Environmental Risk Factors for Inflammatory Bowel Disease

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Abstract: Crohn's disease (CD) and ulcerative colitis (UC) are chronic immunologically mediated diseases that often have a relapsing-remitting course in young persons. Genetic-risk polymorphisms explain less than one third of the heritability of disease. Epidemiologic and laboratory data suggest that environmental factors play a significant role in influencing the risk and natural history of disease. Smoking is the most widely and consistently described risk factor. It, however, increases the risk of CD while conferring protection against UC. The gut microbiome is a key component in the development of inflammatory bowel disease (IBD). Several external factors potentially exert an effect by influencing the composition of the gut microbiome or disrupting the intestinal barrier. These external influences include the use of antibiotics or nonsteroidal anti-inflammatory drugs and the presence of enteric infections. Data on diet have been inconsistent, but high fiber intake, particularly of soluble fiber, appears to protect against CD, whereas protein intake may increase disease risk. Vitamin D may also play an important protective role, particularly in patients with CD. Neurobehavioral factors, such as stress and depression, also influence the risk of IBD. Systematic and rigorous studies of environmental exposures in the management of IBD are needed. In particular, studies of whether environmental factors can be modified to reduce the likelihood of relapse or improve patient outcomes would be valuable.

Keywords
Crohn's disease, ulcerative colitis, environmental factors, cigarette smoking, diet, vitamin D

Inflammatory bowel disease (IBD) is a chronic intestinal disease that often has its onset during young adulthood and has a chronic relapsing-remitting course.[1,2] IBD comprises Crohn's disease (CD) and ulcerative colitis (UC). Treatment of refractory disease or disease-related complications frequently requires immunosuppressive therapy, hospitalization, or surgery.[2,3] The key mechanism underlying CD and UC is a dysregulated immune response to commensal flora in a genetically susceptible host.[4,5]

Considerable advances have been made in recent years in the understanding of the role of genes, the intestinal immune system,

