analyzed the data from a case-control study conducted in Okinawa, Japan from 1988 to 1991. The analysis, based on 333 cases and 666 age-, sex- and residence-matched controls, provided the following major findings. (a) The greater the intake of Okinawan tea (a partially fermented tea), the smaller the risk, particularly in women. For females, the odds ratios (and 95% confidence intervals) for those who consumed 1-4, 5-9, and 10 cups or more of Okinawan tea every day, relative to non-daily tea drinkers, were 0.77 (0.28-2.13), 0.77 (0.26-2.25) and 0.38 (0.12-1.18), respectively (trend: $P=0.032$). The corresponding odds ratios for males were 0.85 (0.46-1.55), 0.85 (0.46-1.56) and 0.57 (0.31-1.06) (trend: $P=0.053$). (b) The risk reduction by Okinawan tea consumption was detected mainly in squamous cell carcinoma. Daily tea consumption significantly decreased the risk of squamous cell carcinoma in males and females, the odds ratios being 0.50 (95% confidence interval 0.27-0.93) and 0.08 (0.01-0.68), respectively. These findings suggest a protective effect of tea consumption against lung cancer in humans.

Key words: Tea — Lung cancer — Protective effect — Case-control study — Okinawa

Many laboratory studies have revealed inhibitory effects of tea preparations and their polyphenols against tumor formation and growth.¹⁾ Several epidemiological studies have detected a negative association between tea consumption and the development of human cancers.²⁻⁵⁾

Concerning lung cancer, several investigators have reported that the extracts from various kinds of tea or their major polyphenols inhibited lung neoplasms chemically induced in mice.⁶⁻¹⁰⁾ Komori *et al.*¹¹⁾ reported that green tea extract and EGCG,⁹ a major constituent of the polyphenols in tea, inhibited the growth of lung cancer cell lines.

Epidemiological studies, however, have not fully endorsed these inhibitory effects against lung cancer. Oguni *et al.*¹²⁾ reported a negative association between amount of green tea production and lung cancer mortality in a correlation study in Shizuoka prefecture, Japan. In an international ecological study,¹³⁾ however, national consumption of tea was positively correlated with lung cancer mortality in females. An increasing lung cancer risk with increasing tea consumption (mainly black tea)

was also observed in men in a cohort study conducted in London.¹⁴⁾ A case-control study in Hong Kong indicated that consumption of green tea increased lung cancer risk in females.¹⁵⁾ Three other studies (one cohort study¹⁶⁾ and two case-control studies^{17,18)} failed to find a significant association between tea consumption and lung cancer.

To cast more light on this issue, we analyzed a part of the data obtained from a case-control study in Okinawa, where the highest lung cancer mortality rate has long been observed among the 47 prefectures in Japan¹⁹⁾; in Okinawa, lung cancer mortality rate (per 100,000 population, age-adjusted by world population²⁰⁾) was 38.2 for males and 10.2 for females in 1990,²¹⁾ with the corresponding rates being 30.3 and 7.9 for all Japan.²²⁾

MATERIALS AND METHODS

Study subjects We conducted this study from January 1988 to November 1991 in Okinawa, Japan. To be eligible as cases in the present study, patients had to have been initially diagnosed as having primary lung cancer in the National Okinawa Hospital at 40 years of age or older, and were required to be residents of the Okinawan main islands (Okinawa, Miyako and Ishigaki islands) at diagnosis. Patients aged 90 years or over were not eligible for a direct interview, and those with other malignancies

⁸ To whom correspondence should be addressed.

⁹ The abbreviations used are: EGCG, (–)-epigallocatechin-3-gallate; OR, odds ratio; CI, confidence interval; AHH, aryl hydrocarbon hydroxylase; GST, glutathione S-transferase.

were excluded. All lung cancers were histopathologically diagnosed and classified according to cell type by one pathologist in the hospital.

A total of 477 eligible cases were identified in the study period. Of these patients, 130 (27%) had died or were too ill to be interviewed when we tried to contact them. Fourteen (3%) patients refused an interview. Finally, we interviewed 333 patients (70%).

Controls were randomly selected from the general population of the Okinawan main islands (40–89 years old), using the electoral registers for the study period from 1988 to 1991. In Japan, the electoral registers are updated annually and are complete lists of residents aged 20 years or older. The random sampling was designed to select 5 eligible controls who were matched to each case for sex, age (± 2 years) and residence (within the area covered by one health center), and two controls per case were taken from them. Those with a previous history of lung cancer or other malignancies were excluded from the controls.

