LIFESTYLE-RELATED RISK FACTORS FOR PEPTIC ULCER DISEASE: A HOSPITAL-BASED CASE-CONTROL STUDY IN AKITA PREFECTURE

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Abstract

A case-control study was carried out to determine lifestyle-related risk factors for peptic ulcer disease (PUD). The subjects, who resided in Akita, Japan, were 161 patients with PUD and 322 control subjects without PUD who underwent medical checkups, matched with patients by gender and age. All of the subjects underwent endoscopy and provided information on psychosocial factors and lifestyle practices through self-administered questionnaires. Blood samples were collected for determination of *Helicobacter pylori* (*H. pylori*) status. Lifestyle-related variables were assessed for their associations with PUD and *H. pylori* infection by using multiple logistic regression analysis. The prevalences of *H. pylori* infection were 97.5% in the patients and 84.8% in the controls, which were higher than those in Japanese adults (i.e., from 23% to 73%). Significant risk factors for PUD were positive *H. pylori* status (odds ratio (OR)=14.1), leanness (OR=2.68), urban residency (OR=2.57), irregular meal times (OR=2.17), smoking habit (OR=1.98), shift work (OR=2.15), non-professional occupation (OR=2.64), lack of morale in job (OR=2.13), and difficulty in mood change (OR=2.20). Significant risk factors for *H. pylori* infection were age of 40 years or over (OR=4.28) and rural origin (OR=3.17).

These findings suggest that smoking, leanness, and psychosocial stress in daily life are associated with PUD in the northeastern region of Japan where the prevalence of *H. pylori* infection is considerably high.

Key words: lifestyle, risk factors, peptic ulcer disease, *Helicobacter pylori*, case-control study

Introduction

Since the identification of *Helicobacter pylori* (*H. pylori*) in 1982, there have been many epidemiological studies on *H. pylori* infection[1-7]. *H. pylori* infection is now considered to be a major factor contributing to the occurrence of peptic ulcer disease (PUD)[8-10]. However, in previous studies, the prevalence of PUD in *H. pylori*-infected individuals in populations, whose prevalence of *H. pylori* infection ranged from 53.7% to 59.2%, were only 2.0%[11] and 5.7%[12], respectively. The prevalence of PUD is influenced not only by *H. pylori* infection but also by lifestyle-related factors[10]. Lifestyle-related risk factors for PUD have been reported to be smoking[10,13-15], salty food intake[15], and self-

perceived stress[16]. However, the association between *H. pylori* infection and PUD was not examined in most of those studies[14–16]. The studies also lacked endoscopic verification of PUD status[14–16]. Regarding the relationship between self-perceived stress and PUD, previous studies in general dealt with major stressful life events or stress, but not psychosocial stresses encountered in daily life[16–20]. Furthermore, there have been only a few case-control studies on lifestyle-related risk factors for PUD in Japan[19,20]. In the present study, the authors focused on the impact of stresses related to urban residency and work environment on PUD prevalence. *H. pylori* infection itself may be influenced by lifestyle-related factors[10,21–24].

The aim of the present study was to determine lifestyle-related risk factors for PUD and for *H. pylori* infection, as well as whether there are interactions between factors relating to the occurrence of PUD. In this case-control study, we analyzed various lifestyle-related factors, including work-related stress, in subjects who underwent upper gastrointestinal endoscopy and provided blood samples for *H. pylori* status. The subjects all lived in Akita Prefecture in northeastern Japan where the prevalence of *H. pylori* infection ranked among the highest in the world[1,23–25].

Subjects and Methods

Selection of patient population

The study population included 161 inpatients and outpatients who had peptic ulcers diagnosed endoscopically between December 1997 and November 1998 at the Gastroenterological Division of H hospital in Honjo City, located in the Tohoku district of Japan. Active ulcers were regarded as gastric ulcers when craters of appreciable depth were located in the stomach (fundal, corpal or antral area), and ulcers with craters in the pyloric canal or in the duodenum were regarded as duodenal ulcers. Ulcers with craters both in the stomach and in the pyloric canal or duodenum were regarded as gastroduodenal ulcers. Ninety-four patients had gastric ulcers, 39 had duodenal ulcers and 28 had gastroduodenal ulcers. Patients were excluded if they had neoplasmic lesions (group 3 or higher according to pathological diagnostic criteria), if they had previously undergone esophagogastric surgery, or if other overhelming physical or mental diseases were present. The subjects used in this study were 117 males (72.7%) and 44 females (27.3%) with a mean age 50.1±10.9 years. Informed consent was obtained from all patients.

