Abstract

Smoking is a major environmental factor that interferes in the establishment and clinical course of ulcerative colitis (UC). Firstly, the risk of smoking status impact in the development of UC is reviewed, showing that current smoking has a protective association with UC. Similarly, being a former smoker is associated with an increased risk of UC. The concept that smoking could have a role in determining the inflammatory bowel disease phenotype is also discussed. Gender may also be considered, as current smoking delays disease onset in men but not in women. No clear conclusions can be driven from the studies trying to clarify whether childhood passive smoking or prenatal smoke exposure have an influence on the development of UC, mainly due to methodology flaws. The influence of smoking on disease course is the second aspect analysed. Some studies show a disease course more benign in smokers than in non-smokers, with lower hospitalizations rates, less flare-ups, lower use of oral steroids and even less risk of proximal extension. This is not verified by some other studies. Similarly, the rate of colectomy does not seem to be determined by the smoking status of the patient. The third issue reviewed is the use of nicotine as a therapeutic agent. The place of nicotine in the treatment of UC is unclear, although it could be useful in selected cases, particularly in recent ex-smokers with moderate but refractory attacks of UC. Finally, the effect of smoking cessation in UC patients is summarised. Given that smoking represents a major worldwide cause of death, for inpatients with UC the risks of smoking far outweigh any possible benefit. Thus, physicians should advise, encourage and assist UC patients who smoke to quit.

INTRODUCTION

The development of inflammatory bowel disease (IBD) is the result of an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host. Some environmental factors, such as cigarette smoking and appendectomy, have been shown to play a significant role in the pathogenesis of IBD. Cigarette smoking may cause lung cancer, atherosclerotic vascular disease, other kinds of cancers and chronic obstructive pulmonary disease.
Nowadays, smoking represents a major cause of preventable morbidity and is probably the most important and preventable cause of premature mortality in developed and developing countries.

As smoking is a major environmental factor that interferes in the clinical course of ulcerative colitis (UC), in this article we will review its influence on patients with UC.

**RISK OF DEVELOPING UC**

It is now fully accepted that UC predominantly affects non-smokers and former smokers, and that smoking exerts a universal protective effect against developing UC\(^1\).

This relationship between smoking and UC has been described for more than 30 years. The first to report this association was Samuelsson\(^1\), who noted a lack of smokers among UC patients compared with matched control subjects. The author attributed this observation to interaction with medication rather than to pathogenesis. In 1982, Harries et al\(^3\) confirmed this observation; in a study on 23 UC patients, they found only 8% were current smokers compared with 44% of matched control subjects [patients with Crohn’s disease (CD) or a cohort evaluated for fractures]. After the first reports, numerous other studies also confirmed this association. The first meta-analysis, including nine case-control studies, revealed a pooled odds ratio (OR) for non-smoking as the risk factor for acquiring UC of 2.9 (95% CI: 2.6-3.2)\(^5\). The authors also demonstrated a higher risk for former smokers compared to non-smokers with a pooled OR of 1.64 (95% CI: 1.36-1.98). Additionally, they found a dose-response association with an overall pattern of decreased risk of disease with increased level of smoking. A subsequent meta-analysis\(^6\) that included new information from 11741 patients with UC in 13 studies confirmed the previous data. When they compared current smoking with never smoking, all studies, with the exception of one, found an OR of less than 1.0, indicating a protective association of current smoking and UC. Current smoking decreased the risk for UC (OR: 0.58, 95% CI: 0.45-0.75), suggesting that current smoking is associated with an approximately 42% reduced risk of an UC diagnosis. In contrast to current smoking, when former smokers were compared with never smokers among patients with UC vs controls, being a former smoker was associated with an increased risk of UC, with an overall OR of 1.79 (95% CI: 1.37-2.34).

