Does active smoking really influence the course of Crohn's disease? A retrospective observational study

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Abstract

Background: Active smoking has been associated with a higher risk of developing Crohn's disease (CD). However, its impact on clinical outcomes has been controversial among studies.

Aims: To evaluate the influence of active smoking on initial manifestations of CD, the development of disease-related complications, and therapeutic requirements.

Methods: Patients diagnosed with CD within a ten-year period (1994–2003) were identified. Clinical and therapeutic features until October 2008 or loss of follow-up were recorded. Smoking status was assessed at each major disease-related event (e.g. penetrating and stricturing complications, perianal disease, intestinal resection, introduction of immunomodulators or biological agents).

Results: A total of 259 patients were included in the study with a median follow-up period of 91 months. At diagnosis, 50.5% were active smokers and only 12% of them quit smoking during follow-up, mostly after a major disease-related event occurred. Smoking at diagnosis was not associated with a particular CD presentation. Active smoking did not influence the development of strictures, intraabdominal and perianal penetrating complications, or increased resectional surgery, biological therapy or immunomodulators requirements.
1. Introduction

The current hypothesis for the pathogenesis in Crohn's disease (CD) suggests that genetic susceptibility in combination with environmental factors compose a complex pathogenic system that causes a characteristic dysregulation of mucosal immunity. Among environmental factors, smoking has been the only one repeatedly associated with a higher risk for CD development as well as with a worse disease prognosis as judged by increased clinical activity, lower quality of life, disease-related complications, increased need for immunosuppressive drugs and early post-operative recurrence. Initial retrospective studies suggested that disease outcomes improved after giving up smoking when compared with continuing smokers. These results were reproduced in the only prospective study assessing the effect of smoking cessation on the course of CD. The impact of smoking does not seem to be the same in all CD patients. It has been suggested that women and patients with small bowel involvement are particularly susceptible to the deleterious effects of tobacco. Moreover, the impact of smoking seems to vary depending on the genetic background. In this regard, no effect of active smoking has been found among Jewish CD patients, as well as in Hungarian population.

The influence of active smoking on disease progression is poorly characterized mainly because of the heterogeneity of disease phenotypes and because smoking status has only been assessed at the time of disease diagnosis but not later on, leading to controversial results. Therefore, the aim of our study was to evaluate the influence of active smoking on phenotypic changes based on the Montreal's classification basis as well as on the therapeutic requirements, in a cohort of CD patients who were followed-up right from disease diagnosis.

2. Patients and methods

2.1. Study population and data collection

CD patients diagnosed between January 1994 and December 2003 were identified from the Inflammatory Bowel Disease (IBD) databases of three Spanish tertiary centres. Only those patients who were diagnosed, treated, and followed in the same centre were included. Diagnosis of CD was based on the conventional Lennard-Jones criteria. Demographic, epidemiological, and clinical features (including treatment with steroids, immunomodulators, biological agents, or surgery, as well as changes in the Montreal's classification during the follow-up period) were collected from diagnosis until October 2008, loss of follow-up, or patient's death. A careful history of smoking habit (recording dates of starting and stopping smoking) was obtained from medical records or by telephone call, if this was not available or for patients that had not visited in the outpatient clinic within 6 months prior to data compilation.

For the purpose of this study, we defined non-smokers as those patients who had never smoked or smoked less than 7 cigarettes/week, and former smokers as those that had given up smoking at least 12 months before diagnosis in agreement with previous studies. Those patients who smoked at CD diagnosis or within the previous year but who quit smoking for more than 12 months during the follow-up period were considered as quitters. In all other situations patients were considered to be active smokers. In order to assess the influence of heaviness of smoking, the number of cigarettes per day was also recorded. Heavy smokers were those who smoked 15 or more cigarettes/day, taking into account the increased risk that has been found within this threshold in CD patients. However, due to the retrospective design of the study, this variable was only available at CD diagnosis but not thereafter. Treatment requirements at baseline included all treatments started within the first three months after disease diagnosis.