Data collection Epidemiological information was collected by a direct interview of the study subject him/herself, using a standardized questionnaire, by well-trained public health nurses. The interviews were usually conducted at the subjects' homes, but some patients were interviewed during admission.

We examined Okinawan tea consumption in the present study, since most middle-aged or old people in Okinawa predominantly drink it instead of Japanese green tea, and 'tea' usually means Okinawan tea for them. It is somewhat different from Japanese green tea, being partially fermented during its production, but not so thoroughly as oolong tea. Therefore, it would retain tumor-inhibiting catechins, such as EGCG, (–)-epigallocatechin, (–)-epicatechin-3-gallate, at a rather high level.²³⁾

A subject was asked about the weekly frequency of Okinawan tea intake during 5 years before the interview. If the subject consumed Okinawan tea every day, he/she

was then asked about the daily amount of its intake by the Japanese tea cup (about 150 ml). Other epidemiological information collected at the direct interview included routine demographic data such as date of birth, marital status, and educational attainment; residential history; previous episodes of illness; family history of cancer; occupational history; smoking and drinking habits; diet; consumption of various beverages such as coffee, black tea, milk, juice, and soft drinks; reproductive history for women; and personality.

We also included questions on intake frequency of such green-yellow vegetables as carrot, spinach, pumpkin, sweet pepper, tomato and others. We classified the subjects into the high intake category when they consumed one or more of these green-yellow vegetables almost every day. Those who consumed green-yellow vegetables 2 times per week or less were included in the low intake category, and others were in the middle intake group.

Statistical methods Ex-smokers who had quit smoking less than 5 years ago were classified as current smokers in the analyses, since some might have stopped smoking because of lung cancer itself. The chi-square or Wilcoxon test was used to detect case-control differences in background factors and Okinawan tea consumption. The strength of the association between lung cancer and Okinawan tea intake was measured as OR. The ORs were obtained by using conditional multiple logistic regression analysis²⁴⁾ adjusted for the potentially confounding covariates. Unconditional logistic models including age (continuous variable), residence and other covariates,²⁵⁾ however, were used when analyzing data by cell type or smoking status. In the analysis by cell type, the ORs were calculated for squamous cell carcinoma and adenocarcinoma by sex, since all the male patients with small cell carcinoma were previous or current smokers, so that the ORs adjusted for smoking could not be computed. Small cell carcinomas in women and carcinomas of other cell types were too few for the analysis by cell type. The test

Table I. Distribution of the Study Subjects by Sex and Age

Age	Males				Females			
	Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%
40–49	13	5.3	22	4.5	13	14.8	26	14.8
50–59	29	11.8	60	12.2	17	19.3	33	18.8
60–69	104	42.4	214	43.7	27	30.7	57	32.4
70–79	83	33.9	162	33.1	25	28.4	46	26.1
80–89	16	6.5	32	6.5	6	6.8	14	8.0
Total	245	100.0	490	100.0	88	100.0	176	100.0
Mean age		66.9		67.1		63.7		63.7
SD		9.2		9.1		11.7		11.9

for trend in the logistic regression analysis²⁶⁾ was performed using the score for Okinawan tea intake: not daily, 0; 1–4 cups/day, 1; 5–9 cups/day, 2; 10 or more cups/day, 3.

Missing values in the covariates were replaced by median or mode values. One patient with unknown weekly frequency of Okinawan tea intake was excluded from the analysis. In the multivariate analysis, subjects with missing information on the daily intake of the tea were included as an additional category.

Table II. Distribution of Cases by Cell Type

Cell type	Males		Females	
	N	%	N	%
Squamous cell	115	46.9	19	21.6
Adenocarcinoma	106	43.3	59	67.0
Small cell	20	8.2	8	9.1
Others	2	0.8	1	1.1
Unknown	2	0.8	1	1.1
Total	245	100.0	88	100.0

RESULTS

Table I shows the distribution of our study subjects by sex and age. The mean ages were not statistically significantly different between cases and controls in both sexes. Table II presents the distribution of the cases by cell type. In males, squamous cell carcinoma and adenocarcinoma accounted for 47% and 43%, respectively. In females, adenocarcinoma was the most frequent cell type (67%), followed by squamous cell carcinoma (22%).

