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Original Contribution

Population-based Prospective Study of the Combined Influence of Cigarette Smoking and *Helicobacter pylori* Infection on Gastric Cancer Incidence

The Hisayama Study

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The authors assessed the separate and joint influences of cigarette smoking and *Helicobacter pylori* infection on the development of gastric cancer in a population-based prospective study. A total of 1,071 Japanese men aged ≥40 years were followed up prospectively for 14 years (1998–2002). Compared with that for current nonsmokers, the multivariate-adjusted hazard ratios of gastric cancer for smokers of 1–9, 10–19, and ≥20 cigarettes per day were 1.36 (95% confidence interval (CI): 0.50, 3.71), 1.93 (95% CI: 1.01, 3.67), and 1.88 (95% CI: 1.02, 3.43), respectively. The risk of gastric cancer increased steeply for subjects who had both a smoking habit and *H. pylori* infection compared with those who did not have both risk factors (hazard ratio = 11.41, 95% CI: 1.54, 84.67). If causal, the estimated population attributable fraction of gastric cancer for cigarette smoking was approximately half that for *H. pylori* infection (28.4% vs. 56.2%). The overlap of the population attributable fractions for the 2 factors was 49.6%. Findings suggest that cigarette smoking and *H. pylori* infection are significant risk factors for gastric cancer in Japanese men, and the magnitude of their combined influence is considerable.

cohort studies; *Helicobacter pylori*; smoking; stomach neoplasms

Abbreviations: CI, confidence interval; HR, hazard ratio; PAF, population attributable fraction.

A number of epidemiologic and clinical studies have demonstrated clear associations between cigarette smoking and the risk of gastric cancer, and smoking is thought to be causally related to development of the cancer (1, 2). A particular limitation of previous available studies on this issue is a lack of control for confounding factors, especially *Helicobacter pylori* infection, which has been established as a major risk factor for gastric cancer (3). To our knowledge, cigarette smoking and *H. pylori* infection, 2 major causal factors for gastric cancer, have never been considered together in the same prospective cohort study, and the joint influence of the 2 factors remains unclear. On the other hand, Japan has high rates of both smoking (4) and *H. pylori* infection (5) as well as high mortality and incidence of gastric cancer (6). Our aim was to examine the separate and joint influences of cigarette smoking and *H. pylori* infection on the development of gastric cancer by prospectively studying a population of Japanese men.

MATERIALS AND METHODS

Study population

The town of Hisayama is a suburban community adjacent to Fukuoka City, a metropolitan area in the southern part of Japan. The population of the town is approximately 7,500 and has been stable over 40 years. According to the 1985 census, the ages and occupational distributions of the town's residents were almost identical to those of Japan as a whole (7). In 1988, 2,742 Hisayama residents (1,165 men and 1,577 women) aged 40 years or older (80.9% of the total population in that age group) underwent a screening

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examination for the present study. Subjects were limited to men because the frequency of smoking was low among women. After exclusion of 91 individuals with a history of gastrectomy or gastric cancer (individuals with a history of cancer other than gastric cancer were not excluded) and 3 who died during the examination, a total of 1,071 men (mean age, 58.2 years) were enrolled in the study.

Follow-up survey

The methods used for the follow-up survey were described in detail in our previous report (5). In brief, this population was followed up for 14 years between December 1988 and November 2002 by repeated health checkups conducted every 1–2 years. Approximately 60%–80% of the subjects regularly returned for their checkups, whereas 5.9% of the total subjects moved away from Hisayama during the follow-up period. For all subjects who did not undergo a regular checkup or who moved away, health status was checked every year by mail or telephone. In addition, a daily monitoring system was established by the study team and local physicians or members of the Division of Health and Welfare of the town. To identify new occurrences of gastric cancer in the cohort, we monitored the records of endoscopic biopsies of the stomach as well as the records of radiographies and endoscopies generally performed at local clinics or general hospitals in and around the town. We also checked all of the records of annual mass screenings for gastric cancer by barium radiographic examination. Furthermore, to find any cases of occult gastric cancer, autopsies were performed on 221 (76.7%) of 288 subjects who died during the follow-up period.

