JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.12616

GASTROENTEROLOGY

Second peak in the distribution of age at onset of ulcerative colitis in relation to smoking cessation

Haruhiko Takahashi,* Toshiyuki Matsui,* Takashi Hisabe,* Fumihito Hirai,* Noritaka Takatsu,* Kozue Tsurumi,* Takao Kanemitsu,* Yuho Sato,* Ken Kinjyo,* Yutaka Yano,* Yasuhiro Takaki,* Takashi Nagahama,* Kenshi Yao† and Masakazu Washio‡

Departments of *Gastroenterology and †Endoscopy, Fukuoka University Chikushi Hospital, Chikushino-City, and ‡Department of Community Health and Clinical Epidemiology, St. Mary's College, Kurume Fukuoka, Japan

Key words
age distribution, smoking cessation, ulcerative colitis.

Accepted for publication 12 March 2014.

Correspondence
Toshiyuki Matsui, Department of Gastroenterology, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino, Fukuoka 818-8502, Japan. Email: matsui@fukuoka-u.ac.jp

Abstract

Background and Aim: The prevalence of ulcerative colitis (UC) is increasing steadily in Japan. In Western countries, a bimodal distribution, with UC onset peaks in youth and middle age, is observed, and smoking cessation is reported as a risk factor for UC. However, there are few reports on a bimodal distribution of onset age among Japanese patients. Therefore, the distribution of onset age and factors related to late onset (i.e. onset at 50 years old or later) were investigated in UC patients in Japan.

Methods: A questionnaire survey of UC patients was conducted to investigate the distribution of the age of onset and factors that may be related to UC onset in a Japanese university hospital.

Results: Among 465 UC patients, 343 patients responded. In the distribution of onset age, a large peak was seen in patients aged 10–20s, and small peaks were seen at age 40–44 years and then in 50–60s. In addition, the onset age was older in the UC patients diagnosed in 2001 or later than in those diagnosed in 2000 or earlier. Late onset was more common among the UC patients diagnosed in 2001 or later (*vs* 2000 or earlier: interaction odds ratio = 4.98, 95% CI: 2.21–11.25, $P < 0.01$) and among former smokers (*vs* never-smokers: interaction odds ratio = 2.93, 95% CI: 1.40–6.14, $P < 0.01$) on multivariate analysis.

Conclusions: Similar to UC patients in Western countries, a bimodal distribution of onset age was also observed in Japanese UC patients, and smoking cessation may partly contribute to the increase in late-onset UC patients in recent years in Japan.

Introduction

The prevalence and morbidity rates of inflammatory bowel disease (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are lower in Japan than in Western countries, but they are increasing steadily.[1] Factors related to this are thought to include Westernization of the diet and other living habits in Asian countries.[2,3] Research in recent years has shown that genetic factors and various environmental factors may also contribute to IBD onset.[2–5]

IBD is thought to occur more commonly in young people, but as society ages, there are increases in the number of patients with onset at older age and in the number of patients under long-term observation, and elderly patients with IBD are encountered with greater frequency. Older age at onset has been seen in UC in particular in recent years, and it has been pointed out that, in Western countries, the distribution of onset age has shown bimodality, with onset at a young age and at a fairly old age.[5–11]

UC is increasing in many parts of the Asia-Pacific region and is diagnosed at a slightly older age than in the West.[2,3,12–14] In Asia, there is rarely a second incidence peak as in the West.[2,3,12]

Among the onset factors, smoking in particular is said to be an important factor in the onset of UC and its clinical course in Western countries and Asia-Pacific countries, and several case–control studies and cohort studies have been reported.[2–4,12,13,15–19] In Japan, on the other hand, very few reports have closely examined the most recent prevalence and incidence rates and their generational changes.

Therefore, the distribution of onset age of UC, generational changes in age at onset, and factors related to the onset age of UC were investigated in the UC outpatients of our university hospital in Fukuoka, Japan.

Methods

A questionnaire survey was distributed at the time of outpatient visits and by mail to 465 UC patients seen as outpatients at our hospital between April 2006 and March 2010. The subjects of the present analysis were the 343 patients who responded. The diagnosis of UC was based on clinical, endoscopic, and histological criteria. The protocol of this study was approved by theInstitutional

Review Board of Fukuoka University Chikushi Hospital. All participants provided their written, informed consent to participate.

