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Environmental Risk Factors for Inflammatory Bowel Diseases: A Review

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Abstract

Inflammatory bowel diseases (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC) are chronic immunologically mediated diseases. The key mechanism underlying the pathogenesis of these diseases is a dysregulated immune response to commensal flora in a genetically susceptible host. Thus intestinal microbial dysbiosis, host genetics, and the external environment all play an important role in the development of incident disease and in determining subsequent disease behavior and outcomes. There are several well-defined or putative environmental risk factors including cigarette smoking, appendectomy, diet, stress and depression, vitamin D as well as hormonal influence. The effect of some of the risk factors appears to differ between CD and UC suggesting that despite shared genetic and immunologic mechanisms, distinct pathways of pathogenesis exist. There is a growing body of literature identifying risk factors for incident disease. There is less rigorous literature defining triggers of relapse, and few controlled clinical trials examining if modification of such risk factors results in an improvement in patient outcomes. This is an area of considerable patient, physician, and scientific interest, and there is an important unmet need for rigorous studies of the external environment in disease pathogenesis and subsequent course.

Keywords

Crohn's disease; ulcerative colitis; environment; smoking; diet; vitamin D

Inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) are chronic immunologically mediated diseases affecting nearly 1.5 million Americans and an estimated 2.2 million people in Europe[1, 2]. They often have their onset during young adulthood and a protracted course characterized by periods of remission and relapse, disease progression, and need for hospitalizations or surgery[2, 3]. The pathogenesis of both CD and UC is felt to be driven by a dysregulated immune response to intestinal flora in a genetically susceptible host[1, 4]. Several studies have highlighted a key role for the intestinal microbiome in the pathogenesis of these conditions[5–7]. Patients with IBD exhibit a dysbiosis in their intestine with reduced diversity of their gut microbiome in comparison to healthy

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individuals[5–7]. This dysbiosis is apparent at diagnosis[5], and is further characterized by a reduction in potentially protective bacterial subpopulations such as *Firmicutes*[8, 9] and an increased representation of potentially pathogenic bacteria such as enteroinvasive *Escherichia coli* (*E.coli*) in specific subsets of ileal CD[10]. A recent international analysis of genetic risk factors for IBD including over 75,000 patients with CD and UC identified a total of 163 distinct genetic risk loci with a majority of risk alleles being shared between both diseases[11]. The risk loci highlight several key pathways in the pathogenesis of IBD including innate immunity, adaptive immune responses, maintenance of intestinal barrier function, pathogen sensing, endoplasmic reticulum stress, and response to oxidative stress. This further emphasized the role of the intestinal microbiome and the regulation of host responses to it as key influences in the development of IBD.

The external environment is an important influence on the gut microbiome and could also influence the host immune response and integrity of the epithelial barrier. Several epidemiologic clues point to the importance of environmental influences in the development of IBD. First, there has been a significant increase in incidence of disease over the past five decades. Such an increase is consistent across several distinct ethnic groups and geographic regions, and parallels ‘westernization’ or industrialization of life style[12]. Furthermore, the regions of the world experiencing a recent increase in disease incidence are quite distinct from the classically high-risk regions of Europe and North America[13]. Furthermore, immigrants from low-incidence to high-incidence areas quite rapidly within a generation or two assume the risk of disease associated with their area of residence and in most cases, much greater than the risk associated with their country or origin. Finally, the sum total of heritability explained by the expanded genetic risk pool is still less than one-third for both CD and UC, and the concordance rate in monozygotic twins is 50% at best[4]. Thus, there appear to be several pieces of evidence from epidemiology, clinical observation, and the laboratory that suggests an important role for the external environment in mediating risk of CD and UC. Not only does this offer intriguing clues to the pathogenesis of these diseases, but also suggests that alteration of such environmental influences could potentially play a role in either primary prevention of disease or improvement of natural history in those with established disease.