The diagnosis of all cases of gastric cancer was confirmed by histologic examination of tissue specimens obtained by surgery, including gastrectomy and endoscopic mucosal resection, or autopsy. The tumors were categorized as either intestinal type or diffuse type according to the classification of Lauren (8). The location of the tumor within the stomach was determined by combined evaluation of the clinical and histopathologic records.

During the follow-up period, no subject was lost to follow-up, and gastric cancer developed in 68 subjects. Among them were 7 patients (10.3%) who had 2 synchronous gastric cancers. One (1.5%) occult case was first diagnosed at autopsy. Of the 75 lesions in 68 cases, 59 were classified as intestinal type and the remaining 16 as diffuse type. With regard to the anatomic subsite of the cancers, 18 were on the cardia and proximal one-third, and the remaining 57 were on the distal two-thirds. The interval time from baseline to time of diagnosis of cancer varied from 0.5 to 13.7 years.

Risk factor measurement

Information regarding smoking habits, alcohol intake, history of peptic ulcer disease, and family history of cancer was obtained by means of a questionnaire administered to each subject. On the basis of smoking status, subjects were classified as never smokers, former smokers, or current smokers, and the latter were further subdivided into those smoking 1–9, 10–19, or $\geq$20 cigarettes per day.

To assess the independent influence of cigarette smoking on gastric cancer occurrence, baseline risk factors in addition to age were used for analysis as confounding factors. Serum immunoglobulin G antibodies to *H. pylori* were measured by means of a quantitative enzyme immunoassay using a commercial kit (HM-CAP; Enteric Products Inc., Westbury, New York). The assay values were interpreted as positive and negative based on the manufacturer's instructions. Diabetes was revealed by medical history, glucose levels (fasting glucose level $\geq$7.8 mmol/L or postprandial glucose level $\geq$11.1 mmol/L), or a 75-g oral glucose tolerance test (using the 1985 World Health Organization criteria (9)), which was administered to most of the subjects aged 40–79 years (7), with plasma glucose measured by the glucose-oxidase method. Serum cholesterol levels were determined enzymatically. Body mass index (weight (kg)/height $(m)^2$) was used as an indicator of obesity. Those subjects engaging in sports more than 3 times per week during their leisure time made up the physically active group. The dietary survey was conducted by using a semiquantitative food frequency method (10), and the nutritional elements were adjusted for energy intake using the method of Willet and Stamper (11) to assess their independent contribution. Nutritional intake was calculated by using the fourth revision of the *Standard Tables of Food Composition in Japan* (12).

Statistical analysis

The incidence of first-ever gastric cancer was estimated with the person-year method and was compared by using the Cox proportional hazards regression model. The Cox proportional hazards model was also used to estimate hazard ratios and 95% confidence intervals. In analysis according to histologic type and location of gastric cancer, each of the double cancers was stratified into its respective category. All male subjects were used as a standard population for age adjustment. The population attributable fractions (PAFs) of gastric cancer for cigarette smoking and *H. pylori* infection were calculated by using the observed multivariate-adjusted hazard ratio of each risk factor and its frequency in gastric cancer cases (13). The confidence interval of the PAF was estimated by the method proposed by Greenland (14). All tests were 2 sided, and P values of <0.05 were considered statistically significant.

RESULTS

Table 1 shows the mean values or frequencies of the potential risk factors in our cohort of male subjects. The frequencies of cigarette smoking and *H. pylori* infection were 49.7% and 76.9%, respectively.

