The impact of smoking in Crohn's disease: no smoke without fire

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Smoking habit is the most widely accepted environmental factor affecting the incidence and disease progression in the inflammatory bowel diseases. The contrasting effects in Crohn's disease (CD) and ulcerative colitis are unexplained. The purpose of this review is to summarise the existing data on the effects of smoking in CD on disease history, recurrence after surgery, effects on drug responses and to review available evidence that carriage of some of the known susceptibility genes may be disproportionate in smokers with CD. The review also highlights potential mechanisms involved and factors that might affect patients' smoking habits. The clinical and scientific implications of the data are discussed.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are related chronic inflammatory bowel diseases (IBD) which have increased in incidence over recent years. Both genetic and environmental factors are implicated in disease pathogenesis. The genetic contribution is now well characterised—genome wide association studies (GWASs) have identified a number of susceptibility genes that predispose to CD and/or UC.[1–4] Certain susceptibility genes are important in some but not all populations. NOD2 mutations, the strongest genetic determinant for CD in Europeans, are not found in Asians[5 6] and are less frequent in northern than southern Europeans,[7] even though the incidence of IBD is similar.

Environmental factors affect the incidence and disease history of IBD; smoking, oral contraceptive use, antibiotic use, diet, alcohol, breast feeding and immunisations have all been investigated[8 9] but it is difficult to ascertain the individual contribution of these factors to particular patients. Smoking is the most widely accepted lifestyle factor affecting the incidence and disease history of IBD.[10] Gene–environmental interactions almost certainly occur in CD pathogenesis, as CD is a complex genetic disease with various genes involved to different extents in individuals.

The purpose of this review is to summarise the available data on the effects of smoking on CD history, recurrence after surgery, drug responses and whether carriage of known susceptibility genes is disproportionate in smokers with CD. We also indicate potential mechanisms involved and factors that might affect the ease for patients to stop smoking.

Methods

A PubMed search was carried out using the terms 'CD' and 'smoke' or 'smoking' with further searches on 'smoking' and 'genetics'.

Smoking and susceptibility to CD

It is clear from various studies (table 1) that current smoking predisposes to CD but is protective against UC. UC incidence is higher in ex-smokers whereas in CD non-smokers and ex-smokers have a similar disease risk. There are exceptions to this observation: an Israeli study showed no effect of smoking on the susceptibility to CD[11] which confirmed previous Israeli studies also showing no association[12 13]; the authors suggested that this was due to their higher genetic predisposition to CD.[11] In contrast, another study showed a higher percentage of current smokers in French Canadian CD patients compared with other Caucasians with CD but no difference in disease phenotype; the authors suggested this reflects a stronger genetic sensitivity to the effects of smoking.[14] Thus gene–environmental interactions with smoking might differ across populations. Such interactions may also explain the differential effect of smoking on CD and UC: a study of sibling pairs with similar genetic predisposition to IBD, but discordant for smoking, found that smokers developed CD while non-smokers developed UC.[15]

Table 1 Studies of the association between smoking habit and the risk of developing Crohn's disease or ulcerative colitis

Study	Type	Comparison	CD OR (95% CI, p Value)	UC OR (95% CI, p Value)
Mahid *et al*[113]	Meta-analysis*	Current versus never smokers Former versus never smokers	OR 1.79 (1.4 to 2.22, p<0.001) OR 1.30 (0.97 to 1.76, p<0.08)	OR 0.58 (0.45 to 0.75, p<0.001) OR 1.79 (1.37 to 2.74, p<0.001)
Bridger *et al*[15]	UK family study	Current versus never smokers at diagnosis	OR 3.55 (2.50 to 5.02, p<0.001)	OR 0.28 (0.2 to 0.4, p<0.001)
Regueiro *et al*[31]	USA case-control study	Prevalence of smoking in patients vs. general population	OR 1.53 (1.01 to 2.27, p=0.04)	OR 0.25 (0.12 to 0.45, p<0.0001)
Bernstein *et al*[9]	Canadian case-control study	Current smokers patients versus controls	OR 1.96 (1.38 to 2.78, p<0.001)	No difference
		Former smokers patients versus controls	No difference	OR 2.07 (1.43 to 2.98, p 0.0001)
Halvarson *et al*[114]	Danish-Swedish twin study	Smoking status in diseased versus healthy twin	OR 2.9 (1.2 to 7.1)	OR 0.4 (0.2 to 0.9)
Gearry *et al*[8]	New Zealand case-control study	Current versus never smokers Former versus never smokers	OR 1.83 (1.41 to 2.39, p<0.001) OR 0.86 (0.64 to 1.16, p=0.57)	OR 0.67 (0.49 to 0.91, p=0.021) OR 1.82 (1.40 to 2.37, p=0.005)

