Familial Occurrence of Inflammatory Bowel Disease in Korea

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Background: Little information is available about the familial aggregation of inflammatory bowel disease (IBD) in Asian populations. We therefore determined the risk of familial aggregation of IBD among first-degree relatives of patients with ulcerative colitis (UC) or Crohn’s disease (CD) in an ethnically distinct Korean population.

Methods: Familial aggregation of IBD was evaluated in terms of family history, prevalence, lifetime risk, and population relative risk in first-degree relatives of 1440 unrelated patients with UC (n = 1043) or CD (n = 397).

Results: A positive first-degree family history of IBD was observed in 27 probands (1.88%): 21 of 1043 (2.01%) with UC and 6 of 397 (1.51%) with CD. The crude prevalence of IBD in first-degree relatives of probands with IBD was 0.31%. The lifetime risk of IBD was 0.54% in all first-degree relatives of IBD probands, 0.52% in UC probands, and 0.67% in CD probands, with overall lifetime relative risks of 0.12% in parents, 0.79% in siblings, and 1.43% in offspring. The age- and sex-adjusted population relative risk of IBD was 13.8 in first-degree relatives of probands with IBD.

Conclusions: Although a positive family history, prevalence, and lifetime risk of IBD among first-degree relatives of Korean IBD patients are much lower than among relatives of Western patients, the population relative risk in first-degree relatives is about equal in Koreans and Westerners. This finding indicates that a positive family history is an important risk factor for IBD in Koreans and in Westerners.

Key Words: family history, ulcerative colitis, Crohn’s disease, inflammatory bowel disease

Although the origin of inflammatory bowel disease (IBD) is still not known, it is thought to be related to genetic susceptibility coupled with environmental factors. The risk of developing IBD is increased in relatives of patients with ulcerative colitis (UC) or Crohn’s disease (CD), and a positive family history has been found to be the strongest risk factor for the development of IBD. Familial aggregation of IBD may be due to genetic factors and to a shared environment. Although it is impossible to quantify the relative importance of these genetic and environmental factors, data from studies in twins, spouses, and distant family members suggest that the principal contributor to familial aggregation is genetic susceptibility. Therefore, studying the familial aggregation of IBD may be crucial in revealing the genetic component of this disease.

The prevalence of IBD in Asian populations is lower than in Western populations, which may be due to genetic influences, environmental factors, or a combination of both. Recent studies from Japan and Korea have shown that the incidence rates of UC and CD are increasing in these countries. This rapid increase, which has occurred over a relatively short period of time, strongly suggests that environmental factors are responsible because changes in genetic factors are not expressed that quickly. Thus, if the environments of Asian and Western countries are similar, the ultimate prevalence rate of IBD in Asian countries may approach or exceed that of Western countries, depending on genetic factors. Because the genetic background of patients with IBD may vary widely among different populations, a better determination of familial aggregation of IBD in various populations may help in understanding both the genetic and pathogenetic aspects of this disease. We therefore sought to determine the risk of familial aggregation of IBD among first-degree relatives of patients with UC or CD in an ethnically distinct Korean population. Thus, we evaluated the family history, prevalence, population relative risk, and lifetime risk of IBD in first-degree relatives of patients with IBD.
MATERIALS AND METHODS

Study Population

The background study population consisted of patients with a firmly established diagnosis of either UC or CD who attended the IBD clinics of Asan Medical Center, a university hospital, and Song Do Colorectal Hospital, a community hospital, in Seoul, Korea, from 1989 through 2001. Together, these 2 hospitals registered ≈2000 patients with IBD by the end of 2001. Patients were diagnosed with UC or CD according to accepted clinical, endoscopic, radiological, and histological criteria. This study, performed in 2002, enrolled 1440 consecutive unrelated patients with UC or CD who attended the IBD clinic at either hospital (889 at Asan Medical Center, 551 at Song Do Colorectal Hospital) during the study period. The other patients were excluded from the study because they did not attend the IBD clinic during the study period. Most of them had visited the IBD clinic of either hospital simply to get a second opinion and therefore had not undergone diagnostic evaluation at either hospital. Of the 1440 patients in the present study, 208 also were included in our previous study. Of these 1440 patients, 1135 (78.8%) were residents of Seoul and its metropolitan area, and 305 (21.2%) were residents of other parts of Korea.