The age-adjusted incidence of gastric cancer according to smoking status is shown in Table 2. Because the incidence of gastric cancer did not differ between never smokers and former smokers, these 2 groups were combined as a current nonsmoking group in all subsequent analyses. The incidence of gastric cancer significantly increased among subjects who smoked 10 cigarettes or more per day compared

Table 1. Mean Values or Frequencies[a] of Potential Risk Factors for Gastric Cancer and Laboratory Variables at Baseline for Men in the Hisayama Study, Japan, 1988

Risk Factor	Mean Value or Frequency
Age, years	58 (12)
Cigarette smoking	49.7
Helicobacter pylori infection	76.9
History of peptic ulcer	23.1
Family history of cancer	9.8
Body mass index, kg/m^2	22.9 (3.0)
Diabetes	15.3
Total cholesterol, mmol/L	5.10 (1.05)
Physically active group	12.4
Alcohol intake	61.7
Total energy intake, kcal/day	1,912 (451)
Protein intake, g/day	52.4 (9.6)
Carbohydrate intake, g/day	225 (36)
Salt intake, g/day	13.0 (4.6)
Vitamin A intake, mg/day	2,631 (1,066)
Vitamin B_1 intake, mg/day	0.76 (0.39)
Vitamin B_2 intake, mg/day	1.08 (0.31)
Vitamin C intake, mg/day	68.7 (30.8)
Fiber intake, g/day	9.6 (3.1)

[a] Values and frequencies are expressed as mean (standard deviation) or percentage, respectively.

with subjects in the current nonsmoking group ($P < 0.05$). The age-adjusted hazard ratio was 2.07 (95% confidence interval (CI): 1.11, 3.85; $P = 0.022$) for those who smoked 10–19 cigarettes per day and 2.18 (95% CI: 1.21, 3.92; $P < 0.01$) for those who smoked 20 cigarettes or more per day (Table 3). The age-adjusted hazard ratio for overall current smoking was 2.02 (95% CI: 1.23, 3.32; $P = 0.006$). This association was substantially unchanged even after adjusting for other potential risk factors, namely, *H. pylori* infection, history of peptic ulcer, family history of cancer, body mass index, diabetes, total cholesterol, physical activity, alcohol intake, and dietary factors (intake of total energy, protein, carbohydrate, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and fiber). As shown in Table 3, *H. pylori* infection was also a significant risk factor for gastric cancer after adjustment for other confounding factors, including cigarette smoking (multivariate-adjusted hazard ratio (HR) = 2.68, 95% CI: 1.21, 5.93; $P = 0.015$). We estimated the PAF of gastric cancer for cigarette smoking and *H. pylori* infection: 28.4% (95% CI: 1.2, 48.1) of the cancers that developed were attributable to smoking and 56.2% (95% CI: 11.0, 78.5) to *H. pylori* infection.

Table 2. Age-adjusted Incidence Rate (per 1,000 Person-Years) of Gastric Cancer According to the Cigarette Smoking Status of Men in the Hisayama Study, Japan, 1988–2002

	No. of Person-Years	No. of Cases	Incidence Rate	*P* Value[a]
Current nonsmoking	6,290	25	3.7	
Never smoking	2,539	11	4.3	
Former smoking	3,751	14	3.0	
Current smoking	6,064	43	7.8	0.001
1–9 cigarettes/day	741	5	4.9	0.421
10–19 cigarettes/day	2,347	17	8.2	0.022
≥20 cigarettes/day	2,976	21	7.8	0.001

[a] Compared with current nonsmoking.

We next analyzed the risk of gastric cancer according to smoking and *H. pylori* infection status (Table 4). When compared with that for current nonsmokers without *H. pylori*, the multivariate-adjusted hazard ratios of gastric cancer were 5.82 (95% CI: 0.69, 49.13; $P = 0.11$) for current smokers without *H. pylori*, 6.93 (95% CI: 0.93, 51.56; $P = 0.06$) for current nonsmokers with *H. pylori*, and 11.41 (95% CI: 1.54, 84.67; $P = 0.02$) for current smokers with *H. pylori*. The interaction term between cigarette smoking and *H. pylori* infection was not statistically significant ($P = 0.20$). The PAFs of gastric cancer for cigarette smoking alone, *H. pylori* infection alone, and cigarette smoking with *H. pylori* infection were 7.3% (95% CI: −0.4, 14.5), 30.1% (95% CI: 12.5, 44.3), and 49.6% (95% CI: 30.8, 63.4), respectively (Table 4, Figure 1).

