

U-shaped Effect of Drinking and Linear Effect of Smoking on Risk for Stomach Cancer in Japan

Shogo Kikuchi,¹ Toshifusa Nakajima,² Osamu Kobayashi,³ Tatsuo Yamazaki,^{4,15} Masahiro Kikuichi,⁵ Kiyoshi Mori,^{6,16} Shinsuke Oura,^{9,17} Hideaki Watanabe,¹⁰ Hirokazu Nagawa,⁷ Reiji Otani,^{12,18} Naoyuki Okamoto,¹³ Michiko Kurosawa,¹¹ Haruyuki Anzai,⁴ Toshiro Konishi,^{6,19} Shunji Futagawa,⁹ Noboru Mizobuchi,¹⁰ Oichiro Kobori,¹⁴ Ruriko Kaise,¹² Yutaka Inaba¹¹ and Osamu Wada^{8,20}

¹Department of Public Health, Aichi Medical University School of Medicine, ²Department of Surgery, Cancer Institute Hospital, ³Department of Surgery, Kanagawa Cancer Center Hospital, ⁴1st Department of Surgery, Saitama Medical School, ⁵Department of Surgery, Mitsui Memorial Hospital, ⁶2nd Department of Surgery, ⁷Department of Surgical Oncology, ⁸Department of Hygiene and Preventive Medicine, Graduate School of Medicine, University of Tokyo, ⁹2nd Department of Surgery, ¹⁰1st Department of Surgery, ¹¹Department of Epidemiology and Environmental Health, Juntendo University School of Medicine, ¹²Sempo Tokyo Takanaawa Hospital, ¹³Department of Epidemiology, Kanagawa Cancer Center Research Institute and ¹⁴International Medical Center

A case-control study was conducted to evaluate the relationship between smoking or drinking doses and risk for stomach cancer, and to clarify whether the relationship is dose-dependent or U-shaped. Smoking dose was categorized as 0, 1–399, 400–799, or 800+ cigarette-years, and drinking dose as 0, occasional/0.1–134.9, 135–1349.9, or 1350+ alcohol-years (ml of pure alcohol intake per day multiplied by years of drinking). *Helicobacter pylori* status was determined by serology for adjustment. Using logistic regression, the adjusted effects of smoking and drinking doses on risk for stomach cancer were calculated for both genders. Among male subjects, the odds ratios (95% confidence intervals (CIs)) were 1.29 (0.76, 2.18) for 1–399, 1.71 (1.05, 2.80) for 400–799 and 2.46 (1.49, 4.07) for 800+ cigarette-years compared with never-smokers, and 1.89 (0.97, 3.69) for never-drinkers, 2.82 (1.63, 4.86) for 135–1349.9 and 2.84 (1.97, 4.83) for 1350.0+, compared with occasional/0.1–134.9 alcohol-years. Among female subjects, they were 0.44 (0.20, 1.00) for 1–399 and 2.471 (0.91, 6.68) for 400+ cigarette-years compared with never-smokers, and 1.54 (0.90, 2.63) for never-drinkers and 1.39 (0.66, 2.93) for 135.0+ alcohol-years. Smoking seems to exert a linear effect and drinking, a J- or U-shaped effect on risk for stomach cancer, although there might be a dip of risk in light smokers among female subjects.

Key words: U-shaped effect — Drinking — Smoking — Stomach cancer

Many studies have reported that smoking is a risk factor for stomach cancer, although several have yielded contradictory results. An effect of alcohol intake on risk for stomach cancer has been suspected, and both affirmative and negative results have been reported. However, few studies have evaluated the effect of smoking or drinking on stomach cancer with consideration of their doses. Alcohol intake is known to have a U- or J-shaped effect on cardiovascular diseases,¹ stroke,² all causes of death^{1,3} and cancer mortality⁴; that is, those who consume a little alcohol have the lowest risk. Therefore, it would seem important to evaluate the relationship between smoking or

drinking dose and risk for stomach cancer, and to clarify whether the relationship is dose-dependent or U-shaped.

Although it is known that *Helicobacter pylori* is a strong risk factor for stomach cancer,^{5–9} few studies to date have evaluated the effect of smoking or drinking with consideration of *H. pylori* status.