Environmental Risk factors

Cigarette Smoking

The most well characterized risk factor for IBD is cigarette smoking; yet the pathogenic mechanism behind its effect is yet to be firmly established[14–18]. Current smoking confers a two-fold increase in risk of CD compared to non-smokers and this effect is slightly attenuated on smoking cessation[19, 20]. Similarly, in patients with established CD, current smoking is associated with a greater likelihood of aggressive disease including need for surgery, and earlier risk of severe recurrence and re-operation following bowel resection in CD[15–18]. In contrast, current but not former smoking appears to be protective against UC with a halving of the risk in current smokers compared to never smokers[19, 20]. However, smoking cessation is associated with a significant increase in risk of incident UC when compared to never smokers, and this effect can last as long as 10 years after cessation of

smoking[20]. The protective effect of current smoking extends to those with established UC as well; current smoking is associated with milder disease while quitting cigarette smoking has been associated with flares[21]. The exact mechanism behind the effect of cigarette smoking remains unclear[15, 16]. Use of oral moist snuff was associated with an increased risk for CD and UC in a case-control study from Stockholm[22]. However, this association was not seen in those who had never smoked suggested a synergy with cigarette smoking[22]. Passive smoking also demonstrates an effect similar in direction to active smoking but with a weaker effect[23]. The mechanism of effect, and in particular the contrasting influences on CD and UC is unclear but may be mediated in part through the effect of constituents of cigarette smoke on oxidative stress response in the mononuclear cells relevant to disease pathogenesis[24].

Appendectomy

Appendectomy similarly appears to have a divergent effect on CD and UC. Appendectomy, particularly when done prior to age 20 years, is inversely associated with risk of UC with no effect or a slight increase in disease risk for CD[25]. The exact mechanism of action remains yet to be defined, but two possibilities exist. First, it is possible that the appendectomy results in an altered intestinal microbiome that also has a protective effect on ulcerative colitis. Secondly and supported by emerging data, there is recognition of a distinct microbiome in the appendix particularly in the context of appendicitis[26–28]. This suggests that perhaps a microbiome composition predisposing to appendicitis may be protective against UC. In established UC, it has been hypothesized and supported by scattered studies that appendectomy may ameliorate disease course, though data are conflicting and of insufficient quality[29–31].

Dietary Factors

Most patients believe that diet plays a role in CD and UC[32]. Yet, this remains one of the most challenging associations to study because of its time-varying nature, difficulty in tracking it through the course of childhood and adult life, potential restrictive influence of pre-diagnosis symptoms on diet resulting in spurious associations, and differential recall between cases and controls[33–35]. However, recently several large cohort studies in the United States and Europe have brought to attention some potentially important dietary factors.

In a large prospective cohort study including 170,776 female registered nurses followed over 26 years, we identified 269 incident cases of CD and 338 cases of UC[36]. Compared to women with the lowest energy-adjusted fiber intake, intake of fiber in the highest quintile (median 24 grams per day) was associated with a significant reduction in risk of CD (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.39 – 0.90) but not UC. Interestingly, this association seemed specific for fiber from fruits in particularly, and to a lesser degree from vegetables and cruciferous vegetables. We identified no association between intake of fiber from other sources such as cereals, whole grains, or legumes. This association was also slightly stronger from small bowel compared to colonic CD. These findings support previous case control studies in pediatric CD which demonstrated a similar inverse association[37], and is supported by significant biologic plausibility. First, fiber intake may

maintain epithelial integrity and reduce translocation of potentially pathogenic bacteria such as the enteroinvasive *E.coli* proposed to play a role in the pathogenesis of CD[38]. Secondly, ligands in some sources of dietary fiber may activate the aryl hydrocarbon receptor (AhR) which is expressed widely in intestinal intraepithelial lymphocytes[39]. The AhR plays a role in protection against environmental antigens; mice deficient in AhR are more susceptible to chemical models of colitis[39]. Aryl hydrocarbon receptor ligands may also influence formation of intestinal lymphoid follicles through their effect on the innate lymphoid cells[40]. In an elegant experiment by Buonocore S *et al*., stimulation of colonic leukocytes with interleukin (IL)-23 resulted in colitis that was driven by the production of IL-17 and interferon-gamma by such innate lymphoid cells, further supporting the potential role of AhR ligands[41]. In a subsequent study, we identified that a diet high in long-chain n-3 poly unsaturated fatty acids (PUFA) was associated with a reduced risk of UC (HR 0.72, 95% CI 0.51 – 1.01) while high trans-unsaturated fatty acid intake was associated with a trend towards a greater incidence of UC (HR 1.34, 95% CI 0.94 – 1.92)[42]. Neither total fat nor specific fatty acid intake modified risk of CD. Additional work from the European Prospective Investigation into Cancer and Nutrition (EPIC) suggested a potential association between high protein intake, specifically animal protein, and IBD[43]. However, the cohort lacked power to tease out the effect on CD and UC separately. While case-control studies suggested an association between high intake of carbohydrates and refined sugars and risk of IBD, such as association has not been established from the more rigorous cohort studies[34, 35]. A third mechanism through which diet may influence risk of CD and UC is through its well recognized effect on the intestinal microbiome. Seminal work by Wu *et al*. demonstrated that long-term diet exerts a strong influence on the development of distinct enterotypes[44]. The first enterotype, rich in *Bacteroides* with reduced proportion of *prevotella* was strongly associated with animal protein intake as in a Western diet while the second enterotype rich in *prevotella* was associated with a carbohydrate-based diet. Gut microbial adaptations to diet may be an important evolutionary mechanism and conserved across different mammalian and human species[45]. Childhood diet is an important determinant of gut microbial composition[46]. In a controlled feeding environment, dietary modifications can result in early changes in the gut microbiome supporting the hypothesis that alteration in diets may trigger flares of disease[44, 47]. Dietary fat could also plausibly exert its exert through its influence on the gut microbiome. High-fat diets result in expansion of specific bacterial subpopulations that are associated with a pro-inflammatory response in the gut and mesenteric fat[48, 49].