Selection of control population

Controls were selected from persons who underwent medical checkups at H hospital during the same period (Dec. 1997–Nov. 1998) and in whom neither peptic ulcers nor ulcer scars were detected endoscopically. The 161 patients were individually matched with the 322 controls by gender and age within 5 years. The exclusion criteria for the patients were also used for the selection of controls. The controls were 234 males (72.7%) and 88 females (27.3%) with a mean age 50.3±10.4 years, not significantly different from that of the patients. Informed consent was obtained also from all controls.

Methods for determination of H. pylori status

Blood samples were collected for determination of *H. pylori* status. Levels of specific anti-*H. pylori* IgG antibodies in sera were measured with an enzyme-linked immunosorbent assay (ELISA) kit using solid-phase antigens derived from inactivated *H. pylori* (HEL-pTEST supplied worldwide by Amrad Co., Melbourne, Australia). A titer of more than 50 U/ml was judged positive for anti-*H. pylori* IgG antibodies. Based on the results of histology and urease testing of gastric biopsies in an Asian population, the assay has been shown to be 93.5% sensitive and 92.5% specific for active infection[26]. In the present study, *H. pylori* infection was defined as a positive ELISA result.

Study variables

A self-administered questionnaire was completed

Table 1 Variables assessed in univariate analyses for peptic ulcer disease and *Helicobacter pylori* infection

1) Sociodemographic factors: gender, age
2) BMI (body mass index)*
3) Socioeconomic status: residency†, birthplace, number of siblings, educational base, present main occupation
4) Dietary habits:
   a. salty food intake (daily consumption of soybean paste soup and weekly consumption of pickles and other salty food)
   b. numbers and regularity of meals
   c. alcohol intake (weekly consumption of Japanese sake, distilled liquor, beer, whisky, and wine)
   d. coffee and green tea intake (number of cups drunk daily or weekly)
5) Lifestyle practices:
   a. working conditions (frequency of shift work, working time, resting time, home-arrival time, commuting means and time, and numbers of monthly holidays)
   b. fatigability (degree of fatigue and easiness of recovery from fatigue, sleeping time)
   c. leisure-time physical activity (hobbies, sports)
   d. degree of stress (stress in work, easiness of mood change)
   e. morale in job
   f. behavioral character (type A behavior pattern)[27]
   g. family conditions (stress in family, satisfaction in life)
   h. changes in life within the previous year
   i. smoking habit (cumulative numbers of cigarettes smoked daily, cumulative years of smoking).

*BMI values were calculated by height (meter) and weight (kilogram), and a value less than 19.8 was judged positive for leanness.
†Regarding residency, the hospital serves residents of mainly Honjo City (urban) and its satellite 10 towns of Yuri County (rural).

on the same day as the blood examination or on a day before the patient's next attendance. The study variables assessed in the statistical analyses are listed in Table 1.

Statistical analyses

All data for the variables were divided into two categories and converted into binary data by assigning a value of 0 to 1 to each of the two categories. Statistical analyses were performed using the chi-squared test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. P values less than 0.05 were regarded as significant. Univariate analyses for the association of the study variables with PUD and *H. pylori* infection were performed. Based on the results, multivariate analyses were performed using stepwise logistic regression with backward elimination. Variables with p values less than 0.1 in univariate analyses were used in multivariate analyses. The independent variables used in multivariate analysis for PUD status were BMI, residency, occupation, number of meals a day, regularity of mealtime, smoking habit, shift work, working time, stress in job, decrease in sleep quality, morale in job, self-confidence, family discord, easiness of mood change, and *H. pylori* status. The independent variables used in multivariate analysis for *H. pylori* status were gender, age, birthplace, soybean paste soup consumption frequency, decrease in sleep quality, anger, and PUD status.

Independent variables with p values greater than 0.1 were removed stepwise in multivariate analyses. All data were analyzed using the statistical package SPSS 11.0 for Windows (SPSS Inc., USA).

Results

Prevalence of *H. pylori* infection

Fig. 1 shows the distributions of *H. pylori* seroprevalence by age classes in the patients and controls. One hundred fifty-seven patients (97.5%) were positive for *H. pylori* infection and 273 controls (84.8%) were positive for *H. pylori* infection. The prevalence of *H. pylori* infection was 89.0% in the subjects overall. The prevalence of *H. pylori* infection in the controls in the present study was higher than the average rates in Japanese adults, which ranged from 23% (in healthy adults aged 20 ～29 years) to 73% (in healthy adults aged ≧70 years)[25].

Factors related to PUD status

Table 2 shows those variables which were related to PUD status ($p<0.1$) in the univariate analysis. Table 3 shows those variables which were significantly related to PUD status ($p<0.05$) in the multivariate analysis. They were *H. pylori* status, BMI, residency, occupation, meal time, smoking habit, shift work, morale in job and easiness of mood change.