In this study, the effects of smoking and drinking on risk of stomach cancer were evaluated according to their doses, using data including *H. pylori* status from 718 stomach cancer patients and 883 control subjects. Analyses were also carried out for intestinal, diffuse type, early advanced, proximal and distal stomach cancer, respectively.

SUBJECTS AND METHODS

The case subjects were stomach cancer patients who were newly hospitalized in one of nine hospitals in the Tokyo Metropolitan Area between June 1993 and July

E-mail: kikuchis@aichi-med-u.ac.jp

Present address: ¹⁵Maruyama Memorial Hospital, ¹⁶Department of Surgery, Higashi Kobe Hospital, ¹⁷Department of Surgery, Yanagibashi Hospital, ¹⁸Sempo Shibaura Clinic, ¹⁹Department of Surgery, NTT Tokyo Hospital, ²⁰Department of Hygiene, Saitama Medical School.

1995. Patients aged over 70 years and those who had undergone prior therapy for stomach cancer were excluded. The control subjects were recruited from several health check programs in a hospital in the same area between June 1993 and November 1994, so that numbers of subjects were about 100 men and 100 women in each 10-year age-class, in order of admission.⁹⁾ The subjects were asked to provide sera and to fill out a questionnaire regarding their smoking and drinking habits. Informed consent was obtained from all subjects. In the questionnaire, the case subjects were asked whether they had been diagnosed clinically or in screening programs for stomach cancer. Diagnoses were confirmed using the pathology reports for resection or biopsy specimens. The case subjects were classified by type (intestinal or diffuse), stage (early or advanced), and subsite of the lesions (proximal, middle or distal). Those with both intestinal and diffuse type lesions were classified according to the most prevalent lesion. Proximal, middle and distal cancers were cancers the main lesion of which was within the proximal, middle or distal third of the stomach.

Of 787 stomach cancer patients and 1007 control subjects, 69 patients and 124 control subjects were excluded from the analyses, because the information they provided on smoking or drinking habits was incomplete. The age and gender distribution of the subjects included in the analyses is shown in Table I. The smoking dose for ex- and current smokers was calculated by multiplying cigarettes consumed per day by years of smoking (cigarette-years). The drinking dose for ex- and current drinkers was calculated by multiplying the amount of pure alcohol consumed (ml) per day by years of drinking (alcohol-years). A cup (180 ml) of sake (Japanese rice wine) contains 27 ml of pure alcohol. Thus, consumption of one cup of sake a day for 5 years equals 135 alcohol-years.

The presence of *H. pylori* antibody was measured by the SRL Co., Ltd. (Tokyo) using Pilika-Plate G Helicobacter produced by Biomerica Co., Ltd. (Newport, CA). In the present study, (±) was defined as negative.

At first, analyses restricting case subjects to those who were diagnosed in screening programs were carried out, and then analyses using all stomach cancer patients were carried out. Each analysis was conducted separately by gender. Age, *H. pylori* status, smoking and drinking doses were put into an unconditional logistic regression model as explanatory variables, and their mutually adjusted odds ratios for risk of stomach cancer were calculated. In the analysis of male subjects, smoking and drinking doses were classified into 4 categories with similar numbers of subjects in each: smoking dose: never, 1–399, 400–799, and 800 or more; drinking dose: never, occasional and 1–134.9, 135–1349.9, and 1350 or more. As female subjects showed smaller smoking and drinking doses than male subjects, the third and the fourth categories of the smoking and drinking doses were combined in the analysis of female subjects.

In order to observe whether any relationship between stomach cancer and the risk factors depends on the type, stage or subsite of the lesion, analyses were also carried out using all control subjects and the case subjects with the types, stages and subsites.

RESULTS

About half of the stomach cancer patients were diagnosed in screening programs (Table I). Both smoking and drinking habits depended more on gender than on diagnosis. Smoking and drinking were more frequent among male subjects. Ex-smokers and ex-drinkers accounted for a larger proportion of stomach cancer patients than control subjects. As separate analyses by *H. pylori* status gave similar results, they are not shown in this study.