Data Collection

All 1440 patients were interviewed on >1 occasion while attending the outpatient clinic or during hospitalization, and all answered detailed questionnaires to evaluate the familial occurrence of IBD. Data collected included diagnosis, age, sex, age at diagnosis, and a complete family pedigree, including the number, year of birth (and death), and sex of first-degree relatives (parents, siblings, and offspring). Patients also were asked to identify relatives with IBD. When relatives reported to have IBD were not patients of our own hospitals, we evaluated their diagnoses by asking the index patients detailed information regarding the symptoms, treatment, and course of disease in their relatives. If this information indicated the possibility of IBD in their relatives, we requested their medical records for review, and only subjects in whom we could confirm a diagnosis of IBD were regarded as having IBD. The order in which family members were diagnosed also was ascertained. Whenever ≥2 members of the same family were registered, only the member in whom UC or CD was first diagnosed was considered the proband; the others were regarded as relatives. The study protocol was approved by the ethics committee for clinical investigation at our institutes, and informed consent was obtained from all patients included in the study.

Statistical Analysis

A positive family history was defined as the percentage of probands with at least 1 first-degree relative having UC or CD. Concordance for type of IBD was estimated by dividing the number of relatives having the same disease as the proband by the total number of affected relatives.

The crude prevalence of UC or CD in relatives was calculated by dividing the number of relatives with either disease by the total number of relatives of the same category. In addition, analyses were performed for each category of probands’ first-degree relatives (i.e., parents, siblings, and offspring).

The risk of familial occurrence also was assessed by estimating the population relative risk of the disease in first-degree relatives. The age- and sex-adjusted population relative risk of IBD was calculated by dividing the observed number of affected first-degree relatives by the number expected according to the prevalence rates in the population. The latter number was calculated by adding the products of the age- and sex-specific rates and the number of relatives within each corresponding age-sex category using the age- and sex-specific prevalence rates of UC and CD in Seoul on December 31, 2001. The overall prevalence of UC and CD was 14.51 and 5.30 per 100,000 inhabitants, respectively.

Age-adjusted empirical risk for IBD in first-degree relatives was estimated using Strömgren’s method of age correction. The cumulative proportional risk of developing IBD up to age 70 was calculated from the age-specific incidence data in Seoul from 1986 to 2001 (Table 1). The calculation method for estimating age-adjusted empirical risk was described elsewhere in detail. Briefly, the age-specific incidence rates of IBD provided the basis for calculating the correction factor for the age adjustment by Strömgren’s method (Table 1). The number of first-degree relatives in each group was multiplied by a correction factor to give an age-adjusted number of relatives at risk. The number of relatives with IBD divided by the age-adjusted total number of relatives at risk yields the theoretical risk of IBD up to age 70, i.e., the

<table>
<thead>
<tr>
<th>Age, y</th>
<th>i</th>
<th>a_i</th>
<th>b_i, %</th>
<th>c_i, %</th>
<th>d_i</th>
</tr>
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<tbody>
<tr>
<td>&lt;10</td>
<td>1</td>
<td>0.15</td>
<td>1.50</td>
<td>1.50</td>
<td>0.0075</td>
</tr>
<tr>
<td>10–19</td>
<td>2</td>
<td>1.35</td>
<td>13.47</td>
<td>14.97</td>
<td>0.0824</td>
</tr>
<tr>
<td>20–29</td>
<td>3</td>
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<td>20.56</td>
<td>35.53</td>
<td>0.2525</td>
</tr>
<tr>
<td>30–39</td>
<td>4</td>
<td>1.50</td>
<td>14.97</td>
<td>50.50</td>
<td>0.4302</td>
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<tr>
<td>40–49</td>
<td>5</td>
<td>1.88</td>
<td>18.76</td>
<td>69.26</td>
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</tr>
<tr>
<td>50–59</td>
<td>6</td>
<td>1.33</td>
<td>13.27</td>
<td>82.53</td>
<td>0.7590</td>
</tr>
<tr>
<td>60–69</td>
<td>7</td>
<td>1.53</td>
<td>15.27</td>
<td>97.80</td>
<td>0.9017</td>
</tr>
<tr>
<td>70+</td>
<td>8</td>
<td>0.22</td>
<td>2.20</td>
<td>100.00</td>
<td>0.9890</td>
</tr>
<tr>
<td>Total</td>
<td>10.02</td>
<td>100.00</td>
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a_i, age-specific incidence rates (per 100,000) of UC and CD in Seoul, Korea, 1986–2001; b_i, proportion of total risk by age group [b_i(%)] = a_i × 100%/Σa_i; c_i, cumulative proportional risk [c_i(%) = Σb_i(%)]; and d_i, correction factor for its age group [d_i = (b_i/2 + c_i−1)/100].
prevalence of IBD assuming that all relatives will reach 70 years of age. The result is therefore independent of the actual age of the probands and their relatives.