The role of diet in established disease is less well established. Surveys of large cohorts of patients suggest considerable heterogeneity in dietary beliefs of patients[32]. While over half the surveyed patients believed that food played a role in causing relapses, the proportion of patients reporting a specific food group as a culprit for either triggering flares varied widely[32]. A study from a North American cohort similar identified a wide spectrum of foods identified as culprits resulting in worse symptoms[50]. Furthermore, both studies relied on self-report and assessed patient perception rather than a true effect of diet on intestinal inflammation.

Vitamin D

There is considerable interest in the immunologic role of vitamin D, distinct from its effect on calcium metabolism and maintenance of bone health[51–53]. The incidence of IBD tends to be higher in northern latitudes. Several groups including ours have examined geographic variation in IBD incidence even within a specific country and have suggested a greater incidence in areas associated with reduced exposure to UV light[54]. Khalili *et al*. using the Nurses' Health Study cohort described above demonstrated a lower risk for both CD (HR 0.48, 95% CI 0.30 – 0.77) and UC (HR 0.62, 95% CI 0.42 – 0.90) in women residing in southern latitudes at age 30 compared to those residing in northern latitudes[54]. Using a previously validated regression model to predict plasma vitamin D levels, we examined the effect of pre-diagnosis plasma vitamin D on risk of subsequent development of CD and UC[55]. Compared to women in the lowest quartile of predicted plasma vitamin D (median 22ng/mL), those in the highest quartile of predicted vitamin D (median 32ng/mL) had a lower risk of CD (HR 0.54, 95% CI 0.30 – 0.99). Higher dietary vitamin D intake was inversely associated with reduced risk of UC suggesting that vitamin D may have a role in the pathogenesis of both diseases with a greater strength and plausibility of association for CD. The effect of vitamin D does not appear to be restricted to incident disease. In a large multi-institutional cohort of 3,217 patients with established IBD, we demonstrated that lower plasma 25(OH)D was associated with an increased risk of surgery and IBD-related hospitalizations in both CD and UC[56]. In addition, CD patients who were subsequently able to achieve a normal vitamin D level had a reduced likelihood of surgery (odds ratio (OR) 0.56, 95% CI 0.32 – 0.98) compared to those who remained deficient. This effect is also supported by laboratory data suggesting amelioration of colitis and suppression of tumor-necrosis factor related genes in the colon of mice with administration of $1,25(OH)_2D_3$ [53, 57]. The effect of vitamin D does not appear to be restricted to disease activity alone. We also demonstrated the IBD patients with low plasma vitamin D may have increased risk of cancers, in particular colorectal cancer, and *clostridium difficile* infection[58, 59] suggesting a panoply of adverse health outcomes associated with low vitamin D levels in patients with IBD. As most of the literature on vitamin D and IBD has been observational in nature and retrospective, it has been hypothesized that vitamin D deficiency may merely be a marker of severe disease and a confounder rather than a true biologic mediator. However, animal studies support a causal role of 25(OH)D in mediating colitis in various experimental models, and limited controlled trial data suggests that vitamin D administration may reduce risk of relapses. In an elegant small clinical trial by Jorgensen *et al*., patients with CD most of whom were not on immunosuppression were randomized to receive 1200 IU vitamin D3 or placebo for 12 months. At the end of the study period, vitamin D administration was associated with a borderline statistically significant reduction in risk of relapse (13% vs. 29%, p=0.06)[60].

