Cigarette Smoking and its Association with Overlapping Gastroesophageal Reflux Disease, Functional Dyspepsia, or Irritable Bowel Syndrome

Yasuhiro Fujiwara, Makiko Kubo, Yukie Kohata, Hirohisa Machida, Hirotoshi Okazaki, Hirokazu Yamagami, Tetsuya Tanigawa, Kenji Watanabe, Toshio Watanabe, Kazunari Tominaga and Tetsuo Arakawa

Abstract

Background  Gastroesophageal reflux disease (GERD), functional dyspepsia (FD), and irritable bowel syndrome (IBS) are common gastrointestinal diseases. Several studies have shown a significant occurrence of overlap among these 3 diseases. The purpose of this study was to examine the factors associated with such disease overlap in Japanese adults.

Methods  We performed a cross-sectional study on Japanese workers who visited a clinic for a routine health check-up and asked them to fill out a self-report questionnaire. GERD was defined as episodes of heartburn and/or acid regurgitation at least once a week, and the diagnosis of FD and IBS was based on Rome III criteria. A logistic regression model was used to identify risk factors, and odds ratio (OR) was calculated with 95% confidence intervals (CIs).

Results  Disease overlaps were found in 160 (6.0%) of the 2680 eligible subjects. Female gender was associated with GERD + IBS (OR=1.99; 95% CI, 1.06-3.75), and FD + IBS (OR=1.72; 95% CI, 1.03-2.85), and lower body mass index was negatively associated with FD + IBS (OR=0.54; 96% CI, 0.34-0.87). Cigarette smoking was a common factor associated with the overlaps: GERD + FD (OR=2.14; 95% CI, 1.22-3.76), GERD + IBS (OR=3.16; 95% CI, 1.75-3.71), FD + IBS (OR=2.26; 95% CI, 1.40-3.66), and GERD + FD + IBS (OR=4.08; 95% CI, 1.66-10.07). The associations between smoking habits and overlaps were stronger in smokers who smoked >1 pack per day as compared to those who smoked <1 pack per day.

Conclusion  Cigarette smoking was significantly associated with overlaps among GERD, FD, and IBS in Japanese adults.

Key words: gastroesophageal reflux disease, functional dyspepsia, irritable bowel syndrome, overlapping, smoking

(Intern Med 50: 2443-2447, 2011)  
(DOI: 10.2169/internalmedicine.50.6012)

Introduction

Gastroesophageal reflux disease (GERD), functional dyspepsia (FD), and irritable bowel syndrome (IBS) are common gastrointestinal (GI) diseases in adults (1-3). GERD is caused by an abnormal reflux of gastric contents into the esophagus and is characterized by bothersome symptoms such as heartburn and acid regurgitation (4). FD is a disorder in which upper abdominal symptoms occur in the absence of organic disease that explains them (5). Patients with FD complain of meal-induced dyspeptic symptoms such as postprandial fullness and early satiation, and/or epigastric pain or burning sensation according to the Rome III criteria (5). IBS is characterized by abdominal pain or discomfort, and is associated with disturbed defecation (5).
incidence of such functional GI diseases, especially GERD, has been increasing in Japan (6).

Several studies showed that some patients may develop a condition that involves an overlap of these 3 diseases (7-9). Our previous study showed that overlaps among GERD, FD, and IBS were common, accounting for 47% of GERD, 48% of FD, and 34% of IBS patients (9). Patients with GERD, FD, or IBS reported significantly poor health-related quality of life (HR-QOL), and the HR-QOL was markedly worse in the overlapping condition as compared with GERD, FD, and IBS alone. In particular, the physical component summary for overlapping GERD and mental component summary for overlapping IBS were poor (9). Therefore, physicians should pay attention to the overlapping of functional GI disorders. There are several studies concerning risk factors associated with GERD, FD, or IBS (10-26). Our previous study showed that smoking and drinking habits were associated with GERD (13); female gender, low body mass index (BMI), smoking and drinking habits with FD (18); younger age, female gender, low BMI and presence of allergic diseases with IBS (22). However, factors associated with the disease overlaps are not well known. The purpose of this study was to identify factors associated with disease overlaps among GERD, FD, and IBS.

Materials and Methods

Subject

We included 6,334 Japanese workers who visited the Nagahori Clinic for a routine health check-up between May 2008 and January 2009 in this study. The participants were employees of several companies in the Kansai area, which has the second largest population in Japan. Japanese law requires all employers to conduct annual health screening for all employees. Subjects with a history of GI tract surgery, peptic ulcer diseases, Crohn’s disease, and ulcerative colitis were excluded. Subjects who submitted incomplete questionnaires were also excluded. Our study was approved by the Osaka City University Ethics Committee, and informed consent was obtained from all participants. Among the participants, 3,152 subjects (49.8%) submitted their written informed consent and filled out the questionnaires. Of these 3,152 subjects, 472 were excluded on the basis of the above-mentioned exclusion criteria. Finally, 2,680 subjects were included in the analysis and the overall response rate was 42.3%.