2.2. Study outcomes

To assess the impact of smoking status on disease outcomes we arbitrarily defined some major disease-related events that included the development of any stricturing and/or penetrating disease complication (bowel strictures, intra-abdominal penetrating complications, or perianal disease), and therapeutic requirements (introduction of immunomodulators -thiopurines or methotrexate-, biological agents -infliximab or adalimumab-, and intestinal resection). To define stricturing or penetrating disease behaviour at disease presentation or during follow-up, we used the Montreal's classification criteria. For each of these events, patients were classified according to their smoking status at the time the event occurred. Patients were classified according to their smoking status at CD diagnosis if no event occurred by the end of the follow-up period. In agreement with smoking status definitions, for patients who quit or started smoking during the study period, their follow-up finished one year after their change in smoking status. While steroids have been the widest used therapy in CD, we did not consider steroid use as a major-disease related event. Hence, we did not collect the time for the first course of steroids but the total time on steroids.

This was an observational study according to the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the Institutional Review Board of the steering centre (Hospital Universitari Germans Trias i Pujol).

2.3. Statistical analysis

Descriptive statistics are expressed as percentages for qualitative data and mean with standard deviation or median and interquartile range (IQR) for quantitative data. Univariate
analysis (Chi-squared test and Mann–Whitney test) was used to evaluate differences in baseline characteristics. Two sided \( P \)-values less than 0.05 were considered significant. Time to each major disease-related event was compared between smokers and non-smokers using the Kaplan–Meier method from the date of CD diagnosis to the date of each event or end of follow-up. The impact of smoking status in each event was assessed using the log rank test, or linear regression model for time on steroids. As the impact of smoking has been reported to be influenced by disease location and gender, a Cox proportional-hazards regression was performed. It included potential confounding variables, in the case of those major disease-related events in which log rank test \( P \) value was <0.2, as well as year of diagnosis, as it may influence the availability of immunosuppressive or biological therapy. All statistical tests were two-tailed and were performed using the SPSS 18.0 package for Windows (Inc. Chicago IL, USA).

3. Results

3.1. Smoking status and disease presentation

A total of 259 patients were included in the study. Regarding smoking status at disease diagnosis, 131 patients (50.5%) were active smokers (median of 15 cigarettes/day, IQR 10–20), 13 patients (5%) were former smokers (median time since quitting smoking until CD diagnosis 108 months, IQR 30–180) and 115 patients (44.4%) were non-smokers.

Given that former smokers represented a minority in the study group, we arbitrarily decided to exclude them from comparative analyses. Baseline characteristics of the main groups (active smokers vs. non-smokers) are shown in Table 1. There were neither differences in demographic features nor the pattern of disease presentation between active smokers and non-smokers. Similar results (not shown) were obtained when heaviness of smoking was considered (29% heavy smokers).

3.2. Disease-related events during follow-up

The median follow-up of the whole cohort was 91 months (IQR 70–139) with no significant differences between smokers and non-smokers. At the end of follow-up, 48 out of 183 patients (26%) with initial inflammatory pattern changed their disease behaviour: 24/183 (13%) to stricturing and 24/183 (13%) to penetrating pattern. Additionally, 14% (30/221) of patients without perianal disease at diagnosis developed perianal lesions during follow-up.

In terms of therapeutic requirements, 183 (74%) patients used steroids, 163 (66%) immunomodulators, 49 (20%) anti-TNF agents, and 92 (37%) patients required intestinal resection during follow-up. Smokers were exposed to steroids for significantly longer periods of time (9 months, IQR 3–15) than non-smokers (4 months, IQR 0–9; \( P=0.031 \)) but this effect could not be maintained when analysing time on steroids with a linear regression model, including confounding variables (year of diagnosis, age, gender; \( P=0.26 \)).

The rates of major disease-related events according to smoking status (active vs. non-smoker) during follow-up are shown in Figures 1 and 2. Only one patient with severe aortic stenosis died during the follow-up because of congestive heart failure.

