

# Role of smoking in inflammatory bowel disease: implications for therapy

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## Abstract

**The relationship between smoking and inflammatory bowel disease is now firmly established but remains a source of confusion among both patients and doctors. It is negatively associated with ulcerative colitis but positively associated with Crohn's disease. In addition, it has opposite influences on the clinical course of the two conditions with benefit in ulcerative colitis but a detrimental effect in Crohn's disease. These differences have been the subject of much interest and scrutiny with the hope that they may offer some insight into the pathogenesis of the two conditions and possibly lead to alternative therapeutic options. Nicotine is probably the principal active ingredient in smoking responsible for the association; trials have shown it to be of some benefit in ulcerative colitis, but further research is required to establish its therapeutic role, and the relevant mechanisms responsible for its action. In this article, we review the role of smoking in inflammatory bowel disease and its implication for therapy.**

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Smoking has been shown to be negatively associated with ulcerative colitis but positively associated with Crohn's disease. These relationships are the most striking and firmly established epidemiological factors associated with the two conditions. The first association of non-smoking with ulcerative colitis was made 17 years ago,<sup>1</sup> followed within two years by the observation that patients with Crohn's disease were more often smokers.<sup>2</sup> It also has opposite effects on the clinical course of the two conditions with possible benefit in ulcerative colitis<sup>3</sup> and a detrimental effect in Crohn's disease.<sup>4</sup>

This remarkable finding of "opposite associations" for smoking with inflammatory bowel disease has been the subject of intense scrutiny in the hope that it may help to identify important pathogenic mechanisms responsible for the two conditions, and perhaps provide the key to alternative therapeutic options. Historical, clinical, and therapeutic aspects of the association between smoking, nicotine, and inflammatory bowel disease are reviewed.

## Smoking and ulcerative colitis

The initial observation in 1982 by Harries and colleagues,<sup>1</sup> that ulcerative colitis was largely a disease of non-smokers was made almost by serendipity, when a population of patients with

colitis were used as controls in a study of nutritional aspects of Crohn's disease. Only 8% of 230 patients with colitis were current smokers compared with 44% of the matched controls. Since this initial observation, there have been many published case-control studies in different countries which have consistently identified the association. Although there are variations in the calculated relative risks, most of the case-control studies confirm that the relative risk of colitis in ex-smokers is greater than life-long non-smokers, with a reduced risk in current smokers. In one study, which is representative of the literature, the relative risks in ex-smokers, non-smokers, and smokers were 2.5, 1.0, and 0.6, respectively, with a high figure of 4.4 for ex-smokers who smoked more than 11 cigarettes daily.<sup>5</sup>

In 1989, Calkins reviewed the available studies on the association of smoking with inflammatory bowel disease<sup>6</sup>. A critical appraisal of the studies included strict inclusion criteria. A meta-analysis of data from nine suitable case-control studies of ulcerative colitis showed a remarkably consistent association of smoking with ulcerative colitis in terms of direction. Pooled odds ratios and 95% confidence intervals calculated for current smokers compared with life time non-smokers were 0.41 (0.34 to 0.48). When the analysis was reversed, with non-smoking as the "risk factor" for ulcerative colitis, the risk to life time non-smokers was 2.9 (2.6 to 3.2). When the risk of ulcerative colitis in ex-smokers to non-smokers was examined, the odds ratio was 1.64 (1.36 to 1.98). These values are significant and indicate an increased risk of ulcerative colitis among lifelong non-smokers and ex-smokers compared with current smokers. The Surgeon General's criteria for causality were applied and found consistent with a causal relationship.<sup>7</sup>

## Other supportive evidence

Case-control studies may be criticised for various reasons, particularly with respect to recall bias. This may be a particular problem for a patient trying to accurately recall the time of smoking cessation and the onset of disease; prospective studies would overcome this but are more difficult to perform. However, additional support for a negative association has come from a number of other sources. In the Boston Drugs Surveillance Program, there was a relative deficiency of smokers in patients with ulcerative colitis.<sup>8</sup> Mortality figures from a group of 109 patients with ulcerative colitis in Birmingham, England, showed a relative absence of smoking related diseases at necropsy, particularly cardiovascular and respiratory

