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EDITORIAL

Smoking in inflammatory bowel diseases: Good, bad or ugly?

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Abstract

Smoking is an important environmental factor in inflammatory bowel disease (IBD), having different effects in ulcerative colitis (UC) and Crohn's disease (CD). A recent meta-analysis partially confirmed previous findings that smoking was found to be protective against ulcerative colitis and, after onset of the disease, might improve its course, decreasing the need for colectomy. However, smoking increases the risk of developing Crohn's disease and worsens its course, increasing the need for steroids, immunosuppressants and re-operations. Smoking cessation aggravates ulcerative colitis and improves Crohn's disease. Data are however, largely conflictive as well as the potential mechanisms involved in this dual relationship are still unknown. In this review article, the authors review the role of smoking in inflammatory bowel diseases.

Key words: Smoking; Crohn; Ulcerative colitis; Phenotype

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INTRODUCTION

The pathogenesis of ulcerative colitis (UC) and Crohn's disease (CD) has only been partly understood. Inflammatory bowel disease (IBD) is a multifactorial disease with probable genetic heterogeneity[1,2]. In addition, several environmental (eg, diet, smoking, measles or appendectomy) risk factors may contribute to its pathogenesis.

During the past decades, the incidence pattern of both diseases has changed significantly[3], showing some common but also quite distinct characteristics for the two disorders. Differences in geographic distribution, and particularly changes in incidence over time within one area, may provide insight into possible etiological factors[4]. It is very unlikely however, that these rapid changes attributed to variations in the genetic factors. On the contrary, environmental factors are likely to play an important role. Diet, as a luminal antigen, was thought to be an important factor in the pathogenesis of IBD[1,5]. In the last two decades, there has been a shift in the lifestyle in Eastern Europe, Asia, and Central America, as the lifestyle, including the diet, became more "Westernized". This possibility is further supported by the differences in incidence and prevalence found within one region.

A further important environmental factor studied extensively in both diseases is smoking. The link between smoking and (IBD) was first made in 1982 when Harries *et al*[6] noticed a low proportion of ulcerative colitis patients were smokers. Two years later a case-control study by Somerville *et al*[7] reported that the relative risk of developing Crohn's disease was 4.8 in those who smoked before disease onset, and 3.5 for those with a current smoking habit. In recent years, IBD has been classified into subtypes/phenotypes that are distinct and based on age at onset, disease location, and clinical behaviour. Knowledge of this heterogeneity has led to the re-examination of genetic and environmental influences on IBD. The relationship between smoking and IBD however, is far more complex than previously realized as clinical subtypes have become apparent. In this article, the authors give an updated review on the role of smoking in IBD.

EFFECT OF SMOKING CESSASION AND SMOKING ON THE RISK OF DEVELOPING INFLAMMATORY BOWEL DISEASES

Risk for developing ulcerative colitis

Ulcerative colitis affects predominantly non-smokers and former smokers. The percentage of current smokers (smoking more than seven cigarettes per week) in a group of patients with UC is about 10%-15%[8,9]. These percentages are significantly lower than those observed in a control population matched for sex and age (25%-40%). The meta-analysis by Calkins[10], conducted more than 15 years ago, yielded a pooled odds ratio of 0.41 (0.34-0.48) for current smokers compared with lifetime non-smokers. The effect of smoking seems to only postpone the event, as the relative risk of UC was also higher in former smokers (OR: 1.64; 95% CI: 1.36-1.98). In a recent meta-

analysis by Mahid *et al*[11] comparable values were reported, which also included new available data. Current smoking decreased the risk for UC (OR: 0.58; 95% CI: 0.45-0.75), while former smoking was associated with an increased risk (OR: 1.79; 95% CI: 1.37-2.34). Interestingly, in patients who stopped smoking, UC developed in 52% of patients, in the first three years after cessation, as reported by Motley *et al*[12] in concordance with other studies[13]. In contrast, active smoking in early childhood was associated with a gradually increased risk for developing UC (OR for smoking start < 10 years: 7.02 and < 15 years: 3.46)[14]. The same trend was observed for passive smoking by the mother (OR: 1.53, 95% CI: 0.93-2.49).