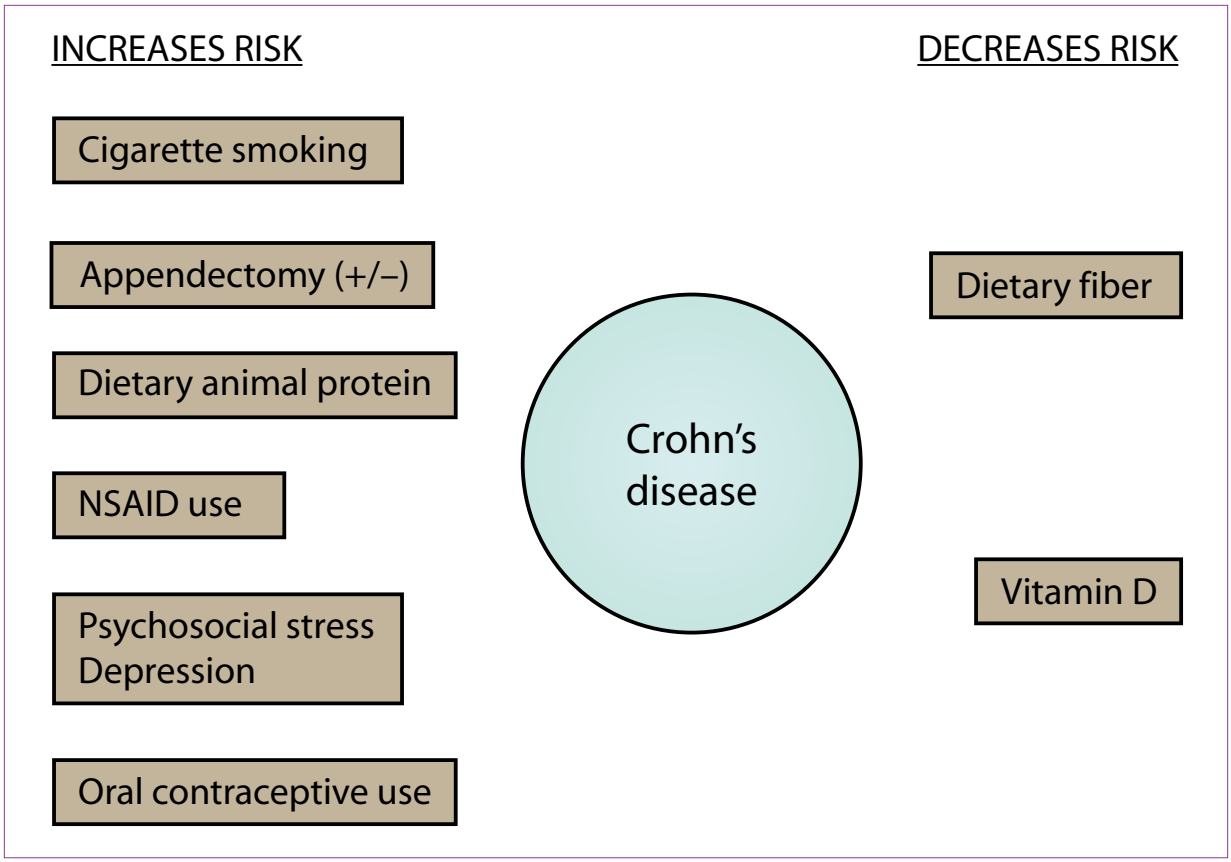

Figure 1. Environmental risk factors for Crohn's disease.
NSAID=nonsteroidal anti-inflammatory drug.

and the gut microbiome in the pathogenesis of CD and UC.[5,6] An international collaborative effort, including over 75,000 patients with CD or UC, identified 163 distinct genetic loci that modulate the risk of either disease.[6] Over two thirds of the loci were shared between both diseases; 30 loci were associated with CD alone, and 23 were UC-risk alleles.[6] Interestingly, several of the identified risk loci also play significant roles in determining susceptibility to infections and the host-microbial response, further strengthening the interaction between the gut microbiome and intestinal immune system in the development of IBD.

Yet, the expanded panel of genes explain less than one third of the heritability of either disease.[6] Epidemiologic data suggest that external environmental factors could explain a significant fraction of this gap. The rapidity of the increase in incidence of IBD in countries where IBD was previously considered uncommon—in many cases, paralleling industrial development—points to a potential role of environmental factors that are associated with the westernization of lifestyle.[7] Within 2 generations, immigrants from low-risk to high-risk countries assume the disease risk of the country of residence over that of the country of origin.[8] This review highlights several recent studies that examine environmental risk factors for IBD, confirming previously described associations and suggesting novel environmental triggers. Figure 1 and Figure 2 provide quick-glance schematics of risk factors for CD and UC, respectively.

Classic Risk Factors: Cigarette Smoking and Appendectomy

The earliest described environmental factor that is consistently associated with CD is cigarette smoking.[9-13] Current smokers have a 2-fold increased risk of CD compared with persons who have never used tobacco products.[12-14] Former smokers experience an increase in CD risk of a magnitude in between that of never and current smokers.[9,14,15] The risk of CD in former smokers lasts several years after smoking cessation.[12] In contrast, current smokers appear to be protected against the development of UC.[9,12,13,15] However, smoking cessation significantly increases the risk of development of UC. This elevation is seen within the first year of smoking cessation and can last