Questionnaire

All participants were asked to fill in a self-report questionnaire to assess age, gender, height, body weight, smoking habits, drinking habits, and several GI symptoms concerning GERD, FD, and IBS. Body mass index (BMI) was calculated as body weight divided by the square of body height in meters (kg/m²). The questions concerning GERD symptoms were on the presence or absence of heartburn (a burning sensation or discomfort behind the breast bone in the chest) and/or acid regurgitation (a bitter or sour-tasting fluid coming into the throat or mouth), and the frequency of these symptoms (every day, more than 1 day a week, 1 day a week, 2-3 days a month, 1 day a month, and less than 1 day a month). Subjects who had heartburn and/or acid regurgitation at least 1 day a week were defined as having GERD (4, 6). The self-report questionnaire also included key questions regarding FD and IBS from the Rome III Integrative Questionnaire (5). The questions concerning FD were on the presence or absence of dyspeptic symptoms, including epigastric pain (pain or burning in the middle of abdomen above the belly button; the location was shown pictorially), postprandial fullness (the feeling of being uncomfortably full after a regular-sized meal), and early satiation (inability to finish a regular-sized meal); the frequency of these symptoms (every day, more than 1 day a week, 1 day a week, 2-3 days a month, 1 day a month, and less than 1 day a month) during the last 3 months; and their onset (more than or less than 6 month ago) and severity (very severe, severe, moderate, mild, and very mild). Persons who had postprandial fullness and/or early satiation for more than 1 day a week or those who had epigastric pain on at least 1 day a week with more than mild severity for more than 6 months were defined as having FD (5). The questions concerning IBS were on the presence or absence of abdominal pain or discomfort in the last 3 months, the frequency of these symptoms (every day, more than 1 day a week, 1 day a week, 2-3 days a month, 1 day a month, and less than 1 day a month), and the time of onset of these symptoms (more than or less than 6 months ago). The questions also covered 3 criteria, including association between the improvement of symptoms and defecation, onset associated with a change in frequency of stool, and onset associated with a change in the form (appearance) of stool. Persons who satisfied 2 of these 3 criteria with abdominal pain or discomfort for at least 2-3 days a month for more than 6 months were defined as having IBS (5).

Statistical analysis

We compared several factors such as age (per 10 years), gender, BMI (≤25 kg/m² or >25 kg/m²), smoking habits (smoker or non-smoker), and drinking habits (drinker or non-drinker) between controls and GERD, FD, IBS, or their overlaps. Controls were participants without GERD, FD, or IBS. A forward stepwise multiple logistic regression model was created to assess the independence of the associations between risk factors and the presence of GERD, FD, IBS, or their overlaps. To clarify the association between smoking habits and disease overlaps, we divided smokers into persons who smoked 1 pack per day or more and persons who smoke less than 1 pack per day. p values less than 0.05 were considered to indicate statistical significance. Data were expressed as odds ratio (OR) with 95% confidence intervals (CI). Statistical analyses were performed using the SPSS (SPSS; Chicago, IL, USA).


**Table 1. Characteristics of Control and Overlapping among GERD, FD, and IBS**

<table>
<thead>
<tr>
<th></th>
<th>Control n = 2012</th>
<th>GERD + FD n = 65</th>
<th>GERD + IBS n = 61</th>
<th>FD + IBS n = 92</th>
<th>GERD + FD + IBS n = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.4 ± 14.2</td>
<td>37.3 ± 11.3</td>
<td>37.8 ± 12.4</td>
<td>35.1 ± 11.1</td>
<td>35.1 ± 11.0</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>67.1</td>
<td>61.5</td>
<td>54.1</td>
<td>48.9</td>
<td>51.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5 ± 3.4</td>
<td>21.6 ± 2.8</td>
<td>21.8 ± 3.0</td>
<td>21.2 ± 3.0</td>
<td>21.8 ± 3.4</td>
</tr>
<tr>
<td>BMI (&gt;25 kg/m², %)</td>
<td>20.6</td>
<td>24.6</td>
<td>21.3</td>
<td>12.0</td>
<td>20.7</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>33.1</td>
<td>52.3</td>
<td>55.7</td>
<td>47.8</td>
<td>58.6</td>
</tr>
<tr>
<td>Drinkers (%)</td>
<td>63.2</td>
<td>61.5</td>
<td>63.9</td>
<td>63.0</td>
<td>62.1</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease; FD, functional dyspepsia; IBS, irritable bowel syndrome; BMI, body mass index. Data were expressed as mean ± SD, or frequency.