Characteristics of the study subjects are summarized in Table III. As expected, never-smokers were more common among controls than among cases in both sexes ($P < 0.001$), and cases were more likely to be heavy smokers than controls in both men and women. Medical history of lung diseases was also positively associated with the malignancy in males ($P < 0.001$). Among socio-economic factors, we examined educational attainment. Female patients were seemingly less well educated than controls ($P = 0.063$). Then, we treated these factors as confounding variables and included them in the multivariate analysis. Family history of lung cancer and intake

Table III. Characteristics of the Study Subjects

	Males				Females			
	Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%
Education								
Primary school	61	24.9	108	22.0	33	37.5	50	28.4
Junior high school	132	53.9	272	55.5	41	46.6	83	47.2
High school, college, university or higher	52	21.2	110	22.5	14	15.9	43	24.4
Test for gradient ^{a)}			$P = 0.436$				$P = 0.063$	
Smoking ^{b)}								
Never smoked	10	4.1	65	13.4***c)	50	57.5	145	83.8***
Ex-smokers	54	22.4	140	28.9#	5	5.7	5	2.9
Current smokers Cigarette-years: 0–599	34	14.1	94	19.4#	20	23.0	18	10.4**
600–1199	77	32.0	155	32.0	10	11.5	4	2.3**
1200–1799	36	14.9	19	3.9***	2	2.3	1	0.6
1800–	30	12.4	12	2.5***	0	0.0	0	0.0
Family history of lung cancer (father or mother)								
No	241	98.4	487	99.4	85	96.6	171	97.2
Yes	4	1.6	3	0.6	3	3.4	5	2.8
Medical history of lung disease (chronic bronchitis, pneumonia and pulmonary tuberculosis)								
No	167	68.2	418	85.3***	76	86.4	162	92.1
Yes	78	31.8	72	14.7***	12	13.6	14	8.0
Intake frequency of green-yellow vegetables								
Low	30	12.2	48	9.8	6	6.9	6	3.4
Middle	55	22.5	112	22.9	16	18.4	45	25.6
High	160	65.3	329	67.3	65	74.7	125	71.0
Test for gradient			$P = 0.494$				$P = 0.667$	

a) Wilcoxon test for case-control difference.

b) Ex-smokers who quit smoking 0–4 years ago were classified as current smokers.

c) Chi-square test for case-control difference; # $P < 0.10$, ** $P < 0.01$, *** $P < 0.001$.

frequency of green-yellow vegetables did not demonstrate a significant case-control difference in the present study. Nevertheless, we also took these characteristics into consideration in the multivariate analysis, because they have been found significant in earlier epidemiological studies of lung cancer.²⁷⁻²⁹⁾

For all the covariates except smoking, the strata specified in Table III were used in the logistic regressions. We adjust for smoking in finer strata, since smoking is the most prominent risk factor for lung cancer, and therefore careful adjustments are needed to reduce its confounding effect. The strata used in the logistic models were as follows: non-smokers, ex-smokers who had quit smoking 15+, 10-14, and less than 10 years ago, and current smokers with 0-299, 300-599, 600-899, 900-1199, 1200-1499, 1500-1799, 1800-2099 and 2100+

cigarette-years for males; ex-smokers, and current smokers with 0-299, 300-599 and 600+ cigarette-years for females. Ex-smokers were categorized according to the period after cessation for males, because this period is the major determinant of lung cancer risk among ex-smokers.³⁰⁾ Fewer strata than those used in males were applied for females, since the number of ex-smokers and current smokers among women was much smaller than that among men.

Table IV shows the ORs with 95% CIs for lung cancer according to the level of Okinawan tea intake. The ORs for daily tea drinkers relative to non-daily drinkers were 0.73 (95% CI: 0.43-1.24) in men, and 0.66 (0.26-1.72) in women. Decreasing risk with increasing tea intake was detected in both sexes. In males, the ORs (and 95% CIs) for those who daily consumed 1-4, 5-9, and 10 cups or

Table IV. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer according to Okinawan Tea Intake by Sex^{a)}

Okinawan tea intake	Males				Females			
	Cases/Controls		OR	95% CI	Cases/Controls		OR	95% CI
Not daily	40	58	1.00		11	15	1.00	
Daily any ^{b)}	205	432	0.73	0.43-1.24	76	161	0.66	0.26-1.72
1-4 cups/day	65	129	0.85	0.46-1.55	32	66	0.77	0.28-2.13
5-9 cups/day	58	121	0.85	0.46-1.56	20	38	0.77	0.26-2.25
10- cups/day	77	160	0.57	0.31-1.06 ^{c)}	21	50	0.38	0.12-1.18 ^{c)}
Test for trend				P=0.053				P=0.032

a) Adjusted for education, smoking, family history of lung cancer, medical history of lung disease and intake frequency of green-yellow vegetables.

b) Subjects with missing information on the level of daily intake were also included.

c) $P < 0.10$.