The relationship between smoking and ulcerative colitis has also been examined at a population level. The prevalence of UC was five-fold increased in patients from the Mormon Church in Britain and Ireland, where smoking is strongly discouraged, compared with that of the general population. In contrast, CD was equally as common[15]. In addition, a review of 56 epidemiological studies in Sweden over the time period from 1930 to 1990[16] demonstrated that the sex distribution of UC had changed from an earlier female predominance to a later male predominance. Over the same period, the proportions of smokers and ex-smokers among men and women have undergone reciprocal changes with an increase in women smokers relative to men, while the same change in predominance was not observed in contemporary pediatric studies. Somewhat contradictory, in a recent population-based case-control study[17], among others, ever smoking was also associated with increased risk (1.66; 95% CI: 1.17-2.35).

There are only very few data regarding the effect of smoking in indeterminate colitis[8,18]. The effect seems to be similar to that observed in UC, that is, a protective effect against the development of colitis and a possible beneficial effect on disease course.

Risk for developing Crohn's disease

The percentage of current smokers in a group of patients with CD is significantly higher than that observed in a control population matched for sex and age (45%-55% *vs* 30%-40%)[19]. In concordance, an increased life-time risk was reported in current smokers when compared to non-smokers by both Calkins *et al*[10] (OR: 2.0; 95% CI: 1.65-2.47) and in the more recent meta-analysis by Mahid *et al* (OR: 1.76; 95% CI: 1.40-2.22).

Compared to never-smokers, former smokers were reported to have an increased risk of developing CD[10]. This risk decreased only after four years of having quit smoking. In a recent population-based study by Bernstein *et al*[19], similar data were reported, both current smoking (OR: 1.96) and ever smoking (OR: 1.78) were associated with increased risk to develop CD. However, this later association could not be replicated in the recent meta-analysis by Mahid *et al* although a trend was observed ($P = 0.08$). In contrast, ever smoking was associated with increased risk (OR: 1.61; 95% CI: 1.27-2.03). The effect of passive smoking remains controversial[20]. In one recent prospective study[14] CD patients were more likely than controls to have prenatal smoke exposure (OR: 1.72; 95% CI: 1.1-2.71). In addition, the passive smoke exposure during childhood, with parents or other household members being smokers (OR: 2.04; 95% CI: 1.28-3.31) was also associated with increased risk, in concordance with previous data by Lashner *et al*[21].

EFFECT OF SMOKING AND ITS CESSATION ON DISEASE PHENOTYPE AND COURSE

Effect of smoking and its cessation on clinical course and extent of ulcerative colitis

Although the extent at diagnosis is not affected by smoking, UC usually runs a more benign disease course in smokers compared to non-smokers. Flare-up, hospitalization rates[13], the need for oral steroids[22] and colectomy rates[22,23], are reported to be lower, while age at onset is older in smokers compared to non-smokers, though not in all studies. Relapse rates are lower in patients who began smoking after the diagnosis of UC[24]. In concordance, in a recent Europe-wide population-based cohort[25] the relapse rate was lower (Hazard Ratio: 0.8; 95% CI: 0.6-0.9) in smokers compared to non-smokers, while it was higher in women. In a retrospective analysis of a large series of patients with UC, current smoking was found to decrease the 10-year cumulative colectomy risk from 0.42 to 0.32[22]. In concordance, a meta-analysis of several large series with a total of 1489 UC patients also found the risk for colectomy to be lower (OR: 0.57; 95% CI: 0.38-0.85) in current smokers compared to non-smokers[26].

In addition, in smokers with distal UC at diagnosis, the proximal extension of the disease is less frequent[22,27], while primary sclerosing cholangitis is observed almost exclusively in non-smokers[28]. Disease regression[29] was also more likely to occur in smokers compared to non-smokers or ex-smokers 5 years (30% *vs* 5% *vs* 8%), but not 10 years after the diagnosis. Also, those with extensive disease were the lightest smokers, whereas those with healthy colons were the heaviest smokers. Finally, current smokers have a lower incidence of pouchitis following coloproctectomy with ileal reservoir when compared to non-smokers[30,31].

