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Smoking Habit and Load Influence Age at Diagnosis and Disease Extent in Ulcerative Colitis

Marian C. Aldhous, Ph.D.,[1] Hazel E. Drummond, B.Sc.(Hons.),[1] Niall Anderson, Ph.D.,[2] M. Reza Baneshi, M.Sc.,[2] Linda A. Smith, R.N.,[1] Ian D.R. Arnott, M.D.,[1] and Jack Satsangi, D.Phil.[1]
[1]*Gastrointestinal Unit, Molecular Medicine Centre, School of Molecular and Clinical Medicine, and* [2]*Public Health Sciences, Division of Community Health Sciences, University of Edinburgh, Western General Hospital, Edinburgh. Scotland, UK*

INTRODUCTION: Cigarette smoking affects susceptibility to ulcerative colitis (UC), but its effects on age at diagnosis, disease extent, and need for surgery are less well defined. We examined these parameters in a detailed retrospective analysis of a large cohort of well-characterized UC patients.

METHODS: 499 UC patients (254 male, median age 34.3 yr) were studied. Data were collected on smoking habits, smoking load (pack-years), age at recruitment, age at diagnosis, surgery, and disease extent. Colonoscopic and histological data at both diagnosis and follow-up (median follow-up time 4.6 yr) were available on 349 patients.

RESULTS: Ex-smokers were older at diagnosis than current or nonsmokers, (46.5 yr *vs* 31.1 or 29.4 yr, respectively, $P < 0.001$). Before diagnosis, ex-smokers had a higher smoking load than current smokers (13.0 *vs* 6.94 pack-years, $P < 0.001$). A Cox model for age at diagnosis, with smoking as a time-dependent covariate, showed that at any age, ex-smokers were significantly more likely to develop UC than current smokers (hazard ratio 1.8, 95% CI 1.41–2.44, $P < 0.001$). For current smokers at latest colonoscopy, those with extensive disease were the lightest smokers (median 0.320 pack-years), whereas those with healthy colons were the heaviest smokers (median 9.18 pack-years, $P = 0.006$). At 5 yr, regression of extensive disease was more frequent in current than ex-smokers or nonsmokers (30% current smokers *vs* 8% nonsmokers and 5% ex-smokers, $\chi^2 = 30.4$, $P < 0.001$) but these differences were not maintained over a longer time period.

CONCLUSIONS: Smoking habit influences the age at diagnosis and changes in disease extent in UC. Mechanisms are likely to be complex and require further investigation.

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INTRODUCTION

Ulcerative colitis (UC) is a common cause of gastrointestinal disease in the western world with both genetic and environmental influences important in disease etiopathogenesis (1–4). It is clear that UC is clinically heterogeneous; variations in disease extent and severity are well documented among patients (4). For a given individual, variation is also common over the course of the disease: changes in disease activity are characteristic of the condition represented by clinical relapse and remissions. Proximal extension of distal disease is well recognized (5–9); the proportions of patients whose disease progressed ranged from 14–54% in different studies. Extension was associated with abdominal pain and diarrhea (5), disease severity, and extent of disease at diagnosis (7). Progression was inversely associated with smoking in one study (9) but was independent of smoking habit in another (8).

The influences on these dynamic processes are poorly understood. Genetic factors have been shown to influence clinical aspects of UC. Variants of the multidrug resistance gene MDR1 have been associated with total colitis (10), and the human leukocyte antigen (HLA) gene HLADRB*0103 with need for surgery (11). However, the genetic contribution in UC is relatively smaller than in Crohn's disease (CD), evidenced by twin data (12).

Smoking is the best-described environmental factor implicated in determining susceptibility to, and phenotype of, IBD (2). Susceptibility to UC is reduced in smokers (odds ratio [OR] 0.57, 0.35–0.85) (13), and stopping smoking has been clearly defined as a risk factor for the development of disease (14, 15). In the United Kingdom, 25–30% of the population smoke (27% men and 25% women), with relatively little regional variation (28% in Scotland, 26% in England, and 27% in Wales) (16).

The dichotomous effect of cigarette smoking on the course of CD and UC is well described (reviewed in (17)). Active smoking has been associated with a more benign disease course of UC and this is reflected by lower colectomy rates

in some studies (15, 18–20), while others have been unable to confirm this association (21–24). Smoking cessation has been found to be detrimental to the clinical course of UC in an intervention study (25), data that are compounded by the efficacy of nicotine patches in the treatment of mild to moderate active UC (26). The risk of colectomy is associated with disease extent, those with more extensive colitis requiring more frequent surgery (21, 23), and smokers have been found to have less extensive disease (18, 20).

While differences between numbers of cigarettes smoked has been analyzed for age at diagnosis of UC (27), there are few studies on the influence of smoking load on the dynamic nature of disease extent in UC. There are also few studies comparing the disease course in those who stop smoking prior to diagnosis (referred to here as ex-smokers), those who continue to smoke (current smokers), and those who never smoke (nonsmokers). In Crohn's disease, ex-smokers have been found to have a more benign disease course than nonsmokers (28), and we wished to investigate whether differences between ex-smokers and nonsmokers were apparent in UC.