The questionnaire was administered with the aim of investigating onset factors, with question items limited to smoking habit, alcohol consumption, and family history of IBD. Subjects were divided into three groups by smoking habit before the diagnosis of UC: never-smokers, former smokers, and current smokers. For the former smokers, information about duration since they stopped smoking, duration of past smoking, and the number of cigarettes they smoked a day was obtained.

The duration of non-smoking since they stopped smoking among former smokers was classified into three categories (1 year or less, 1–9 years, and 10 years or more). Intensity of smoking was measured by the Brinkman index (BI) (never-smokers, BI = 1–499, BI = 500–999, BI = 1000, or greater). The BI was determined as the number of cigarettes per day multiplied by the number of years smoking.[20]

The patients were similarly divided into three groups by alcohol drinking habit before the diagnosis of UC: never-drinkers, former drinkers, and current drinkers.

In the present study, UC patients were considered to have a family history if they had a relative within the third degree of kinship who had CD or UC.

The age at onset and clinical features were based mainly on the individual clinical survey of their medical records. The distribution of the age at onset was investigated for all subjects and for men and women separately. Patients were divided into two date groups according to onset (2000 or earlier and 2001 or later), and the generational changes in age at onset and related factors were compared between these two groups.

Comparisons were also made between the two groups of 20–49 years old and ≥ 50 years old. As 50 years of age showed a small peak in the overall distribution of age at onset, 50 years of age was used as a cut-off point. In addition, the correlations between smoking habit and disease extent and severity, and the relationships between age at onset and disease extent, severity, and course (surgery and hospitalization rates) were investigated.

Statistical analysis. All statistical analyses were conducted using the Statistical Analysis System (SAS) package (SAS Institute, Cary, NC, USA). In comparisons between groups, Student's *t*-test (for continuous variables) and the χ^2 test (for categorical variables) were used to compare the two groups. Unconditional logistic regression was used to compute the odds ratios (ORs) and their 95% confidence intervals (CIs) with adjustments for covariates. The dose-dependent trend was tested by evaluating the regression coefficient when the categories were treated as equally spaced numerical variables in the logistic regression model. Differences were assessed with two-side tests, with an alpha level of 0.05.

Results

The clinical backgrounds of the subjects ($n = 343$) are shown in Table 1. The distribution of age at onset in all patients is shown in Figure 1. A large peak was seen in the 10–20s, and small peaks were seen at age 40–44 years and then at age 50–64 years.

Table 1 Clinical background of subjects ($n = 343$)

Sex (male : female)	173:170
Age at onset (year)	34.7 ± 15.8
Mean year at onset	2001.7 ± 7.6
Smoking status	
Never-smoker	215 (62.7%)
Former smoker	74 (21.6%)
Current smoker	54 (15.7%)
Drinking status	
Never-drinker	218 (63.6%)
Former drinker	9 (2.6%)
Current drinker	116 (33.8%)
Has family history	31 (9.0%)

Each set of value represents the mean ± SD or number (%).

Figure 1 also shows a comparison of male and female patients. The mean (± standard deviation [SD]) age at onset of UC was significantly higher in male patients than in female patients (36.5 ± 16.0 years *vs* 32.8 ± 15.4 years, $P = 0.03$). There was also a significant difference between men and women in the distribution of age at onset ($P = 0.04$). The proportion of old patients tended to be greater in male patients than in female patients (22.0% *vs* 15.4%, $P = 0.07$).

Table 2 shows the generational changes in age at onset and related factors in both groups. The mean year of onset was 2001.7 ± 7.6 years; thus, the subjects were divided into two groups according to onset (2000 or earlier and 2001 or later). The mean (± SD) age of onset was significantly younger in the 127 patients diagnosed in 2000 or earlier than in the 216 UC patients diagnosed in 2001 or later (30.8 ± 12.1 years *vs* 36.9 ± 17.2 years; $P < 0.01$). In addition, the proportion of late-onset patients (≥ 50 years) was significantly smaller in the patients diagnosed in 2000 or earlier than in the patients diagnosed in 2001 or later (6.3% *vs* 25.9%, $P < 0.01$). There was also a significant difference between the two groups in the distribution of age at onset ($P < 0.01$). In the investigation of onset factors, the 2001 or later onset group had a significantly larger proportion of smokers before onset than the 2000 or earlier onset group ($P = 0.03$). No significant differences were seen in alcohol consumption and family history.