The influence of smoking in genetically predisposed IBD patients has been analyzed in family studies. It is well known that there is high concordance within a family between smoking habits and the IBD phenotype, with UC developing in non-smokers and CD in smokers\(^3\). Thus, some of the apparent protection that smoking exerts on sporadic UC may be due not only to a therapeutic effect of tobacco usage, but rather that in some instances, it is CD rather than UC which develops as a result of the influence of smoking on the pathogenic processes. Bridger et al\(^6\) examined 89 sibling pairs with CD or UC discordant for both smoking and IBD phenotype to investigate whether smoking determines the type of IBD that develops in individuals with very similar genetic susceptibility. Of 89 sibling pairs discordant for smoking at diagnosis, 23 were also discordant for disease type. In 21 of these, CD occurred in the smoker and UC in the non-smoker, suggesting that tobacco consumption may act on the IBD genetic predisposition to shift the phenotype from UC towards CD. This role of smoking habits on the IBD phenotype has been confirmed in twins\(^7\). Among 103 pairs (at least one twin who suffered from IBD), the frequency of smokers was lower among twins with UC. Furthermore, smoking habits were found to be of significance for discordance of disease.

Another issue that should be noted is whether gender may influence the effect of tobacco smoking on UC. Motley et al\(^8\) noticed that current smoking delayed disease onset in men but not in women. The effect of gender was also described in the aforementioned article by Bridger et al\(^6\), who noted different effects of smoking on the incidence of CD or UC in females and males. This paper showed more pronounced protection from UC (OR 0.18, 95% CI: 0.11-0.3) in females smoking at diagnosis compared with non-smokers (OR 0.47, 95% CI: 0.28-0.79). Later, Cosnes et al\(^9\) studied a cohort of 1784 consecutive adult patients (978 with UC). In this study, the beneficial effect of smoking in UC was modulated importantly by gender: they described a more marked increase in disease presentation in men during the few years after smoking cessation.

One important question that should be resolved is whether childhood passive smoking or prenatal smoke exposure has the same influence on the development of UC. This issue was analyzed in a meta-analysis of 13 studies\(^10\); the results revealed that, in contrast to the inverse association between active smoking and UC development, there was no significant association between childhood passive smoke exposure or prenatal smoke exposure and the development of UC. A dose-response relationship is a possible explanation for the failure of this meta-analysis to show a protective effect of childhood passive smoke exposure on UC; thus it is possible that the level of exposure does not reach a threshold level which is required for the protective effect that has been well documented in active smokers. Moreover, the size of the studies regarding prenatal smoke exposure and the development of IBD were too small to reach a definitive conclusion. After the publication of the meta-analysis, van der Heide et al\(^11\) published a new study that addressed this issue; the authors did not find that passive smoking had a beneficial effect. Furthermore, passive smoking UC patients had a higher prevalence of ileal disease (pouchitis and backwash ileitis) than non-passive smoking UC patients.

All the presented data support the view that current smoking is associated with a low risk of UC, but before drawing conclusions we should be aware of the possible
bias that may be present in the studies analyzed, such as differences in study methods, measurement error, or a lack of verification of self-reported smoking status. The lack of uniformity in smoking definitions is probably a serious weakness in many of the published studies. Another important issue that should be noted is that most of the studies are based strictly on the effects of smoking on the non-Jewish white population. Certain races have not demonstrated associations between smoking behaviors and IBD, suggesting that different races may have varying degrees of susceptibility to IBD, although these differences are probably more important in CD than in UC. In fact, in Israeli Jewish patients, there was no association between smoking and CD patients, although the opposite association exists in UC.

**INFLUENCE OF SMOKING ON DISEASE COURSE**

Active tobacco smoking has a protective effect on the severity of UC; the disease course is more benign in smokers than in non-smokers. Flare-up, hospitalization rates, the need for oral steroids and, more importantly, colectomy rate are reported to be lower in smokers compared with non-smokers, though this has not been observed in all studies.

The link between smoking and colectomy in UC patients is controversial. In a retrospective analysis of a large series of UC patients, current smoking was found to decrease the 10-year cumulative colectomy risk from 0.42 to 0.32. A subsequent meta-analysis with a total of 1489 UC patients found the risk for colectomy to be lower (OR: 0.57, 95% CI: 0.38-0.85) in current smokers compared with non-smokers.