While the age at diagnosis of UC is generally thought to be under the age of 40 yr, there remains controversy as to whether another peak in diagnosis occurs in older patients (29). In a Belgian study of patients aged >60 yr, 50% of the new IBD cases in this age group were diagnosed as UC (30) and Regueiro *et al.* (31) observed that it was the ex-smokers who tended to be older at diagnosis of UC.

We have assessed the relationship between smoking habit at diagnosis and during the course of disease on age at diagnosis, disease extent, and surgery rates in a large well-defined retrospective cohort of Scottish patients with UC. We report some striking differences among smokers ex-smokers, and nonsmokers, providing additional explanation for the observed heterogeneity in UC, raising critical issues related to disease pathogenesis which need to be considered in future epidemiological, laboratory, and therapeutic studies.

PATIENTS AND METHODS

Patients

The Medicine/Oncology subcommittee of the Lothian Research Ethics Committee approved the study protocol. Patients were recruited from the IBD clinic at the Western General Hospital, Edinburgh, a local center for IBD management and research as well as a tertiary referral center for southeast Scotland. Consecutive consenting patients (N = 513) with a confirmed diagnosis of UC (32) were recruited between June 2001 and May 2005. Retrospective data were collected by interview, patient questionnaire, and case-note review, and comprised dates of diagnosis and follow-up, demographic details, family history of IBD, disease extent by endoscopic and histological assessment, disease behavior, and surgical history. Patients were diagnosed with UC between 1957 and 2005: four patients were diagnosed before 1959, eight patients in 1960–1969, 37 patients in 1970–1979, 85 patients in 1980–1989, 235 patients in 1990–1999, 144 patients in 2000–2005. For all patients, the median time from diagnosis to recruitment was 5.96 yr (interquartile range [IQR] 2.43–13.1 yr). There was significantly less time between diagnosis and recruitment for ex-smokers (N = 162, median 4.76, IQR 1.55–9.55 yr) compared with nonsmokers (N = 237, median 7.4, IQR 2.74–15.0 yr) or current smokers (N = 100, median 6.93, IQR 3.28–16.0 yr, Kruskal-Wallis $P = 0.002$). Patients aged <16 at diagnosis were not included, nor were those for whom smoking data were not available (N = 14).

A total of 499 patients were studied (254 men and 245 women), with a median age at diagnosis of 34.3 yr, IQR 25.6–50.3 yr. Ninety-eight percent of patients were Caucasian. Baseline demographic details are given in Table 1.

Analysis According to Smoking Status at Diagnosis/Follow-up

Patients completed a questionnaire at recruitment in which they were asked whether they had ever smoked and if so, the dates of starting and stopping smoking. From the dates given, each patient's smoking habit (ex-smoker, nonsmoker, or current smoker) was matched with his dates of diagnosis, last follow-up colonoscopy, or surgery. Ex-smokers at diagnosis were defined as those who had stopped smoking more than a year before the date of diagnosis. Twenty-seven patients were smoking at diagnosis of UC, but had stopped for more than a year prior to their last follow-up investigation: these were classed as ex-smokers at follow-up. Nonsmokers were those patients who said they had never smoked. Patients who said they smoked at least seven cigarettes per week were classed as current smokers. Three patients started smoking at least three yr after diagnosis and at least four yr prior to their last follow-up colonoscopy; these were classed as current smokers at follow-up.

Amount Smoked by Patients

Patients stated how many cigarettes per day they smoked. Smoking load was calculated, where the number of packs/day (assuming 20 cigarettes in a standard pack) was multiplied by the number of years smoking (either before or since diagnosis), and given units of pack-years.

Disease Extent in Ulcerative Colitis

Disease extent at diagnosis was assessed on the basis of endoscopic and histological reports and categorized according to the Montreal classification for UC disease extent (33): proctitis (E1, rectum only), left-sided disease (E2, from rectum to the splenic flexure), or extensive disease (E3, disease extended proximally to the splenic flexure, Table 1). Disease extent at latest follow-up colonoscopy was similarly classed on the basis of endoscopic and histological reports, with an extra category of normal for those patients in whom endoscopic appearances were normal and colonic biopsies showed no

Table 1. UC Patients at Diagnosis: Univariate Analyses of Demographics and Disease Extent by Smoking Status