Table 5 shows the associations of smoking and *H. pylori* infection with gastric cancer by location and histologic type of cancer. The risk of cancer located in the distal two-thirds of the stomach was significantly higher for current smokers than for current nonsmokers (age-adjusted HR = 1.83, 95% CI: 1.06, 3.18; $P = 0.032$), and a similar association was observed for the risk of cancer in the proximal one-third, although the hazard ratio did not reach the level of statistical significance (age-adjusted HR = 2.81, 95% CI: 0.98, 8.03; $P = 0.054$). Similarly, *H. pylori* infection was a significant risk factor for cancer located in the distal two-thirds of the stomach (age-adjusted HR = 2.94, 95% CI: 1.17, 7.37; $P = 0.022$) but not for cancer in the proximal one-third (age-adjusted HR = 2.25, 95% CI: 0.51, 9.82; $P = 0.283$).

When cancer was classified according to histologic type, smoking and *H. pylori* infection had an impact on the intestinal type of cancer (smoking: age-adjusted HR = 2.31, 95% CI: 1.31, 4.05; $P < 0.01$; *H pylori* infection: age-adjusted HR = 2.38, 95% CI: 1.02, 5.57; $P = 0.045$) but not on the diffuse type (smoking: age-adjusted HR = 1.28, 95% CI: 0.47, 3.45; $P = 0.63$, *H. pylori* infection: age-adjusted HR = 1.36, 95% CI: 0.39, 4.79; $P = 0.63$).

DISCUSSION

In a population-based prospective study of a male Japanese cohort, we demonstrated a positive association between cigarette smoking and the subsequent incidence of gastric cancer. This association remained substantially unchanged even after adjustment for *H. pylori* infection and other confounding factors, namely, age, history of peptic ulcer, family history of cancer, body mass index, diabetes, total cholesterol, physical activity, alcohol intake, and

Table 3. Age-adjusted and Multivariate-adjusted Hazard Ratios and 95% Confidence Intervals for Development of Gastric Cancer According to Smoking Status and *Helicobacter pylori* Infection in Men in the Hisayama Study, Japan, 1988–2002

	Population at Risk, No.	No. of Cases	Age Adjusted			Multivariate Adjusted			PAF, %	95% CI
			HR	95% CI	*P* Value	HR	95% CI	*P* Value		
Cigarette smoking										
Current nonsmoking	539	25	1.00			1.00				
1–9 cigarettes/day	69	5	1.48	0.57, 3.89	0.421	1.36[a]	0.50, 3.71	0.548		
10–19 cigarettes/day	211	17	2.07	1.11, 3.85	0.022	1.93[a]	1.01, 3.67	0.046		
≥20 cigarettes/day	252	21	2.18	1.21, 3.92	0.001	1.88[a]	1.02, 3.43	0.042		
P for trend					0.004			0.024		
Overall current smoking	532	43	2.02	1.23, 3.32	0.006	1.82[a]	1.08, 3.05	0.024	28.4	1.2, 48.1
H. pylori infection										
(−)	247	7	1.00			1.00				
(+)	823	61	2.61	1.19, 5.71	0.016	2.68[b]	1.21, 5.93	0.015	56.2	11.0, 78.5

Abbreviations: CI, confidence interval; HR, hazard ratio; PAF, population attributable fraction.
[a] Adjusted for age, *H. pylori* infection, history of peptic ulcer, family history of cancer, body mass index, diabetes, total cholesterol, physical activity, alcohol intake, and dietary factors (intake of total energy, protein, carbohydrate, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and fiber).
[b] Adjusted for age, cigarette smoking, history of peptic ulcer, family history of cancer, body mass index, diabetes, total cholesterol, physical activity, alcohol intake, and dietary factors (intake of total energy, protein, carbohydrate, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and fiber).

dietary factors. In the stratified analysis, the risk of gastric cancer increased steeply for subjects who had both a smoking habit and *H. pylori* infection. The PAF of gastric cancer for cigarette smoking was approximately half as great as that for *H. pylori* infection. To the best of our knowledge, this prospective study is the first to investigate the combined influence of cigarette smoking and *H. pylori* infection on gastric cancer occurrence, taking into account other comprehensive confounding factors.