Table V. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer according to Okinawan Tea Intake by Sex and Cell Type^{a)}

Cell type	Okinawan tea intake	Males			Females		
		Cases/Controls	OR	95% CI	Cases/Controls	OR	95% CI
Squamous cell	Not daily	23	58	1.00	3	15	1.00
	Daily any ^{b)}	92	432	0.50	16	161	0.08
	1-4 cups/day	25	129	0.50	6	66	0.10
	5-9 cups/day	27	121	0.59	5	38	0.05
	10- cups/day	37	160	0.46	4	50	0.04
	Test for trend			P=0.082			P=0.047
Adenocarcinoma	Not daily	15	58	1.00	6	15	1.00
	Daily any	91	432	0.85	52	161	0.74
	1-4 cups/day	35	129	1.63	22	66	0.77
	5-9 cups/day	24	121	1.15	13	38	0.84
	10- cups/day	32	160	0.94	15	50	0.62
	Test for trend			P=0.129			P=0.416

a) Adjusted for age, residence, education, smoking, family history of lung cancer, medical history of lung disease and intake frequency of green-yellow vegetables.

b) Subjects with missing information on the level of daily intake were also included.

c) $P < 0.05$.

d) $P < 0.10$.

Table VI. Okinawan Tea Intake of the Study Subjects by Sex and Smoking Status

Okinawan tea intake	Males								Females							
	Never smoked				Ever smoked ^{a)}				Never smoked				Ever smoked			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Not daily	3	30.0	9	14.5	37	16.1	48	11.9	8	17.0	14	10.0	3	8.1	1	3.4
Daily 1-4 cups/day	5	50.0	22	35.5	60	26.1	107	26.4	21	44.7	59	42.1	11	29.7	7	24.1
5-9 cups/day	1	10.0	15	24.2	57	24.8	106	26.2	10	21.3	30	21.4	10	27.0	8	27.6
10+ cups/day	1	10.0	16	25.8	76	33.0	144	35.6	8	17.0	37	26.4	13	35.1	13	44.8
Test for gradient ^{b)}				$P=0.079$				$P=0.254$				$P=0.124$				$P=0.323$

a) Subjects with missing information on cigarette-years were also included.

b) Wilcoxon test for case-control difference.

Table VII. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Lung Cancer according to Okinawan Tea Intake by Sex and Smoking Status^{a)}

Smoking status	Okinawan tea intake	Males				Females			
		Cases/Controls	OR	95% CI		Cases/Controls	OR	95% CI	
Never smoked	Not daily	3	9	1.00		8	14	1.00	
	Daily ^{b)}	7	56	0.44	0.06-3.17	41	131	0.56	0.20-1.57
Ever smoked ^{c)}	Not daily	37	48	1.00		3	1	1.00	
	Daily	198	376	0.70	0.43-1.14	35	30	0.43	0.03-6.77

a) Adjusted for age, residence, education, family history of lung cancer, medical history of lung disease and intake frequency of green-yellow vegetables.

b) Subjects with missing information on the level of daily intake were also included.

c) Subjects with missing information on cigarette-years were also included.

more, relative to non-daily tea drinkers, were 0.85 (0.46-1.55), 0.85 (0.46-1.56), 0.57 (0.31-1.06), respectively (test for trend: $P=0.053$). In females, the corresponding ORs were 0.77 (0.28-2.13), 0.77 (0.26-2.25) and 0.38 (0.12-1.18), respectively (test for trend: $P=0.032$).

Table V presents the ORs and 95% CIs for lung cancer according to the level of Okinawan tea intake by sex and cell type. Risk reduction by Okinawan tea consumption was detected mainly in squamous cell carcinoma. Daily tea consumption was associated with a significantly reduced risk of squamous cell carcinoma in males and females; the ORs being 0.50 (95% CI 0.27-0.93) and 0.08 (0.01-0.68), respectively.

Table VI summarizes the consumption of Okinawan tea by smoking status among the study subjects. Controls were likely to consume more tea than cases irrespective of sex and smoking status, though no significant case-control difference was detected. Ever-smokers tended to drink more Okinawan tea than never-smokers in cases and controls as well ($P=0.033$ for male cases, 0.081 for male controls, 0.021 for female cases, and 0.013 for female controls by Wilcoxon test). Table VII shows the ORs with 95% CIs for lung cancer according to Okinawan tea intake by smoking status. All the ORs were

revealed to be smaller than unity, though none reached the level of statistical significance.