	All UC N = 499 (%)	Smoking Status at Diagnosis			χ^2	*P* Value
		Ex, N = 162 (%)	Non, N = 237 (%)	Current, N = 100 (%)		
Age at diagnosis*						
<50	373 (75)	89 (55)	203 (86)	82 (82)	51.7	<0.001
≥50	126 (25)	73 (45)	34 (14)	18 (18)		
Sex						
Male	254 (51)	92 (57)	107 (45)	55 (55)	6.06	0.048
Female	245 (49)	70 (43)	130 (55)	45 (45)		
Age and sex at diagnosis						
Male	N = 254 (%)	N = 92 (%)	N = 107 (%)	N = 55 (%)		
Male <50	186 (73)	53 (58)	91 (85)	42 (76)	19.4	<0.001
Male ≥50	68 (27)	39 (42)	16 (15)	13 (24)		
Female	N = 245 (%)	N = 70 (%)	N = 130 (%)	N = 45 (%)		
Female <50	188 (77)	35 (50)	113 (87)	40 (89)	39.3	<0.001
Female ≥50	57 (23)	35 (50)	17 (13)	5 (11)		
Family history of IBD	N = 495‡ (%)	N = 160‡ (%)	N = 235‡ (%)	N = 100 (%)		
Yes	90 (18)	28 (17)	39 (17)	23 (23)	2.01	0.336
No	405 (82)	132 (83)	196 (83)	77 (77)		
Disease extent at diagnosis	N = 441 (%)	N = 149 (%)	N = 200 (%)	N = 92 (%)		
Proctitis	152 (34)	52 (35)	71 (36)	29 (32)		
Left-sided disease	182 (41)	64 (43)	80 (40)	38 (41)	1.08	0.897
Extensive	107 (24)	33 (22)	49 (24)	25 (27)		

Ex-smokers were those who had stopped at least a year before diagnosis date. Nonsmokers were those who said they had never smoked. Current smokers were those who smoked.
*50 yr was chosen to differentiate between early and late onset in adult UC.
‡Four patients were adopted and family history data were not available.

evidence of disease by histological analysis. Disease extent at diagnosis was available on 441 patients. Disease extent at last follow-up colonoscopy was available on 411 patients. Disease extent at both diagnosis and follow-up colonoscopy was available on 349 patients with a median follow-up of 4.6 yr, range 1–45 yr.

Statistical Analysis

All data were stored on a Microsoft Access® database. The χ^2 test was used for analysis of discrete variables and odds ratios (OR) were calculated where appropriate (34). Mann-Whitney and Kruskal-Wallis tests were used to compare quantitative results between groups. Kaplan-Meier survival curves were plotted according to smoking habit of the patients at follow-up colonoscopy. These were used to compare the times to regression or progression of disease extent after diagnosis in patients, in all patients for whom disease extent at both diagnosis and follow-up were available. For analysis of regression of disease, patients who progressed or had the same disease extent as at diagnosis were censored, whereas those who regressed to left-sided disease, proctitis, or a healthy colon were counted. Progression of disease was only analyzed for those with proctitis or left-sided disease at diagnosis (as those with extensive disease at diagnosis could not progress any further in terms of disease extent); progression to left-sided or extensive disease was counted, whereas if a patient's disease extent decreased or stayed the same after diagnosis, these data were censored. Kaplan-Meier survival curves were also plotted for time to colectomy *after* diagnosis. Patients who had a colectomy after diagnosis were considered as having the event, while patients who had not had a colectomy by the time their case notes were reviewed were censored. Patients who had been diagnosed with UC at colectomy were not included in this analysis. A Cox model was fitted for age at diagnosis, with a correction factor for age at recruitment: smoking behavior was fitted as a time-dependent covariate, as from birth to age at diagnosis would have remained the same for nonsmokers, but changed for ex-smokers and current smokers at diagnosis. Hazard ratios were calculated for nonsmokers or ex-smokers relative to current smokers at diagnosis; other covariates included sex (men as baseline), family history (no family history as baseline), and disease extent (left-sided and extensive disease were compared with proctitis as baseline). Patients for whom disease extent at diagnosis was unknown were excluded from the analysis (N = 58).

Data were analyzed using Minitab™ Statistical Software, version 13.32 (Minitab Inc, State College PA), GraphPad Prism® version 4 (GraphPad Software, San Diego, CA), and SPSS version 13.0 (SPSS UK Ltd, Woking, UK). Results were considered significant at $P \leq 0.05$.

RESULTS

Smoking Habit Was Associated With Age at Diagnosis

Overall, ex-smokers were significantly older at diagnosis (median 46.5, IQR 34.9–61.1 yr) than current smokers (median 31.1, IQR 25.4–41.6 yr) or nonsmokers (median 29.4, IQR 22.6–41.7 yr, Kruskal-Wallis, $P < 0.001$).