Possible pathogenesis

Several plausible biologic mechanisms have been suggested to explain the influence of cigarette smoking on the development of gastric cancer. It is known that tobacco smoke contains nitrosamines and other nitroso compounds that have been implicated in the carcinogenesis of gastric carcinoma (15). Smokers have also been shown to have lower plasma levels of free radical scavengers such as ascorbic acid and β-carotene (16) and to have high levels of DNA adducts (17).

Association with *H. pylori* infection

In this cohort, the magnitude of the association between cigarette smoking and gastric cancer did not change even after adjustment for other confounding factors, including *H. pylori* infection. This finding implies that *H. pylori* may have a small confounding effect on the association between cigarette smoking and gastric cancer. For our subjects, the risk of gastric cancer was similar for those who had only a smoking habit and those who had only *H. pylori* infection (Table 4), suggesting that the magnitude of the absolute impact of smoking on the development of gastric

Table 4. Age-adjusted and Multivariate-adjusted Hazard Ratios and 95% Confidence Intervals for Development of Gastric Cancer According to Cigarette Smoking and *Helicobacter pylori* Infection in Men in the Hisayama Study, Japan, 1988–2002

	Population at Risk, No.	No. of Cases	Age Adjusted			Multivariate Adjusted			PAF, %	95% CI
			HR	95% CI	*P* Value	HR	95% CI	*P* Value		
Current smoking (−) and *H. pylori* (−)	126	1	1.00			1.00				
Current smoking (+) and *H. pylori* (−)	121	6	7.42	0.89, 61.72	0.06	5.82[a]	0.69, 49.13	0.11	7.3	−0.4, 14.5
Current smoking (−) and *H. pylori* (+)	412	24	7.42	1.00, 54.85	0.049	6.93[a]	0.93, 51.56	0.06	30.1	12.5, 44.3
Current smoking (+) and *H. pylori* (+)	411	37	13.16	1.80, 95.95	0.01	11.41[a]	1.54, 84.67	0.02	49.6	30.8, 63.4

Abbreviations: CI, confidence interval; HR, hazard ratio; PAF, population attributable fraction.
[a] Adjusted for age, history of peptic ulcer, family history of cancer, body mass index, diabetes, total cholesterol, physical activity, alcohol intake, and dietary factors (intake of total energy, protein, carbohydrate, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and fiber).

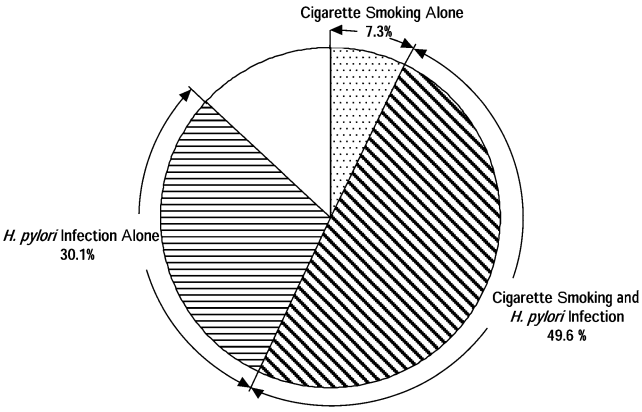

Figure 1. Estimated population attributable fractions of gastric cancer incidence for cigarette smoking and *Helicobacter pylori* infection in men, the Hisayama Study, Japan, 1998–2002. The white portion of the circle refers to risk factors other than cigarette smoking and *H. pylori* infection.

cancer is comparable to that of *H. pylori* infection. The combination of cigarette smoking and *H. pylori* infection increased the risk of gastric cancer more than smoking alone or *H. pylori* infection alone, leading to an 11-fold increase in the risk of gastric cancer, which reveals a synergistic association between cigarette smoking and *H. pylori* infection. This finding is in accordance with the those of previously reported case-control studies (18, 19).

