Ulcerative colitis and colorectal cancer: a follow-up study in Fukuoka, Japan

Naoaki Ishibashi, Yoshio Hirota, Masato Ikeda and Tomio Hirohata

Background Our goal was to study the higher death rate and the causes of such deaths among ulcerative colitis (UC) patients in the Japanese population, and to compare our findings in such cases with those for Crohn's disease (CD).

Methods In all, 174 UC (male/female: 54/120) and 66 CD (34/32) patients who were registered for the research promotion programme in Fukuoka prefecture (1971–1981) were traced up to the end of 1994. The standardized mortality ratios (SMR) were calculated based on the death rates of the Japanese population by age, sex and calendar year.

Results The overall follow-up rate was 96.7%. Among the UC patients, the SMR for all causes were 0.84 (95% CI: 0.11–4.31) for men; 1.05 (95% CI: 0.08–4.69) for women; and 0.94 (95% CI: 0.09–4.50) for both sexes combined. When excluding deaths due to colorectal cancer, the SMR for the same groups were 0.43, 0.94 and 0.67, respectively. The SMR for both sexes were 1.82 (95% CI: 0.17–5.96) for malignant neoplasms and 9.93 (95% CI: 4.67–17.3) for colorectal cancer. Patients who died from colorectal cancer showed onset at a younger age (mean: 25.5 years) as well as a longer disease course of UC (mean: 17.0 years). Regarding the CD patients, the SMR for all causes were 1.75 (95% CI: 0.15–5.75) for both sexes. Most deaths were caused by gastrointestinal complications.

Conclusions An excess mortality from colorectal cancers was indicated in the UC patients, especially in males. The overall SMR in male UC patients decreased by 50% when the deaths from colorectal cancer were excluded. The excess mortality in those with CD over UC patients was attributed to gastrointestinal complications rather than malignant diseases. Some carcinogenic factors therefore seem most likely to exist in the pathogenesis of UC.

Keywords Ulcerative colitis, SMR, follow-up study, colorectal cancer, Crohn's disease

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insurance programmes in the community and followed them up until death for 14–25 years.

Materials and Methods

Background

The Ministry of Health and Welfare of Japan has underwritten a financial support system, as part of a research promotion programme, for patients with specific rare diseases, including UC and CD. The system subsidizes the usual patient contribution when participating in the regular national health insurance programme, so that patients are encouraged to receive sufficient medical care, and as a result, more research on such diseases can become possible. Eligibility for this system is thus not based on family income. The patients simply submit annual application forms to the prefecture government where their residences are located, along with a medical certificate and examination results such as colonoscopy and/or a biopsy in the case of UC or CD. Each prefecture government has a special committee comprised of medical specialists, who then verify the diagnosis according to the submitted materials. We thus recruited the present study subjects using the information from this programme.

Briefly, the health insurance system in Japan consists of four main programmes: Government-managed Health Insurance (GHI) for employees at small companies; Social Health Insurance (SHI) for employees at large companies; National Health Insurance (NHI) for self-employed individuals; and others, including Mutual Health Insurance for national and local public employees, Seamen’s Insurance, and Daily Laborers Health Insurance. At the beginning of 1971, the proportions of the total population covered by each insurance programme were 25.2% for GHI, 23.4% for SHI, 39.4% for NHI, and 12.0% for the others; the ratio of those insured to their dependents was 0.89, 0.73, 0.47 and 0.69, respectively. The medical care benefits for the insured people except for those of NHI were full, while the coverage for their dependents ranged from 70% to 90%; both the insured and dependent in the NHI have to pay 10–30% of the medical costs. Therefore, all the patients with UC and CD who were registered for the abovementioned rare-disease research programme and recruited to the present study were the insured and their dependents of the NHI and dependents of insured people of the other health insurance programmes.

Subjects and follow-up

The study subjects were 174 patients with UC (male/female: 54/120) and 66 with CD (male/female: 34/32) who had been diagnosed between 1 January 1971 and 31 December 1981, and registered for the programme in Fukuoka prefecture, in southwestern Japan. They were followed up until the end of 1994. Of the 240 patients, 105 patients (UC: 80, CD: 25) were determined to be alive because of continued annual application. Vital status of the remaining 135 patients (UC: 94, CD: 41) was confirmed by obtaining a copy of the family register (Honseki in Japanese) at the city office where all citizens legally register their permanent domiciles: this was 107 alive (UC 75, CD 32), 20 deceased (UC 13, CD 7), and 8 unknown (UC 6, CD 2). Vital status of the eight patients was unknown primarily because the patients’ Honseki was not properly recorded.