Frequency distribution analysis for age at diagnosis according to smoking status at diagnosis showed a bimodal distribution, with peaks at 25 and 60 yr and a trough at 50 yr (Fig. 1A). Therefore, using 50 yr to differentiate between older and

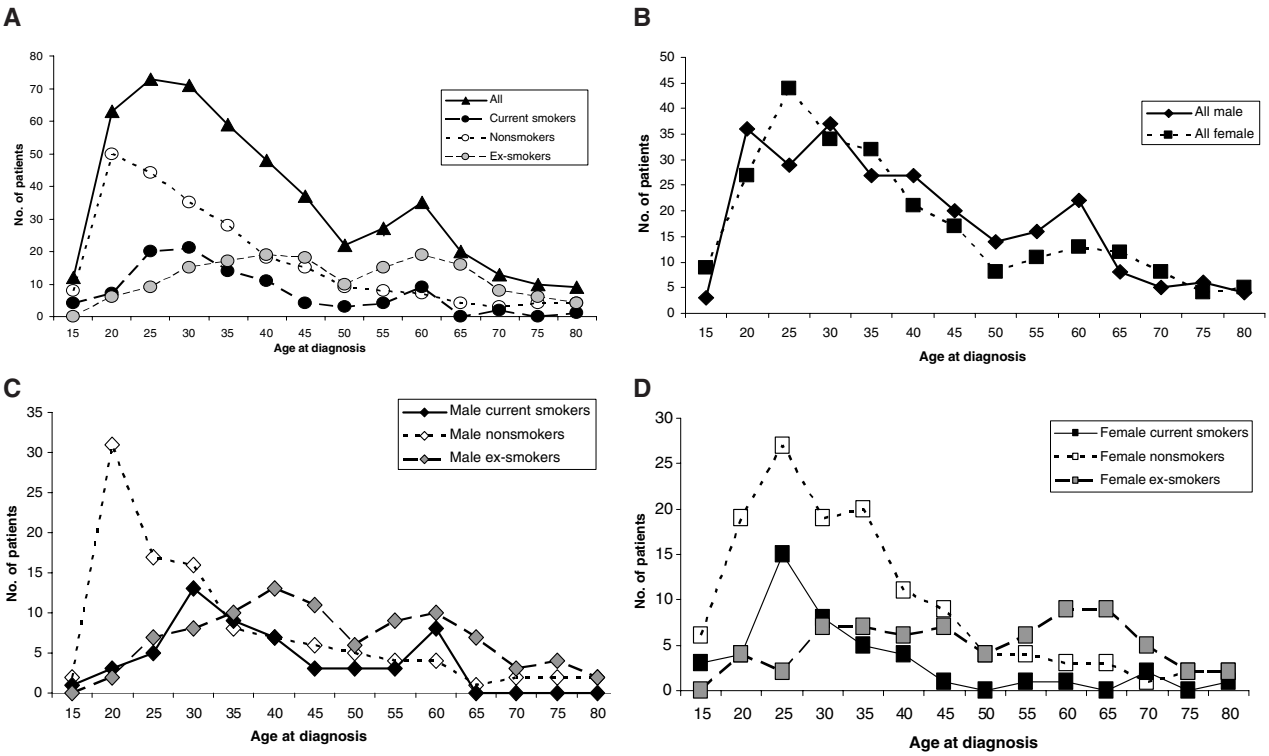

Figure 1. Frequency distribution analysis of age at diagnosis for UC patients. (*A*) All UC patients by smoking habit. Ex-smokers were those who had stopped smoking at least a year prior to diagnosis. Nonsmokers were those who said they had never smoked. Smokers were those who said they were smoking at diagnosis. (*B*) All UC patients by gender. (*C*) Male UC patients by smoking habit. (*D*) Female UC patients by smoking habit.

younger ages at diagnosis, we found that ex-smokers were overrepresented in the second peak compared with nonsmokers or ex-smokers (45% *vs* 14% or 18%, respectively, $\chi^2 = 51.7$, $P < 0.001$, Table 1).

Age at recruitment also differed according to smoking habit. Ex-smokers were older (median age 56.0, IQR 43.5–67.5 yr) than nonsmokers (median age 41.5, IQR 32.7–55.1 yr) or current smokers (median age 43.5, IQR 34.4–57.9 yr).

To determine whether the older age at diagnosis in ex-smokers was not just a reflection of the older age of the ex-smokers at recruitment leading to "inadequate follow-up time bias" (35), we accounted for calendar age by comparing ages at diagnosis in the subgroup of patients who had been recruited at >40 yr of age but diagnosed with UC at <40 yr of age. Ex-smokers were still significantly older at diagnosis (N = 22, median 35.3, IQR 32.9–38.1 yr) than nonsmokers (N = 63, median 30.2, IQR 24.1–34.6 yr) or current smokers (N = 32, median 30.6, IQR 28.8–37.0 yr, Kruskal-Wallis $P = 0.004$).

Gender and Smoking Habit at Diagnosis Were Associated With Age at Diagnosis

Female smokers (median age 28.9, IQR 23.8–33.8 yr) were significantly younger at diagnosis than male smokers (median age 36.4, IQR 28.7–49.5 yr, Mann-Whitney $P = 0.004$). Daily cigarette doses before diagnosis were similar in these two groups (males median 10, IQR 5–20 *vs* women median 10, IQR 5–15 cigarettes/day). Smoking load before diagnosis was lower in female smokers than males but this was not significant (women median 5.75, IQR 1.76–10.9 *vs* men median 8.10, IQR 2.06–23.9 pack yr, Mann-Whitney, $P = 0.113$).