Population attributable fraction

If causality is assumed, the PAF for cigarette smoking was 28.4% for our male subjects, which is larger than that estimated by most other studies. A meta-analysis estimated that the proportion of cases of gastric cancer attributable to cigarette smoking is 11% for men in developing countries and 17% in developed countries (20). Other epidemiologic studies have reported the PAF of gastric cancer for smoking to be 20% for men and women in a Polish population (21) and 21.5% for men in a European population (22), while it was similar to ours in a US male population (28%) (23). Since the PAF is a function of the frequency of cigarette smoking and its hazard ratio for gastric cancer, one of the reasons for this difference is considered to be the higher frequency of cigarette smoking by our subjects (49.7%) compared with other populations (13%–32%), although the strength of the association was moderate (adjusted HR = 1.82).

Table 5. Age-adjusted Hazard Ratios and 95% Confidence Intervals for Gastric Cancer Incidence by Cigarette Smoking and *Helicobacter pylori* Infection Status According to Cancer Location and Histology in Men in the Hisayama Study, Japan, 1988–2002

Characteristic	Population at Risk, No.	No. of Cases	HR	95% CI	*P* Value
Cancer location					
Proximal one-third					
Current smoking (−)	539	5	1.00		
Current smoking (+)	532	12	2.81	0.98, 8.03	0.054
H. pylori (−)	247	2	1.00		
H. pylori (+)	823	15	2.25	0.51, 9.82	0.283
Distal two-thirds					
Current smoking (−)	539	21	1.00		
Current smoking (+)	532	33	1.83	1.06, 3.18	0.032
H. pylori (−)	247	5	1.00		
H. pylori (+)	823	49	2.94	1.17, 7.37	0.022
Cancer histology					
Intestinal type					
Current smoking (−)	539	19	1.00		
Current smoking (+)	532	35	2.31	1.31, 4.05	0.004
H. pylori (−)	247	6	1.00		
H. pylori (+)	823	48	2.38	1.02, 5.57	0.045
Diffuse type					
Current smoking (−)	539	7	1.00		
Current smoking (+)	532	9	1.28	0.47, 3.45	0.629
H. pylori (−)	247	3	1.00		
H. pylori (+)	823	13	1.36	0.39, 4.79	0.629

Abbreviations: CI, confidence interval; HR, hazard ratio.

In our study, the PAF of gastric cancer for *H. pylori* infection was 56.2%, which was lower than that in other studies: in a meta-analysis, the PAF of gastric noncardia cancer for *H. pylori* infection was estimated to be 65% in developed countries and 80% in developing countries (3). The prevalence of *H. pylori* infection in our study (76.9%) was higher than that in developed countries (35% on average) but was almost the same as that reported for other locations in Japan (70%–80%) (24) and developing countries (85% on average). Thus, the lower PAF for *H. pylori* infection for our subjects seems to have been caused by the relatively low strength of the association between *H. pylori* infection and gastric cancer (adjusted HR = 2.68). The latter was attributed to the fact that our gastric cancer cases included not only noncardia cancers but also cardia cancers, which are not susceptible to *H. pylori* infection.

For the men in our study, the PAFs of gastric cancer for cigarette smoking alone and *H. pylori* infection alone were 7.3% and 30.1%, respectively, and the PAF for overlap of both factors was 49.6% (Figure 1). When their independent and joint influences on gastric cancer are taken into account, the impact is large (sum of PAFs, 87.0%), and a large part is due to their cooccurrence. This finding suggests that combination of these 2 factors accounts for almost all of the population burden of gastric cancer in Japanese men.