*The nine studies used in this meta-analysis for CD and 13 studies for UC were not included on this table. This meta-analysis also remarked on the lack of consistency of definitions for smoking status (ie, current, ever, never and former smokers) and differences in defining smoking amount (eg, pack years versus definitions of heavy versus light smokers).[113]
CD, Crohn's disease; UC, ulcerative colitis.

Whether a threshold exists of smoking amount is unclear. Dose–response relationships have been shown,[16 17] although for the latter study, this only became significant when patients smoked >20 cigarettes/day. Others showed that the increased CD susceptibility was associated with smoking at diagnosis.[15] However, no threshold level of smoking was seen in studies from Sweden[18] or Spain.[19] Patients who stopped smoking reduced the likelihood of developing CD, regardless of the amount they had smoked previously (see table 1). Thus smoking at diagnosis appears to be the risk factor for developing CD rather than the cumulative amount smoked.[15]

The association between childhood exposure to passive smoking and development of CD has been investigated. Two main outcomes were: (1) perinatal and childhood exposure to passive smoking increased the likelihood of CD[9 20 21] or (2) maternal smoking during pregnancy affected later development of CD but not passive smoking in childhood.[8 22] In contrast, a New Zealand study showed no association with either maternal smoking during pregnancy or childhood exposure to passive smoking.[16] In further contrast, a Swedish study showed that children of mothers who smoked during early pregnancy had a significantly reduced risk of later IBD development.[23] The confusion arising from these reports may be due to differences in study design. Indeed, a meta-analysis confirmed the heterogeneity across these studies but concluded that the evidence for an association between passive smoking and CD is inconclusive.[24]

Smoking and disease history of CD

Studies of the disease history of CD have used different criteria for disease severity and/or complications. The Vienna[25] and Montreal[26] classifications were compiled to define CD location and behaviour for comparing studies (table 2). CD location is thought to be stable whereas disease behaviour can progress from purely inflammatory to stricturing and/or penetrating disease. Patients progress to a more complicated phenotype with time since diagnosis.[27 28]

Smoking predisposes patients to non-colonic disease (ie, involving the small bowel) and complicated (ie, stricturing/penetrating) disease behaviour (table 3). Our studies found an association between smoking and non-colonic disease and an indirect effect of smoking on disease behaviour,[28 29] substantiating that small bowel location predisposes to complicated disease.[27] Another study found a direct association between smoking and progression to stricturing/penetrating disease, which was dose dependent, as the proportion of patients with inflammatory (B1) disease was highest in non-smokers and light smokers and decreased with increasing amount smoked.[30] In contrast, several studies have found no association between smoking and disease location[19 20 31–33] or disease behaviour[19 20] but small numbers or short follow-up times might explain these differences. Two Israeli studies confirmed their lack of association with smoking as they found no association between smoking and disease severity.[11 34] Those studies that found associations between smoking and disease location and/or behaviour were consistent in showing that smoking predisposes to non-colonic and complicated CD whereas not smoking predisposes to colonic CD with its associated more benign disease course.

A study of osteoporosis in IBD found an association between being a current or ex-smoker and increased development of osteoporosis or osteopaenia.[35] This could be due to levels of vitamin D which are lower in CD smokers.[36 37] However, other studies have found no association between smoking and osteoporosis in CD.[38 39]

Smoking and surgery in CD

The requirement for surgery is increased in smokers compared with non-smokers in CD.[40–42] In a 1992 study, patients who smoked >10 cigarettes/day required more surgery and were more likely to have undergone ≥2 operations at 10 years post-diagnosis compared with lighter or non-smokers.[43] In patients with stricturing disease, smokers had a shorter time from first dilation to requiring a second intervention (surgery or another dilation) than non-smokers.[44] We found no association between smoking and surgery[29] but excluded those who were diagnosed with CD at their first operation. Another study found no association between risk for surgery and smoking habit[45] but gave no details of their criteria for smoking status or length of disease follow-up which might affect the results.