Further analysis of the frequency distribution by gender (Fig. 1B) showed that the second peak at 60 yr of age was higher in men, but still present in women. Frequency distribution analysis according to gender and smoking habit at diagnosis showed that in both sexes, the ex-smokers were the main contributors to this second peak (Fig. 1C, D). From Table 1 it can be seen that for both sexes, ex-smokers are overrepresented in the group of patients who were diagnosed at over 50 yr of age (men $\chi^2 = 19.4$, $P < 0.001$, women $\chi^2 = 39.3$, $P < 0.001$).

To assess whether the differences by sex were not just inadequate follow-up time bias, age at diagnosis for male and female smokers who were over 40 yr at recruitment but less than 40 yr at diagnosis were compared. Female smokers (N = 15, median 29.5, IQR 25.3–32.8 yr) were significantly younger than male smokers (N = 17, median 35.1, IQR 29.6–37.4 yr, Mann-Whitney $P = 0.029$).

Smoking Load Was Associated With Age at Diagnosis

To investigate whether smoking prior to diagnosis had an effect, we compared the time between starting smoking and diagnosis of UC in current smokers, with the time

between starting and stopping smoking in ex-smokers, as well as the number of cigarettes per day and smoking load prior to diagnosis in the two groups. Ex-smokers at diagnosis had smoked for longer times prior to stopping (median 19.0, IQR 10.0–35 yr) than current smokers (median 14.0, IQR 7.15–25.2 yr, Mann-Whitney $P = 0.016$). Prior to stopping, the ex-smokers had smoked a significantly higher daily number of cigarettes (median 15, IQR 10–20) than the current smokers (median 10, IQR 5–20, Mann-Whitney $P < 0.001$), leading to a significantly higher smoking load in ex-smokers prior to stopping (median 13.0, IQR 5.0–31.8 pack-years) than current-smokers at diagnosis (median 6.94, IQR 1.87–15.8 pack-years, Mann-Whitney $P < 0.001$).

Smoking Habit Was Not Associated With Disease Extent at Diagnosis

From Table 1, it can be seen that there was no difference in the disease extent at diagnosis of the patients according to their smoking habit at diagnosis.

Cox Regression Analysis for Age at Diagnosis

A Cox model for age at diagnosis was fitted, with smoking behavior prior to diagnosis as a time-dependent covariate and corrected for age at recruitment. Other covariates were sex, family history of IBD, and disease extent at diagnosis. Results are summarized in Table 2. Smoking habit at diagnosis affected age at diagnosis as the hazard ratios (HR) for both nonsmokers (HR = 1.60, 95% CI 1.24–2.07, $P < 0.001$) and ex-smokers (HR = 1.85, 95% CI 1.41–2.44, $P < 0.001$) were significantly raised for diagnosis of UC at any given age compared with current smokers, all other covariates being equal. The model also showed that disease extent at diagnosis may be slightly different in terms of age at diagnosis, but this was a weak effect ($P = 0.049$).

Table 2. Summary of Results from Cox Model With Smoking as Time-Dependent Covariate for Age at Diagnosis of UC

Variable	Hazard Ratio	950% CI	*P* Value
Smoking behavior at diagnosis‡			<0.001
Nonsmoking	1.60	1.24–2.07	<0.001
Ex-smoking	1.85	1.41–2.44	<0.001
Recruitment age	0.850	0.836–0.864	<0.001
Sex*	0.988	0.813–1.201	0.905
Disease extent at diagnosis†			0.049
Left-sided	0.761	0.608–0.952	0.017
Extensive	0.807	0.624–1.04	0.101
Family history of IBD§	1.04	0.807–1.34	0.772

*Hazard ratio calculated relative to males.
†Hazard ratios calculated relative to proctitis. Patients for whom disease extent at diagnosis was unknown were excluded from the analysis.
‡Smoking behavior was fitted as a time-dependent covariate, as from birth to age at diagnosis would have remained the same for nonsmokers, but changed for ex-smokers and current smokers. Hazard ratios calculated relative to current smokers.
§Hazard ratios calculated relative to no family history of IBD.

Smoking Load Was Inversely Associated With Disease Extent at Follow-up

In current smokers (N = 50), disease extent at latest follow-up colonoscopy was compared by smoking load at the same time point. Smoking load was highest in patients with healthy colons (median 9.18, IQR 2.94–14.8 pack-years), less for those with proctitis/left-sided disease (median 2.23, IQR 0.542–7.48 pack-years) and those with extensive disease were the lightest smokers (median 0.32, IQR 0.04–1.95 pack-years, Kruskal-Wallis $P = 0.003$, Fig. 2A).