Results of male subjects are shown in Table II. When stomach cancer patients were restricted to those from screening, the odds ratios (95% confidence intervals (CIs)) were 1.29 (0.76, 2.18) for 1–399, 1.71 (1.05, 2.80) for 400–799 and 2.46 (1.49, 4.07) for 800+ cigarette-years compared with never-smokers, and 1.89 (0.97, 3.69) for

Table I. Age and Gender Distribution of the Subjects (%)

Age	Whole stomach cancer patients		Screening-diagnosed (again) ^{a)}		Control subjects	
	Male	Female	Male	Female	Male	Female
20–29	1 (0.2)	2 (0.9)	0 (0.0)	1 (1.0)	87 (19.4)	89 (20.5)
30–39	15 (3.0)	19 (8.5)	10 (3.4)	6 (5.9)	95 (21.2)	89 (20.5)
40–49	95 (19.2)	53 (23.7)	60 (20.5)	29 (28.7)	90 (20.1)	84 (19.3)
50–59	161 (32.6)	77 (34.4)	105 (35.8)	37 (36.6)	87 (19.4)	87 (20.0)
60–69	222 (44.9)	73 (32.6)	118 (40.3)	28 (27.7)	89 (19.9)	86 (19.8)
Total	494 (100.0)	224 (100.0)	293 (100.0)	101 (100.0)	448 (100.0)	435 (100.0)

a) Stomach cancer patients diagnosed in screening programs for stomach cancer.

Table II. Odds Ratios for Stomach Cancer among Male Subjects Adjusted for Age and the Shown Variables Using Logistic Regression

Explanatory variable Category	Stomach cancer diagnosed in screening			Whole stomach cancer		
	Patients/Subjects	OR (95% CI)	OR (95% CI) ^{a)}	Patients/Subjects	OR (95% CI)	OR (95% CI) ^{a)}
Smoking dose (cigarette-years ^{b)})		<i>P</i> =0.004			<i>P</i> <0.001	
0 (Never-smoker)	52/188	1.0		87/223	1.0	
1–399	52/211	1.29 (0.76, 2.18)		75/234	1.21 (0.76, 1.92)	
400–799	84/178	1.71 (1.05, 2.80)		149/243	2.00 (1.31, 3.05)	
800+	105/164	2.46 (1.49, 4.07)		183/242	2.63 (1.69, 4.10)	
Drinking dose (alcohol-years ^{c)})		<i>P</i> <0.001			<i>P</i> <0.001	
0 (Never-drinker)	34/91	1.0	1.89 (0.97, 3.69)	62/119	1.0	1.75 (1.00, 3.07)
Occasional and 0.1–134.9	31/177	0.53 (0.27, 1.03)	1.0	60/206	0.57 (0.33, 1.00)	1.0
135.0–1349.9	90/233	1.49 (0.82, 2.70)	2.82 (1.63, 4.86)	135/278	1.23 (0.73, 2.06)	2.15 (1.39, 3.39)
1350.0+	138/240	1.50 (0.85, 2.65)	2.84 (1.67, 4.83)	237/339	1.40 (0.85, 2.31)	2.45 (1.57, 3.83)
<i>H. pylori</i> serology		<i>P</i> <0.001			<i>P</i> <0.001	
Negative	24/216	1.0		48/240	1.0	
Positive	269/525	4.57 (2.78, 7.54)		446/702	3.50 (2.34, 5.22)	

a) Odds ratios when the risk of the second category is defined as 1.0.

b) Cigarettes/day multiplied by years of smoking.

c) Pure alcohol intake (ml)/day multiplied by years of drinking. Male.

Table III. Odds Ratios for Stomach Cancer among Female Subjects Adjusted for Age and the Shown Variables Using Logistic Regression

Explanatory variable Category	Stomach cancer diagnosed in screening			Whole stomach cancer		
	Patients/Subjects	OR (95% CI)	OR (95% CI) ^{a)}	Patients/Subjects	OR (95% CI)	OR (95% CI) ^{a)}
Smoking dose (cigarette-years ^{b)})		<i>P</i> =0.021			<i>P</i> =0.003	
0 (Never-smoker)	84/412	1.0		178/506	1.0	
1–399	8/105	0.44 (0.20, 1.00)		23/120	0.70 (0.40, 1.22)	
400+	9/19	2.47 (0.91, 6.68)		23/33	3.61 (1.57, 8.30)	
Drinking dose (alcohol-years ^{c)})		<i>P</i> =0.291			<i>P</i> =0.016	
0 (Never-drinker)	57/227	1.0	1.54 (0.90, 2.63)	138/308	1.0	1.86 (1.22, 2.83)
Occasional and 0.1–134.9	29/227	0.65 (0.38, 1.12)	1.0	55/253	0.54 (0.35, 0.82)	1.0
135.0+	15/82	0.91 (0.45, 1.83)	1.39 (0.66, 2.93)	31/98	0.75 (0.43, 1.30)	1.38 (0.77, 2.48)
<i>H. pylori</i> serology		<i>P</i> <0.001			<i>P</i> <0.001	
Negative	9/212	1.0		24/227	1.0	
Positive	92/324	6.37 (3.07, 13.2)		200/432	5.10 (3.13, 8.28)	

a), b), c) See the footnotes of Table II.