DISCUSSION

One potential weakness of this study is that the cases were not collected in a population-based setting. Nevertheless, the geographical distribution of the patients who visited the National Okinawa Hospital during the study period was almost identical to that of patients who died of lung cancer in Okinawa prefecture; 20.2% of the patients in the hospital came from the Nago and Ishikawa areas, 19.7% from the Koza area, 23.6% from Naha city, 22.7% from the Nanbu area, and 13.8% from the Miyako and Yaeyama areas; the corresponding figures for those who died of lung cancer in Okinawa were 20.1%, 20.0%, 23.4%, 24.2% and 12.2%, respectively.²¹⁾ This implies that the cases identified in the hospital well represent lung cancer in Okinawa.

Another issue in our study might be a non-respondent bias. Thirty percent of the patients could not be interviewed, usually because they were dead or too ill. It is unlikely, however, that poor prognosis is associated with large Okinawan tea consumption, and thus a non-

respondent bias in the cases would not exaggerate the protective effect of the tea. The exact response rate of the controls could not be obtained. However, we can assume the response rate to be well above 50%, since we successfully set up two controls from the first and second potential controls on most occasions, and only rarely required candidates from the remaining eligible controls or additional ones. We found some difficulties in setting up the controls for male cases in their forties and fifties. The negative association between Okinawan tea consumption and lung cancer risk in males, however, was not attenuated, even if these age groups were excluded from the analysis, the OR for daily drinkers versus non-daily drinkers being 0.62 (95% CI 0.34–1.14). Therefore, the association could not be explained by non-respondent bias in the controls.

The present study detected a negative association between Okinawan tea consumption and lung cancer risk. Although we adjusted for smoking in very fine strata in the analysis, one may wonder whether tea drinkers were less exposed to the deleterious effects of smoking, so that this confounding might produce the apparent protective effect of tea. This is, however, unlikely, because daily tea drinkers with no history of smoking also showed odds ratios smaller than unity. Also, from Table VI, ever-smokers were likely to consume more Okinawan tea than never-smokers in cases and controls as well. These findings essentially raise the possibility that the residual confounding effect of smoking might have diluted the favorable effect of Okinawan tea, if the confounding effect of smoking was not totally removed in the multivariate analysis.

To our knowledge, this is the first case-control study which suggests a protective effect of tea consumption against lung cancer. Tea catechins have been demonstrated to possess inhibitory effects against various types of tumors. The features of the catechins that may affect tumorigenesis are their antioxidant activities, inhibition of nitrosation reactions, modulation of carcinogen-metabolizing enzymes, trapping of activated carcinogens, and inhibition of activities related to cell proliferation.¹⁾

The protective effect of tea consumption against lung cancer suggested in our study, however, is not necessarily substantiated by the previous epidemiological investigations. What are the possible explanations for the different findings regarding risk modification by tea consumption?

First, the composition of tea as a beverage is known to be different according to how the tea leaves are prepared, and the main categories are green tea, Okinawan tea, oolong tea and black tea.²³⁾ Green tea contains catechins at a level of 30–42% of tea extract solids. The corresponding value for black tea is only 3–10%, because the catechins undergo oxidative polymerization to theaflavins, thearubigins, and other oligomers in the produc-

tion processes, that is, fermentation.^{1, 23)} Although theaflavins, thearubigins, and other black tea polyphenols might also have inhibitory effects on carcinogenesis, their potencies might not be the same as those of the catechins. Moreover, green tea beverage also contains another antioxidant, vitamin C, whose protective effect against lung cancer has been detected in several epidemiological studies.^{29, 31)} About 4 mg of vitamin C is found in 100 ml of green tea beverage, while black tea or oolong tea contains virtually no vitamin C.³²⁾ (Unfortunately, we have no data on the vitamin C content in Okinawan tea.) Thus, the kind and amount of tea beverage consumed, that is, the different amounts of catechins and vitamin C intake from tea leaves differently prepared, would have to be considered in further epidemiological investigations.

We did not ask the study subjects specifically about the consumption of Japanese green tea or oolong tea. Some subjects might have consumed Okinawan tea and Japanese green tea in combination. Therefore, we should not emphasize the specific effect of Okinawan tea too much. Nevertheless, there seems no reason to deny the protective effect of tea catechins in general, suggested in the present study.