Smoking Habit Was Associated With Early But Not Long-Term Changes in Disease Extent from Diagnosis to Follow-Up

Kaplan-Meier survival curves were plotted to compare the effects of smoking on the change in disease extent from diagnosis to follow-up. Patients with extensive disease (pancolitis) at diagnosis (N = 81) were analyzed for regression at follow-up. Patients whose disease extent had regressed were included whereas those whose disease extent remained extensive were classed as censored data. At 5 yr after diagnosis, 30% of current smokers but only 5% of ex-smokers or 8% of nonsmokers had less extensive disease ($\chi^2 = 30.4$, $P < 0.001$), although there was no significant difference in the survival curves overall, as they converged at 10 yr (logrank test $\chi^2 = 2.00$, $P = 0.367$, Fig. 2B). In a similar analysis for regression of disease extent for all patients (N = 349), again at 5 yr, 22% of current smokers but only 6% of nonsmokers and 9% of ex-smokers had less extensive disease ($\chi^2 = 13.4$, $P = 0.001$). However, the curves were not significantly different at 10 yr or overall (Fig. 2C, logrank test $\chi^2 = 4.92$, $P = 0.086$). For patients with proctitis or left-sided disease at diagnosis (N = 268), time to progression of disease extent was analyzed using a Kaplan-Meier survival curve, but no differences were seen according to smoking habit at latest colonoscopy (Fig. 2D, logrank test $\chi^2 = 0.113$, $P = 0.945$).

Smoking Habit Was Not Associated With Requirement for Surgery

Surgery data were available on all patients at case-note review. Only four patients were diagnosed with UC at colectomy. The proportions of patients requiring surgery (22% [15/67] current smokers *vs* 16% [37/232] nonsmokers *vs* 20% [40/200] ex-smokers) were not significantly different, according to their smoking habit at case-note review date or date of colectomy, $\chi^2 = 1.98$, $p = 0.372$. Kaplan-Meier analysis of time to surgery after diagnosis was not significantly different according to smoking habit at case-note review date or colectomy date (logrank test $\chi^2 = 4.40$, $P = 0.111$).

DISCUSSION

The present study provides information clearly demonstrating that smoking habit is a key determinant of phenotype in UC. Age at diagnosis and rate of change of disease extent