never-drinkers, 2.82 (1.63, 4.86) for 135–1349.9 and 2.84 (1.97, 4.83) for 1350.0+, compared with occasional/0.1–134.9 alcohol-years. Similar results were obtained when all stomach cancer patients were included. The risk of stomach cancer increased linearly with smoking dose, but not with drinking dose. Subjects with less than 135 alcohol-years and occasional drinkers showed the lowest risk

for stomach cancer, while the other subjects had significantly elevated risk. Heavy drinkers with 1350 or more alcohol-years had the highest risk for stomach cancer.

Among female subjects, when stomach cancer patients were restricted to those from screening, the odds ratios (95% CIs) were 0.44 (0.20, 1.00) for 1–399 and 2.47 (0.91, 6.68) for 400+ cigarette-years compared with never-

Table IV. Odds Ratios for Intestinal, Diffuse Types, Early, Advanced, Proximal, Middle and Distal Stomach Cancer among Male Subjects

	Intestinal type	Diffuse type	Early	Advanced	Proximal ^{a)}	Middle ^{a)}	Distal ^{a)}
(Number of patients)	(330)	(164)	(271)	(221)	(111)	(218)	(165)
Smoking dose (cigarette-years ^{b)})							
0	1.0 <i>P</i> <0.01 ^{c)}	1.0 <i>P</i> <0.01	1.0 <i>P</i> <0.01	1.0 <i>P</i> <0.01	1.0 <i>P</i> <0.01	1.0 <i>P</i> =0.01	1.0 <i>P</i> <0.01
1-399	1.25 (0.73, 2.15)	1.06 (0.57, 1.97)	1.42 (0.81, 2.47)	0.98 (0.54, 1.78)	1.15 (0.51, 2.57)	0.87 (0.49, 1.85)	1.95 (0.99, 3.84)
400-799	2.13 (1.31, 3.44)	1.63 (0.93, 2.87)	2.26 (1.37, 3.75)	1.71 (1.02, 2.89)	2.11 (1.06, 4.17)	1.22 (0.72, 2.07)	3.20 (1.75, 5.86)
800+	2.70 (1.65, 4.42)	2.44 (1.37, 4.33)	2.83 (1.68, 4.78)	2.45 (1.45, 4.15)	2.83 (1.44, 5.59)	2.10 (1.24, 3.55)	3.47 (1.86, 6.45)
Drinking dose (alcohol-years ^{b)})							
0	1.76 (0.94, 3.32)	1.74 (0.80, 3.79)	1.76 (0.90, 3.44)	1.88 (0.94, 3.77)	2.72 (1.13, 6.53)	1.74 (0.84, 3.57)	1.28 (0.60, 2.76)
0.1-134.9 ^{d)}	1.0 <i>P</i> =0.02 ^{c)}	1.0 <i>P</i> <0.01	1.0 <i>P</i> <0.01	1.0 <i>P</i> =0.02	1.0 <i>P</i> =0.06	1.0 <i>P</i> <0.01	1.0 <i>P</i> =0.25
135.0-1349.9	2.07 (1.22, 3.53)	2.20 (1.19, 4.07)	2.23 (1.29, 3.87)	2.17 (1.21, 3.89)	2.24 (1.01, 4.96)	2.34 (1.30, 4.19)	1.85 (1.00, 3.41)
1350.0+	2.14 (1.29, 3.55)	3.05 (1.68, 5.56)	2.50 (1.48, 4.23)	2.38 (1.36, 4.17)	2.46 (1.17, 5.17)	3.29 (1.88, 5.76)	1.56 (0.86, 2.84)

Adjusted for age, *Helicobacter pylori* status and the shown factors.