Table 3 shows the cumulative effects of the interactions between onset age and smoking status, drinking status, and family history of UC at onset limited to adult UC patients (≥ 20 years). Even after controlling for all factors in the table, the late-onset patients (≥ 50 years) were more common among the patients with onset in 2001 or later (interaction odds ratio [ORi] = 4.98, 95% CI: 2.21–11.25, $P < 0.01$) and among former smokers (ORi = 2.93, 95% CI: 1.40–6.14, $P < 0.01$) on multivariate analysis.

As shown in Table 4, compared with never-smokers, former smokers were more common among late-onset adult UC patients than early-onset adult patients even after controlling for sex (sex-adjusted ORi = 3.42, 95% CI: 1.69–6.93). In addition, former smokers with longer years had higher ORi (*vs* never-smokers, 1 year or less: sex-adjusted ORi = 2.34, -------; *P* for trend < 0.01). Furthermore, the BI was positively associated with late onset (*vs* never smokers, BI = 1–499: sex-adjusted ORi = 2.55, 95% CI: 1.19–5.47; BI = 500–999: sex-adjusted ORi = 8.02, 95% CI: 2.14–30.10; BI = 1000 or greater; sex-adjusted ORi = 22.33, 95% CI: 2.33–214.43; *P* for trend < 0.01).

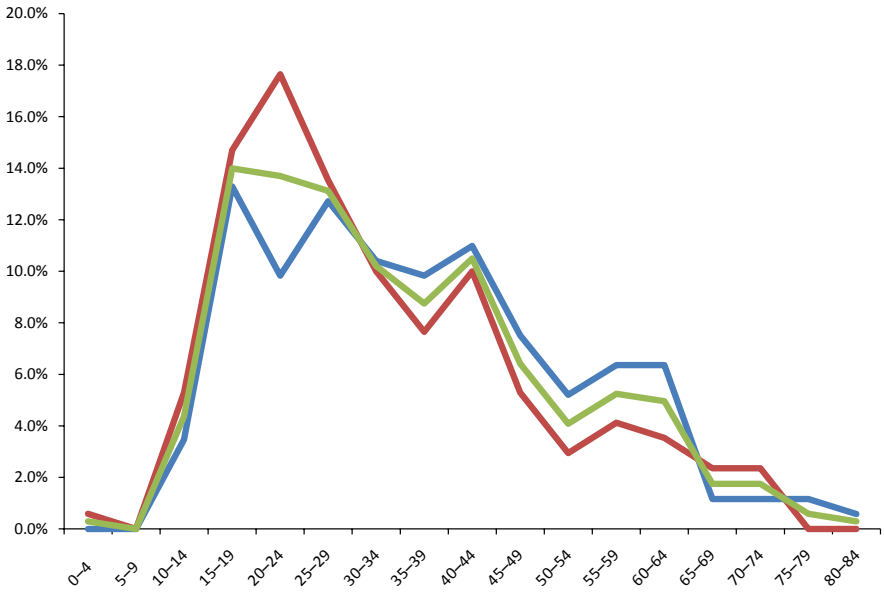

Figure 1 Distribution of age at onset in all subjects (n = 343). A large peak is seen in the 10–20s, and small peaks are seen at age 40–44 years and then at age 50–64 years. Distribution of age at onset in men and women (173 men, 170 women). The mean age at onset is 36.5 ± 16.0 years for men and 32.8 ± 15.4 years for women (P = 0.03). There is a significant difference in the distribution of age at onset. ——, male; ——, female, ——, total.