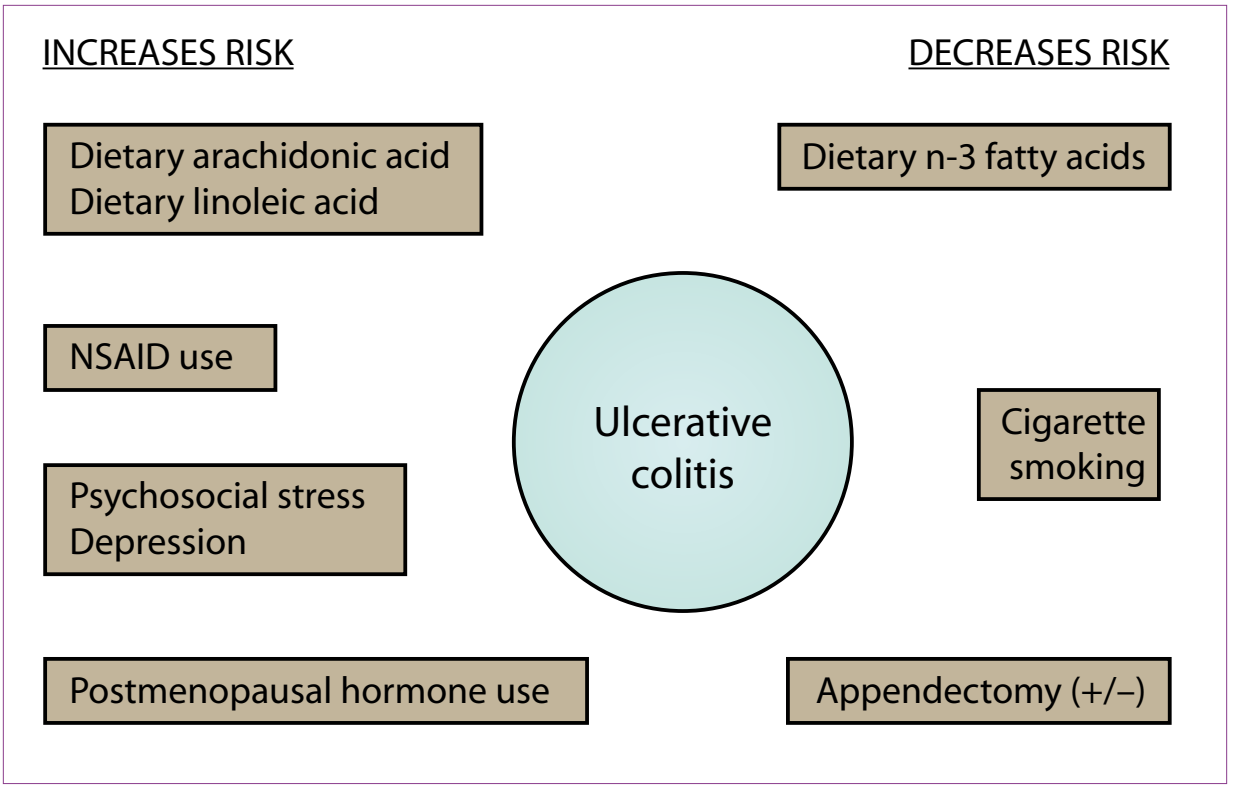

Figure 2. Environmental risk factors for ulcerative colitis.
NSAID=nonsteroidal anti-inflammatory drug.

for more than 10 years after cessation of cigarette smoking.[12] Similarly, both current and former cigarette smoking are associated with a more aggressive course of CD, including higher rates of surgery, need for therapy escalation, and disease recurrence after bowel resection.[10,11,15] Patients who stop smoking experience an improvement in disease course within 1 year of cessation.[16] In contrast, patients with UC who stop smoking cigarettes may have an increased risk of relapse.

Trials of nicotine replacement in patients undergoing treatment for UC have yielded divergent results but cumulatively suggest that nicotine replacement may have a weak effect on disease course.[17] The effect of cigarette smoking may be mediated through alteration of the composition of the intestinal microbiome, influencing the reactivity of intestinal immune cells and the generation of free radical-mediated oxidative stress.[9,18] One of the as-yet unexplained mysteries of IBD pathogenesis is why cigarette smoking exerts divergent—indeed, opposite—effects in CD and UC and why smoking cessation, in particular, is a trigger for the relapse of UC.

