REVIEW

Environment and the inflammatory bowel diseases

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Inflammatory bowel diseases (IBD), which consists of Crohn disease and ulcerative colitis, are chronic inflammatory conditions of the gastrointestinal tract. In genetically susceptible individuals, the interaction between environmental factors and normal intestinal commensal flora is believed to lead to an inappropriate immune response that results in chronic inflammation. The incidence of IBD have increased in the past century in developed and developing countries. The purpose of the present review is to summarize the current knowledge of the association between environmental risk factors and IBD. A number of environmental risk factors were investigated including smoking, hygiene, microorganisms, oral contraceptives, antibiotics, diet, breast-feeding, geographical factors, pollution and stress. Inconsistent findings among the studies highlight the complex pathogenesis of IBD. Additional studies are necessary to identify and elucidate the role of environmental factors in IBD etiology.

Key Words: *Crohn disease; Environment; Epidemiology; Inflammatory bowel disease; Ulcerative colitis; Risk factors*

L'environnement et les maladies inflammatoires de l'intestin

Les maladies inflammatoires de l'intestin (MII), qui incluent la maladie de Crohn et la colite ulcéreuse, sont des maladies inflammatoires chroniques du tube digestif. Chez les personnes qui y sont génétiquement susceptibles, on pense que l'interaction entre les facteurs environnementaux et la flore commensale intestinale normale entraîne une réponse immunitaire inadéquate qui suscite une inflammation chronique. L'incidence de MII a augmenté depuis un siècle dans les pays industrialisés et les pays en développement. La présente analyse vise à résumer les connaissances actuelles sur l'association entre les facteurs de risque environnementaux et les MII. Les chercheurs ont exploré plusieurs facteurs de risque environnementaux, y compris le tabagisme, l'hygiène, les microorganismes, les contraceptifs oraux, les antibiotiques, le régime, l'allaitement, les facteurs géographiques, la pollution et le stress. Les résultats contradictoires entre les études font ressortir la pathogenèse complexe des MII. D'autres études s'imposent pour déterminer et clarifier le rôle des facteurs environnementaux dans l'étiologie des MII.

Inflammatory bowel disease (IBD), which includes Crohn disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract whose pathogenesis is not completely understood. The prevailing theory is that IBD arises from a combination of genetic susceptibility and exposure to environmental risk factors (1). Genome-wide association scans have identified more than 100 genes that increase susceptibility to CD and UC (2-3). The identification of genetic determinants have provided insight into the pathogenesis of IBD but have not fully explained disease pathogenesis. This is highlighted by a Swedish twin study (4), which demonstrated a stronger heredity factor in CD over UC among monozygotic twins, with a concordance rate of 58% for CD and only 6% for UC. Incomplete gene penetrance suggests that additional factors influence disease pathogenesis (5). Furthermore, genetic susceptibility does not explain the rise in incidence of IBD observed in developed and, now, in developing nations (6).

IBD was primarily recognized in westernized countries following the rise of the industrial revolution. The incidence of IBD dramatically increased during the 20th century (7). IBD is most prevalent in developed nations such as Canada, the United States and Western Europe (7,8). The incidence of IBD in these developed nations is as high as 20 and 24 cases per 100,000 person-years for CD and UC, respectively (8). As developing countries, such as India and China, became industrialized, the incidence of IBD has risen in parallel (9-11). Additionally, as individuals move from areas of low to high prevalence of IBD, first-generation offspring acquire the same risk of developing IBD as the local population (12,13). This shift in risk suggests that changes in environment – in addition to genetic predisposition – contribute to the development of IBD.

Multiple studies have explored the relationship between IBD and environment; however, these studies have not completely elucidated the association between the environment and IBD (14). In the present review, we explore the current knowledge of the association between commonly studied environmental exposures and IBD (Table 1).

SMOKING

Smoking has long been known to affect IBD. A meta-analysis implicated smoking as a risk factor for CD and a protective factor for UC (15). In patients with CD, smoking worsens prognosis by increasing the frequency of disease flares and the the need for surgery, in addition to increasing postoperative recurrence (16,17). Smoking cessation is a key therapeutic strategy in patients with CD (16). In contrast, smoking appears to be protective against UC, with the majority of UC patients being nonsmokers or exsmokers (18). The relationship between IBD and smoking follows a dose-response relationship, with current smokers followed by exsmokers at greatest risk for development of CD, and exsmokers followed by nonsmokers at greatest risk for UC (19-21).

However, another meta-analysis did not demonstrate an association between IBD and childhood passive smoke exposure, or prenatal smoke exposure (19). Smoking may only influence the development of IBD in adults. Passive smoking may not contribute sufficient levels of

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smoke and associated chemicals to elicit a response. However, measuring an individual's exposure to passive smoking is more difficult compared with direct smoking exposure. Thus, methodological challenges in studying passive smoking exposure may account for the lack of an observed association (22).

Smoking may influence the development of IBD through nicotinic acetylcholine receptors, which are present in mucosal epithelial cells of the bowel (23), and on T cells (24). Clinical trials of nicotine replacement in UC have yielded modest yet inconsistent results; thus, nicotine alone may not be the sole component of smoking that influences IBD (25). Other proposed mechanisms are that chemicals in smoking modulate cellular immunity (26), alter cytokine levels (27), modify colonic mucus production (28), and predispose to the development of microvascular thrombi or altered blood flow (25,29).