Table 2 Comparison of distribution of age at onset and onset factors by generation

	Onset in 2000 or earlier (n = 127)	Onset in 2001 or later (n = 216)	P-value
Age at onset (year)	30.8 ± 12.1	36.9 ± 17.2	< 0.01**
Men	49 (39.2%)	124 (56.9%)	< 0.01**
Distribution of age at onset (year)			
< 10	1 (0.8%)	0 (0%)	
10–19	24 (18.9%)	40 (18.6%)	
20–29	40 (31.5%)	50 (23.1%)	
30–39	25 (19.7%)	40 (18.5%)	
40–49	29 (22.8%)	30 (13.9%)	< 0.01**
50–59	6 (4.7%)	26 (12.0%)	
60–69	2 (1.6%)	21 (9.7%)	
70–79	0 (0%)	8 (3.7%)	
≥ 80	0 (0%)	1 (0.5%)	
Proportion ≥ 50	8 (6.3%)	56 (25.9%)	< 0.01**
Smoking status before onset			
Never-smoker	91 (71.7%)	124 (57.3%)	
Former smoking	17 (13.3%)	57 (27.1%)	0.03*
Current smoker	19 (15.0%)	35 (16.2%)	
Drinking status before onset			
Never-drinker	83 (65.4%)	135 (62.4%)	
Former drinking	2 (1.6%)	8 (3.2%)	0.65
Current drinker	42 (33.0%)	73 (34.4%)	
Has family history	14 (11.0%)	17 (7.8%)	0.29

*P < 0.05; **P < 0.01.
Each set of value represents the mean ± SD or number (%).
Student's t-test or χ^2 test.

Although not shown in a table, the age at onset by smoking habit was 31.2 ± 14.7 years in never-smokers, 46.1 ± 13.9 years in former smokers, and 32.7 ± 15.1 years in current smokers. The age at onset was thus significantly higher in former smokers (P < 0.01). There was no correlation between age at onset and disease extent, severity, or course (surgery rate and hospitalization rate), and there was no correlation between smoking habit and disease extent or severity.

Discussion

The present study is the first large-scale report to show a bimodal distribution of onset age and relationship with smoking cessation in Japanese UC patients.

The mean age of onset in the years since 2001 was 36.9 years, which is older than the age of onset in the years 2000 and earlier. The results of a multivariate analysis of people with early onset (20–49 years) and people with late onset (≥ 50 years) showed that the risk of onset after smoking cessation was about three times higher in people with late onset. Moreover, the risk of onset at an older age has increased fivefold since 2001, suggesting the possibility that smoking cessation is a risk for late onset. When the BI was high, the risk of late onset was also high, and there was a risk of late onset even 10 years after smoking cessation.

On the other hand, the rate of current smokers did not differ between the patients with onset in 2001 or later and those with onset in 2000 or earlier (15.6% *vs* 12.8%). These findings suggest that smoking cessation may partly contribute to an increase in late-onset UC patients and to the bimodal distribution of the age at onset in recent years in Japan. Moreover, these trends strengthened with the later generational changes in this study.

In a survey of IBD patients in Japan by Asakura *et al.*,[1] the prevalence of IBD was 63.6/100 000 persons for UC and 21.2/100 000 persons for CD in 2005. These rates are lower than those in Western countries, but they are increasing steadily. Fujimoto *et al.*[21] reported that the proportion of UC patients aged ≥ 60 years

Table 3 Comparison of smoking and drinking status and family history of adult patients at the diagnosis of ulcerative colitis according to the onset age

Age category	20–49 years old (n = 215)	50–89 years old (n = 64)	OR (95% CI)	Adjusted OR (95% CI)
Female	109 (50.7%)	26 (40.6%)	1.00 (reference)	1.00 (reference)
Male	106 (49.3%)	38 (59.4%)	1.50 (0.85–2.65)	0.91 (0.45–1.80)
Year of diagnosis				
2000 or earlier	93 (43.3%)	8 (12.5%)	1.00 (reference)	1.00 (reference)
2001 or later	122 (56.7%)	56 (87.5%)	5.34 (2.43–11.74)**	4.98 (2.21–11.25)**
Smoking status				
Never-smoker	136 (63.3%)	26 (40.6%)	1.00 (reference)	1.00 (reference)
Former smoker	45 (22.3%)	29 (46.9%)	3.27 (1.76–6.08)**	2.93 (1.40–6.14)**
Current smoker	34 (14.4%)	9 (12.5%)	1.35 (0.56–3.27)	1.22 (0.46–3.27)
Drinking status				
Never-drinker	136 (63.3%)	35 (54.7%)	1.00 (reference)	1.00 (reference)
Former drinker	4 (1.9%)	5 (7.8%)	4.86 (1.24–19.04)*	3.37 (0.78–14.62)
Current drinker	75 (34.9%)	24 (37.5%)	1.24 (0.69–2.25)	1.00 (0.51–1.96)
Family history of IBD				
No	196 (91.2%)	58 (90.6%)	1.00 (reference)	1.00 (reference)
Yes	19 (9.4%)	6 (9.4%)	0.94 (0.36–2.46)	0.56 (0.20–1.57)