Gender also appears to be associated with susceptibility in relation to cigarette smoking and IBD risk. In a French study, the adverse effect of smoking was particularly prominent among women with CD.[19] That the incidence of IBD has traditionally been low in countries that have the highest rates of smoking supports the concept of variability in susceptibility to environmental influences. Conversely, the rate of smoking is lower than average in those countries with a high incidence of IBD, such as Sweden and Canada.

Similar to observations regarding smoking and IBD incidence, appendectomy also has divergent effects on CD and UC. Early appendectomy (before age 20 years) is associated with a reduction in the risk for UC[20]; however, appendectomy does not alter CD risk and may even be associated with an initial increase in risk, although whether this represents true causality or is due to diagnostic bias remains to be definitively established.[21,22]

Vitamin D: A Role Beyond Bone Health

Vitamin D usually has been examined for its role in calcium metabolism and maintenance of bone health; however, data are increasing on the immunologic role of vitamin D, particularly on the innate immune system.[23-25] This immunologic effect is mediated through the binding of the active form of vitamin D, 1alpha,25-dihydroxyvitamin D3

($1,25[OH]_2D_3$), to the vitamin D receptor (VDR). The $1,25(OH)_2D_3$ also decreases production of regulatory Th17 cells and influences function of natural killer T cells.[23,25-28] In laboratory studies, VDR-knockout mice have an increased expression of inflammatory cytokines in the colon and are more susceptible to experimental models of colitis.[26,27,29] Colitis is ameliorated[30] and tumor necrosis factor alpha–related gene expression in the colon is suppressed[31] when these mice are administered $1,25(OH)_2D_3$.

Genetic association studies of VDR polymorphisms and IBD have yielded conflicting results, with some studies supporting a positive association and others not.[32-34] The incidence of IBD demonstrates a north-south gradient, with a higher incidence of IBD in residents of northern latitudes compared with southern latitudes.[35] This variation in incidence could relate to differences in ultraviolet (UV) light exposure, a key determinant of vitamin D status. Indeed, studies have demonstrated such an inverse association between UV light exposure and incidence of CD.[35,36]

In a prospective examination of the Nurses Health Study, a large cohort of female registered nurses prospectively followed through biennial questionnaires on lifestyle exposure and health information, Ananthakrishnan and colleagues described an association between pre-illness predicted plasma vitamin D levels and the risk of CD.[37] A regression model was used to predict each woman's plasma vitamin D status. The model incorporated the region of residence, diet, body mass index, physical activity, and supplemental vitamin D use. Women who were in the highest quartile of predicted plasma vitamin D level had a 40% reduction in the risk of CD over the subsequent 22 years of follow-up compared with those in the lowest quartile (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.30–0.99).[37] There was no effect on the risk of UC. Patients with CD and vitamin D deficiency were more likely to have greater disease activity and lower health-related quality of life than those whose vitamin D levels were sufficient.[38]

A randomized controlled trial examined the role of vitamin D in the treatment of CD, with disease activity rather than bone health as the primary endpoint.[39] Patients in clinical remission who were randomly selected to receive daily oral vitamin D supplementation had a reduced risk of relapse over the subsequent 12 months compared with those receiving placebo. There have been no published studies examining whether vitamin D has a role as an active treatment modality in IBD. In light of the promising experimental and epidemiologic data and the relative safety of vitamin D, there is a need for careful and well-designed studies examining the value of therapeutic vitamin D supplementation in patients with IBD.

Disruption of the Microbiome and Intestinal Barrier: Antibiotics and NSAIDs

The interaction among the gut microbiome, the immune system, and intestinal barrier function plays a key role in IBD. Consequently, alteration of commensal flora following antibiotic use or disruption of the intestinal barrier through agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of disease.