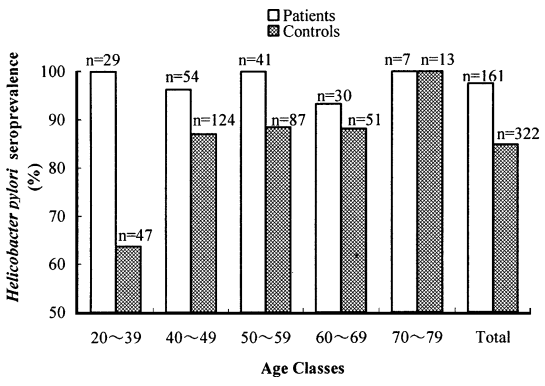

Fig. 1 Distributions of *Helicobacter pylori* seroprevalence by age classes in both patients and controls according to results of immunoglobulin G enzyme-linked immunosorbent assays.

Factors related to *H. pylori* status

Table 4 shows those variables which were related to *H. pylori* status ($p<0.1$) in the univariate analysis. Of these variables, age and birthplace were significantly related to *H. pylori* status in the multivariate analysis (Table 5).

Discussion

The hospital from which subjects were enrolled in this case-control study serves residents mainly of the Honjo-Yuri area, located in Akita Prefecture. This area includes Honjo City (population of 45,491 in March 2004) and Yuri County (population of 77,025 in March 2004). The hospital is one of the three major hospitals in the area. Therefore, the patient population in the present study is thought to represent PUD patients in this area. PUD status was verified by endoscopy in the same hospital in both the patient and control groups. PUD prevalence based on clinical history is inaccurate and may underestimate or overestimate the real prevalence[28]. Lack of endoscopic proof of ulcers has been pointed out as a weakness of epidemiologic studies on PUD[29]. Endoscopic verification of PUD status in a control group could exclude apparently healthy subjects with ulcer scars who have a risk of recurrent PUD. Singh *et al.* reported that the point prevalence and lifetime prevalence of active peptic ulcer in the general population were 3.4% and 8.8%, respectively[12], according to the results of their endoscopic study on PUD prevalence.

In the present study, the authors reconfirmed an association between leanness and PUD. Kato *et al.* reported a higher prevalence of PUD in lean persons and speculated that this is because lean persons have greater susceptibility to stress[30].

Regarding the urban-rural difference in PUD prevalence, the authors found higher prevalence in urban residents than in rural residents. This finding is similar to the finding in a community-based

Table 2 Odds ratios with 95% confidence intervals, adjusted for age and gender, for the association between peptic ulcer disease and study variables, including *Helicobacter pylori* status

Variables	OR*	*p* value	95%CI*
*H. pylori** status			
Positive/Negative	7.05	0.00	2.50–19.9
BMI*			
＜19.8/≧19.8	2.90	0.00	1.70–4.93
Residency			
Urban/Rural	2.63	0.00	1.77–3.90
Occupation			
Non-professional/Professional	1.89	0.05	0.97–3.70
Number of meals			
≦2 times a day/3 times a day	2.17	0.01	1.22–3.88
Meal time			
Irregular/Regular	2.39	0.00	1.62–3.54
Smoking habit			
Present smoker/Never or ex-smoker	2.55	0.00	1.73–3.76
Shift work			
Yes/No	2.45	0.00	1.53–3.98
Working time			
≧9 hours a day/＜9 hours a day	2.03	0.00	1.27–3.25
Stress in job			
Yes/No	2.04	0.01	1.24–3.37
Decease in sleep quality			
Yes/No	2.04	0.01	1.24–3.37
Morale in job			
No/Yes	1.78	0.04	1.01–3.17
Easiness of mood change			
No/Yes	2.52	0.00	1.42–4.47
Self-confidence			
No/Yes	1.82	0.01	1.16–2.85
Family discord			
Yes/No	1.68	0.01	1.14–2.47

*OR, odds ratio ; CI, confidence interval ; *H. pylori*, *Helicobacter pylori* ; BMI, body mass index.

study in Akita Prefecture by Kamiyama *et al.*, who reported that the frequency of past history of PUD in urban workers was significantly higher than that in rural farmers[31].

Regarding the association between dietary practices and PUD, the authors reconfirmed the importance of mealtime regularity[32] and could not prove the association between dietary items and PUD. It has been reported that PUD was influenced by both circadian and ultradian variations in gastric acid secretory pattern[33], and mealtime irregularity could desynchronize these variations.