Continuous variables were compared by the use of Student’s t test. Comparisons of the frequency of discrete variables were analyzed by the χ² test or, when appropriate, by Fisher’s exact test. The 95% confidence intervals of population relative risks were calculated by Vandenbroucke’s formula. Values of P < 0.05 were considered statistically significant. Statistical evaluations were performed with SPSS (version 12.0) and SAS (version 8.02) software.

RESULTS

Patient Demographics
Of the 1440 enrolled subjects, 1043 had UC and 397 had CD. The male-to-female ratio was 0.99:1 among probands with UC and 2.13:1 among those with CD (P < 0.001). The age at diagnosis was significantly younger in the probands with CD (24.0 ± 8.3 years) than in those with UC (37.5 ± 13.1 years; P < 0.001). The family pedigrees of all 1440 probands included a total of 9236 first-degree relatives: 2880 parents, 4427 siblings, and 1929 offspring. Family size (number of first-degree relatives) ranged from 2 to 16, with a median of 6.

Positive Family History
A positive first-degree family history of IBD could be confirmed in 27 probands (1.88%): 21 of 1043 (2.01%) with UC and 6 of 397 (1.51%) with CD (Table 2). Twenty-five probands had only 1 affected first-degree relative each, and 2 had 2 each, resulting in 29 first-degree relatives with IBD. In 21 families in which UC was diagnosed in the proband, 20 relatives (87.0%) had UC and 3 (13.0%) had CD. Similarly, in 6 families in which the proband had CD, 4 relatives had CD (66.7%) and 2 had UC (33.3%). Therefore, the overall concordance for type of IBD among first-degree relatives was 82.8%.

The rate of positive family history did not differ between patients from Asan Medical Center (2.02%) and those from Song Do Colorectal Hospital (1.63%; P = 0.595) or between patients from Seoul and its metropolitan area (1.67%) and those from other parts of Korea (2.62%; P = 0.278).

Prevalence of IBD in First-degree Relatives
The crude prevalence of IBD in first-degree relatives of probands with IBD is shown in Table 3 separately by type of relationship (i.e., parents, siblings, and offspring) and type of IBD (i.e., UC or CD). The prevalence of IBD at the time of the study was highest in siblings (0.45%) and lowest in parents (0.05%). There was no difference in prevalence of IBD between first-degree relatives of UC and CD probands.
TABLE 4. Age- and Sex-adjusted Population Relative Risk of IBD in First-degree Relatives of Patients with UC or CD

<table>
<thead>
<tr>
<th>Disease in Proband</th>
<th>Disease in First-degree Relatives (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>UC (10.15 (1.91–24.87)</td>
</tr>
<tr>
<td>CD</td>
<td>6.34 (0.60–18.16)</td>
</tr>
<tr>
<td>IBD</td>
<td>12.77 (7.99–18.66)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

(0.31% versus 0.35%; P = 0.965). In addition, the prevalence of UC among first-degree relatives of UC probands was similar to that of CD among first-degree relatives of CD probands (0.27% versus 0.23%; P = 1).

### Population Relative Risk of IBD in First-degree Relatives

The age- and sex-adjusted population relative risk of IBD was estimated in first-degree relatives of probands with UC or CD (Table 4). Compared with the prevalence rates in the general population, the rates of UC and CD among first-degree relatives of the probands with UC were increased by factors of 14.2 and 10.2, respectively, and the rates of UC and CD among first-degree relatives of probands with CD were increased by factors of 6.3 and 49.3, respectively. The population relative risk of CD among first-degree relatives of CD probands tended to be higher than that of UC among first-degree relatives of UC probands (49.3 versus 14.2). The overall prevalence of IBD in first-degree relatives of IBD probands was estimated to be 13.8 times higher than that in the general population.

### Lifetime Risk of IBD in First-degree Relatives

The age-adjusted empirical risk (i.e., lifetime risk) for IBD in first-degree relatives as calculated by Strömberg’s method is shown in Table 5. Lifetime risk of developing IBD was 0.52% for all first-degree relatives of UC probands and 0.67% for relatives of CD probands (P = 0.617). The highest lifetime risk of IBD in first-degree relatives of all IBD probands was observed among offspring (1.43%); the lowest was among parents (0.12%).

### DISCUSSION

Both genetic and environmental factors may influence the prevalence of IBD in general populations, as well as the degree of familial aggregation of IBD. The relative importance of these factors in causing familial aggregation may differ between low- and high-prevalence areas, although genetic susceptibility is thought to supply the principal contribution. Differences in genetic backgrounds for IBD have been reported in Asian and Western countries. For example, the NOD-2 mutation is not associated with CD in Japan, China, or Korea, whereas it is in Western countries. In addition, HLA-DRB1 alleles associated with UC differ between Asian and Western countries. Therefore, comparing the pattern and degree of familial aggregation of IBD in Asian and Western populations may optimize genetic counseling and increase our understanding of the genetic mechanisms underlying IBD.