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illnesses in men.<sup>9</sup> Further support comes from a study in which a large cohort of 17 032 women registered on the Oxford Family Planning Association contraceptive study were subsequently followed up—31 developed ulcerative colitis; smoking habit which had been recorded on entry to the programme showed a relative absence of smokers among those who later developed colitis.<sup>10</sup>

The relationship between smoking and ulcerative colitis has been examined at a population level. The first was a study of the prevalence of ulcerative colitis and Crohn's disease in the Mormon church in Britain and Ireland; smoking is strongly discouraged in the Mormon community. The prevalence of ulcerative colitis was fivefold compared with that of the general population, but Crohn's disease was equally common.<sup>11</sup> In the second, a review of 56 epidemiological studies in Sweden over the period 1930 to 1990, showed the sex distribution of ulcerative colitis 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. The change in predominance of the disease between sexes has not been borne out in contemporary paediatric studies and one explanation is that the changes in adults may be related to changes in smoking patterns.<sup>12</sup>

Data on the relationship between passive exposure and inflammatory bowel disease are scanty and difficult to interpret. In one study, childhood exposure to environmental tobacco smoke decreased the risk of developing ulcerative colitis in adulthood.<sup>13</sup> In another, the relative risk of Crohn's disease was increased in those exposed to environmental tobacco smoke in childhood.<sup>14</sup>

In a recent study of families with multiple members affected by inflammatory bowel disease, 24 (28%) of those with ulcerative colitis were smokers, while the other 61 (72%) were ex or lifelong non-smokers. An opposite trend was seen for Crohn's disease with smokers significantly outnumbering non-smokers. This relationship existed if patients were from families with multiple cases of ulcerative colitis, Crohn's disease, or a mixture of the conditions.<sup>15</sup> Similar findings were discovered in sibling pairs with inflammatory bowel disease who were discordant for their smoking habit before diagnosis.<sup>16</sup> These studies suggest that smoking is an important environmental influence in those with a genetic predisposition to ulcerative colitis or Crohn's disease.

#### **Temporal relationship between disease onset and smoking habit**

The time at which patients stopped smoking in relation to the onset of colitis has been of particular interest. Motley *et al*, in a study of 138 patients, found that 107 (70%) developed colitis after stopping smoking with a peak in the first year and 52% in the first three years after cessation.<sup>17</sup> Similar findings have been reported

by others.<sup>5 18</sup> A further study by Motley *et al* showed male lifelong non-smokers developed colitis earlier than those who were ex-smokers—50% of “never smokers” developed their colitis by the age of 25 years compared with 42 years for ex-smokers; the apparent delay of 17 years in onset of disease for ex-smoking males did not hold true for females. This difference between the sexes was found in another study<sup>20</sup> and remains unexplained. It suggests the observation is not simply due to a difference in the mean age of the population cohorts of non-smokers and ex-smokers.

#### **Effect of smoking on the clinical course of ulcerative colitis**

If smoking reduces the risk of ulcerative colitis, and most previous smokers develop the disease soon after stopping, one must question whether smoking may have a favourable effect on active disease and perhaps maintain clinical remission. Studies on the effect of smoking on the clinical course of colitis are difficult to conduct for obvious reasons, and have produced some conflicting results. There are anecdotal case reports of patients relapsing on cessation only to improve again on recommencing cigarettes,<sup>21 22</sup> but formal studies would be both impossible and unethical to perform. Thirty patients with ulcerative colitis who were intermittent smokers were questioned—half of them thought their colitis symptoms improved over a six week period while smoking 20 cigarettes daily.<sup>23</sup> More recently, we identified a group of 51 patients with ulcerative colitis who smoke and confirmed that they had quiescent disease on symptomatic, sigmoidoscopic, and histological criteria; 11 were on no treatment and most others were on very little maintenance therapy. None felt smoking had a detrimental effect on their symptoms.<sup>3</sup> The effect of smoking on the quality of life of patients with inflammatory bowel disease has been examined. Males with ulcerative colitis who continued to smoke reported fewer bowel complaints than their non-smoking counterparts.<sup>24</sup> Some studies have shown no clear pattern between smoking habit and the clinical course of the disease measured either symptomatically, or by hospitalisation or colectomy rates.<sup>25 26</sup> It must be stressed there were relatively few patients who were current smokers in both of these studies. By contrast, other studies have demonstrated a beneficial effect. In one, patients smoking at the onset of colitis had lower hospitalisation rates but there was no difference in the colectomy rates between non-smokers and smokers after diagnosis—ex-smokers who stopped smoking before the onset of their colitis had higher hospitalisation and colectomy rates.<sup>27</sup> Another showed that non-smokers and ex-smokers had a higher colectomy rate than current smokers who continued to smoke after diagnosis, but clinical relapse rates in the groups were similar. Patients who began smoking after diagnosis had reduced rates of clinical relapse.<sup>28</sup> Additional support for a beneficial effect of smoking comes from the observation