Smoking has been consistently associated with CD recurrence after surgery. A meta-analysis of smoking on outcome after ileocolonic resection showed increased clinical relapse and 5 and 10 year reoperation rates in smokers versus non-smokers[46] which was confirmed by other data.[47–49] Similarly, failure of surgery to repair perianal[50] or rectovaginal[51] fistulae was increased in smokers versus non-smokers. Comparison of smokers with ex-smokers showed that smokers experienced an increased incidence of clinical relapse and significantly higher reoperation rates.[46] This is strong evidence that stopping smoking reduces the levels of complications to that of non-smokers. Thus smoking cessation should be encouraged in CD smokers (see box 1).

Effect of smoking on drug responses

The relationship between smoking and drug use or response was highlighted in a recent study where smokers had higher usage of 5-aminosalicylic acid than ex-smokers or non-smokers.[52] In a French study, smokers

Table 2 Summary of the Vienna and Montreal classifications for Crohn's disease

Variable	Vienna classification[25]		Montreal classification[26]	
Age at diagnosis	A1	<40 years	A1	<17 years
	A2	>40 years	A2	17–40 years
			A3	>40 years
Location	L1	terminal ileum only	L1	terminal ileum
	L2	colonic only	L2	colonic
	L3	ileocolonic only	L3	ileocolonic
	L4	any upper GI disease* regardless if elsewhere in gut	L4	upper GI
			+L4	modifier to signify co-localisation upper GI disease and either L1, L2 or L3.
Behaviour	B1	inflammatory	B1	inflammatory
	B2	stricturing	B2	stricturing
	B3	penetrating, including perianal fistulae and abscesses	B3	internal penetrating disease
			+p	modifier to signify co-existence of perianal fistula/abscess

*Proximal to terminal ileum.

Table 3 Summary of the associations found between smoking and disease location and behaviour in Crohn's disease

Study	Nationality of study	Number of CD patients	Classification used	Association with smoking	
				Location	Behaviour
van der Heide *et al*[52]	Dutch	380	Vienna	–	Higher proportion of smokers had B2/B3 disease
Lakatos *et al*[40]	Hungarian	340	Montreal	–	Progression from B1 to B2/B3 disease
Aldhous *et al*[29]	Scottish	408	Montreal	Non-colonic	Non-colonic disease associated with B2/B3 disease progression
Chatzicostas *et al*[41]	Greek	116	Vienna	Non-colonic	Progression from B1 to B2/B3 disease
Smith *et al*[28]	Scottish	231	Vienna	Non-colonic	Non-colonic disease associated with B2/B3 disease progression
Brant *et al*[42]	USA	275	Vienna	Ileal (OR=2.25)	–
Louis *et al*[27]	Belgian	163	Vienna	–	Increased perianal disease. Progression from B1 to B3 disease
Picco and Bayless[30]	USA	311	Vienna	Ileal	Non-inflammatory (B1) behaviour
Russel *et al*[115]	Dutch	457	–	Non-colonic	–
Lindberg *et al*[43]	Swedish	231	–	Small bowel	Increased occurrence of fistulae/abscesses

CD, Crohn's disease.

of >10 cigarettes/day required more immunosuppressive therapy (methotrexate or azathioprine) than lighter or non-smokers. Of those who did not receive immunosuppressive therapy, smokers were more likely to undergo surgery.[33] A study of tolerance and outcome of 6-mercaptopurine therapy showed no difference in responses between smokers and non-smokers.[53]

There has been much discussion about smoking and responses to the antitumour necrosis factor α therapies. Data from adalimumab are limited; the only study so far showed a non-significant but lower response in smokers compared with non-smokers at 4–6 weeks.[54] However, there have been concerns over the safety and efficacy of the use of infliximab in smokers. Some studies demonstrated no difference in infliximab response according to smoking habit.[55 56] Conversely, others found that smokers have a lower response rate, shorter response duration and higher relapse rate.[57–59] A recent case report described an increased risk of developing lung cancer in infliximab treated patients.[60] Infliximab therapy in chronic obstructive pulmonary disease also showed an increased incidence of lung cancer,[61] leading to questions regarding the safety of infliximab treatment in long term smokers with CD.