*P < 0.05; **P < 0.01.

Each set of value represents number (%).

95% CI, 95% confidence interval; adjusted OR, odds ratio adjusted for factors in the table; OR, odds ratio.

Table 4 Cumulative effects of interaction between onset age and sex, smoking status, duration of quit smoking, Brinkman index at the onset of ulcerative colitis risk: case-only analysis among adult never and former smokers

Factors	Early onset adult UC patients, 20–49 years old (n = 181)	Late onset adult UC patients, 50–89 years old (n = 55)	Sex-adjusted ORi (95% CI)
Gender			
Female	101 (50.8%)	24 (43.6%)	1.00 (reference)
Male	80 (44.2%)	31 (56.4%)	0.61 (0.33–1.13)
Smoking status			
Never smokers	136 (75.1%)	26 (47.3%)	1.00 (reference)
Former smokers	45 (24.9%)	29 (52.7%)	3.42 (1.69–6.93)**
Duration of quit smoking			
Never smokers	136 (75.1%)	26 (47.3%)	1.00 (reference)
1 year or less	10 (5.5%)	6 (10.9%)	3.20 (1.04–9.98)*
1–9 years	23 (12.7%)	10 (18.2%)	2.34 (0.94–5.83)***
10 years or more	12 (6.6%)	13 (23.6%)	5.84 (2.23–15.31)**
			P for trend < 0.01
Brinkman index (BI)			
Never smokers	136 (75.1%)	26 (47.3%)	1.00 (reference)
1–499	39 (21.6%)	18 (32.7%)	2.55 (1.19–5.47)*
500–999	5 (2.8%)	7 (12.7%)	8.02 (2.14–30.10)**
1000 or greater	1 (0.6%)	4 (7.3%)	22.33 (2.33–214.43)**
			P for trend < 0.01

*P < 0.05; **P < 0.01; ***P < 0.1.

Each set of value represents number(%).

95% CI, 95% confidence interval; ORi, interaction odds ratio.

increased 6.5-fold from 1981 to 2000. These results indicate that UC does not occur more commonly in young people.

UC is increasing in many parts of the Asia-Pacific region and is diagnosed at a slightly older age than in the West.[2,3,12,13] Looking at the distribution of age at onset of UC in Western countries, a bimodal distribution is seen, with young people in their 20–30s and older people in their 50–70s.[4–7] In contrast, there is rarely a second incidence peak in Asian populations.[2,3,12] In a recent Korean study, Yang *et al.*[14] were able to demonstrate this smaller second peak in incidence for UC, similar to that seen in the present study.

In Asia, some studies have shown that smoking has a protective effect in the development of UC.[2,3,12,22] Other possible environmental factors associated with UC in the Asian population include a

Western diet. Several studies have shown genetic polymorphisms associated with UC in the Asian population.[2,3,12]

The results of the present investigation are similar to those of Western countries and other Asian countries, suggesting that there may be bimodality in the age at onset and an increase in patients with onset at older age among Japanese as well. The effect of an aging society is not the only factor involved in this. Environmental factors such as diet, smoking habit, and alcohol consumption are also thought to be related to onset. Smoking in particular has been said for some time to be an important environmental factor.