that patients who had a restorative proctocolectomy for ulcerative colitis were less likely to develop pouchitis if they were smokers than non-smokers.<sup>29</sup>

### Smoking and Crohn's disease

The initial observation that smoking is associated with an increased risk of Crohn's disease was made shortly after the link between ulcerative colitis and smoking was established,<sup>2</sup> subsequent studies have shown a greater risk of Crohn's disease in current smokers than non-smokers.<sup>30-31</sup> Logan summarised the relative risk of Crohn's disease in patients, relative to "never smokers" at diagnosis, as 2.7 for current smokers, 1.5 for ex-smokers, and 2.4 for those who had ever smoked during their life.<sup>32</sup> A meta-analysis on seven suitable studies of Crohn's disease confirmed a pooled odds ratio and a 95% confidence interval of 2.0 (1.65 to 2.47) for current smokers compared with life time non-smokers, and 1.83 (1.33 to 2.51) for former smokers compared with life time non-smokers. In this non-smoking group the risk was greatest for those who had quit smoking within four years of developing Crohn's disease, and least for those who had been non-smokers for more than 10 years.<sup>6</sup> The relative risk associated with smoking for women may be greater than for men: one study demonstrated a threefold difference.<sup>14</sup> The site of Crohn's disease has been linked with the duration of smoking habit and number of cigarettes smoked, suggesting that small bowel and ileocolonic disease are more common in heavy smokers.<sup>33</sup>

### Effect of smoking on the clinical course of Crohn's disease

In addition to the risk identified in epidemiological studies, smoking also appears to have an adverse effect on the clinical course of the disease. Several studies have followed up clinical and surgical recurrence, with the latter defined as a further bowel resection. In one, patients with Crohn's disease were monitored for six months using a disease activity scoring system. Smokers with Crohn's disease had a 34% higher relapse rate than non-smokers.<sup>34</sup> In another, patients with Crohn's disease who continued to smoke after bowel resection had an increased risk of further resection compared with non-smokers.<sup>35</sup> Cottone *et al* studied the influence of smoking on the clinical course of Crohn's disease in 182 patients followed up over a 20 year period.<sup>4</sup> After surgery, the risks of clinical, endoscopic, and surgical recurrence were all increased in smokers compared with non-smokers. In an intermediate group of 19 patients, who had stopped smoking at least one year before surgery, and were defined as ex-smokers, the outcome was substantially better than for current smokers, and was similar to that observed in non-smokers. This study also suggested that smokers developed more severe lesions at the anastomotic site, with strictures and nodular distortion, compared with non-smokers and ex-smokers. The effect of smoking on the quality of life of patients with Crohn's disease has been examined:

#### Box 1: Factors affected by smoking (and in some cases by nicotine)

- Immune system
- Inflammatory cascade
- Gut motility
- Mucus production
- Gut permeability
- Gut blood flow
- Platelet activation

young females who continued to smoke suffered more bowel and systemic symptoms, in addition to more emotional dysfunction than female non-smokers with Crohn's disease.<sup>24</sup>