In agreement with these results, a population-based cohort study performed in Europe with 771 UC patients prospectively included and followed for 10 years revealed a lower relapse rate (Hazard ratio: 0.8, 95% CI: 0.6-0.9) in smokers compared with non-smokers. Another similar study carried out in the Netherlands by van der Heide et al. with 295 UC patients identified smoking after diagnosis as a protective factor for colectomy (OR 0.27, 95% CI: 0.11-0.67), whereas pancolitis at diagnosis (OR 3.18, 95% CI: 1.85-5.48) was a risk factor.

On the other hand, a study by Beaugerie et al. designed to determine the impact of cessation of smoking on the course of UC, analyzed the disease severity in 32 patients with UC who stopped smoking after the diagnosis compared with 32 non-smokers and 32 continuing smokers matched for sex, age, and age at onset. There was no significant difference in colectomy rate among quitters during the 5-year period after smoking cessation and either non-smokers or continuing smokers during the matched periods. Nevertheless, smokers who quit experienced 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.

As well as the study by Beaugerie et al., Boyko et al. reported a lower hospitalization rate in patients who were smoking at the onset of UC, but could not identify a difference in the colectomy rate between smokers and non-smokers.

In agreement with the presented data, improvements in symptoms and a milder course of disease have been reported in ex-smokers who returned to smoking. In fact, many patients noted symptom exacerbation when they stopped smoking, followed by symptom relief when they smoked again. Interestingly, some studies reported a gender association; when compared to non-smokers, male UC who smoked ran a more benign disease course as assessed by the decreased need for immunomodulators, whereas this difference was not observed in females. Additionally, smoking delayed the onset of the disease, although only in males.

Smoking seems to be a protective factor against proximal extension. In patients with distal UC at diagnosis, retrograde extension of the disease process was less frequent in smokers than in non-smokers. A retrospective analysis in France showed that in a subgroup of patients with limited disease at onset of symptoms, the percentage of smokers developing pancolitis was lower than among non-smokers. More recently, Meucci et al., in a cohort of 273 patients, described proximal extension of the disease in 27.1%. The cumulative rate of proximal extension was higher in non-smokers, in patients with more than three relapses per year and in patients requiring systemic steroid or immunosuppressive treatment.

Not all the studies could identify a protective effect of smoking on the retrograde extension of UC. Pica et al. retrospectively reviewed 138 patients with ulcerative proctitis; in this series, proximal extension of the disease was seen in 30% of patients. The prevalence of smoking habit was not higher in patients with extended disease.

Finally, it is important to note that many studies failed to identify a beneficial effect of smoking on the course of UC. For instance, Roth et al. included 102 consecutive patients in a survey to assess the natural history of the disease and to determine predictors of future disease severity at the time of diagnosis. Delay from symptoms to diagnosis of UC, gender, family history of IBD, smoking status and disease severity at the time of diagnosis did not significantly predict the disease severity. Similar results were described by Romberg-Camps et al. in a population-based survey designed to predict the disease course in 630 UC patients. In this study, disease severity, cumulative medication use, and “surgical” and “nonsurgical” recurrence rates were calculated as outcome parameters. A protective effect of smoking on disease recurrence in UC could not be confirmed in this study.

Tobacco smoking also influences other clinical scenarios in patients with UC. Smoking may also prevent the development of primary sclerosing cholangitis (PSC), or pouchitis after colectomy and ileal pouch anal anastomo-
Table 1  Studies of the use of nicotine in ulcerative colitis