When patients were known to be deceased, we received copies of their death certificates from the District Legal Affairs Bureau. These procedures were performed by obtaining a special permission from the Ministry of Legal Affairs.

Based on patients’ death certificates, the cause of death was assigned according to the Ninth Revision of the International Classification of Disease, Injuries and Causes of Deaths (ICD-9). The categories used for the analyses were all causes and malignant neoplasms of all sites (140–208), large bowel (153–154), and haemopoietic tissues (200–208).

Data analysis

To assess the potential effect of participating in different health insurance programmes, we computed sex- and age-adjusted hazard ratio of total death for each insurance programme using the Cox proportional hazard model; NHI was used as a reference category because the largest number of subjects subscribed to this type of insurance.

Standardized mortality ratios (SMR) were derived from the observed number of deaths divided by the expected number of deaths, which was calculated by multiplying the patients’ calendar (class of each 5 years)-, sex-, and age- (class of each 5 years) specific person-years at risk by sex- and age-specific mortality rates for the selected causes in 1970, 1975, 1980, 1985 and 1990 in Japan.14

We also calculated the SMR of the deaths excluding colorectal cancer, in which deaths from colorectal cancer were not counted as death cases in both our study and the Japanese population. The statistical significance and 95% CI of the SMR were computed by assuming that the observed number of deaths followed the Poisson distribution. These calculations were conducted using the Statistical Analysis System (SAS).15

Results

The follow-up rate was 96.6% (168/174) for UC patients, 97.0% (64/66) for CD patients, and 96.7% (232/240) for total subjects. Results of the follow-up among the 174 UC patients were: alive 15, dead 13, lost to follow-up 6. The corresponding figures in the 66 CD patients were: alive 57, dead 7, lost to follow-up 2. The 8 cases, 6 UC and 2 CD, lost to follow-up were excluded in the subsequent analysis. The adjusted hazard ratios of death for each insurance programme as compared with NHI among UC patients were 0.4 (95% CI : 0.0–3.1) for SHI, 1.2 (95% CI : 0.2–6.4) for GHI, and 1.1 (95% CI : 0.2–6.4) for the others. The corresponding figures among CD patients were 2.8 (95% CI : 0.3–30.5), 3.3 (95% CI : 0.3–36.8) and 6.3 (95% CI : 0.6–70.0), respectively. Likelihood ratio test showed no material effect of insurance type on mortality pattern in either UC ($\chi^2 = 1.21, P = 0.82$) or CD ($\chi^2 = 3.03, P = 0.40$).

Among UC patients, overall person-years were 2690 (male: 849, female: 1844), and the average observation period was 16.0 years. Of the patients, 57% were followed up for more than 20 years. Among CD patients, the overall person-years were 1004 (male: 545, female: 459). The average observation period was 15.7 years. Of the patients, 58% were followed up more than 20 years. Table 1 summarizes number of patients and deaths by sex and age at diagnosis for UC and CD.

Table 2 shows the causes of death, the age at UC diagnosis, and the periods up to death in patients with UC. The mortality percentage for each of the categorized causes was 54% (7/13) from all malignant neoplasms; 39% (5/13) from gastrointestinal
malignancies; and 15% (2/13) from haematopoietic neoplasms. The patients who died from colorectal cancer seem to have been diagnosed at a younger age (mean 25.5 years, range 19–33 years), and also showed a longer disease period up to death (mean 17.0 years, range 14.5–19.0 years). The corresponding figures were 36.7 (range 26–66) and 13.5 (range 4.3–14.5) for neoplasms of other sites, 50.3 (range 25–68) and 10.2 (range 0.2–25.0) for non-malignant diseases, respectively. Therefore, all patients who died from colorectal cancer had contracted UC before the age of 35 and also had a long disease course up to death, in excess of 14 years.