Most of the present subjects did not consume black tea. Black tea drinkers (those who drank it at least once a month) accounted for only 16%, 14%, 6% and 22% of male cases, male controls, female cases and female controls, respectively. The ORs for black tea drinkers relative to those who did not drink it were 1.15 (95% CI 0.70–1.91) in males and 0.10 (0.02–0.46) in females, after adjusting for the same covariates as in Table IV. The apparent protective effect found for black tea against lung cancer in females, but not in males, may largely be due to chance, because there were very few black tea drinkers among our female cases.

Second, the genetic susceptibility to tea might possibly vary according to the population studied. Wang *et al.*³³⁾ reported that the catechins derived from green tea inhibited cytochrome P-450-dependent AHH of rat hepatic microsomes. Black tea leaves,³⁴⁾ water extract of green tea,⁹⁾ and green tea polyphenols^{9, 35)} have been reported to enhance the GST activity in mouse liver and small intestine. AHH activates carcinogens such as benzo(a)pyrene,³⁶⁾ and GST catalyzes the conjugation of activated carcinogens, including hydroquinones and epoxides of polycyclic aromatic hydrocarbons.^{36, 37)} Therefore, the modification of carcinogen-metabolizing enzymes might well play an important role in the preventive effects of tea against lung cancer. Since AHH inducibility shows a genetically determined variation,³⁸⁾ and deficiency of GST1 (GST1 is an isozyme of GST) is frequently observed,³⁹⁾ it is reasonable to assume that the genetic susceptibility to tea might vary among individuals and populations. Thus, stratification by the phenotype or

genotype of these enzymes might be useful in future studies, when analyzing the association between tea consumption and lung cancer.

Finally, tea is known to have not only antimutagenic effects, but also some mutagenic activities.^{15,40)} This mutagenicity might partly explain the observation of elevated lung cancer risk by tea consumption.¹³⁻¹⁵⁾

Risk reduction by Okinawan tea consumption appeared to be larger for squamous cell carcinoma than for adenocarcinoma. Antioxidant activities of the catechins, like those of carotenoids,²⁹⁾ may be related to protective effects chiefly on squamous cell carcinoma of the lung.

The findings in the present study are consistent with those in laboratory animals. Further investigations, however, are undoubtedly needed, since there was only weak evidence of a dose-response relationship, and confounding by dietary factors other than tea intake could not possibly be fully adjusted. We adjusted intake frequency of green-yellow vegetables in our multivariate analyses, but the method of assessing the consumption level of green-yellow vegetables might be too crude to properly remove any confounding effect. Fat, animal or saturated fat in particular, has recently been incriminated as a lung cancer risk factor,^{41,42)} though such an association has not yet been proved in Japan. Dietary fat intake could not be adjusted in the present study, since we only examined the intake frequency of some selected food

items. It is, therefore, possible that the observed risk reduction by tea might be biased due to incomplete assessment of dietary factors other than tea. We are now conducting another case-control study to elucidate the effect of nutrients on lung cancer risk in Okinawa.

In short, our study found that the greater the intake of Okinawan tea, the smaller the lung cancer risk, and suggested an inhibitory effect of tea consumption on the development of lung cancer in humans. The risk reduction by Okinawan tea consumption was found chiefly for squamous cell carcinoma. More detailed studies to determine the effects of the kind of tea beverage consumed and the amounts of catechins and vitamin C taken from the drink, as well as the role of genetic factors and the effects of other dietary factors such as carotene or fat intake, would be warranted to confirm the protective action of tea consumption suggested in our study.

ACKNOWLEDGMENTS

The authors thank the public health nurses of the health centers in Okinawa prefecture for the control selection and the data collection. This work was supported by a Smoking Research Foundation Grant for Biomedical Research, and a Grant-in-Aid (4-2) for Cancer Research from the Ministry of Health and Welfare of Japan.

(Received July 3, 1995/Accepted August 30, 1995)