Any increase in genetic predisposition in smokers?

We suggested that gene–environmental interactions might occur in smokers with CD. Direct evidence for such interactions is the disproportionate carriage of CD susceptibility genes in smokers versus non-smokers. No difference in NOD2 allele frequency was found between smokers and non-smokers with CD,[42 62–66] apart from one study with a higher proportion of smokers carrying the G908R variant than the wild-type genotype.[67] Neither the matrix metalloproteinase genes[48] nor the ATP binding cassette transporter genes[68] showed any association between smoking and genotype in CD.

Interestingly, an Australian study investigating the A to G variant of ATG16L1, previously identified as a susceptibility gene,[69 70] found an increased risk of CD in smokers versus non-smokers with the GG genotype.[71] This suggests that some interaction occurs between smoking and the GG genotype, which may have a functional effect. Combinations of genes could also predispose smokers to CD: a study of interleukin 10 gene mutations stratified by NOD2 variants showed that, in patients carrying one or more NOD2 mutations, a specific interleukin 10 mutation was more common in smokers than non-smokers.[72] Thus potentially 'unrelated' genes might work together to confer the susceptibility to CD in smokers.

An alternative mechanism of gene–environmental interactions in smoking may be differential gene expression (see box 2). In colonic biopsies from smoking versus non-smoking CD patients, three genes were upregulated in smokers although there was no indication of smoking duration or amount in these patients. The genes identified were involved in signalling pathways, control of cell cycling and/or apoptosis, all potentially important pathways in CD pathogenesis.[73] Similar studies are required to establish whether specific genes or pathways are affected by smoking thus providing insights into the aetiology of CD.

Is nicotine the active compound in cigarette smoke?

Nicotine is a major candidate as the active compound in cigarette smoke with the observed effects. In animal models of colitis, chronic nicotine administration ameliorated colonic inflammation but exacerbated jejunal inflammation, without affecting uninflamed intestine.[74–76] In peripheral blood mononuclear cells, we found that cytokine profiles were associated with specific alterations in cell cycle responses and that these were modified by nicotine.[77] Nicotine also differentially modified the β-defensin-2 production from cultured gut biopsies in response to lipopolysaccharide stimulation.[78] The potential mechanisms of the effects of nicotine on the intestine have been reviewed.[79–81]

The gut–brain axis might be important in IBD[82] suggesting that similar factors might affect both brain and gut function and therefore studies of smoking dependence may be relevant. Several GWASs have shown specific genes associated smoking dependence, including genes coding for nicotinic acetylcholine receptor (nAChR) subunits on chromosomes 15[83–87] and 8.[85 88] Intestinal lamina propria T cells from CD patients expressed the nAChRα7 receptors. Chronic stimulation of these cells with nicotine in vitro led to proinflammatory cytokine production.[89] The use of nicotine in the treatment for UC has had limited success.[90–93] A pilot study of nicotine enemas in Crohn's colitis showed decreased symptoms in ~50% of patients. Larger randomised controlled trials are needed to give long term outcome data.[94]

Other potential mechanisms

Apart from nicotine, there are few studies of other mechanisms behind the effects of smoking in CD. Cigarette smoke contains over 4000 compounds and studies in smoking related respiratory diseases have used cigarette smoke extract. A study in a rat model of colitis showed that both cigarette smoke extract and nicotine reduced inflammation, with a concomitant decrease in neutrophil activity.[95] Other GWASs of smoking dependence identified genes important in processes involved in establishment of neuronal connections[96–98] and pathways crucial to synapse formation and maintenance.[97–99] Similar gene variants may be affected in CD patients with implications for both smoking dependence and effects on cells in the gut. Another GWAS of smokers identified genes at putative transcription factor binding sites near the interleukin