Psychologic and behavioral factors

IBD has been long associated with personality types, in particular neuroticism, dependency, anxiety, and perfectionism. Furthermore, psychosocial stressors are among the most common patient-reported triggers. Studies relying on patient recall of major life events have variably demonstrated an association between major life stressors, anxiety, or depression

and risk of incident IBD[61–72]. Using a large prospective cohort with assessment of depressive symptoms at different time points, we demonstrated that both recent and remote stress was associated with increased risk of CD with a stronger effect seen for recent stress[73]. A recent (within 4 years prior to diagnosis) mental health index-5 (MHI-5) score ≤ 52 was associated with two-fold increase in risk of CD (HR 2.39, 95% CI 1.40 – 3.98) with a weaker effect seen for baseline depressive symptoms (HR 1.62, 95% CI 0.94 – 2.77). Depression, anxiety, and stress have also been associated with increased rates of relapse and surgery for IBD[62, 74]. The exact mechanism behind the effect of stress on intestinal inflammation is unclear. Mice subjected to stress demonstrate increased susceptibility to both acute and re-activation of chronic colitis with more severe histologic activity[75]. Interestingly, the inflammatory response to stress through elevation of interleukin-6 levels can be ameliorated in mice by administration of antibiotics suggesting that the influence of stress on the gut microbiome may be a mechanism of its influence[76, 77].

An interesting environmental influence with emerging data is sleep. Both reduced and increased sleep has been associated with worse health outcomes. Using the Crohn's and Colitis Foundation of America (CCFA) Partners cohort, we demonstrated that reduced sleep quality during remission was associated with increased risk of relapse at 6 months in CD[78]. In a prospective cohort study, both reduced and increased sleep duration (≤ 6 hours, ≥9 hours) was associated with an increased risk of UC, further supporting the association between sleep and intestinal inflammation[78]. Further work is necessary to establish these factors as being causally linked to incident disease or relapses rather than markers of disease severity.

Other factors

Several other environmental influences have been proposed to modify the risk of IBD. Consistent with the hypothesis of the central role of the host microbiome in the pathogenesis of both diseases, antibiotic exposure has been associated with increased risk of both adult and pediatric-onset IBD[72, 79–81]. In particular, exposure during infancy or early childhood is associated with the greatest increase in risk[79, 81]. Other medications that may play a role potentially through their effect on the disruption of the epithelial barrier or host immune responses are non-steroidal anti-inflammatory drugs[82], oral contraceptives[83], and post-menopausal hormone replacement therapy[84]. Enteric infections are well recognized triggers for relapses of IBD, in particular infection with *clostridium difficile*[72, 85, 86]. The role of such infections in disease pathogenesis is less certain as symptoms from enteric infection are often indistinguishable from clinically active IBD. Infections with salmonella and campylobacter have been associated with increased risk of incident IBD, particularly within a few years of such infections[87–89]. However, this association is at least in part due to an ascertainment bias as the risk in those with a negative stool culture seems to be as high if not higher than in those with a defined infection[88]. Intriguing hypotheses have also been proposed linking air pollution exposure to both incident disease and IBD-related hospitalizations[90, 91]. However, further work in the area is required to establish or refute this association. In an elegant study, Khalili *et al*. also demonstrated rigorous physical activity to be inversely associated with CD independent of the effect of body mass index[92].

Can changing the environment prevent disease or improve outcomes?

While there is growing literature providing data in support of the association between various environmental influences, there is a significant dearth of high-quality data supporting the role of modifying such environmental influences to improve outcomes of established disease. In a large cohort of 1,115 patients with CD who were prospectively followed across six cities in Australia, those who ceased smoking prior to diagnosis had a reduced likelihood of progressing to complicated disease behavior or need for intestinal surgery[93]. The TABACROHN study demonstrated that up to a third of patients were able to achieve complete smoking cessation within 18 months of an advice-based smoking cessation strategy[94]. Smoking cessation was associated with reduced rates of relapse during a median follow-up of 29 months with the rates of flare-ups in quitters similar to non-smokers. Similarly, the need for steroids or immunosuppressive therapy was lower in quitters and nonsmokers when compared to current smokers[95]. There have been few studies of dietary intervention; a large randomized controlled trial of fish oil for the maintenance of remission of CD showed no effect[96]. Smaller studies in UC where there is greater mechanistic plausibility suggested a weak effect and merit investigation in larger cohorts[97]. The only dietary intervention consistently shown to improve outcomes in CD is the elemental diet[98, 99]. Both partial and complete enteral nutrition are associated with rates of response superior to placebo but perhaps slightly weaker than corticosteroids. Other diets popularized in the lay press such as the specific carbohydrate diet are supported only by small uncontrolled case series demonstrating efficacy and merit much more rigorous study[100]. As noted above, in a small Scandinavian study, vitamin D supplementation was associated with reduced risk of relapse in patients with CD who are in remission[60].