### Possible mechanisms involved in the relationship between smoking and inflammatory bowel disease

Through which mechanisms does smoking influence the course of inflammatory bowel disease? Strong epidemiological associations with disease should point toward causative factors and help elucidate mechanisms responsible for the pathological process. In spite of intense scrutiny the principal mechanisms remain unclear, although there are many potential routes by which smoking could influence a disease process (box 1). The effects of smoking and nicotine are numerous and while the pathogenesis of inflammatory bowel disease remains poorly understood any discussion about possible mechanisms can only be speculative. Although nicotine is thought to be the principal pharmacological agent responsible for the effect of smoking, one should be careful not to use the terms "smoking" and "nicotine" interchangeably as some effects from smoking may not follow the use of nicotine formulations used for therapeutic purposes.

#### IMMUNE SYSTEM

Smoking influences cellular<sup>36</sup> and humoral immunity.<sup>37-38</sup> Alterations in immunoregulatory T cells have been reported with heavy smokers having an increased level of suppressor OKT8+ cells, and decreased ratio of OKT4+ to OKT8+ cells. These changes, which imply immune suppression, revert to normal on cessation of smoking.<sup>36</sup> There are reports that heavy smokers may have reduced levels of IgA in both saliva<sup>37</sup> and intestinal secretion.<sup>38</sup> In addition, smokers have a reduced skin response to challenges from lauryl sulphate and ultraviolet radiation.<sup>39</sup> In an attempt to establish whether smoking causes clinically significant immunosuppression, patients with systemic lupus erythematosus have been studied and no correlation between smoking habit and the disease was found, either at diagnosis or interview. There was no evidence to suggest the effect of smoking was sufficient to influence the clinical course of lupus.<sup>40</sup>

## INFLAMMATORY PATHWAY

Both smoking and nicotine affect the cytokine profile, predominantly by reducing the production of proinflammatory cytokines. Smokers with active inflammatory bowel disease have significantly lower concentrations of interleukin (IL)-1 $\beta$  and IL-8 than non-smokers.<sup>41</sup> Nicotine inhibits the *in vitro* production of IL-2 and tumour necrosis factor (TNF)- $\alpha$  from the isolated mononuclear cells of healthy volunteers<sup>42</sup> and also reduces the formation of IL-1 $\beta$  and TNF- $\alpha$  from mouse colonic mucosa, but the production of lipid mediators like eicosanoids and platelet activating factor are unaffected.<sup>43</sup> In contrast, when healthy volunteers wear nicotine patches for a week, the production of TNF- $\alpha$  and IL-2 by non-adherent mononuclear cells isolated from peripheral blood is unaffected, while IL-10 formation is significantly reduced.<sup>44</sup> In patients with active ulcerative colitis, transdermal nicotine, up to 22 mg daily for four weeks, significantly reduces mucosal IL-8 mRNA concentrations, but has no effect on other cytokines or mucin gene expression.<sup>45</sup> The effect on rectal eicosanoids is of some interest—levels of certain eicosanoids are lower in rectal biopsy specimens of cigarette smokers compared with normal healthy controls.<sup>46</sup> In rabbits given subcutaneous nicotine, changes were demonstrated in eicosanoid tissue concentrations and the thickness of adherent surface mucus in the rectum.<sup>47</sup>

Smokers also have a greater capacity for generation of free oxygen radicals, with reduced antioxidant capacity.<sup>48</sup> However, the effect of nicotine on *in vitro* production of oxygen free radicals from neutrophils only showed an effect at concentrations far too high to be of clinical relevance.<sup>49</sup>

## INTESTINAL MOTILITY

We have been aware for some time, both through anecdotal reports from patients who smoke to control symptoms and from studies with nicotine patches in active disease, that the first symptom to improve is often the urgency to defecate—a particularly troublesome problem for many patients. Both smoking and nicotine have been shown to affect motility at various sites in the gastrointestinal tract.<sup>50, 51</sup> *In vivo*, intraluminal nicotine reduces smooth muscle tone and contractile activity in the human distal large bowel.<sup>52</sup> *In vitro*, animal studies have shown that nicotine produces smooth muscle relaxation in the gastrointestinal tract, largely through the release of nitric oxide which acts as a non-adrenergic, non-cholinergic neurotransmitter.<sup>53, 54</sup> We have recently demonstrated that this may also be the case in human colonic smooth muscle.<sup>55</sup>