To the best of our knowledge, this study is the first to describe in detail the familial aggregation of IBD in an Asian population. We found that the prevalence of IBD among relatives of IBD patients was higher than that of the general population in Korea and in Western countries. Therefore, familial aggregation can be regarded as a common feature of IBD in both low- and high-prevalence areas.

It has been reported that the familial aggregation of IBD is greater among relatives of CD than of UC probands in Western populations. In contrast, we found that a positive family history in first-degree relatives tended to be higher in UC (1.73%) than in CD (1.01%) patients. This finding is in agreement with results showing that, among Japanese IBD patients with disease onset before age 16, 6.0% of UC patients had a positive family history of UC, whereas only 2.8% of CD patients had a positive family history of CD. Together, these results suggest that, in contrast to Western populations, familial aggregation in Asian populations is more common in UC than in CD patients. We also

### TABLE 5. Lifetime Risk for IBD Among First-degree Relatives of Patients with UC or CD

<table>
<thead>
<tr>
<th>Disease in Proband</th>
<th>Category of First-degree Relatives, no. (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Parents</td>
</tr>
<tr>
<td>UC</td>
<td>1/1812* (0.06)</td>
</tr>
<tr>
<td>CD</td>
<td>2/602 (0.33)</td>
</tr>
<tr>
<td>IBD</td>
<td>3/2414 (0.12)</td>
</tr>
</tbody>
</table>

*The numerator represents the observed number of affected relatives; the denominator represents the age-adjusted number of relatives at risk calculated according to Strömberg’s method.
found, however, that the population relative risk of CD among first-degree relatives of CD probands tended to be higher than that of UC among first-degree relatives of UC probands. This discrepancy probably reflects the fact that, among the general population in Korea, the prevalence of UC is 2.7 times higher than that of CD, whereas the UC and CD prevalence rates are rather similar in Western populations. Therefore, in Korea and in Western countries, familial aggregation is more important in CD than in UC.

The risks for IBD in first-degree relatives of IBD patients in Korea and in Western countries can be compared (Table 6). In Korean patients, the rate of a positive family history was 5 to 10 times less than that of Western patients. Similar findings were also noted for the prevalence and lifetime risk for IBD in first-degree relatives of IBD patients, all of which may reflect the much lower prevalence of IBD in Koreans compared with Western populations. We found, however, that the population relative risk was about the same in Korean as in Western populations, indicating that a positive family history is an important risk factor for IBD in both Korea and Western countries.

Our study has several limitations. Although it surveyed a relatively large patient population, it may have been limited by the small number of affected first-degree relatives. Because there were only 6 affected first-degree relatives of patients with CD, the inclusion of 1 or 2 unusual families would make a big difference in the risk estimation. We therefore determined the risk for IBD and for either UC or CD. Second, because our study was hospital based, we may have overestimated the real degree of familial aggregation of IBD. Although we found no differences in the rate of positive family history between patients seen at a university hospital (Asan Medical Center) and at a community hospital (Song Do Colorectal Hospital), we may not have completely overcome the limitations of a hospital-based study. In our earlier population-based study, we found that the rate of a positive family history in first-degree relatives of Korean IBD patients was 1.3%, slightly lower than the 1.88% reported here. We were unable to use our population-based study for the comprehensive evaluation of familial aggregation of IBD because the number of probands with IBD was too small to calculate risk estimates. An additional limitation of this study was that, to calculate the lifetime risk for IBD in first-degree relatives of IBD patients, we needed its incidence in the background population. However, we used incidence data from Seoul, not from throughout Korea, even though our patient population came from all over the country. Similar limitations were seen in the 3 Western studies that calculated lifetime risk in that they used incidence data from other areas or other countries because these figures were not available for the study area. We regarded it as legitimate to use data from Seoul because almost 80% of our study population was from Seoul or its metropolitan area and because both demographic characteristics (data not shown) and rates of positive family history were similar between patients from Seoul or the metropolitan area and other parts of Korea.

In conclusion, although a positive family history, prevalence, and lifetime risk of IBD among first-degree relatives of Korean IBD patients are much lower than among relatives of Western patients, the population relative risk in first-degree relatives is about equal in Koreans and Westerners. This finding indicates that a positive family history is an important risk factor for IBD in Koreans and in Westerners.

### REFERENCES