A relationship between IBD and smoking was first reported in 1982 by Harries *et al*.,[15] who reported that there were fewer smokers among UC patients than among healthy people. Later, smoking habit was thought to an important factor in the onset of UC and its clinical course in Western countries and Asia-Pacific countries, and several case–control studies and cohort studies have been reported.[16–19,22–24]

Aldhous *et al*.[17] found that a group of former smokers had significantly higher age at onset than current smokers and never-smokers (46.5 years *vs* 31.1 years or 29.4 years, $P < 0.01$). They also showed a bimodal distribution of age at onset and a significantly higher proportion of former smokers in the group with onset at age ≥ 50 years. These results are the same as those of the present investigation. Moreover, the second peak in age at onset is conjectured to be formed by smoking cessation in middle-aged people,[23,24] and the high proportion of onset at older age in men in particular is conjectured to be because the smoking cessation rate is higher in men than in women.[24] There are several reports that the proportion of onset at an elderly age increases with later generations, a tendency that is particularly strong in men.[6–8,10,11,24] The proportion of late onset (≥ 50 years) in this study was 38/173 (22.0%) in men and 26/170 (15.4%) in women. Although the difference was not significant, the incidence rate had a male preponderance. This is thought to be because of the high smoking cessation rate in men. In Japan, the "People's Health Promotion Campaign for the 21st Century" (Healthy Japan 21) was formulated in 2000 as a measure to promote health and vitality in all citizens. Programs in Healthy Japan 21 are implemented with cigarette smoking as a priority issue. To prevent lifestyle-related diseases, a health promotion law was enacted in 2002 that incorporates the concept of health promotion through lifestyle improvements in the areas of nutrition, exercise, and alcohol and tobacco consumption. Since that time, the smoking rate has remained relatively flat in women (1990–2010: 14.3–12.1%), but it declined over time in men (1990–2010: 58.8–36.6%).[25]

In the present study, no correlation was seen between smoking habit and disease extent or severity, and no correlation was seen between age at onset and disease extent, severity, or course (surgery and hospitalization rates). There are many reports of greater severity at time of onset[26] and more extensive disease[11,26] in early-onset patients than in late-onset patients, but there are also reports showing no difference,[17,19] and no consensus has been reached.

Similar to the report by Higuchi *et al*.,[27] when the BI was high, the risk of late onset was also seen to be high, and there was a risk of late onset even 10 years after smoking cessation. Thus, it was found that smoking cessation was a risk for the onset of UC, regardless of the length of time between smoking cessation and onset.

While smoking is thus thought to have a positive effect for UC patients, the mechanism is not clear. Since smoking is known to increase risks for cardiovascular events such as myocardial infarction and stroke, lung diseases such as emphysema, and lung cancer and other malignancies, it is difficult to recommend smoking to our UC patients. The mechanisms are likely to be complex and require further investigation.

In the present study, there was no causal association between family history of IBD and onset, but Ha *et al*.[19] reported that, while smoking cessation was an onset factor in the older onset group ($P < 0.001$), family history was an onset risk in the young onset group ($P = 0.008$). In Japan, Ishige *et al*.[28] found that family history of IBD was significantly higher in a young onset group when young onset was defined as onset at age ≤ 16 years. Various studies have been conducted in recent years with gene analysis of IBD patients, and we look forward to elucidation of this in the coming years.

The present study has several limitations. First, the number of UC patients was small because the participants in the present study were not from hospitals all over the Japan but from one university hospital in Fukuoka, Japan. Second, the present study was not a case–control study. Thus, one can evaluate the risk of UC onset but not the interaction between factors related to UC onset. Further studies are needed.

In conclusion, a bimodal distribution of the age at onset in UC patients was seen in our hospital, similar to the distribution in Western countries. Moreover, these trends strengthened with the later generational changes. The present results also suggest that smoking cessation may contribute as a factor in the second peak.

Acknowledgments

This study was supported by Health and Labour Science Research Grants (Chief researcher Dr M Watanabe) from the Ministry of Health, Labour and Welfare of Japan.