The number of control subjects was 448 in each analysis.

a) The main lesion was within the proximal, middle and distal third of the stomach, respectively.

b) See the footnote of Table II.

c) *P*-value for smoking dose or drinking dose.

d) Including occasional drinker.

Table V. Odds Ratios for Intestinal, Diffuse Types, Early, Advanced, Proximal, Middle and Distal Stomach Cancer among Female Subjects

	Intestinal type	Diffuse type	Early	Advanced	Proximal ^{a)}	Middle ^{a)}	Distal ^{a)}
(Number of patients)	(89)	(135)	(113)	(111)	(39)	(111)	(70)
Smoking dose (cigarette-years ^{b)})							
0	1.0 <i>P</i> =0.20 ^{c)}	1.0 <i>P</i> =0.04	1.0 <i>P</i> =0.08	1.0 <i>P</i> =0.12	1.0 <i>P</i> =0.05	1.0 <i>P</i> =0.29	1.0 <i>P</i> =0.06
1-399	0.76 (0.33, 1.77)	0.69 (0.35, 1.35)	0.66 (0.31, 1.40)	0.78 (0.38, 1.60)	0.34 (0.76, 1.49)	0.98 (0.51, 1.87)	0.50 (0.16, 1.51)
400+	2.50 (0.83, 7.56)	2.89 (1.10, 7.61)	2.57 (0.95, 6.95)	2.65 (0.95, 7.35)	3.43 (0.94, 12.47)	2.25 (0.81, 6.25)	2.90 (0.97, 8.69)
Drinking dose (alcohol-years ^{b)})							
0	2.18 (1.18, 4.03)	1.74 (1.07, 2.84)	1.48 (0.88, 2.49)	2.48 (1.42, 4.33)	1.50 (0.70, 3.21)	2.07 (1.22, 3.53)	1.69 (0.85, 3.35)
0.1-134.9 ^{d)}	1.0 <i>P</i> =0.04 ^{c)}	1.0 <i>P</i> =0.06	1.0 <i>P</i> =0.22	1.0 <i>P</i> <0.01	1.0 <i>P</i> =0.21	1.0 <i>P</i> =0.02	1.0 <i>P</i> =0.28
135.0+	1.39 (0.55, 3.53)	1.02 (0.48, 2.19)	0.88 (0.38, 2.05)	1.54 (0.68, 3.44)	0.43 (0.10, 2.05)	1.34 (0.64, 2.84)	1.78 (0.67, 4.71)

Adjusted for age, *Helicobacter pylori* status and the shown factors.

The number of control subjects was 435 in each analysis.

a), b), c), d) See the footnotes of Table IV.

smokers, and 1.54 (0.90, 2.63) for never-drinkers and 1.39 (0.66, 2.93) for 135.0+ alcohol-years (Table III). Similar odds ratios were obtained when all stomach cancer patients were included. Smokers with 1-399 cigarette-years had a reduced risk compared with never-smokers, and the difference was significant only in the analysis restricting stomach cancer patients to those from screening. Smokers with 400 or more cigarette-years showed an elevated risk, and the difference was significant in the analysis using all patients. Subjects with less than 135 alcohol-years and occasional drinkers showed the lowest

risk, and the difference with never-drinkers was significant in the analysis using all patients.

H. pylori status was positively related to the risk for stomach cancer after adjustment for smoking and drinking doses irrespective of gender or the way of diagnosis.

The odds ratios for the types, stages and subsites of cancers are shown in Tables IV for male and V for female subjects. When case subjects were restricted by type, stage, or subsite, the association of smoking and drinking doses with the cancers showed the same pattern as with the cancer overall. However, when restricted by subsites, a

difference in the strength of the associations was observed. In both male and female subjects, smoking dose was more closely associated with proximal and distal cancers than with middle cancer, whereas drinking dose showed a stronger association with middle cancer.

DISCUSSION

The stomach cancer patients and control subjects were from different hospitals, which may be a limitation of this study. The control subjects were screenees who attended health check programs, and most of them underwent stomach examination (contrasted X-ray) as screening for stomach cancer in the programs. They would often have been admitted to the hospitals where the stomach cancer patients were recruited, if their diagnoses had been stomach cancer. Sampling bias between the stomach cancer patients and the control subjects may have had little influence on the results of this study.