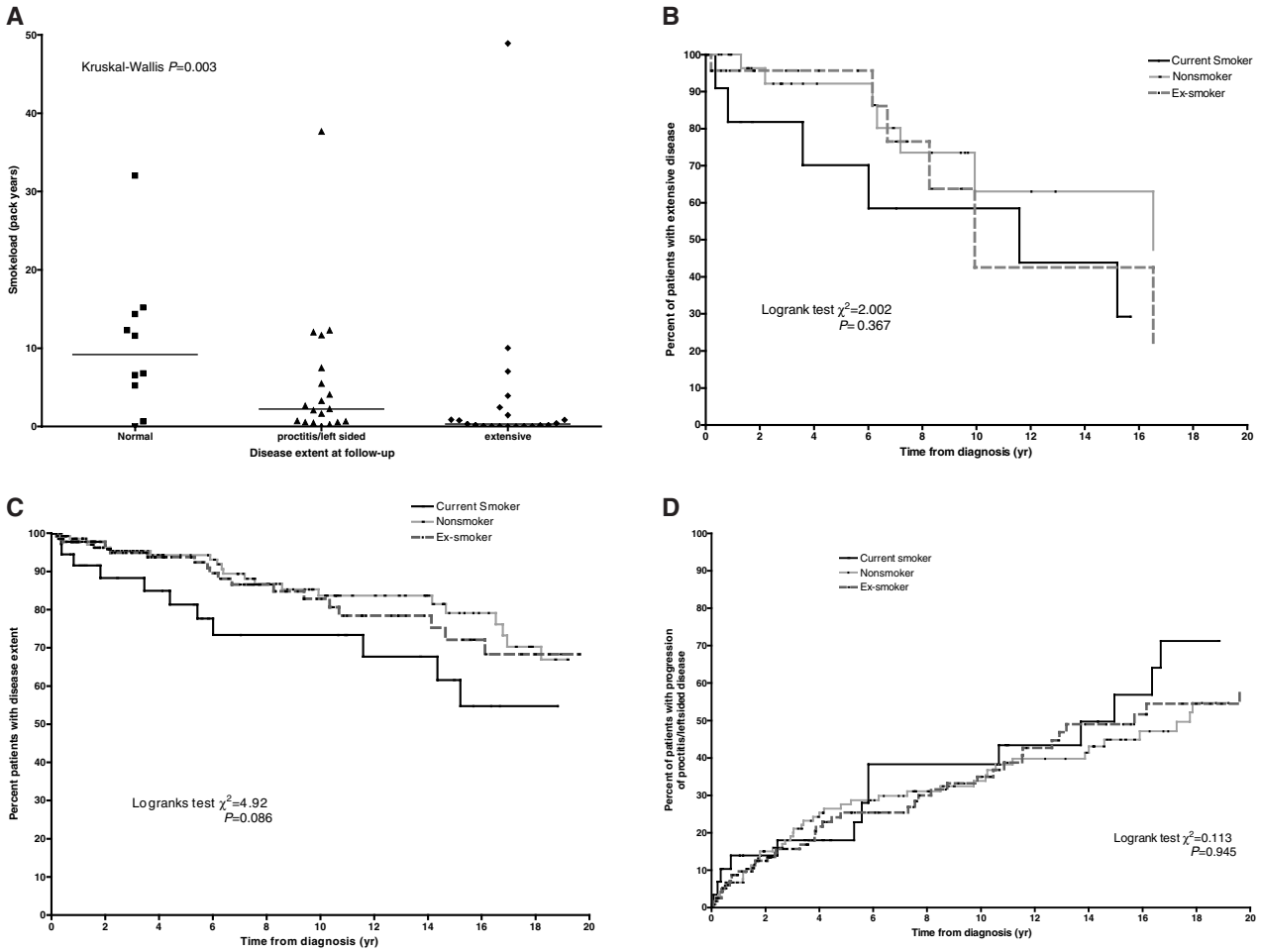

Figure 2. Disease extent, regression, and progression of disease extent. (*A*) For current smokers, the graph shows the smoking load (pack-years) at follow-up by the disease extent. Due to small numbers, those with proctitis and left-sided disease were combined. (*B*) Kaplan-Meier plot for time after diagnosis (up to 20 yr) to regression of extensive disease, according to smoking habit at follow-up. The χ^2 and *P* values relate to a logrank test of comparison of the curves. (*C*) Kaplan-Meier plot for time after diagnosis (up to 20 yr) to regression of any disease extent, according to smoking habit at follow-up. Logrank test χ^2 and *P* values are given. (*D*) Kaplan-Meier plot for time after diagnosis to progression of proctitis/left-sided disease, according to smoking habit at follow-up. Logrank test χ^2 and *P* values are given.

are both influenced by smoking habit and load. Our results confirm that smoking not only has a protective effect on the susceptibility to UC, but also has a beneficial effect on the disease course of UC as shown by a faster regression rate of disease extent in current smokers. This was a retrospective study of a large cohort of UC patients followed up in one center over a long period of time (up to 45 yr). Our data were not population based and there was always the possibility of unintentional recruitment bias throughout the study, *e.g.*, patients with quiescent disease may have not been recruited or followed up as vigorously as those with more active UC.

A bimodal distribution of age at diagnosis of UC was observed and a higher proportion of ex-smokers were diagnosed at $\geq$50 yr of age. These data provide support for Hanauer's hypothesis that "ex-smokers account for the preponderance of the second age peak for UC in patients over 40 yr of age" (36). There is still some debate as to whether this bimodal distribution exists, as some studies (37, 38), but not all (39–41), previously described such a peak. "Inadequate follow-up" bias is a potential problem, as has been believed to happen in IBD families, where the age at diagnosis appeared to decrease with successive generations due to increased awareness and ease of diagnosis, but may actually be due to a shorter length of follow-up (35, 42). Although it is possible that the older age at diagnosis of ex-smokers was another example of this, we found that it remained true even when only older patients were compared. However, the Cox model, including a correction for age at recruitment to eliminate follow-up time bias and using smoking as a time-dependent covariate, showed that ex-smokers had higher hazard ratios for diagnosis of UC than current smokers; *i.e.*, all else being equal, an ex-smoker at any particular age is more likely to develop UC than an individual of the same age who is currently smoking. The patients studied form a retrospectively defined cohort, with no known selection bias. Nevertheless, caution must be advised in deriving broad conclusions about the population relative risks of development of UC due to smoking behavior. This would require a randomly selected prospective cohort.

It is well established that smoking reduces the susceptibility to UC (13) until they stop smoking (14, 15). Indeed, in our results the Cox model showed that the hazard ratios for ex-smokers *versus* current smokers were higher than those for nonsmokers *vs* current smokers. Others have suggested (14), that ex-smokers have a higher risk of developing UC than nonsmokers, possibly because underlying disease mechanisms have been triggered (or stopped being suppressed by some factor(s) within cigarette smoke). If smoking is protective, then those who develop UC while smoking (current smokers) must have less "protection" than those who developed UC after they stopped smoking (ex-smokers). The present study suggests that smoking "dose" may be critical, as an obvious difference between these groups was that current smokers at diagnosis were also lighter smokers: the ex-smokers (prior to stopping and subsequent diagnosis of UC) smoked more cigarettes over a longer time with a resultant higher smoking load (13.0 *vs* 6.94 pack-years). In the absence of other obvious contributory factors, we postulate that a protective smoking threshold exists, below which UC was able to develop in our current smokers. Corrao *et al.* (27) analyzed the number of cigarettes/day and found that in their former smokers, those who had smoked *fewer* cigarettes daily were at a higher risk of developing UC. Our data confirm that of others that smoking reduces susceptibility to UC (14, 15).