## OTHER EFFECTS: GUT PERMEABILITY, BLOOD FLOW, PROTHROMBOSIS

The effect of smoking on gut permeability has been examined, but results have been conflicting. Initial observations suggested smoking may decrease permeability and “tighten” the gut,<sup>56</sup> but a recent study by the same authors has failed to confirm this.<sup>57</sup>

Changes in the microvasculature of the bowel wall have been described in Crohn’s disease consistent with ischaemia.<sup>58</sup> Whether these changes should be interpreted as a primary event or simply a consequence of the disease process from inflammation and oedema in the gut wall remains unresolved. Smoking produces a transient reduction of blood flow in the rectum,<sup>59</sup> and is known to increase the thrombotic tendency with associated vascular damage.<sup>60</sup> Both effects might conceivably aggravate a situation in which ischaemia plays a part. It is noteworthy that nicotine administered by transdermal patches to non-smokers is not associated with any changes in the markers usually taken as an index of thrombotic risk.<sup>61</sup>

**Hypothesis**

The “opposite” effect of smoking on these two inflammatory conditions offers an opportunity to define relevant mechanisms involved in the two diseases. Any beneficial effect is unlikely to be due to a direct action on mediators in the inflammatory cascade as this should result in improvement in both conditions, although different mechanisms may well be influenced by smoking in the two diseases. One could hypothesise that in Crohn’s disease where changes in the microvasculature may play a part by producing ischaemic damage, smoking would be expected to have an adverse effect on this process; comparable changes in the microvascular circulation have not been described in ulcerative colitis. In colitis, an effect on gut motility or mucus may be of more relevance but these are only a few of the different possibilities. The opposite effects of smoking may not apply to nicotine itself since all the effects of smoking are not reproduced by nicotine alone.<sup>62</sup>

**Clinical trials of nicotine in ulcerative colitis**

It would be both unethical and impractical to ask patients to stop and start smoking in order to assess the effect on their disease. However, with the advent of nicotine replacement therapy for cessation of smoking it became possible to examine this compound more formally. Initial studies with nicotine gum were inconclusive and uncontrolled<sup>63, 64</sup> but with the introduction of transdermal nicotine it became possible to examine nicotine in controlled trials. In the first, 72 patients with active left sided disease, were treated with either transdermal nicotine patches or placebo for six weeks.<sup>65</sup> Patients continued their usual medication and incremental doses of nicotine were given; most patients tolerated 15–25 mg/24 hours. Seventeen of 35 patients in the nicotine group had complete remissions compared with only nine in the placebo group. The serum concentrations of nicotine and cotinine were only a third of the values for smokers of 20 cigarettes a day. Side effects were more common in the nicotine group and were more frequent in lifelong non-smokers than in ex-smokers—the most common were nausea, light headedness, headache, and sleep disturbance. A second study of similar design involving 64 patients has recently confirmed these results.<sup>66</sup> In a third study,