**Table 2. Factors Associated with Overlapping GERD, FD, or IBS**

<table>
<thead>
<tr>
<th></th>
<th>GERD + FD</th>
<th>GERD + IBS</th>
<th>FD + IBS</th>
<th>GERD + FD + IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 year)</td>
<td>0.91 (0.73-1.12)</td>
<td>1.00 (0.81-1.24)</td>
<td>0.86 (0.72-1.04)</td>
<td>0.87 (0.62-1.13)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>1.28 (0.69-2.39)</td>
<td>1.99 (1.06-3.75)</td>
<td>1.72 (1.03-2.85)</td>
<td>1.60 (0.62-4.13)</td>
</tr>
<tr>
<td>BMI (&gt;25 kg/m²)</td>
<td>0.68 (0.38-1.19)</td>
<td>0.71 (0.40-1.28)</td>
<td>0.54 (0.34-0.87)</td>
<td>0.55 (0.23-1.32)</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Smokers</td>
<td>2.14 (1.22-3.76)</td>
<td>3.16 (1.75-3.71)</td>
<td>2.26 (1.40-3.66)</td>
<td>4.08 (1.66-10.07)</td>
</tr>
<tr>
<td>Drinking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinkers</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Drinkers</td>
<td>1.14 (0.63-2.08)</td>
<td>1.04 (0.56-1.94)</td>
<td>0.85 (0.50-1.47)</td>
<td>0.54 (0.19-1.54)</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease; FD, functional dyspepsia; IBS, irritable bowel syndrome; BMI, body mass index. Data were odds ratio (OR) (95% CI) after adjustment for age, gender, BMI, smoking habits, and drinking habits.

**Results**

GERD was found in 207 (7.7%), FD in 269 (10.0%), and IBS in 381 (14.2%) of the total 2,680 subjects. The remaining 2,012 subjects who did not have GERD, FD, or IBS were controls. Overlaps were found in 160 (6.0%) of all 2,680 subjects, including 65 (2.4%) with GERD and FD (GERD + FD), 61 (2.3%) with GERD and IBS (GERD + IBS), and 92 (3.4%) with FD and IBS (FD + IBS). Further, 29 (1.1%) subjects had overlap of all the 3 diseases (GERD + FD + IBS).

Table 1 showed clinical characteristics of control and overlaps among GERD, FD, and IBS. After adjusting for age, gender, BMI, smoking habits, and drinking habits, we observed that smokers were significantly associated with an increased OR for GERD (OR=1.60, 95% CI 1.17-2.21) and FD (OR=1.05, 95% CI 1.12-2.01) but not IBS (OR=1.10, 95% CI 0.85-1.43), female gender for FD (OR=1.49, 95% CI 1.08-2.04) and IBS (OR=1.88, 95% CI 1.44-2.45) but not GERD (OR=0.99, 95% CI 0.69-1.44), drinkers only for FD (OR=1.51, 95% CI 1.12-2.04), while high BMI (defined as ≥25 kg/m²) was associated with a low OR for FD (OR=0.62, 95% CI 0.46-0.82) and IBS (OR=0.74, 95% CI 0.58-0.95).

Table 2 shows OR for disease overlaps among GERD, FD, and IBS after adjusting for age, gender, BMI, smoking habits, and drinking habits. Female gender was associated with increased OR for GERD + IBS and FD + IBS, while high BMI was negatively associated with only FD + IBS. Interestingly, smoking habits were significantly associated with all types of overlaps. Other factors such as age and drinking habits were not associated with overlaps. To clarify associations between smoking habits and overlaps in detail, we further analyzed the status of smoking habits on the basis of the number of packs smoked per day. After adjusting for age, gender, BMI, smoking habits, and drinking habits, the OR for overlaps in smokers who smoked ≥1 pack per day was high as compared to those who smoked <1 pack per day in all overlap types, except FD + IBS (Table 3).

**Discussion**

The present study showed that cigarette smoking was a common factor associated with any type of overlap among GERD, FD, and IBS. In addition, the association between smoking and overlaps was stronger in smokers who smoked ≥1 pack per day as compared to those who smoked <1 pack per day. These results suggest that cigarette smoking might affect the development of disease overlaps among GERD, FD, and IBS, or it might be associated with the common pathogenesis of the overlapping diseases.

There are several points of evidence of positive associations between smoking habits and Crohn’s disease or peptic ulcer disease, and negative associations between smoking habits and ulcerative colitis, celiac disease, or pouchitis (27).
Previous epidemiological findings concerning the associations between smoking habit and GERD, FD, or IBS have been inconclusive (10-26). Several studies have shown that smoking is significantly associated with GERD (10-13), uninvestigated dyspepsia (14-16), postprandial distress syndrome (a subtype of FD) (17, 18), and IBS (19, 20), especially, in female IBD (21) and diarrhea-predominant IBS (22). However, other studies have failed to show positive associations between smoking habits and GERD (23), FD (24), and IBS (25, 26). These conflicting results might be attributed to the study design, racial difference, environmental factors, number of subjects, and diagnostic criteria of each disease.