In this study, about half of the stomach cancer patients were diagnosed in screening programs, and there might be a difference depending on the way of diagnosis among the stomach cancer patients. Analyses restricting stomach cancer patients to those diagnosed in screening programs were carried out, because screenees might be biased as control subjects for stomach cancer patients not diagnosed in screening programs. However, no difference was observed between analyses using all stomach cancer patients and analyses using case subjects from screening programs. The only exception was a slight difference in significance among female subjects, which may be because of the difference in sample sizes. Thus, we concluded that in this study the difference between stomach cancer patients from screening and those diagnosed clinically was negligible, and further analyses were carried out using all stomach cancer patients.

In Japan, most people, though there is limitation by age, can attend health check programs and screenings for lung, cervical, stomach and colon cancers with little or no charge. This is because local governments, health insurance societies and/or employers meet the cost. This system may have accounted for the high proportion of patients from screening among the stomach cancer patients of this study and may have minimized the difference between the patients from and not from screening programs.

As there was a considerable difference in smoking and drinking doses between male and female subjects, analyses were carried out separately by gender. Both analyses gave similar results, which seems to reinforce the reliability of the results in this study. Ex-smokers and ex-drinkers were more frequent among stomach cancer patients. This may be because some patients stopped smoking or drinking after their hospitalization. However, this may have

exerted little effect, because cigarette-years and alcohol-years are used for smoking and drinking doses.

It is a well-known fact that *H. pylori* is closely related with the risk of stomach cancer.⁵⁻⁹⁾ No remarkable difference was found between analyses restricting subjects by *H. pylori* status, though the results are not shown. Therefore, the effect of smoking and drinking doses were evaluated with adjustment for *H. pylori* status, which differs from most studies to date. Although a Russian study has reported a synergic effect of *H. pylori* infection and smoking,¹⁰⁾ we could not find any such effect in Japanese subjects.

Smoking Many studies have evaluated the relationship between smoking and risk of stomach cancer. Although some studies obtained negative results,¹¹⁻¹³⁾ other studies had positive results,¹⁴⁻²⁴⁾ several of which showed a linear association between smoking dose and risk of stomach cancer.^{10, 25-28)}

Among male subjects, smoking dose showed a dose-dependent linear association with risk of stomach cancer. Among female subjects, smokers with 1-399 cigarette-years showed the lowest risk, which was different from the results among male subjects. If the gender difference in effect of light smoking on risk for stomach cancer is a true one, two explanations may be possible. One is that biological gender difference may influence the effect of smoking, and the other is that there may be a difference in the backgrounds of light smokers depending on gender, because male smoking is socially considered to be not as bad as female smoking in Japan. Nevertheless, the possibility still remains that the gender difference is a seeming one caused by the socially negative evaluation of female smoking. It is possible that some female smokers kept their past smoking habit secret from the questionnaire in this study, and the frequency of smokers may be underestimated among the patients, because most patients had quit smoking due to disease and/or hospitalization at the time when they answered the questionnaire. Thus, it is impossible to say whether the gender difference in the risk of light smokers is a true or a seeming one, from the results of this study. It is concluded that smoking elevates the risk of stomach cancer dose-dependently, although there might be a dip of risk in light smokers among female subjects.

Drinking Although many studies have produced negative results on the relationship between drinking and risk of stomach cancer,^{13, 16, 20, 21, 25, 26, 29)} some studies have shown positive results.^{11, 12, 19, 22, 23)} A few studies found a linear association.^{11, 23)}

In this study, light drinkers showed the lowest risk among both male and female subjects, and heavy drinkers the highest risk among male subjects. In other words, the association was J-shaped among male subjects, and U-shaped among female subjects, which is different from the

linear association shown in preceding studies. The reasons for the discrepancy may be differences in the areas of the studies, incidence of stomach cancer, and background factors such as food intake and lifestyle. Adjustment for *H. pylori* status may have made the J- or U-shaped association clearer. The association of drinking with risk of stomach cancer is very similar to the association with risk of other diseases such as cardiovascular diseases¹⁾ and stroke.²⁾ The J- or U-shaped association can explain the fact that more studies on stomach cancer have demonstrated an association with smoking than with drinking.