In contrast, intriguing new data by Aldhous *et al*[29] showed that current and non-smokers had an almost identical age at onset (31.1 *vs* 29.4 years) and this was delayed only in ex-smokers (46.5 years). Colectomy rates were not different. This group however, had a greater exposure to smoking compared to the group of current smokers.

A link between smoking habits and the course of UC has also been reported. In intermittent smokers, many patients note symptom exacerbation when they stop smoking, followed by symptom relief when they smoke again[12]. In contrast, almost half of the intermittent smokers thought that their colitis symptoms improved while smoking at least 20 cigarettes per day[32]. Moreover, smokers with UC who quit, experience an increase in disease activity, hospital admissions, and the need for major

medical therapy (oral steroids, immunosuppressants), within the first years following the cessation of smoking[33]. However, the risk of colectomy in the short-term was not increased compared to matched non-smokers and continuing smokers.

Effect of smoking and its cessation on disease location, behaviour, and disease progression in Crohn's disease

Smoking is associated with disease location: most, but not all, studies report a higher prevalence of ileal disease and a lower prevalence of colonic involvement in smokers[34-36].

A recent review[36] and previous data have demonstrated that smoking, when measured up to the time point of disease behavior classification, was associated more frequently with complicated disease, penetrating intestinal complications[34,37,38], and greater likelihood to progress to complicated disease, as defined by development of strictures or fistulae[36], and a higher relapse rate[2,39]. Of note, previous severity of the disease, as assessed from the therapeutics needs, was found to be similar in young patients who started smoking and in their matched controls[10]. The need for steroids and immunosuppressants is increased in smokers compared to non-smokers[35]. Whether the daily dose (eg, more than 15 cigarettes per day) or the total pack years smoked is more important in the abovementioned associations remains questionable.

The risk of surgery as well as the risk for further resections during disease course is also higher in smokers, in most studies[34,41,42]. These findings were reinforced by Cottone *et al*[43] who have shown that macroscopic lesions on the ileal site of the anastomosis were observed 1 year after surgery in 70% of smokers, versus 35% of non-smokers and 27% of ex-smokers. The risk of symptomatic postoperative recurrence was more marked in heavy smokers than in mild smokers[43]. Noteworthy, immunosuppressive therapy was found to neutralize the effect of smoking on the need for surgery[40].

However, the harmful effect of smoking on the course of CD is not a universal finding. Studies in patients from Israel and Hungary have not found differences in the need for surgery or for immunosuppressants between smokers and non-smokers[2,44,45], and patients with only colonic involvement are less sensitive to the harmful effects of smoking[8]. Finally, the development and severity of perineal complications do not seem to be influenced by the smoking status[39].

In a recent paper by Aldhous *et al*[46] using the Montreal classification, the harmful effect of smoking was only partially confirmed. Although current smoking was associated with less colonic disease, the smoking habits at diagnosis were not associated with time to development of stricturing disease, internal penetrating disease, perianal penetrating disease, or time to first surgery. Age at diagnosis was also similar in current smokers and non-smokers (28.3 years and 28.9 years) and was only delayed in ex-smokers (43.2 years). However, the way in which they measured tobacco exposure was different from previous studies. "Current smokers" were defined as those who were smoking at the time of diagnosis or event (penetrating or stricturing complication) and "ex-smokers" had stopped for at least one year before the diagnosis or event (eg, a patient could have continued smoking up to 1 year before developing a complication but was considered an "ex-smoker").