REFERENCES

- 1) Yang, C. S. and Wang, Z.-Y. Tea and cancer. *J. Natl. Cancer Inst.*, **85**, 1038-1049 (1993).
- 2) Kono, S., Ikeda, M., Tokudome, S. and Kuratsune, M. A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn. J. Cancer Res.*, **79**, 1067-1074 (1988).
- 3) Kato, I., Tominaga, S., Matsuura, A., Yoshii, Y., Shirai, M. and Kobayashi, S. A comparative case-control study of colorectal cancer and adenoma. *Jpn. J. Cancer Res.*, **81**, 1101-1108 (1990).
- 4) Shibata, A., Mack, T. M., Paganini-Hill, A., Ross, R. K. and Henderson, B. E. A prospective study of pancreatic cancer in the elderly. *Int. J. Cancer*, **58**, 46-49 (1994).
- 5) Gao, Y. T., McLaughlin, J. K., Blot, W. J., Ji, B. T., Dai, Q. and Fraumeni, J. F., Jr. Reduced risk of esophageal cancer associated with green tea consumption. *J. Natl. Cancer Inst.*, **86**, 855-858 (1994).
- 6) Wang, Z. Y., Hong, J.-Y., Huang, M.-T., Reuhl, K. R., Conney, A. H. and Yang, C. S. Inhibition of N-nitrosodiethylamine- and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced tumorigenesis in A/J mice by green tea and black tea. *Cancer Res.*, **52**, 1943-1947 (1992).
- 7) Xu, Y., Ho, C.-T., Amin, S. G., Han, C. and Chung, F.-L. Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and its major polyphenol as antioxidants. *Cancer Res.*, **52**, 3875-3879 (1992).
- 8) Wang, Z. Y., Agarwal, R., Khan, W. A. and Mukhtar, H. Protection against benzo[a]pyrene- and N-nitrosodiethylamine-induced lung and forestomach tumorigenesis in A/J mice by water extracts of green tea and licorice. *Carcinogenesis*, **13**, 1491-1494 (1992).
- 9) Katiyar, S. K., Agarwal, R., Zaim, M. T. and Mukhtar, H. Protection against N-nitrosodiethylamine and benzo[a]pyrene-induced forestomach and lung tumorigenesis in A/J mice by green tea. *Carcinogenesis*, **14**, 849-855 (1993).
- 10) Katiyar, S. K., Agarwal, R. and Mukhtar, H. Protective effects of green tea polyphenols administered by oral intubation against chemical carcinogen-induced forestomach and pulmonary neoplasia in A/J mice. *Cancer Lett.*, **73**, 167-172 (1993).
- 11) Komori, A., Yatsunami, J., Okabe, S., Abe, S., Hara, K., Suganuma, M., Kim, S.-J. and Fujiki, H. Anticarcinogenic activity of green tea polyphenols. *Jpn. J. Clin. Oncol.*, **23**, 186-190 (1993).
- 12) Oguni, I., Nasu, K., Kanaya, S., Ohta, Y., Yamamoto, S. and Nomura, T. Epidemiological and experimental studies on the antitumor activity by green tea extracts. *Jpn. J. Nutr.*, **47**, 93-102 (1989).