Anatomic subsite of gastric cancer

For our subjects, the hazard ratio of cigarette smoking was high for both the proximal one-third and distal two-thirds of the stomach, although it did not reach the level of statistical significance for the proximal one-third of the stomach, probably because of the small number of cancer cases. Several prospective and case-control studies have also demonstrated a significant association between smoking and both anatomic subsites of gastric cancer (22, 25, 26). Thus, it is likely that the influence of smoking on gastric cancer is homogenous across the anatomic subsites of the stomach. On the other hand, the influence of *H. pylori* infection on development of gastric cancer in our male cohort was significant for the distal two-thirds of the stomach whereas it was not significant for the proximal one-third of the stomach, which is in line with the findings of previous studies (3).

Histologic type of gastric cancer

With regard to the histology of gastric cancer, cigarette smoking and *H. pylori* infection were found to be more associated with the risk of intestinal-type than diffuse-type cancer. Cigarette smoking and *H. pylori* infection are known to cause precancerous lesions such as intestinal metaplasia (27, 28). It is generally accepted that intestinal-type cancer arises through a multistep process that originates with chronic gastritis and progresses through stages of atrophy, intestinal metaplasia, and dysplasia, finally resulting in carcinoma (28). It is therefore reasonable to conclude that smoking and *H. pylori* infection are closely associated with intestinal-type cancer. Our finding is in accordance with that of a case-control study by Inoue et al. (29) and supports the hypothesis that the intestinal type of gastric cancer is more closely related to environmental than to genetic factors (30). In contrast, diffuse-type gastric cancer is postulated to be more genetically predetermined and less associated with environmental factors, such as cigarette smoking and *H. pylori* infection (31).

Limitations

Some limitations of this study merit discussion. First, regarding screening for gastric cancer, we did not perform endoscopy on all subjects. It is undeniable that there were presymptomatic gastric cancer patients at baseline. However, after exclusion of those subjects who developed gastric cancer in the initial 2 years of the follow-up period, the magnitude of the major results did not change (data not shown). Thus, the influence of occult cases of gastric cancer is considered to be so small that they can be neglected. Second, we cannot rule out the possibility that smoking status was misclassified or that smoking behavior was modified during the follow-up period. However, such inaccuracies would lead to underestimation of the risk associated with cigarette smoking, suggesting that the true association may be even greater than that reflected in our findings. Third, it has been speculated that the influence of *H. pylori* infection on gastric cancer is underestimated; *H. pylori* is thought to disappear from the stomach after extensive gastric atrophy, which is considered a precursor of gastric cancer (32). Thus, the actual impact of *H. pylori* infection on the development of gastric cancer is probably greater than estimated in this study.

Conclusions

This population-based prospective cohort study is the first known to investigate the relation between cigarette smoking and gastric cancer, with consideration of *H. pylori* infection. The risk of gastric cancer was found to be highest for subjects who had both a smoking habit and *H. pylori* infection. It is recommended that members of this high-risk group quit smoking and undergo regular gastrointestinal examination, especially in countries such as Japan, where the rates of cigarette smoking and *H. pylori* infection and the risk of gastric cancer are considerable.

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Conflict of interest: none declared.