| Ref. | Formulation | Dose (mg) | n | Type of disease | Study | Comparator | Results |
|------|-------------|-----------|---|----------------|-------|------------|---------|
| [44] | Nicotine gum | 4         | 1 | Active UC      | Uncontrolled | --        | 100%    |
| Perera et al. | Nicotine gum | 4         | 11| Active UC     | Uncontrolled | --       | 27%     |
| Watson et al. | Nicotine gum | --        | 10| Active UC     | Uncontrolled | --       | 100%    |
| Srivastava et al. | Transdermal nicotine | 22 | 18| Active UC   | Uncontrolled | --       | 78%     |
| Guslandi et al. | Transdermal nicotine | 15 | 3 | Active UC    | Uncontrolled | --       | 66%     |
| Guslandi et al. | Transdermal nicotine | 15 | 10| Active UC    | Uncontrolled | --       | 70%     |
| Lasnser et al. | Nicotine gum | 20        | 7 | Active UC    | Cross-over | Placebo  | NI 43% vs PL 0% |
| Pullan et al. | Transdermal nicotine | 15-25 | 72| Active UC | Controlled | Placebo  | NI 49% vs PL 24% |
| Sandborn et al. | Transdermal nicotine | 11-24 | 64| Active UC   | Controlled | Placebo  | NI 39% vs PL 9% |
| Thomas et al. | Transdermal nicotine | 15-25 | 61| Active UC    | Controlled | Prednisone | NI 20% vs PR 45% |
| Guslandi et al. | Transdermal nicotine | 15-38 | 38| UC in remission | Controlled | Prednisone  | NI 71% vs PR 88% |
| Thomas et al. | Transdermal nicotine | 15-80 | UC in remission | Controlled | Placebo  | NI 45% vs PL 50% |
| Green et al. | Nicotine enemas | 4        | 22| Active UC    | Uncontrolled | --       | 73%     |
| Sandborn et al. | Nicotine enemas | 6        | 7 | Active UC    | Uncontrolled | --       | 71%     |

NI: Nicotine; PL: Placebo; UC: Ulcerative colitis.

to the nicotine dose and leads to peak nicotine concentrations of approximately two thirds of those measured during smoking[39]. Nevertheless, compared with smoking cigarettes, no sharp increases in blood nicotine concentrations have been observed using transdermal application.

Topical administration of nicotine directly to the colon via enema or delayed release oral capsule formulations decrease the systemic absorption and side effects, and may be clinically beneficial. Nicotine is rapidly and extensively metabolized, primarily in the liver via the cytochrome P450 enzyme pathway[44,45]. When nicotine is ingested orally, bioavailability is low (20%-44%) due to the first pass hepatic metabolism[42,43].

A pharmacokinetic study in healthy volunteers demonstrated that nicotine tartrate administered as a liquid enema had low systemic absorption (mean systemic bioavailability for various formulations ranged from 15% to 25%) and was well tolerated after a single dose[42].

Uncontrolled studies reported that nicotine gum 4 mg, 5-7 sticks/d was beneficial in some ex-smokers with active UC[44-46] but, in contrast, nicotine gum had no benefit[47]. Similarly, uncontrolled studies reported that transdermal nicotine 15 mg/24 h and 30 mg/24 h (22 mg delivered) was beneficial in patients with active and steroid-dependent UC[47,48]. As happened with the nicotine gum, patients who had never smoked were reported to tolerate nicotine poorly[47]. Following the uncontrolled studies, six controlled trials have assessed the utility of nicotine therapy in UC patients[40-50].

A study in seven patients with active UC confirmed that nicotine gum 2 mg administered 5-7 times/d was beneficial compared with placebo in three of four ex-smokers and in none of three who had never smoked[49].

Two randomized, placebo-controlled trials of transdermal nicotine for active UC showed that nicotine was useful when compared with placebo[51,52]. Both studies began with lower nicotine doses (15 mg and 11 mg) to improve patient tolerance, followed by dose escalation after 1-2 wk. The first study, conducted by Pullan et al[39]...
treated 72 patients with active left-sided UC with either transdermal nicotine patches (up to 25 mg/24 h) or placebo over a period of 6 wk. The standard medication, which included mesalamine (all patients) and glucocorticoids (12 patients), continued to be administered during the study. Most patients tolerated the nicotine doses. Patients in both the nicotine and placebo groups improved, although the improvement in clinical and histological grades was greater in the group treated with nicotine. Seventeen of 35 (48.6%) patients in the nicotine group had complete remission, compared with only nine of 37 (24.3%) patients in the placebo group.

Similar results were found by Sandborn et al[52], who compared transdermal nicotine (22 mg/24 h) for 4 wk with placebo. Nicotine treatment led to a clinical benefit in 39% of patients compared with 9% receiving placebo. No improvement in histology was observed.

A fourth randomized controlled trial compared transdermal nicotine at the highest tolerated dose (up to 25 mg/16 h) with prednisolone 15 mg/d in active UC[58]. No significant differences were found between the two groups, although the corticosteroid therapy tended to be more efficacious.