Type, stage and subsite of lesion When stomach cancer was restricted by type, stage or subsite of the lesions, the linear association with smoking and the J- or U-shaped association with drinking were also observed. The linear and the U-shaped association may not depend on type, stage or subsite of the lesions. Although neither type nor stage of cancer was very closely related with the associa-

tion, smoking showed a stronger association with proximal and distal cancers and drinking a stronger association with middle cancer than the other subsites of cancer. The present results on smoking are similar to the results of one Japanese study,³⁰⁾ although they are different from the results of a Swedish study.²⁰⁾ The closeness of the relationship with smoking and probably with drinking may be different according to the subsite of the lesions.

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REFERENCES

- 1) Camargo, C. A., Jr., Stampfer, M. J., Glynn, R. J., Gaziano, J. M., Manson, J. E., Goldhaber, S. Z. and Hennekens, C. H. Prospective study of moderate alcohol consumption and risk of peripheral arterial disease in US male physicians. *Circulation*, **95**, 577–580 (1997).
- 2) Berger, K., Ajani, U. A., Kase, C. S., Gaziano, J. M., Buring, J. E., Glynn, R. J. and Hennekens, C. H. Light-to-moderate alcohol consumption and risk of stroke among U.S. male physicians. *N. Engl. J. Med.*, **341**, 1557–1564 (1999).
- 3) Gaziano, J. M., Gaziano, T. A., Glynn, R. J., Sesso, H. D., Ajani, U. A., Stampfer, M. J., Manson, J. E., Hennekens, C. H. and Buring, J. E. Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. *J. Am. Coll. Cardiol.*, **35**, 96–105 (2000).
- 4) Tsugane, S., Fahey, M. T., Sasaki, S. and Baba, S. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC study Cohort I. Japan Public Health Center. *Am. J. Epidemiol.*, **150**, 1201–1207 (1999).
- 5) Kikuchi, S., Wada, O., Nakajima, T., Nishi, T., Kobayashi, O., Konishi, T. and Inaba, Y. Serum anti-*Helicobacter pylori* antibody and gastric carcinoma among young adults. Research Group on Prevention of Gastric Carcinoma among Young Adults. *Cancer*, **75**, 2789–2793 (1995).
- 6) Nomura, A., Stemmermann, G. N., Chyou, P. H., Kato, I., Perez-Perez, G. I. and Blaser, M. J. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N. Engl. J. Med.*, **325**, 1132–1136 (1991).
- 7) Parsonnet, J., Friedman, G. D., Vandersteen, D. P., Chang, Y., Vogelman, J. H., Orentreich, N. and Sibloy, R. K. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N. Engl. J. Med.*, **325**, 1127–1131 (1991).
- 8) Shimizu, N., Inada, K., Nakanishi, H., Tsukamoto, T., Ikehara, Y., Kaminishi, M., Kuramoto, S., Sugiyama, A., Katsuyama, T. and Tatematsu, M. *Helicobacter pylori* infection enhances glandular stomach carcinogenesis in Mongolian gerbils treated with chemical carcinogens. *Carcinogenesis*, **20**, 669–676 (1999).
- 9) Kikuchi, S., Nakajima, T., Kobayashi, O., Yamazaki, T., Kikuichi, M., Mori, K., Oura, S., Watanabe, H., Nagawa, H., Otani, R., Okamoto, N., Kurosawa, M., Anzai, H., Kubo, T., Konishi, T., Futagawa, S., Mizobuchi, N., Kobori, O., Kaise, R., Sato, T., Inaba, Y. and Wada, O. for the Tokyo Research Group of Prevention for Gastric Cancer. Effect of age on the relationship between gastric cancer and *Helicobacter pylori*. *Jpn. J. Cancer Res.*, **91**, 774–779 (2000).
- 10) Zaridze, D., Borisova, E., Maximovitch, D. and Chkhikvadze, V. Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control*, **11**, 363–371 (2000).
- 11) Jedrychowski, W., Boeing, H., Wahrendorf, J., Popiela, T., Tobiasz-Adamczyk, B. and Kulig, J. Vodka consumption, tobacco smoking and risk of gastric cancer in Poland. *Int. J. Epidemiol.*, **22**, 606–613 (1993).
- 12) Buiatti, E., Palli, D., Decarli, A., Amadori, D., Avellini, C., Bianchi, S., Biserni, R., Cipriani, F., Cocco, P., Giacosa, A., Marubini, E., Puntoni, R., Vindigni, C., Fraumeni, J., Jr. and Blot, W. A case-control study of gastric cancer and diet in Italy. *Int. J. Cancer*, **44**, 611–616 (1989).
- 13) Hoshiyama, Y. and Sasaba, T. A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control*, **3**, 441–448 (1992).
- 14) Hansson, L. E., Baron, J., Nyren, O., Bergstrom, R., Wolk, A. and Adami, H. O. Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Swe-