Box 1 Smoking and Crohn's disease (CD)—what the gastroenterologist and patient need to know

- Current smoking increases the risk of developing Crohn's disease
- Smoking predisposes patients to small bowel CD, with increased likelihood of complications
- Non-smoking predisposes patients to colonic CD with a more benign disease course
- Smoking increases the likelihood of treatment failure
- Smoking increases the likelihood of needing an operation
- Smoking increases the likelihood of disease recurring after surgery
- Smoking cessation reduces the risk of disease complications to levels of never smokers
- Smoking cessation must be considered as a firstline therapy in CD smokers

Box 2 Potential gene–environmental interactions involved in smoking and Crohn's disease (CD).

- Direct interaction with CD susceptibility gene: for example, higher carriage of ATG16L1 variant in smokers versus. non-smokers[71]
- Interactions with combinations of CD susceptibility genes: for example, interleukin 10 mutation carriage increased in smokers with NOD2 risk alleles but not non-smokers[72]
- Gene expression: for example, changes in gene expression in the bowel due to smoking[73]
- Interactions with genes predisposing to smoking identified in genome wide association studies: for example, nicotinic acetylcholine receptors, signalling pathways, protein transport, cell cycle

15 gene, indicating that these genes regulate interleukin 15 gene expression and that interleukin 15 may be important in smoking behaviour.[100] There is some evidence that interleukin 15 is increased in IBD[101] and may protect intestinal epithelial cells from damage during inflammation.[102] A recent study showed that levels of interleukin 15 were higher in CD patients who responded to infliximab treatment than in non-responders.[103] If smoking decreases interleukin 15 levels, this reduction might explain the smoking related loss of infliximab response.

CD and smoking cessation

Smoking cessation in CD is important and may be the most effective treatment.[104] An intervention study of CD, comparing those who stopped smoking after diagnosis (quitters) with non- and continuing smokers, showed that continuing smokers had significantly worse disease than quitters or non-smokers, but no difference in disease severity between quitters and non-smokers.[105] The detrimental effects of smoking in CD are not long term as the increased risk of developing CD disappears after stopping smoking for a year.[17] A 2003 study investigated the knowledge of CD patients about how smoking affected their disease. Most smokers were aware of the associations between smoking and lung disease but only ~10% recognised that smoking increased the risk and severity of CD.[106] Clinicians must ensure that smokers are aware of the effects of smoking on their disease (see box 1).

Clinical staff have a great opportunity and responsibility to encourage CD patients to stop smoking. A recent study of smokers suggested that realisation of risk led to an intention to stop smoking.[107] Successful strategies used to encourage CD patients to stop smoking have been reviewed previously.[104 108 109] A study of CD smokers showed that those with moderate disease activity were more likely to stop smoking than those with mild or severe activity; factors unrelated to CD were more influential in their decision to smoke.[110] Studies of smoking dependence support the hypothesis that a smoker's ability to stop smoking has polygenic genetic components[86 87] and overlaps with vulnerability to dependence on addictive substances.[111] Thus psychological factors should also be considered. A study investigated the impulse sensation seeking personality characteristic (ImpSS) in IBD patients. The ImpSS correlates with cigarette smoking and reflects a need for thrills, excitement, change and novelty. Multiple logistic regression analyses showed that ImpSS was a significant independent factor for CD patients being more likely to smoke than UC patients. Thus CD smokers might have a greater difficulty in stopping smoking and maintaining abstinence.[112]

Conclusions

Cigarette smoking increases susceptibility to small bowel CD and is also associated with a more aggressive disease course, failure of response to medical therapy, need for surgery and postoperative occurrence. Complications of disease and/or therapy (eg, malignancy, osteoporosis, postoperative wound breakdown) are more common in smokers than non-smokers, which has implications regarding treatment costs. In contrast, smoking does not adversely affect purely colonic CD. Smoking cessation must be considered as a primary therapy in CD smokers. The lack of knowledge regarding the pathophysiological mechanisms involved in the

effect of smoking in CD—arguably the only proven environmental determinant yet identified—highlights the need for basic research in this area.

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