A fifth randomized controlled trial compared transdermal nicotine 15 mg/24 h for 5 wk to prednisone 30 mg/d tapered over 5 wk and demonstrated equivalence, although again there was a tendency towards prednisone being more efficacious[54]. After following up 30 patients with remission of distal UC after therapy with either mesalazine plus transdermal nicotine or mesalazine plus oral prednisolone for 12 mo, Guslandi et al[56] suggested that nicotine-induced remission of UC lasts longer than that obtained by therapy with oral corticosteroids. With respect to the maintenance of remission in patients with UC, no beneficial effect was noted with a lower dose of transdermal nicotine (up to 15 mg/16 h) compared with placebo over a period of 6 mo in the sixth randomized, placebo-controlled trial[58].

In two studies in which liquid nicotine enemas were used to treat patients with active distal UC, the results suggested a clinical benefit in the absence of detectable serum nicotine concentrations[57,58]. Adverse events were of minimal consequence. Nevertheless, the liquid enemas were difficult to retain. Further controlled trials are needed to determine the therapeutic value of topical nicotine administration.

Finally, in patients with PSC, a pilot study of oral nicotine tartrate capsules delivered to the gastroduodenum did not report a beneficial effect[69].

Adverse events when nicotine is therapeutically administered are common (>50%), but generally mild. They include contact dermatitis, nausea, lightheadedness, headache, sleep disturbance, central nervous system stimulation, sweating, tremor, and tachycardia. The side effects are more frequent in non-smokers than in ex-smokers. Non-smokers have fewer nicotine-associated adverse events if they are initially administered a low dose patch, subsequently escalating the nicotine dose, presum-

| Table 2 Possible mechanisms in the pathogenic interactions of smoking and inflammatory bowel disease[64] |
|---------------------------------------------------------------|
| Modulation of cellular and humoral immunity                  |
| Changes in cytokine levels                                    |
| Modification of eicosanoid-mediated inflammation             |
| Reduction of antioxidant capacity, production of oxygen free radicals |
| Release of endogenous glucocorticoids                         |
| Colonic mucus effects                                         |
| Alteration of mucosal blood flow                              |
| Pro-thrombotic effects and promotion of microvascular thrombosis |
| Alteration of gut permeability                                |
| Modification of gut motility                                  |

PATHOGENIC MECHANISMS OF SMOKING ON UC PATIENTS

The exact mechanisms of action of nicotine and smoking in UC patients is not well known (Table 2)[61]. Tobacco smoke contains hundreds of different substances including nicotine, free radicals and carbon monoxide. It is suspected that the main metabolite responsible for the impact on the course of UC is nicotine, however there is no absolute proof of nicotine being the sole active moiety. In consequence, probably the mechanisms are diverse and considering that the pathogenesis of UC is only partially understood, any dissertation on their possible mechanisms can only be hypothetical.

Nicotine increases mucin synthesis in UC patients[62]. Patients with active UC are shown to have a significantly thinner mucus layer in the left colon and rectum compared with healthy (smoking and nonsmoking) control subjects[63]. Nevertheless, no effect of transdermal nicotine on mucin gene expression in UC patients could be demonstrated by Louvet et al[64].

Nicotine also affects the immune system. Heavy smokers may have reduced levels of immunoglobulin A in both saliva and intestinal secretions[65,66]. Heavy smoking also influences cellular immune-defense mechanisms, leading to a state resembling immune suppression with an increased level of suppressor CD8+ T cells and a diminished ratio of CD4/CD8 T cells, which is reversible after the cessation of smoking[67]. Nicotine has been shown to decrease the synthesis of proinflammatory molecules, for instance, interleukin (IL)-1 and tumor necrosis factor (TNF)-α by mouse colonic mucosa as well as the production of mucosal eicosanoids[68] and some proinflammatory cytokines by human mononuclear cells (e.g. IL-2[69], IL-8, and TNF-α[70]).