In the present study, smoking habit was found to be related to PUD status. Both epidemiologic and clinical studies have shown a strong association between smoking and PUD[28]. Various possible

Table 3 Multivariate adjusted odds ratios* with 95% confidence intervals for the association between peptic ulcer disease and study variables

Variables	OR†	*p* value	95%CI†
H. pylori† status			
Positive/Negative	14.1	0.00	3.15–63.1
BMI†			
<19.8/≧19.8	2.68	0.01	1.31–5.51
Residency			
Urban/Rural	2.57	0.00	1.55–4.28
Occupation			
Non-professional/Professional	2.64	0.03	1.13–6.14
Meal time			
Irregular/Regular	2.17	0.00	1.27–3.69
Smoking habit			
Present smoker/Never or ex-smoker	1.98	0.01	1.20–3.28
Shift work			
Yes/No	2.15	0.01	1.21–3.83
Morale in job			
No/Yes	2.13	0.04	1.03–4.39
Easiness of mood change			
No/Yes	2.20	0.03	1.08–4.48

*Odds ratios mutually adjusted for all variables in Table 2 using logistic regression analysis.
†OR, odds ratio ; CI, confidence interval ; *H. pylori*, *Helicobacter pylori* ; BMI, body mass index.

mechanisms underlying the adverse effect of smoking have been proposed. Smoking is associated with decreased gastric mucosal blood flow, decreased mucus secretion, decreased epidermal growth-factor secretion, and increased gastric acid and pepsin secretion[23]. Additionally, smoking is thought to express a form of coping with stress negatively, resulting in an increase in PUD prevalence[34,35].

In the present study, work-related factors such as non-professional occupation, shift work and no morale in the job significantly affected PUD prevalence. Regarding the association between occupation and PUD, our result was in accordance with results of previous studies[13,28]. Regarding the association between shift work and PUD, workers on early morning shift or night shift are likely to have mealtime irregularity and sleep disturbance, developing PUD[32]. Sano has suggested on the basis of results of simultaneous polysomnography and measurement of intragastric pH in healthy subjects and duodenal ulcer patients that sleep disturbance induces an increase in nocturnal gastric acid secretion and can result in ulcerogenesis[36]. Moshal reported that duodenal ulcer patients were found in the lowest group in terms of occupational authority compared with control subjects[37], similar to our finding. Lack of occupational authority could increase self-perceived stress of workers, resulting in the development of PUD.

In the present study, a factor such as difficulty in mood change significantly affected PUD prevalence. It was thought to express a form of coping with stress negatively, too. Anda *et al.* found in the cohort study with self-reported PUD prevalence that the risk of PUD due to subjective stress was

Table 4 Unadjusted odds ratios with 95% confidence intervals for the association between *Helicobacter pylori* infection and study variables, including peptic ulcer status

Variables	OR*	*p* value	95%CI*
PUD* status			
Patients/Controls	7.05	0.00	2.50–19.9
Gender			
Male/Female	2.23	0.01	1.26–4.05
Age			
≧40/＜40	2.97	0.00	1.57–5.63
Birthplace			
Rural/Urban	2.03	0.04	1.03–4.00
Soybean paste soup consumption frequency			
≧1 cup a day/＜1 cup a day	1.76	0.09	0.89–3.47
Decrease in sleep quality			
Yes/No	1.96	0.07	0.92–4.19
Anger			
Yes/No	1.68	0.08	0.93–3.01

*OR, odds ratio ; CI, confidence interval ; PUD, peptic ulcer disease.

Table 5 Multivariate adjusted odds ratios* with 95% confidence intervals for the association between *Helicobacter pylori* infection and study variables

Variables	OR†	*p* value	95%CI†
Age			
≧40/＜40	4.28	0.00	1.86–9.84
Birthplace			
Rural/Urban	3.17	0.00	1.44–6.98

*Odds ratios mutually adjusted for all variables in Table 4 using logistic regression analysis.
†OR, odds ratio ; CI, confidence interval.

increased with increase in the extent of stress perceived[16]. However, individual stressful factors in the workplace or in the family, as demonstrated in the present study, were not analyzed in their study.

Helicobacter pylori is one of the most common infections worldwide[12]. In the present study, the prevalence of *H. pylori* infection in healthy adults in this area of Japan (84.8%) was higher than those in large cities such as Tokyo (55.7%)[7] or Sapporo (62.7%)[38]. The risk factors for *H. pylori* infection identified in the present study are age≧40 years and rural birthplace. The result for age was in accordance with results of previous studies[1,3,5,6]. Regarding birthplace, persons born in rural areas may have been brought up under relatively poor personal hygiene conditions compared to persons born in urban areas[2,5,6]. In the present study, associations of dietary factors or lifestyle practices with *H. pylori* infection were not found. Results regarding associations of smoking, alcohol drinking, or other dietary habits with *H. pylori* infection in previous studies have been inconsistent[1,21–25]. Most *H. pylori* infections are acquired during childhood[2,5] before these habits are started.

In conclusion, *H. pylori* infection is ubiquitous in this area. Peptic ulcer disease occurs rarely in *H. pylori*-negative individuals in this population. However, leanness, smoking, and psychosocial stress in daily life, including urban residency and work environment, are significantly associated with PUD in this area.

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