transdermal nicotine alone was compared with 15 mg of prednisolone daily in active disease.<sup>67</sup> There was no significant difference between the outcome in both treatment groups but the trend of improvement suggested prednisolone to be superior to nicotine. In addition, Guslandi and Tittobello found that patients unable to take steroids for one reason or another benefited from the addition of transdermal nicotine to mesalazine therapy.<sup>68</sup> The only available study of maintenance therapy with transdermal nicotine showed it was no better than placebo when given alone for six months.<sup>69</sup> From available evidence, nicotine appears of some benefit in active disease but not as maintenance therapy, a situation analogous to steroids. Its effect on colitis is less than might be expected from the epidemiological data. However, the serum nicotine concentrations in all the studies were lower than in smokers and less than expected on 15 mg/day of transdermal nicotine, which may reflect poor compliance. In addition, plateau serum nicotine profiles produced by transdermal nicotine are quite different from the peaks observed in smokers; these peaks are probably associated with various metabolic changes seen in cigarette smokers, including platelet activation, and addiction. Should the effect of smoking on colitis be dependent on the high serum peaks of nicotine seen in smokers, reproduction of such a profile would carry the unacceptable consequence of promoting addiction and prothrombosis. It is of interest that in our studies with transdermal patches, none of the patients became addicted to nicotine or started smoking. An alternative approach would be to apply nicotine topically to colonic mucosa, either by enema or with delayed release oral formulations. Since 60% of nicotine is converted to its major metabolite cotinine on "first pass" through the liver, systemic concentrations of nicotine, with associated side effects, would be much lower and tissue levels at the inflammatory site much higher. Benefit from such an approach would depend on whether nicotine has a topical effect in ulcerative colitis. Nicotine has been combined with a polyacrylic carbomer for administration as an enema; this gave maximum serum concentrations of 8 ng/ml after a median duration of 60 minutes with an extended half life of nearly three hours.<sup>70</sup> This has been assessed in a pilot study of patients with active left sided ulcerative colitis with encouraging results.<sup>71</sup> The apparent benefit from smoking on devel-

opment of pouchitis in patients with colitis raises the possibility that nicotine enema may be of therapeutic value in this condition which remains difficult to treat. We have also developed a delayed release oral formulation of nicotine for delivery to the colon,<sup>72</sup> this has not yet been tested in patients. The effect of nicotine on Crohn's disease would also be of considerable interest in establishing whether it is the active ingredient in smoking responsible for the detrimental effect observed; it may prove to be of therapeutic value in Crohn's colitis.

### Conclusions

The diametrically opposite relationship of smoking status with ulcerative colitis and Crohn's disease is a source of confusion among both patients and doctors. Efforts should be made to clarify the situation and reduce misunderstanding. As smoking is bad for Crohn's disease but may help ulcerative colitis, those with Crohn's should be strongly dissuaded from smoking, while those with colitis should be clear about the relationship and make their own decision based on the facts (table 1). Some ex-smokers with active disease, in spite of high dose steroids and powerful immunosuppressant therapy, face the prospect of severe drug induced side effects or surgery and possibly life with a stoma. Given these scenarios they may feel the potential benefit of smoking on their disease outweighs the risks of the habit. We would not encourage our patients to smoke. However, we try to inform patients of the association to help them make an informed decision about the management of their disease. It is our experience that when questioned, most patients with ulcerative colitis admit they would be disgruntled to learn of the relationship by "chance" after many years of being on potentially toxic medication or having had surgery. It is somewhat surprising that with occasional exceptions our patients, when told of the relationship, have not chosen to start smoking.

Patients with active ulcerative colitis may benefit from transdermal nicotine but further clinical trials with different delivery systems and doses are required to explore the therapeutic potential. Should these confirm a therapeutic role for nicotine in colitis, its use may be limited by side effects in some patients, particularly lifelong non-smokers. Other clinical areas where nicotine is under investigation and may be of value include Parkinson's disease, Alzheimer's and Tourette's syndrome;

Table 1 Implications for therapy of ulcerative colitis and Crohn's disease

Question	Answer
<i>Ulcerative colitis</i>	
Encourage patient to commence smoking to improve symptoms and clinical course?	No, but patients should be told the facts
Consider nicotine patches in active disease?	Yes, worth considering in patients with mild to moderate disease not responding to conventional treatment (particularly if urgency is a major problem)
Consider nicotine enema in active disease?	Yes, in patients with mild to moderate disease with side effects on transdermal nicotine
Nicotine patches for maintenance of remission	Not on available data but could be revised with future trials
<i>Crohn's disease</i>	
Encourage patient to stop smoking to improve outcome and help maintain remission?	Yes, one of the most useful steps that can be taken by the patient to help the natural history of their disease

clinical trials in these areas may encounter the same difficulties as in ulcerative colitis.

Centuries have passed since nicotine was first used as a therapy, yet the drug still receives a very mixed reception. Its association with tobacco smoking ensures it continues to receive a bad press, and cautious reception from the medical profession. However, the drug in a more presentable form may yet find acceptance, respectability, and an established role as a therapeutic agent.

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