Shaw and colleagues performed a nested case-control study of 36 children with pediatric-onset IBD (median age of onset, 8 years) from the University of Manitoba IBD database matched to 360 controls.[40] Antibiotic use within the first year of life was more common in IBD cases (58%) than controls (39%). In a follow-up study extending to adult-onset IBD, use of antibiotics 2–5 years prior to diagnosis was seen more commonly in patients with IBD than controls.[41] Furthermore, a dose-dependent effect was seen for 1, 2, or 3 or more antibiotic prescriptions. The association was seen across different classes of antibiotics. A nationwide Finnish study similarly confirmed an association between antibiotic use and CD but not UC.[42] Gender differences in susceptibility to the effect of antibiotic use or consequent microbiota disruption also may exist, but further definitive studies are required. However, it has been difficult to ascribe a directly causal role to antibiotic use because of the challenge in identifying whether antibiotics were used to treat symptoms prior to formal diagnosis of disease or if an underlying infection merited the antibiotic prescription that was the true trigger for the development of IBD.

The acute gastrointestinal adverse effects of NSAIDs are well recognized. However, the disruption of the intestinal barrier by NSAIDs also may predispose patients to chronic IBD. A case-control study of new IBD diagnoses found a higher frequency of NSAID use in cases compared with controls.[43,44] Two recent cohort studies prospectively examined this association. Chan and colleagues used the European Prospective Investigation in Cancer and Nutrition (EPIC) cohort in which CD developed in 35 participants and UC developed in 84 participants.[45] Regular aspirin intake was associated with a 6-fold increase in the risk of CD but not UC.[45] In contrast, data from the Nurses Health Study by Ananthakrishnan and colleagues suggested an association between NSAID intake and increased risk of both CD and UC.[46] Furthermore, both a dose and duration effect were identified. The increase in disease risk was most apparent in those patients with the highest frequency, greatest dose, or longest duration of use. Neither aspirin nor acetaminophen use altered disease risk.

There are less high-quality data on the effect of aspirin or NSAIDs on those with established IBD. Anecdotal reports and case-control studies suggest that use of

these agents could potentially trigger IBD flares.[44] A trial examined this hypothesis by randomizing patients to acetaminophen, diclofenac, naproxen, or indomethacin.[47] Just under one third of patients using nonselective NSAIDs experienced a symptomatic relapse of IBD accompanied by an elevation in fecal calprotectin levels within 28 days of initiating treatment. In most of these patients, relapse occurred within the first 2 weeks of NSAID use. In contrast, celecoxib use for 14 days appeared to be safe and not associated with disease relapse.[48] However, studies with a longer time horizon are needed.

Hormonal Influences

In a study of 232,452 women from 2 prospective cohorts, Khalili and colleagues demonstrated a 3-fold elevation in the risk of CD in women who were currently using oral contraceptives (OC; HR, 2.82), with a slight attenuation of risk in past users (HR, 1.39) compared with never users.[49] A consistent effect was not seen for the development of UC. In distinction to this, the meta-analysis by Cornish and colleagues identified an elevated risk for both CD and UC with OC use.[50] Corrao and colleagues postulated that up to 7% of UC and 11% of CD cases could be attributable to OC use.[51] In contrast to the OC data, postmenopausal hormone use was associated with an elevated risk of UC but not CD.[52] These divergent results could potentially be due to the different intrinsic hormonal milieu that exists in premenopausal OC users compared with users of hormonal therapy who are mostly postmenopausal.

In a Danish cohort study, Jess and colleagues identified an association between IBD (both CD and UC) and endometriosis, further supporting the role of hormonal factors in IBD.[53] There are less data on the effect of hormonal factors on disease course. In a study of 65 women with IBD, Kane and colleagues found no difference in disease course by menopausal status.[54] However, women who used hormone therapy had a significantly reduced likelihood of disease flare.