Table 3 presents the SMR with 95% CI according to major causes. Among UC patients, the SMR for all causes were 0.84 (95% CI: 0.11–4.31) for men; 1.05 (95% CI: 0.08–4.69) for women; and 0.94 (95% CI: 0.09–4.50) for both sexes combined. The SMR for the main causes for both sexes were 1.82 (95% CI: 0.17–5.96) for malignant neoplasms; 9.93 (95% CI: 4.67–17.3) for colorectal cancer; 5.05 (95% CI: 1.59–10.7) for haematopoietic neoplasms; and 0.60 (95% CI: 0.18–3.89) for non-malignant disease. When excluding the deaths from colorectal cancer, the SMR was almost halved for men (0.4) as compared to women (0.9).

Among CD patients, the SMR for all causes was 1.75 (95% CI: 0.15–5.75), somewhat greater than that for UC patients (Table 3). Unlike the predominant causes of deaths in UC patients, most of the deaths in CD patients were caused by

### Table 1

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–19</td>
<td>21</td>
<td>0 (0)</td>
<td>22</td>
<td>1 (5)</td>
</tr>
<tr>
<td>20–39</td>
<td>19</td>
<td>5 (26)</td>
<td>49</td>
<td>1 (2)</td>
</tr>
<tr>
<td>40–59</td>
<td>9</td>
<td>0 (0)</td>
<td>36</td>
<td>2 (6)</td>
</tr>
<tr>
<td>60–4</td>
<td>4</td>
<td>1 (25)</td>
<td>8</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>6 (11)</td>
<td>115</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>Period up to death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant neoplasms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Male</td>
<td>19</td>
<td>16.0</td>
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<tr>
<td>Descending colon cancer</td>
<td>Male</td>
<td>25</td>
<td>18.3</td>
</tr>
<tr>
<td>Sigmoid colon cancer</td>
<td>Male</td>
<td>33</td>
<td>14.5</td>
</tr>
<tr>
<td>Chronic lymphocytic leukaemia</td>
<td>Female</td>
<td>66</td>
<td>4.3</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>Male</td>
<td>26</td>
<td>14.5</td>
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<tr>
<td>Haematopoietic neoplasms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Female</td>
<td>56</td>
<td>11.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Female</td>
<td>68</td>
<td>16.3</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Female</td>
<td>25</td>
<td>5.7</td>
</tr>
<tr>
<td>Suicide (hanging)</td>
<td>Female</td>
<td>58</td>
<td>3.0</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Ulcerative colitis</th>
<th>Crohn's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exp&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>All causes</td>
<td>13</td>
<td>13.8</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>7.15</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>6.65</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4</td>
<td>0.40</td>
</tr>
<tr>
<td>Haematopoietic neoplasms</td>
<td>2</td>
<td>0.40</td>
</tr>
<tr>
<td>Non-malignant diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total death excluding colorectal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>7.02</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>6.38</td>
</tr>
</tbody>
</table>

<sup>a</sup> Obs: observed number of deaths.

<sup>b</sup> Exp: expected number of deaths.

*P < 0.01, **P < 0.0001.
gastrointestinal complications, with only one death from malignancy (galbladder carcinoma). Thus, no significant elevation of the SMR was found for malignant neoplasms in CD patients (SMR = 0.95, 95% CI: 0.09–4.43).

Discussion

Because of the long course of IBD disease, a limited number of follow-up studies have so far been undertaken. In such studies, however, observation periods were 10 years at most, and their study subjects tended to be more severe cases recruited from either university hospitals or other specialized facilities. Moreover, the low frequency of IBD in Japan in comparison to Western countries makes it difficult to perform follow-up studies on such a limited number of subjects. We thus tried to conduct a survey using patients registered in the government research programme and then following them thorough the family registry. These methods allowed us to minimize selection bias by recruiting patients and following them for a significant number of years, regardless of whether they moved or changed hospitals.