While there was no overall effect of gender on age at diagnosis, it was found that female smokers were diagnosed at a younger age than male smokers, and there was no evidence of inadequate follow-up time bias in these groups. This may reflect the lower smoking load prior to diagnosis in females compared with males. Alternatively, these data could indicate some hormonal influence on the etiology of UC such that smoking is less protective in women than men. Cosnes *et al.* also found that the protective effect of smoking was less pronounced in women (43). There are few studies investigating the interactions of smoking and sex hormones on the etiology of UC and there is still some debate as to the relative contributions of oral contraceptives (41), breast-feeding (27), and hormone replacement therapy (44) on UC onset.

Despite differences in age at diagnosis, there was little difference in disease extent, regression, progression, or colectomy rates between ex-smokers and nonsmokers, further indicating that there are minimal long-lasting effects of smoking on UC (25). Interestingly the proportions and rates of progression of proctitis/left-sided disease were similar in current smokers, nonsmokers, and ex-smokers, while regression of extensive disease occurred more frequently and in a faster time in current smokers during the first 5 yr of follow-up. Heavier smokers tended to have macroscopically and histologically normal colons at follow-up colonoscopy, in contrast with ex-smokers, nonsmokers, or light smokers, concurring with previous studies that smokers with UC have milder disease (15, 18, 19). The mechanism(s) of disease progression/regression are not known, nor how smoking affects them. Recent studies showed that inducible nitric oxide synthase (iNOS) was found to be increased in the mucosa of UC patients whose disease progressed over 2 yr (45), and that cigarette smoke solution reduced the induction of iNOS in lung epithelial cell lines (46). Whether a similar mechanism occurs in UC patients requires investigation.

The proportion of patients undergoing colectomy in our cohort was approximately 25% of patients over a total median follow-up time of 4.5 yr. The need for surgery for resistant colitis is a clinically important parameter. Despite its effect on disease regression, smoking habit did not affect the proportion of patients who underwent colectomy, nor the time to surgery after diagnosis. Previous studies have found that similar proportions of ex-smokers and continuing smokers required a colectomy (21–25), but did not find differences, or did not differentiate, between ex- and life-time nonsmokers. As disease extent has been associated with requirement for surgery (21, 23), the proportions of patients undergoing colectomy reflect the increase in disease extent, as these were all similar in nonsmokers, ex-smokers, and current smokers.

The important questions still remain: which mechanism(s) initiate the onset of UC? Is this an environmental factor triggering a genetic effect? In both nonsmokers and current smokers the environment stays the same, with opposing effects on susceptibility to UC, whereas in ex-smokers, the environment changed as smoking ceased, either removing a protective factor(s) or unmasking the underlying disease processes (14). This change in environment could affect mechanisms such as gene expression, activity of critical enzymes involved in a pathway, thus contributing to the pathogenic mechanisms involved in the etiology of UC. The constituent of cigarette smoke involved is also unknown. Previous studies have focused on nicotine, which has wide-ranging effects (47–49), with a view to using nicotine for therapy (50). However, there are over 4,700 compounds in cigarette smoke, many of which may also have immunological actions (51–54).

In summary, this study has shown that both smoking habit and load have effects on the age at diagnosis and subsequent disease extent of UC. Despite differences in age at diagnosis, there were no differences in disease extent between ex-smokers and nonsmokers, although times to colectomy were faster in ex-smokers. These results have implications for the pathophysiology and heterogeneity of disease. Furthermore, the effect of smoking needs to be taken into account in the design and recording of outcomes of clinical trials.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Susceptibility to ulcerative colitis (UC) is reduced by smoking and ex-smokers are at a higher risk of developing UC.
- Smokers with UC are more likely to have a more benign disease course.
- An intervention study has shown that stopping smoking worsens the clinical course of UC.

What Is New Here

- Prior to stopping, ex-smokers smoked more than current smokers prior to diagnosis, indicating a possible threshold of protection of smoking. A substantial proportion of patients, especially ex-smokers, were not diagnosed until >50 yr of age.
- Disease extent was related to smoking load and heavy smokers tended to have normal colonic appearance at follow-up, while light smokers had extensive disease. A higher proportion of smokers than ex- or nonsmokers had a decrease in disease extent between diagnosis and follow-up.
- In terms of disease extent and despite the differences in age at diagnosis, there was little difference between the clinical course of UC in ex-smokers and nonsmokers.

Reprint requests and correspondence: Dr. Marian Aldhous, Gastrointestinal Unit, University of Edinburgh, 2nd floor, Molecular Medicine Centre, Western General Hospital, Edinburgh, EH4 2XU, Scotland, UK.

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CONFLICT OF INTEREST

There were no competing interests in this study.