Clostridium difficile and Other Enteric Infections

A bidirectional relationship exists between infections and the development of IBD. Prior infections may lead to chronic IBD in patients with a genetic predisposition. However, coexisting IBD may predispose patients to enteric infection, in particular *Clostridium difficile* infection (CDI). The occurrence of CDI in patients with IBD has steadily increased over the past decade.[38,55,56] CDI in patients with IBD is associated with significant morbidity. Hospitalized patients with CDI-IBD have a 4-fold greater mortality risk than patients who do not have IBD-CDI.[57] In 1 study, nearly 40% of UC flares requiring hospitalization were associated with CDI.[58] Common extrinsic risk factors for CDI—antibiotic use and recent healthcare contact—appear to be less common in patients with IBD-CDI than in patients who do not have IBD but in whom CDI develops.[38] Data on whether CDI increases colectomy risk or modifies natural history of disease have been less consistent. A few studies suggest that an elevation in the risk of colectomy or need for therapy escalation may persist even 1 year after the index CDI episode.[58-60] There are no data on whether prior CDI predisposes patients to the development of IBD.

Several authors have hypothesized that enteric infections, in particular *Salmonella* and *Campylobacter,* may increase the risk of development of CDI. Gradel and colleagues found a 3-fold elevation in risk for IBD following infection with *Salmonella* or *Campylobacter* gastroenteritis, with a weaker effect after the first year postinfection.[61] Although Jess and colleagues also identified a similar association, the magnitude of effect was greater in those patients who had a negative stool study. A similar temporal pattern was seen, suggesting that the increase in IBD risk after enteric infections may be due to a detection bias.[62]

Depression, Stress, Sleep, and Neurobehavioral Factors

Depression and anxiety are common in patients with IBD.[63] However, evidence suggests that pre-illness stress, depression, or anxiety may influence the risk of IBD development.[44] Indeed, significant biologic plausibility exists for such a hypothesis. Mice subjected to depression induced through intracerebroventricular injection of reserpine demonstrate greater susceptibility to reactivation of chronic colitis, an effect blunted through the administration of amitriptyline.[64] Depression and stress also can mediate their effect through the autonomic nervous system, particularly activation of the sympathetic nervous system.[65,66] Furthermore, release of neuropeptides can influence immune cell activation, and stress can increase intestinal permeability. Less consistent epidemiologic data exist in humans.

Tocchi and colleagues found that major life events occurring within the 12 months prior to study entry were more common in hospitalized patients than matched controls (44% vs 11%).[67] A second study confirmed the association between stress and CD but not stress and UC.[68] In contrast, a large study by Li and colleagues that followed participants after major life events found no elevation in the risk of CD or UC.[69] A recent prospective analysis from the Nurses Health Study demonstrated an association between both remote and recent depressive symptoms ascertained using the 5-item mental health

index on the risk of CD but not UC.[70] The elevation in risk was stronger for recent depressive symptoms but continued to demonstrate a trend even 12 years after the assessment of depressive symptoms.

The effect of stress or psychiatric comorbidity on the natural history of disease also has been examined in a few studies. Bitton and colleagues identified an association between disease relapse with higher perceived stress or avoidance as the primary coping mechanism.[71] This was further confirmed in a prospective population-based study by Bernstein and colleagues in which high perceived stress was the only independent predictor of increased risk of disease flare (odds ratio, 2.40; 95% CI, 1.35–4.26).[72]

In a multi-institutional cohort, the presence of depression or anxiety was associated with an increased risk of CD-related surgery.[73] There are less data on whether education on stress management and coping or treatment of depression is associated with an improvement in disease course. In a retrospective study by Goodhand and colleagues, use of antidepressants was associated with a reduction in the rate of symptomatic relapses and the number of hospital admissions in the treated group.[74] Psychologic counseling was similarly associated with an improvement in health-related quality of life as well as reduction in symptomatic relapses and outpatient office visits.[75]

Diet

Diet exerts a strong influence on the composition of the intestinal microbiome.[76] Consequently, pre-illness diet could be a significant risk factor for the pathogenesis of IBD.[77,78] Rising rates of UC and CD—particularly in areas of Asia with westernization of diet, characterized by a reduction in fiber consumption and increase in processed foods and foods with high fat content—provide preliminary evidence that temporal changes in dietary habits may account for some of the regional variations in disease distribution and rising incidence rates of IBD. Until recent analysis based on large prospective cohorts with structured, pre-illness data about diet became available, identifying associations between IBD incidence and diet via retrospective studies had been challenging because of recall bias and the inability to exclude alteration in diet brought on by symptoms prior to the establishment of a formal diagnosis. Furthermore, the existing literature on dietary risk factors has yielded conflicting results.