Although \( P \) values <0.05 were obtained in the log-rank test when comparing survival with anti-TNF requirement (Table 2), Cox regression analysis ruled out any impact of smoking status on major disease-related events when potential confounding variables were included in the model (Table 3). Perianal disease and year of CD diagnosis were the only independent predictors of using anti-TNF agents, whereas perianal disease, year of CD diagnosis and also disease location were predictors of the introduction of immunomodulators. When taking into account heaviness of smoking at diagnosis, no differences

![Figure 1](image-url) Disease-related events according smoking status at the time of event.
were noted with changes of Montreal classification (development of strictures, fistulae or perianal disease) or requirements of immunomodulators, biological therapy or resectional surgery between light and heavy smokers upon follow-up.

3.3. Clinical outcomes in former smokers and quitters

As previously mentioned, 13 patients (5% of the whole cohort) were former smokers at the time of CD diagnosis. Disease location was colonic in 5, ileal in 3 and ileocolonic in the remaining 5 patients. Most of them (11/13 patients) had an initial inflammatory pattern and 2 were diagnosed with perianal disease. After a median follow-up of 89 months (IQR 66.5–130), 5 patients changed disease behavioural pattern (3 to stricturing and 2 to penetrating disease) and 4 patients developed perianal disease. Nine patients required immunomodulators, three anti-TNF agents and three underwent intestinal resection.

Among initial smokers, only 30 patients (12%) quit smoking, most of them (82%) after developing stricturing or penetrating complications and/or after immunomodulators or biologicals were introduced. This finding suggests that the occurrence of such events during follow-up may be the main reason for quitting. Sixty-three percent of quitters (19/30) had an inflammatory pattern at the time they met the criteria for "quitters" and after a median follow-up of 96 months (IQR 75–141.5), four of them changed their initial pattern (two to penetrating and two to stricturing disease) and three developed perianal disease. Twelve patients required immunomodulators, three anti-TNF agents (two for luminal disease, one for perianal disease) and five underwent intestinal resection (Figure 3). After a median follow-up of 72 months (IQR 55–148.5), only five of the quitters did not present with any major disease-related event.

4. Discussion

While smoking is the best-characterized environmental factor associated with a higher risk for CD development, its impact on the disease course remains controversial due to several reasons. Firstly, the standardization of phenotypic disease changes by means of the Vienna or the Montreal classification has been only used in a few studies evaluating the effect of smoking on disease progression. Second, most studies characterize smoking status only at disease diagnosis but not at the time a particular event occurs, underestimating the real impact of tobacco exposure or withdrawal. Third, there is only one prospective study to date that looked into the impact of smoking cessation on the course of CD. All these

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**Table 2** Cumulative probabilities to remain free of each major disease-related event.

| Major disease-related event | Months | P
|-----------------------------|--------|-------
|                            | 12     | 60    | 120   | 0.276 |
| Stricturing disease         | AS     | 0.934 | 0.815 | 0.745 |
|                            | NS     | 0.949 | 0.836 | 0.791 |
| Penetrating disease         | AS     | 0.958 | 0.825 | 0.717 | 0.884 |
|                            | NS     | 0.935 | 0.828 | 0.788 |
| Immunomodulators            | AS     | 0.746 | 0.432 | 0.290 | 0.155 |
|                            | NS     | 0.784 | 0.507 | 0.398 |
| Intestinal resection        | AS     | 0.846 | 0.719 | 0.615 | 0.355 |
|                            | NS     | 0.784 | 0.654 | 0.607 |
| Perianal disease            | AS     | 0.966 | 0.875 | 0.807 | 0.078 |
|                            | NS     | 0.970 | 0.931 | 0.918 |
| Anti-TNF therapy            | AS     | 0.947 | 0.825 | 0.713 | 0.031 |
|                            | NS     | 0.982 | 0.928 | 0.833 |

AS = active smokers; NS: non-smokers.
reasons may explain the reported conflicting results reported when assessing the real impact of smoking on disease evolution. On that note, the strengths of our study are in the use of the Montreal classification for patients' categorization, the analysis of major disease-related events considering smoking status at each event and that our study has a long follow-up. Nevertheless, as patients came from tertiary referral centres, selection bias cannot be completely excluded.