On the other hand, certain weakness in the present study should be taken into account, since the survey was conducted on patients who were registered in a special rare-disease programme. First, the study subjects did not necessarily reflect the Japanese population at large in terms of sex and age distributions. Many of registered patients were the dependents of those insured. Therefore, subjects in the male group consisted mainly of children and in the female group of children and housewives. Second, the sample size was relatively small compared to studies in Western countries, though we did collect subjects on a regional basis. These two weaknesses made our data analysis somewhat unstable. Third, individual characteristics (e.g., lifestyles and medical procedures) were not sufficiently taken into consideration when investigating a group of people using SMR. In this regard, one possible approach was to utilize the information on participating health insurance which could reflect social and occupational background to some extent. In spite our finding of no significant difference in hazard ratios of total mortality for each health insurance, the study results should be cautiously interpreted with respect to pathogenesis associated with mortality pattern.

There were three deaths from rectal cancer, hepatitis and lymphoma in male UC patients, and one death from septic shock in female UC patients. These diseases might be related to homosexuality or drug abuse. However, in Japan, these are extremely rare and so it is unlikely that many UC patients were affected in this way.

The most frequently cited causes of death among UC patients have been reported to be fulminant colitis, and death related to operation or colorectal cancer. However, some changes have been observed in the extent to which UC exposure is correlated with cancer development. Early studies found an excess of colorectal cancer (3–30 times greater incidence) compared to the general population. Other studies have also reported that the risk of developing colorectal carcinoma increases by from 10% to 20% for every decade of disease duration after 10 years. On the other hand, recent studies have shown a low frequency of colorectal cancer, e.g., 3% at 15 years, 5% at 20 years, and 9% at 25 years in patients with extensive disease. Correspondingly, low figures have also been indicated based on population-based studies in Sweden, Israel and the US, thus suggesting that the cancer risk for all UC patients is much lower than previously anticipated. Most of the early studies seemed to involve more severe cases. Besides, early studies all contained cases diagnosed in the 1930s and 1940s, with some even extending back to 1919, long before the era of prednisolone and sulfasalazine treatment. Recently, these chemotherapeutic remedies may decrease the risk of cancer by lowering the chronic inflammatory activity. In addition, the risk might also be influenced by improved surgical and other medical procedures.

However, in our study, a high risk of colorectal cancer death in UC patients was found, similar to the early studies in Western countries. Recent studies in Japan also reported that malignant disease or severe dysplasia of the colon developed in 4 out of 124 UC patients from 10 to 14 years after the onset and postulated that racial factors might possibly play some role in such a high rate. We observed that cases of colorectal cancer tended to be of early onset and to have been of long duration compared to the other causes of death (Table 2). These findings are concordant with previous reports in which patients with a long, continuous course of disease were seen as having a higher risk for malignant degeneration. Long-term chronic irritation may thus affect development of malignant degeneration in the intestine.

In our study, two deaths from haematopoietic malignant diseases were also found. Concerning the association between lymphoma and UC, it was reported that among 5 cases of malignant lymphoma identified in 1156 UC patients (0.4%) over 24 years, 4 patients simultaneously developed colon cancer within the first decade of treatment for UC. In contrast to the characteristically late development of UC-associated colorectal cancer, this finding is quite interesting. It seems likely that not only the irritation of the colonic mucosa but also some immunological defects play a part in the pathogenesis of colorectal malignancies.

As for the overall mortality in UC patients, recent studies in Western countries have mostly shown a favourable survival rate similar to that of the general population. In this regard, the SMR obtained in our study (0.94 for both sexes) is agreement with these Western studies. Excluding the deaths from colorectal cancer, the SMR was reduced to 0.27, which resulted mainly from the reduction in men's SMR (from 0.84 to 0.43). In the present study, a slight excess mortality was found in CD patients, which was higher than that of UC patients, although not significant. This was attributed to gastrointestinal complications rather than to malignant diseases. These results suggest the presence of carcinogenic factors in the pathogenesis of UC, but not in CD, although some previous studies have shown that the risk of developing colorectal cancer in CD patients is comparable to that in UC cases. Further prospective studies would be required to corroborate aetiologic factors and to predict the long-term prognosis of IBD, particularly in Japan.

In summary, among UC patients, we found a significant excess of deaths due to colorectal cancer and haematopoietic neoplasms, although overall mortality rate was generally similar to that of the general population in Japan. We also observed a different cause of death between UC and CD patients. These findings suggest that some carcinogenic factors such as irritation of the colonic mucosa, as well as immunological and racial
factors might play an aetiologic role in the development of colorectal cancer among UC patients.

References