The rationale for this may be that after surgery, the risk of endoscopic and clinical recurrence in former smokers who have not smoked for at least 1 year is similar to that of non-smokers[43]. Similarly, CD activity in ex-smokers is not different from that of non-smokers, and is less marked than in current smokers[39]. The beneficial effect of quitting smoking might be seen within the year following cessation. A large prospective intervention study by Cosnes *et al*[47] performed in a selected group of 59 patients who stopped smoking following a smoking cessation intervention, examined the disease course from 1 year following smoking cessation onwards. The flare-up rate, therapeutic needs, and disease severity were similar in patients who had never smoked and in those who stopped smoking, and both had a better course than current smokers. Quitters had a 65% lower risk of flare-up compared to continuing smokers. The need for corticosteroids, immunosuppressive therapy, or a dose increase of immunosuppressants was also lower. Interestingly, after quitting, some patients developed UC-like lesions of the distal colon, whereas previously they had typical CD.

Finally, in a prospective study during pregnancy, the improvement of disease activity was observed only in smokers, in parallel with a decrease in the daily cigarette smoking[48].

The role of gender, familial disease, and ethnicity

The effect of smoking is to some extent different between male and female patients. In CD, women are affected more drastically by smoking. The relative risk associated with smoking for women may be greater than for men: one study demonstrated a three-fold difference[20].

This was already demonstrated by Sutherland *et al*[42] in 1990, who reported that in a group of 174 patients who required surgery for Crohn's disease, smokers had a 29% greater risk than non-smokers, over 10 years. However, the increased risk was more marked in females than males (OR: 4.2; 95% CI 2.0-4.2 in females and 1.5; 95% CI 0.8-0.6 in males). In Crohn's colitis, smoking is clearly harmful for women, whereas colitis in men is not affected by smoking[8]. In the study by Cosnes *et al* current smoking hastened disease onset (from 35 to 29 years of age) and increased the need for immunosuppressants, only in women.

In UC, current and ex-smoking delayed disease onset in men (from 25 to 42 years of age), but not in women[50]. Similarly, when compared to non-smokers, male UC patients who smoked ran a more benign disease course as assessed by the decreased need for immunosuppressive therapy (8% *vs* 26%), whereas this difference was not observed in females as reported by Cosnes *et al*[8] and again smoking delayed the onset of disease, only in males.

Thus, the effect of smoking in both UC and CD seems to be modulated by gender, with women being affected more disadvantageously than men. This phenomenon deserves even more attention, since smoking habits are changing in the Western population, with a trend to a greater prevalence of smokers among young women[50]. A gender difference in smoking habits may be a possible

Table 1 Smoking in IBD: Practice points

Ulcerative colitis (UC)	Crohn's disease (CD)
Current smoking decreases the risk for UC by app. 50%, in contrast former smoking is associated with an app. 2-fold increased risk	Both current and former smoking (presumable also passive smoke exposure during childhood) increases the risk of CD almost 2-fold
The protective effect is smaller in females	The risk is greater in females compared to males
Proximal extension of the disease is less likely in smokers as well as disease course is milder but the risk of lung cancer and vascular disease is higher	Smoking is associated with complicated (stricturing or penetrating) and ileal disease
Patients who stop smoking experience an increase in disease activity at least during the first year after cessation	Smokers with CD need more steroids, more immunosuppressants and more operations than non-smokers
The effect of smoking is similar in indeterminate colitis (less evidence is available)	Smoking cessation improves rapidly the course of CD
Nicotine-replacement therapies and antidepressants are useful in heavy smokers motivated to stop smoking	
Geographic differences exists (e.g. Israel, Korea)	

explanation, since women use more filtered cigarettes and lighter cigarettes, and might consequently have a higher relative exposure to smoke than to nicotine[51]. In addition, the negative effect of estrogens[52] on proinflammatory cytokine gene regulation and lymphocyte interactions might also play an important role.

In Israel, no association was reported between smoking and CD in Jewish patients, although the opposite association was found for UC[53]. Similarly, smoking was not associated to the risk for CD in some studies from Asia[54]. The reason why CD in Israeli Jews or Koreans is not as sensitive to smoking as in other populations is not clear. Explanations might include differences in genetic and/or environmental factors (eg, type of tobacco, way of smoking or other alimentary factors).