Smokers with UC have a significant reduction in mucosal cytokine levels, specifically, IL-1β and IL-8[71]. Beneficial effects of nicotine in active UC may be associated with a decrease in IL-8 expression. In rats, DNBS-induced colonic damage was improved in passive-smoking rats involving changes in colonic cytokine levels[72]. The increase
of leukotriene B4, TNF-\(\alpha\), IL-1\(\beta\), and IL-6 levels was alleviated. In contrast, the deprivation of IL-10 during UC was preserved. The exact meaning of these changes in the cytokine balance still remains poorly understood.

Smoking has a deleterious effect on phagocyte function, decreasing their bactericidal and bacteriostatic activity\(^7\). 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\(^8\,\(^9\). Smokers have a greater capacity for the generation of free oxygen radicals, with reduced antioxidant capacity\(^5\). This fact correlates with the harmful effect of smoking on patients with CD but does not offer an explanation for the beneficial effects on UC patients.

Other effects of nicotine or smoking on the intestine include hyperfusion of the rectum and of acutely damaged colonic tissue\(^6\), the alteration of gut motility, the reduction of smooth muscle tone and contractility (modulated by nitric oxide)\(^7\), altered permeability\(^5\), and alterations in the microcirculation\(^7\). Patients with IBD have an increased intestinal permeability\(^8\). Smoking was found to decrease the intestinal permeability in healthy control subjects\(^\text{[80]}\). However, no such observation could be made in smokers with UC compared with nonsmokers with UC\(^8\), refuting the notion that the protective effect of smoking on UC is due to the moderation of an increased intestinal permeability.

**SMOKING CESSATION**

Based on all the available data, it is clear that smoking cessation in a patient with UC could exacerbate its symptoms as well as the disease activity. For this reason, in order to decide whether we should recommend that UC patients quit smoking, we need to balance the decision with the patient.

First and foremost, the patient has to be aware that active cigarette smoking causes a broad spectrum of diseases; it is a major cause of vascular disease, cancer and chronic obstructive pulmonary disease. In addition to these, cigarette smoking also causes other respiratory symptoms, adversely affects reproductive outcomes and is a cause of diminished health status. Furthermore, exposure to second-hand smoke is an established cause of coronary heart disease and lung cancer, as well as a host of other adverse health effects.

Secondly, patients should be given truthful information; it is important to explain to them that there is the possibility of disease exacerbation (flares, hospitalization or the need for oral steroids) following cessation of smoking. We should also explain that the risk of colectomy in the short term appears not to be increased in the case of quitting smoking.

Additionally, patients should be given other important information about the effects of smoking on the course of UC. Patients with UC had a significantly decreased risk of pulmonary cancer, which may primarily be explained by the smoking habits of the patients with UC\(^5\). Patients should also be informed about the influence of smoking on the risk of colon cancer (CRC). It is well accepted that UC is associated with an increased risk of colon cancer. A recent meta-analysis of 36 studies showed that current smokers had a significantly increased risk of CRC incidence\(^8\).

Finally, the patient should be aware that nowadays there is an increasing number of treatments that can be used to control inflammation in the case of disease exacerbation after smoking cessation, such as immunosuppressants, leukocyte apheresis or anti-TNF-\(\alpha\) products\(^8\).

Based on all the deleterious health effects combined with the substantial prevalence, cigarette smoking represents a major worldwide cause of death. In patients with UC, the risks of smoking far outweigh any possible benefit, so physicians should advise, encourage and assist UC patients who smoke to quit.

**CONCLUSION**

1. Smoking is protective in UC, with a lower incidence of disease in smokers; (2) Current smoking protects against UC and, after onset of the disease, improves its course, reducing the need for colectomy; (3) Ex-smokers have an increased risk of developing an unfavorable clinical course; (4) PSC is observed almost exclusively in nonsmokers; (5) Nicotine is efficacious for active UC, but in most studies, side-effects (nausea, headache, dermatitis) were frequent and tended to overcome the clinical benefit; (6) The place of nicotine in the algorithm of treatment of UC patients is unclear, although it may be useful in selected cases, particularly in recent ex-smokers with moderate but refractory attacks of UC; and (7) Since smoking is associated with several additional deleterious effects (e.g. 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 an increase in disease activity, without a higher risk for surgery.

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