Given its retrospective approach, it should be considered that our study might underestimate the beneficial effect of smoking cessation. However, we did not address the impact of smoking cessation as represented by former smokers and quitters because former smokers accounted for too small group. In addition, quitters were included as active smokers in the analysis of each major-disease related event until the event occurred or after one year from quitting (if no event occurred) and most of them developed at least one of these major events before giving up smoking. Thus, the real follow-up of quitters should have started one year on after quitting, resulting to shorter follow-up periods. However, it should be kept in mind that we used strict criteria to define former smokers and quitters, as it has been suggested that beneficial effects of quitting smoking on CD are only apparent from one year later. In our study only 12% of initial smokers quit smoking after disease diagnosis. This figure is identical to that obtained after repeated counselling and easy access to a smoking cessation program in the landmark study by Cosnes et al.

In agreement with other studies, no differences in disease behaviour at diagnosis with regards to smoking habits were found. We also failed to show differences in disease location in relation to smoking, a finding reported by some authors in which a lesser ileal involvement among non-smokers or a lesser colonic disease among smokers were found. Although it has been suggested that disease onset might be delayed among former smokers, we were unable to find such a relationship. As the effect of tobacco consumption has been shown to be dose dependent, we assessed this effect in phenotypic features at diagnosis but no further effect in addition to active smoking was found.

A trend towards an association between active smoking and perianal disease on follow-up was noticed, but this was not confirmed when potential confounding variables were included in the logistic regression analysis. Few data are available regarding risk factors for perianal disease. Louis et al. reported that active smoking was significantly more frequent among patients with perianal disease than in those with intrabdominal penetrating disease. However, in a study with a closer design to ours, no risk factor for perianal disease was found. In our study, active smokers did not present a higher risk of developing penetrating or structuring complications on follow-up. In this sense, other studies have shown that disease location but not smoking was independently associated with changes on disease behaviour, although it seems that smoking at the time of diagnosis can be associated with an earlier change in disease pattern. As a consequence of this similar clinical evolution, we did not find any impact of active smoking on major therapeutic requirements.

Many reasons may contribute to the mild influence of active smoking found in our study. First, it has been shown that the impact of smoking on IBD is not the same all over the world. The association between smoking and IBD type has not been demonstrated among Jewish, South-Asian or Hungarian communities. However, only a minimal proportion of our IBD patients were of non-Caucasian origin, and most Spanish Jews are Sephardic (with an IBD incidence significantly lower than American- or European-born Ashkenazi Jews). On the other hand, it has been suggested that immunosuppressive therapy may neutralize the effect of smoking on the need for surgery. Hence, it could be hypothesized that the low impact of active smoking on disease outcomes was due to a more intensive therapeutic approach in our patients. However, this was not the case as long as only a few patients used immunomodulators or anti-TNF agents within the first three months upon diagnosis (7% and 1%, respectively).

In summary, we did not find any relevant differences at clinical presentation or in the disease course between active smokers and never smokers. From this point of view, active smoking may not be considered as a general risk factor for poorer outcomes at disease diagnosis. It is likely that, in those patients with a more aggressive disease, active smoking worsens disease prognosis as it occurs in the postsurgical setting. Although scarce evidence is available yet, the benefit of smoking cessation (resulting in a clinical outcome even better than in never smokers) would suggest a different pathogenetic background between those patients who develop CD while smoking and those who never smoked (in whom other genetic or environmental factors might be of major influence—i.e. diet, stress, infections...). To ascertain the real effect of smoking cessation, better policies to improve the rate of quitters as well as studies with a larger group of former smokers are warranted.

**Author’s declaration of interests**

Authors declare no conflicts of interest.

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