REFERENCES

1. *Tobacco Smoke and Involuntary Smoking*. Lyon, France: International Agency for Research on Cancer; 2004. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; vol 83.
2. 2004 Surgeon General's report—The health consequences of smoking. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004. (http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm).
3. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut*. 2001; 49(3):347–353.
4. Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in the general population in Japan. *J Hypertens Suppl*. 1990;8(5):S9–S15.
5. Yamagata H, Kiyohara Y, Aoyagi K, et al. Impact of *Helicobacter pylori* infection on gastric cancer incidence in a general population: the Hisayama study. *Arch Intern Med.* 2000; 160(13):1962–1968.
6. Tanaka K, Kiyohara Y, Kubo M, et al. Secular trends in the incidence, mortality, and survival rate of gastric cancer in a general Japanese population: the Hisayama study. *Cancer Causes Control*. 2005;16(5):573–578.
7. Ohmura T, Ueda K, Kiyohara Y, et al. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama study. *Diabetologia*. 1993;36(11):1198–1203.
8. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. *Acta Pathol Microbiol Scand.* 1965;64:31–49.
9. WHO Study Group on Diabetes Mellitus. *Diabetes Mellitus, Report of a WHO Study Group*. Geneva, Switzerland: World Health Organization; 1985. (Technical report series 727).
10. Kiyohara Y, Shinohara A, Kato I, et al. Dietary factors and development of impaired glucose tolerance and diabetes in a general Japanese population: the Hisayama study. *J Epidemiol.* 2003;13(5):251–258.
11. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol.* 1986;124(1):17–27.
12. Resources Council of Science and Technology Agency. *Standard Tables of Food Composition in Japan*. 4th ed. Tokyo, Japan: Ministry of Finance Printing Bureau; 1982.
13. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fraction. *Am J Public Health*. 1998; 88(1):15–19.
14. Greenland S. Confidence limits made easy: interval estimation using a substitution method [letter]. *Am J Epidemiol.* 1999; 149(9):884.
15. Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. *Cancer Lett.* 1995;93(1):17–48.
16. Buiatti E, Muñoz N, Kato I, et al. Determinants of plasma antioxidant vitamin levels in a population at high risk for stomach cancer. *Int J Cancer.* 1996;65(3):317–322.
17. Dyke GW, Craven JL, Hall R, et al. Smoking-related DNA adducts in human gastric cancers. *Int J Cancer.* 1992;52(6): 847–850.
18. Siman JH, Forsgren A, Berglund G, et al. Tobacco smoking increases the risk for gastric adenocarcinoma among *Helicobacter pylori*-infected individuals. *Scand J Gastroenterol.* 2001;36(2):208–213.
19. Brenner H, Arndt V, Bode G, et al. Risk of gastric cancer among smokers infected with *Helicobacter pylori*. *Int J Cancer.* 2002;98(3):446–449.
20. Trédaniel J, Boffetta P, Buiatti E, et al. Tobacco smoking and gastric cancer: review and meta-analysis. *Int J Cancer.* 1997; 72(4):565–573.
21. Chow WH, Swanson CA, Lissowska J, et al. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int J Cancer.* 1999;81(6):871–876.
22. González CA, Pera G, Agudo A, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer.* 2003;107(4):629–634.
23. Chao A, Thun MJ, Henley SJ, et al. Cigarette smoking, use of other tobacco products and stomach cancer mortality in US adults: the Cancer Prevention Study II. *Int J Cancer.* 2002; 101(4):380–389.
24. Asaka M, Kimura T, Kubo M, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. *Gastroenterology.* 1992;102(3):760–766.
25. Lindblad M, Rodríguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control.* 2005; 16(3):285–294.
26. Ye W, Ekström AM, Hansson LE, et al. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int J Cancer.* 1999;83(2):223–229.
27. Kneller RW, You WC, Chang YS, et al. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. *J Natl Cancer Inst.* 1992;84(16):1261–1266.
28. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* 1992;52(24):6735–6740.
29. Inoue M, Tajima K, Yamamura Y, et al. Influence of habitual smoking on gastric cancer by histologic subtype. *Int J Cancer.* 1999;81(1):39–43.
30. Sipponen P, Jarvi O, Kekki M, et al. Decreased incidences of intestinal and diffuse types of gastric carcinoma in Finland during a 20-year period. *Scand J Gastroenterol.* 1987;22(7):865–871.
31. Correa P, Shiao YH. Phenotypic and genotypic events in gastric carcinogenesis. *Cancer Res.* 1994;54(7 suppl): 1941s–1943s.
32. Ohata H, Kitauchi S, Yoshimura N, et al. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. *Int J Cancer.* 2004; 109(1):138–143.