- 13) Stocks, P. Cancer mortality in relation to national consumption of cigarettes, solid fuel, tea and coffee. *Br. J. Cancer*, **24**, 215-225 (1970).
- 14) Kinlen, L. J., Willows, A. N., Goldblatt, P. and Yudkin, J. Tea consumption and cancer. *Br. J. Cancer*, **58**, 397-401 (1988).
- 15) Tewes, F. J., Koo, L. C., Meisgen, T. J. and Rylander, R. Lung cancer risk and mutagenicity of tea. *Environ. Res.*, **52**, 23-33 (1990).
- 16) Heilbrun, L. K., Nomura, A. and Stemmermann, G. N. Black tea consumption and cancer risk: a prospective study. *Br. J. Cancer*, **54**, 677-683 (1986).
- 17) Mettlin, C. Milk drinking, other beverage habits, and lung cancer risk. *Int. J. Cancer*, **43**, 608-612 (1989).
- 18) Chengyu, H., Xiuquan, Z., Zhongkai, Q., Li, G., Shusheng, P., Jiangrong, L., Ruming, X. and Li, Z. A case-control study of dietary factors in patients with lung cancer. *Biomed. Environ. Sci.*, **5**, 257-265 (1992).
- 19) Kubo, N., Ohno, Y., Ohmine, K. and Fukuma, S. Descriptive epidemiology and epidemiological background of lung cancer in Okinawa prefecture, the area with the highest mortality rate for male lung cancer in Japan. *J. Health Welfare Stat.*, **36**, 14-21 (1989) (in Japanese).
- 20) Smith, P. G. Comparison between registries: age-standardized rates. In "Cancer Incidence in Five Continents, Vol. VI," ed. D. M. Parkin, C. S. Muir, S. L. Whelan, Y.-T. Gao, J. Ferlay and J. Powell, pp. 865-870 (1992). IARC, Lyon.
- 21) Okinawa Prefecture. "Vital Statistics of Okinawa Prefecture, 1988-1990" (1990-1992). Okinawa Prefecture, Naha.
- 22) Ministry of Health and Welfare of Japan. "Vital Statistics of Japan, 1990, Vol. III" (1992). Health and Welfare Statistics Association, Tokyo.
- 23) Graham, H. N. Green tea composition, consumption, and polyphenol chemistry. *Prev. Med.*, **21**, 334-350 (1992).
- 24) Breslow, N. E. and Day, N. E. Conditional logistic regression for matched sets. In "Statistical Methods in Cancer Research, Vol. I," ed. W. Davis, pp. 248-279 (1980). IARC, Lyon.
- 25) Breslow, N. E. and Day, N. E. Unconditional logistic regression for large strata. In "Statistical Methods in Cancer Research, Vol. I," ed. W. Davis, pp. 192-246 (1980). IARC, Lyon.
- 26) Swanson, C. A., Brinton, L. A., Taylor, P. R., Licitra, L. M., Ziegler, R. G. and Schairer, C. Body size and breast cancer risk assessed in women participating in the Breast Cancer Detection Demonstration Project. *Am. J. Epidemiol.*, **130**, 1133-1141 (1989).
- 27) Ooi, W. L., Elston, R. C., Chen, V. W., Bailey-Wilson, J. E. and Rothschild, H. Increased familial risk for lung cancer. *J. Natl. Cancer Inst.*, **76**, 217-222 (1986).
- 28) Shaw, G. L., Falk, R. T., Pickle, L. W., Mason, T. J. and Buffler, P. A. Lung cancer risk associated with cancer in relatives. *J. Clin. Epidemiol.*, **44**, 429-437 (1991).
- 29) Fontham, E. T. H. Protective dietary factors and lung cancer. *Int. J. Epidemiol.*, **19** (Suppl. 1), S32-S42 (1990).
- 30) Sobue, T., Suzuki, T., Fujimoto, I., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwahara, O., Ichitani, M., Taki, T., Kuwabara, M., Nakahara, K., Endo, S., Sawamura, K., Kurata, M. and Hattori, S. Lung cancer risk among exsmokers. *Jpn. J. Cancer Res.*, **82**, 273-279 (1991).
- 31) Block, G. Vitamin C status and cancer. Epidemiologic evidence of reduced risk. *Ann. N. Y. Acad. Sci.*, **669**, 280-290 (1992).
- 32) Committee on Resources, Science Bureau, Japan. "Standard Tables of Food Composition in Japan," 4th Ed. (1983). Committee on Resources, Science Bureau, Japan, Tokyo.
- 33) Wang, Z. Y., Das, M., Bickers, D. R. and Mukhtar, H. Interaction of epicatechins derived from green tea with rat hepatic cytochrome P-450. *Drug Metab. Dispos.*, **16**, 98-103 (1988).
- 34) Sporn, V. L., Venegas, P. L. and Wattenberg, L. W. Glutathione S-transferase activity: enhancement by compounds inhibiting chemical carcinogenesis and by dietary constituents. *J. Natl. Cancer Inst.*, **68**, 493-496 (1982).
- 35) Khan, S. G., Katiyar, S. K., Agarwal, R. and Mukhtar, H. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. *Cancer Res.*, **52**, 4050-4052 (1992).
- 36) Gelboin, H. V. Benzo[a]pyrene metabolism, activation and carcinogenesis: role and regulation of mixed-function oxidases and related enzymes. *Physiol. Rev.*, **60**, 1107-1166 (1980).
- 37) Mannervik, B. and Danielson, U. H. Glutathione transferases: structure and catalytic activity. *Crit. Rev. Biochem. Mol. Biol.*, **23**, 281-337 (1988).
- 38) Kiyohara, C. and Hirohata, T. A role of aryl hydrocarbon hydroxylase inducibility in susceptibility to lung carcinogenesis. *Jpn. J. Hyg.*, **48**, 1027-1036 (1994) (in Japanese).
- 39) Nakachi, K., Imai, K., Hayashi, S.-I. and Kawajiri, K. Polymorphisms of the *CYP1A1* and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. *Cancer Res.*, **53**, 2994-2999 (1993).
- 40) Nagao, M., Takahashi, Y., Yamanaka, H. and Sugimura, T. Mutagens in coffee and tea. *Mutat. Res.*, **68**, 101-106 (1979).
- 41) Jain, M., Burch, J. D., Howe, G. R., Risch, H. A. and Miller, A. B. Dietary factors and risk of lung cancer: results from a case-control study, Toronto, 1981-1985. *Int. J. Cancer*, **45**, 287-293 (1990).
- 42) Alavanja, M. C. R., Brown, C. C., Swanson, C. and Brownson, R. C. Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. *J. Natl. Cancer Inst.*, **85**, 1906-1916 (1993).