- den. *Int. J. Cancer*, **57**, 26–31 (1994).
- 15) Wu-Williams, A. H., Yu, M. C. and Mack, T. M. Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles County. *Cancer Res.*, **50**, 2569–2576 (1990).
 - 16) Nomura, A., Grove, J. S., Stemmermann, G. N. and Severson, R. K. A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Res.*, **50**, 627–631 (1990).
 - 17) McLaughlin, J. K., Hrubec, Z., Blot, W. J. and Fraumeni, J. F., Jr. Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. *Int. J. Cancer*, **60**, 190–193 (1995).
 - 18) 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).
 - 19) Hu, J. F., Zhang, S. F., Jia, E. M., Wang, Q. Q., Liu, S. D., Liu, Y. Y., Wu, Y. P. and Cheng, Y. T. Diet and cancer of the stomach: a case-control study in China. *Int. J. Cancer*, **41**, 331–335 (1988).
 - 20) Ye, W., Ekstrom, A. M., Hansson, L. E., Bergstrom, R. and Nyren, O. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int. J. Cancer*, **83**, 223–229 (1999).
 - 21) You, W. C., Blot, W. J., Chang, Y. S., Ershow, A. G., Yang, Z. T., An, Q., Henderson, B., Xu, G. W., Fraumeni, J. F., Jr. and Wang, T. G. Diet and high risk of stomach cancer in Shandong, China. *Cancer Res.*, **48**, 3518–3523 (1988).
 - 22) Ji, B. T., Chow, W. H., Yang, G., McLaughlin, J. K., Gao, R. N., Zheng, W., Shu, X. O., Jin, F., Fraumeni, J. F., Jr. and Gao, Y. T. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer*, **77**, 2449–2457 (1996).
 - 23) Correa, P., Fontham, E., Pickle, L. W., Chen, V., Lin, Y. P. and Haenszel, W. Dietary determinants of gastric cancer in south Louisiana inhabitants. *J. Natl. Cancer Inst.*, **75**, 645–654 (1985).
 - 24) Chen, M. J., Chiou, Y. Y., Wu, D. C. and Wu, S. L. Life-style habits and gastric cancer in a hospital-based case-control study in Taiwan. *Am. J. Gastroenterol.*, **95**, 3242–3249 (2000).
 - 25) Kneller, R. W., McLaughlin, J. K., Bjelke, E., Schuman, L. M., Blot, W. J., Wacholder, S., Gridley, G., CoChen, H. T. and Fraumeni, J. F., Jr. A cohort study of stomach cancer in a high-risk American population. *Cancer*, **68**, 672–678 (1991).
 - 26) Chow, W. H., Swanson, C. A., Lissowska, J., Groves, F. D., Sobin, L. H., Nasierowska-Guttmejer, A., Radziszewski, J., Regula, J., Hsing, A. W., Jagannatha, S., Zatonski, W. and Blot, W. J. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int. J. Cancer*, **81**, 871–876 (1999).
 - 27) Lee, J. K., Park, B. J., Yoo, K. Y. and Ahn, Y. O. Dietary factors and stomach cancer: a case-control study in Korea. *Int. J. Epidemiol.*, **24**, 33–41 (1995).
 - 28) De Stefani, E., Boffetta, P., Carzoglio, J., Mendilaharsu, S. and Deneo-Pellegrini, H. Tobacco smoking and alcohol drinking as risk factors for stomach cancer: a case-control study in Uruguay. *Cancer Causes Control*, **9**, 321–329 (1998).
 - 29) Trichopoulos, D., Ouranos, G., Day, N. E., Tzonou, A., Manousos, O., Papadimitriou, C. and Tricopoulos, A. Diet and cancer of the stomach: a case-control study in Greece. *Int. J. Cancer*, **36**, 291–297 (1985).
 - 30) Inoue, M., Tajima, K., Hirose, K., Kuroishi, T., Gao, C. M. and Kitoh, T. Life-style and subsite of gastric cancer—joint effect of smoking and drinking habits. *Int. J. Cancer*, **56**, 494–499 (1994).