There have been only 2 studies on the risk factors of disease overlaps. Jung et al examined the prevalence and risk factors of overlap of GERD and IBS in 2298 subjects in a population-based study (7). They found that GERD and IBS overlap was common in the general US adults and this overlap did not occur by chance. They also identified that insomnia, frequent abdominal symptoms, and higher somatization were associated with overlap of GERD and IBS (7). Recently, Lee et al conducted a cross-sectional survey of 1638 Korean subjects by using modified Rome II criteria (8). They found that anxiety was significantly associated with disease overlaps of GERD, dyspepsia, or IBS (8). There is, however, no study about the factors associated with disease overlaps among GERD, dyspepsia, or IBS based on the Rome III criteria.

Cigarette smoking affects several GI functions that play crucial roles in the pathogenesis of each GERD, FD, and IBS. Smoking decreases lower esophageal sphincter pressure (27) and affects esophageal defensive mechanisms such as reduction of esophageal clearance and saliva secretion (28). In the stomach, smoking increases acid secretion and pepsinogen release (27), and delays gastric emptying (29). Smoking also induces relaxation of colonic smooth muscles and increases intestinal permeability (27). These effects of smoking on GI function might be responsible for the development of GERD, FD, and IBS.

The precise mechanisms of cigarette smoking associated with disease overlaps are unknown. Two hypotheses might be proposed: First, smoking might affect all GI functions including those of the esophagus, stomach, and colon, resulting in susceptibility to several kinds of functional GI diseases including GERD, FD, and IBS. Second, overlapping might have common psychological backgrounds such as anxiety or stress. Thus, such patients prefer to smoke to attain relief from their anxiety or stress. A large epidemiological study showed that smoking was associated with anxiety (30), which has been reported as the risk factor of disease overlaps among GERD, dyspepsia, and IBS (8).

Female gender was associated with some types of overlap such as GERD+IBS and FD+IBS. A previous study showed that female gender was associated with IBS (22). There are gender differences in gastrointestinal motility and brain activation patterns to visceral stimuli in IBS patients (31). Although the reasons why GERD+IBS and FD+IBS were associated with female gender, increased visceral sensitivity (32) and gonadal hormones may be responsible for some types of overlaps.

The present study has some potential limitations. First, the subjects in our study were workers who visited a clinic for routine check-up. Nevertheless, we emphasize that our results can be applied to most of the general Japanese population. Second, we did not include data on the duration of smoking habits or former smokers in this study. Since we evaluated GI symptoms during the last 3 months according to the Rome III criteria (5), we believe that the current status of smoking is the most important factor that affects overlapping among GERD, FD, or IBS. Finally, educational backgrounds, socio-economic status, and the presence of anxiety or depression in the participants in this study were not included. Such factors might affect the present results and should be included in a future study.

In conclusion, cigarette smoking was associated with overlaps among GERD, FD, or IBS. Further studies are necessary to determine whether the cessation of smoking can improve GI symptoms in patients with disease overlaps among GERD, FD, or IBS.

Author’s disclosure of potential Conflicts of Interest (COI).
Arakawa T: Honoraria, Eisai Co. Ltd. and Otsuka Pharmaceutical Co. Ltd.

Acknowledgement
We thank Dr. Hideki Nishikawa (Nagahori Clinic) for his help during data collection. We also thank nurses and officers at Nagahori Clinic for their kind help in the present survey. This study

Table 3. Association between Smoking Habits and Overlapping GERD, FD, or IBS

<table>
<thead>
<tr>
<th>Smoking habits</th>
<th>GERD + FD</th>
<th>GERD + IBS</th>
<th>FD + IBS</th>
<th>GERD + FD + IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 pack/day</td>
<td>1.91 (0.96-3.80)</td>
<td>2.55 (1.28-5.06)</td>
<td>2.44 (1.43-4.15)</td>
<td>2.70 (0.99-7.38)</td>
</tr>
<tr>
<td>≥1 pack/day</td>
<td>3.15 (1.69-5.89)</td>
<td>4.44 (2.30-8.60)</td>
<td>2.41 (1.36-4.27)</td>
<td>5.46 (2.13-13.96)</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease; FD, functional dyspepsia; IBS, irritable bowel syndrome. Data were odds ratio (OR) (95% CI) after adjustment for age, gender, BMI, smoking habits, and drinking habits.

was supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology in Japan. Dr. Arakawa is a consultant to Eisai Pharmaceutical and Otsuka Pharmaceutical. The remaining authors disclose no competing interests.

References