A further interesting question is whether the effect of smoking is similar in familial versus sporadic cases. Family studies have reported a high concordance rate within families, between smoking habits and the phenotype of IBD, CD developing in smokers, and UC in non-smokers[55]. The above association was refined in more recent studies. Tuvlin *et al*[56] reported that ex-smokers made up an increasing percentage of older patients diagnosed with UC, accounting for more than 35% of the attributable risk of late onset (> 45 years) UC and a large component of the second peak in diagnosis. In contrast, current smoking accounted for a large percentage of patients diagnosed at a younger age with familial CD but not with sporadic CD (Table 1).

MECHANISMS BEHIND THE EFFECT OF SMOKING ON IBD

The reason behind the opposite effects of smoking observed in CD and UC remain obscure. The effects of smoking and nicotine are numerous and since the pathogenesis of inflammatory bowel disease is only partially understood, any discussion on the possible mechanisms can only be speculative. In addition, although nicotine is thought to be the most important agent responsible for the effect of smoking, one should be careful, as some effects usually associated with smoking may not follow the use of therapeutic nicotine formulations. Of note in most studies, side-effects (nausea, headache, dermatitis) of nicotine therapies were frequent and tended to be greater than the clinical benefit[57].

Smoking has numerous specific and non-specific effects. It has been shown to affect the immune system, by influencing cellular and humoral immunity. Nicotine has been shown to decrease the synthesis of proinflammatory molecules, for example, interleukin (IL)-1β and TNFα by mouse colonic mucosa as well as the production of mucosal eicosanoids[58] and some proinflammatory cytokines by human mononuclear cells (eg, IL-2[59], IL-8, and TNFα[60]) partly by its action on the nicotinic acetylcholine receptor a7 subunit. Further evidence for anti-inflammatory properties comes from a surgically-induced ileus model, where carbon monoxide-treated mice were shown to have three times higher levels of IL-10. Macrophages from smokers express a selective functional deficiency in their ability to kill intracellular bacteria[61]. Finally, chronic exposure of rats to nicotine inhibits the antibody-forming cell response, impairs the antigen-mediated signaling in T-cells and induces T-cell anergy[62]. Other effects of nicotine or smoking on the intestine include the alteration of gut motility, the reduction of smooth muscle tone and contractility (modulated by nitric oxide)[63], decreased permeability[64], and alterations in the microcirculation[65], Furthermore, smoking also increases lipid peroxidation.

In UC, the colonic mucosal layer is thin or absent, in contrast to CD where it is significantly thicker[66], with nicotine having been shown to increase mucin synthesis[67,68]. Smokers with IBD have a significant reduction in mucosal cytokine levels, specifically, IL-1b and IL-8 in patients with UC, and IL-8 in patients with CD[69]. Beneficial effects of nicotine in active UC may be associated with a decrease in IL-8 expression. Hypoperfusion of the rectum and of acutely damaged colonic tissue may play an additional role[70]. On the contrary, in CD, several plasma antioxidant parameters are altered, the total radical-trapping antioxidant potential is decreased[71], and abnormalities are present in the microvasculature[65]. Smoking through increased carbon monoxide concentration might amplify the impairment in the vasodilation capacity of chronically inflamed microvessels, resulting in ischemia and perpetuating ulceration and fibrosis[70]. Furthermore, smoking is known to increase the thrombotic potential associated with vascular damage. A defect in bacterial clearance or macrophage deficiency might also play an important role.

CONCLUSION

In conclusion, smoking plays a dual role in IBD by increasing the risk for CD and decreasing that of UC. In an individual who is genetically at risk for IBD, smoking might be an important factor in determining disease phenotype. In addition, smoking also affects the disease course. It improves UC and worsens CD, more markedly in women, while smoking cessation is followed rapidly by a reversed effect. Since smoking is associated with several additional deleterious effects (eg, cardiovascular, lung cancer risk), gastroenterologists should encourage both UC and CD patients to quit smoking. Before stopping, UC patients should be informed about the potential risk of increase in disease activity, without a higher risk for surgery. In CD, the benefit of smoking cessation is well-proven, since patients who continue to smoke have a more severe course of disease with more complications, while ex-smokers run a similar course of disease to non-smokers.

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