References

1 Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, Takebayashi T. Prevalence of ulcerative colitis and Crohn's disease in Japan. *J. Gastroenterol.* 2009; **44**: 659–65.
2 Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am. J. Gastroenterol.* 2008; **103**: 3167–82.
3 Prideaux L, Kamm MA, De Cruz P, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. *J. Gastroenterol. Hepatol.* 2012; **27**: 1266–80.
4 Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504–17.
5 Cones J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel disease. *Gastroenterology* 2011; **140**: 1785–94.
6 Loftus CG, Loftus EV Jr, Harmsen WS *et al*. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm. Bowel Dis.* 2007; **13**: 254–61.
7 Johnston RD, Logan RF. What is the peak age for onset of IBD? *Inflamm. Bowel Dis.* 2008; **14**: S4–5.

8 Molinie F, Gower-Rousseau C, Yzet T *et al*. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988–1999). *Gut* 2004; **53**: 843–8.
9 Bernstein CN, Wajda A, Svenson LW *et al*. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am. J. Gastroenterol.* 2006; **101**: 1559–68.
10 Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology* 1991; **100**: 350–8.
11 Langholz E, Munkholm P, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. *Scand. J. Gastroenterol.* 1991; **26**: 1247–56.
12 Ooi CJ, Fock KM, Makharia GK *et al*. The Asia-Pacific consensus on ulcerative colitis. *J. Gastroenterol. Hepatol.* 2010; **25**: 453–68.
13 Jiang XL, Cui HF. An analysis of 10218 Ulcerative colitis cases in China. *World J. Gastroenterol.* 2002; **8**: 158–61.
14 Yang SK, Yun S, Kim JH *et al*. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986–2005: a KASID study. *Inflamm. Bowel Dis.* 2008; **14**: 542–9.
15 Harries AD, Baird A, Rhodes J. Non-smoking: a feature of ulcerative colitis. *Br. Med. J.* 1982; **284**: 706.
16 Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin. Proc.* 2006; **81**: 1462–71.
17 Aldhous MC, Drummond HE, Anderson N *et al*. Smoking habit and load influence age at diagnosis and disease extent in ulcerative colitis. *Am. J. Gastroenterol.* 2007; **102**: 589–97.
18 Bastida G, Beltran B. Ulcerative colitis in smokers, non-smokers and ex-smokers. *World J. Gastroenterol.* 2011; **17**: 2740–7.
19 Ha CY, Newberry RD, Stone CD, Clorba MA. Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. *Clin. Gastroenterol. Hepatol.* 2010; **8**: 682–7.
20 Brinkmann GL, Coates EO. The effect of bronchitis, smoking, and occupation on ventilation. *Am. Rev. Respir. Dis.* 1963; **87**: 684–93.
21 Fujimoto T, Kato J, Nasu J *et al*. Change of clinical characteristics of ulcerative colitis in Japan: analysis of 844 hospital-based patients from 1981 to 2000. *Eur. J. Gastroenterol. Hepatol.* 2007; **19**: 229–35.
22 Jiang L, Xia B, Li J *et al*. Risk factors for ulcerative colitis in a Chinese population: an age-matched and sex-matched case-control study. *J. Clin. Gastroenterol.* 2007; **41**: 280–4.
23 Hanauer SB. Update on the etiology, pathogenesis and diagnosis of ulcerative colitis. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 2004; **1**: 26–31.
24 Riegler G, Tartaglione MT, Carratu R *et al*. Age-related clinical severity at diagnosis in 1705 patients with ulcerative colitis: a study by GISC (Italian Colon-Rectum Study Group). *Dig. Dis. Sci.* 2000; **45**: 462–5.
25 Health, Labour and Welfare Statistics Association. Trend of National Health 2011/2012. Health, Labour and Welfare Statistics Association: Tokyo. 2011/2012.
26 Lee JH, Cheon JH, Moon CH *et al*. Do patients with ulcerative colitis diagnosed at a young age have more severe disease activity than patients diagnosed when older? *Digestion* 2010; **81**: 237–43.
27 Higuchi LM, Khalili H, Chan AT, Richter JM, Bousvaros A, Fuchs CS. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. *Am. J. Gastroenterol.* 2012; **107**: 1399–406.
28 Ishige T, Tomomasa T, Takebayashi T *et al*. Inflammatory bowel disease in children: epidemiological analysis of nationwide IBD registry in Japan. *J. Gastroenterol.* 2010; **45**: 911–17.