Pharmacologic therapy or counseling to treat depression and anxiety has not consistently demonstrated an effect on improving disease outcomes or reducing relapse. In a retrospective case series, patients who were referred for counseling, primarily for disease related stress, demonstrated a reduced rate of relapse, outpatient attendance, steroid usage, and use of other-IBD medications during the year after counseling while the control arm demonstrated no temporal decline[101]. In a small retrospective study, antidepressants were also associated with fewer relapses in the year following initiation of therapy[102]; however another study of psychotherapy identified no effect on disease[103].

Potential for Gene-Environment Interactions

All individuals may not be uniformly susceptible to the effect of the external environment. Using a prospectively recruited cohort of 634 patients with CD, 401 with UC and 337 healthy controls, we demonstrated a significant interaction between smoking and genetic variants in the cytochrome CYP2A6 / EGLN 2 locus and glutathione transferase enzymes (GSTP1) and risk of CD and UC[104]. Individuals with wild types did not demonstrate an increased risk of CD associated with ever smoking and UC with former smoking while a statistically significant effect was seen in those homozygous or heterozygous for polymorphisms at these sites. Costea *et al*. similarly suggested that an increased n-6/n-3 PUFA ratio was associated with risk of CD only in children who were carriers of specific variants of the CYP4F3 and FADS2 genes involved in the regulation of PUFA metabolism[105]. Thus, as our understanding of the role of the external environment and

genetics on disease risk expands and with the availability of larger cohorts with sufficient power to examine such interactions, it is possible that interventions to improve disease outcomes could specifically target those who are most likely to derive benefit from such changes.

Microbiome – the role of the "internal environment"

Several recent studies have highlighted the central role of the gut microbiome in the pathogenesis of IBD. While an extensive review of the work in this area is beyond the scope of this article, the changes in the gut microbiome that occur with IBD can be summarized as one of three phenomena. First, there is a reduced diversity of microbiome in IBD[6, 7, 106]. This reduction is apparent even at the time of diagnosis[5] suggesting that it is not a consequence of treatments used to manage these diseases. It is plausible that such reduction in diversity precedes the development of overt intestinal inflammation though data from ongoing prospective cohorts of high-risk individuals is essential to establish this with certainty. Second, specific disease phenotypes such as ileal CD have been associated with increased frequency of occurrence of pathogenic bacteria such as enteroinvasive *Escherischia coli*[10]. This does not occur across all disease locations, and may be specific to CD. Third, there is a reduction in frequency of 'anti-inflammatory' bacterial subgroups in those with IBD, one important such species being *faecalibacterium prausnitzii*[8, 9]. Reduced representation of this bacterium is associated with increased rates of endoscopic recurrence following resection in CD, and intragastric administration of *F.prausnitzii* results in amelioration of colitis in animal models[8, 9]. In this background, there is a need for high-quality studies linking the effect of environmental exposures outlined above to changes in the internal 'micro-environment' – namely the gut microbiome. Evidence supports this interaction may be important in understanding the role of diet[48, 107, 108], smoking[109], and stress[76, 77]. Further study may also allow for development of targeted microbial manipulations in response to external factors to prevent or treat disease. In addition, while most of the work so far, primarily limited by availability of tools for sequencing and study, have been limited to examining the role of gut bacteria, certainly other components of the intestinal microbiome may play an important role in the development and progression of these diseases. For example, in a laboratory study by Cadwell *et al*., murine norovirus infection in the setting of disordered autophagy was associated with susceptibility to intestinal inflammation[110] suggesting that such microbial factors may be particularly important in the setting of genetic predisposition or altered host-microbial response.

Conclusion

The past two decades have witnessed tremendous advances in defining the pathogenesis of CD and UC. Genetics, the gut microbiome, and the external environment all appear to play important roles in the development of disease. Of these, the external environment offers particular promise as a modifiable risk factor for both incident disease and for outcomes in those with established disease. Rigorous randomized controlled trials examining the effect of dietary and other environmental influences are required to establish or refute the role of these factors in achieving and maintaining disease remission. Genetics may influence susceptibility to specific environmental triggers and can help target an appropriate patient population most likely to benefit from such interventions. There are considerable challenges

to examining the role of environmental factors in disease pathogenesis. However, this remains an area of significant interest to both patients and providers, and one of much needed high-quality research.

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