The most consistently described dietary association with IBD has been intake of dietary fiber, fruits, or vegetables.[77,78] In a pediatric IBD cohort, Amre and colleagues demonstrated that intake of fruits and vegetables was inversely associated with the risk of CD.[79] A larger prospective adult study similarly demonstrated a strong inverse association between intake of dietary fiber and the risk of CD, with a weaker effect on UC.[80] However, the source of dietary fiber was important as well. Fiber intake from fruits and vegetables (soluble fiber) was protective against CD, whereas insoluble fiber intake from cereals, whole grain, or bran did not reduce the risk of CD or UC.[80] The data on dietary fat intake are less consistent. Many studies have failed to identify an association between overall fat intake and the risk of CD or UC.[77,78] In an analysis from the EPIC cohort, de Silva and colleagues demonstrated that higher tissue arachidonic acid content (which correlated well with dietary intake) was associated with an increase in the risk for UC.[81] Similarly, linoleic acid intake also was associated with increased risk of UC.[82] In contrast, dietary n-3 polyunsaturated fatty acid and docosahexaenoic acid intake were protective against UC.[83] Dietary intake of carbohydrates has not been consistently associated with CD or UC risk. However, increased protein intake, particularly animal protein, may be associated with increased risk of CD.[84] There have been few studies examining the association between micronutrient intake and the risk of CD or UC.

There are also limited data on whether diet predisposes patients to disease flare. Data from patient surveys suggest considerable heterogeneity regarding trigger foods.[85,86] The heterogeneity suggests either that uniform dietary triggers of relapse may not exist or that an underlying genetic predisposition may influence susceptibility to metabolic effects of dietary constituents. Given that diet is one of the most commonly reported patient concerns and that diet modification could potentially be a safe and inexpensive adjunct in the management of IBD, rigorous studies of dietary risk factors for relapse of disease as well as intervention studies of dietary modification for treatment of IBD are needed.

Conclusion

Environmental influences appear to be critical to the pathogenesis of CD and UC. Recent high-quality studies have confirmed some of the previously defined associations, such as cigarette smoking, and have identified newer risk factors, including diet, hormone use, stress, and vitamin D level status. However, while many of these factors have been described as risk factors for incident disease, few studies have examined the effect of such environmental factors on the natural history of disease, and fewer still have examined whether interventions that modify these factors can improve patient outcomes. Given the suboptimal rates of response to existing immunosuppressive therapy and persisting concerns about long-term safety and cost, systematic and rigorous studies of environmental exposures in the management of disease are needed, particularly if modification of environmental factors can

be shown to reduce the likelihood of relapse. Advances in genetics and immunology have significantly furthered the understanding of the pathophysiology of IBD. Defining environmental risk factors that may have similar or differential effects on CD and UC will further contribute to our understanding about why IBD develops in some persons as will examining the interaction between genetics and the external environment. However, it should also be recognized that changes in individual environmental factors alone (either in space or over time) are unlikely to sufficiently explain the changing epidemiology of IBD. Significant heterogeneity in susceptibility to each environmental influence likely exists among individuals, both in isolation and in codependence with other exposures in addition to underlying host genetics and microbial composition. Further studies of the role of environment in conjunction with genetics, immunologic mechanisms, and microbiota would significantly contribute to defining the mechanism of development of IBD. Further research would also potentially lead to identification of novel targets for therapy and recommendations for lifestyle and behavioral modifications that may augment existing therapy to achieve and maintain remission, prevent complications, and improve patient outcomes.

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