Although smoking is an important part of IBD pathogenesis, the highest incidence of CD actually occurs in countries with a low prevalence of smoking such as Canada (30,31). In contrast, many countries with a low incidence of CD, such as South Korea, have a much higher smoking prevalence than Canada (32). The majority of CD patients are nonsmokers and the majority of smokers do not develop CD. Thus, smoking's impact on IBD development is multifactorial and not universal.

HYGIENE AND MICROORGANISMS

Hygiene hypothesis
The hygiene hypothesis suggests that improved sanitation and reduced exposure to enteric organisms during childhood leads to inappropriate immunological responses later in life (33). Several proxy markers of childhood hygiene have been studied. Living with multiple siblings increases the exposure to enteric bacteria in childhood, which may reduce the risk of developing of IBD later in life (33,34). One study determined that CD patients are more likely to live in smaller households with fewer siblings (35). However, this was not found in UC (35). Other studies have found that having older siblings is associated with an increased risk of UC, while having younger siblings is associated with a decreased risk of CD (36). Additionally, higher birth rank has been associated with decreased risk of both CD and UC (37). Exposure to cats in early life was a risk factor in pediatric-onset CD (35). However, one study found that patients with adult-onset CD were significantly less likely to have lived with cats before five years of age (38). Living on a farm in childhood, living in more crowded homes and consuming unpasteurized milk are associated with decreased risk of IBD, although this decrease is seen more commonly in CD than UC (35,38,39).

Helicobacter pylori
H pylori, a pathogen involved in peptic ulcer disease, is a bacterium that is associated with larger family size, multiple siblings and poor sanitary conditions (40). A meta-analysis (41) reported that CD and UC are negatively associated with *H pylori*. *H pylori* increases the expression of T cell regulatory genes, such as *Foxp3*, resulting in an anti-inflammatory response (41). Alternatively, *H pylori* may not be causally related to IBD, but instead is a proxy marker of the 'hygiene hypothesis'. Reduced colonization of *H pylori* in IBD patients may be secondary to more frequent antibiotic use before the diagnosis of IBD or a consequence of improved childhood sanitary living conditions (34).

Helminths
Colonization of parasitic worms (ie, helminths) may be associated with a reduced prevalence of IBD. Helminths play an important immunoregulatory role in the intestinal flora (42,43). Open-label clinical trials of helminth treatment demonstrate a potential benefit for both UC and CD, which is likely due to the ability of the parasite to upregulate immunoregulatory and anti-inflammatory cytokines (eg, interleukin-10 and interleukin-4) (44,45). A randomized controlled trial found that UC patients treated with *Trichuris suis* ova, a type of helminth, were more likely to improve their disease state compared with UC patients who received placebo (46).

TABLE 1
Environmental risk factors for the inflammatory bowel diseases

Environmental risk factor	Strength of association*	
	Crohn disease	Ulcerative colitis
Smoking		
Current	Strong positive	Strong negative
Previous	Strong positive	Strong positive
Never	Negative	Positive
Hygiene		
Multiple siblings	Questionable negative	Questionable negative
Farm in childhood	Questionable negative	Questionable negative
Microorganisms		
Helicobacter pylori	Negative	Negative
Helminths	Negative	Negative
Myobacterium avium spp *paratuberculosis*	Positive	Not studied
Dysbiosis	Positive	Not studied
Urban living environment	Questionable positive	Questionable positive
Medication		
Nonsteroidal anti-inflammatory drugs	Positive	Positive
Oral contraceptive pills	Positive	Positive
Isotretinoin	Questionable positive	Questionable positive
Antibiotics	Questionable positive	Questionable positive
Appendectomy	Not associated	Negative
Nutrition		
Fruits and vegetables	Questionable negative	Questionable negative
Fat	Questionable positive	Questionable positive
Sugar/sweeteners	Questionable positive	Questionable positive
Animal protein	Not studied	Questionable positive
Fibre	Questionable negative	Questionable negative
Breastfeeding	Questionable negative	Questionable negative
Northern residence	Positive	Positive
Ambient air pollution		
Sulfur dioxide	Questionable not associated	Questionable positive
Nitrogen dioxide in children	Questionable positive	Questionable not associated
Nitrogen dioxide in middle-age adults	Questionable negative	Questionable not associated
Stress	Questionable positive	Questionable positive

Strength of association based on information from included studies. spp Subspecies

Mycobacterium avium subspecies *paratuberculosis*
Several diseases in animals parallel the clinical presentation of IBD. One such example is Johne's disease in cattle, which has clinical and histological similarities to CD (6). *M avium* subspecies *paratuberculosis* (MAP) has been implicated as a potential cause of CD in humans because of its similar clinical effect on Johne's disease in cattle (6). MAP is detectable in the intestinal tissue and blood of a subset of CD patients, and antimycobacterial drugs have been found, in some cases, to improve disease (47). A meta-analysis of case-control studies (48) reported a positive association between MAP and CD when either ELISA or polymerase chain reaction techniques were used to detect MAP. However, the role of MAP in CD is unclear. MAP may induce CD in a subset of patients, or CD may increase the frequency of intestinal colonization of MAP. The results of a large, double-blinded placebo-controlled trial (49) suggested that treatment of MAP was not associated with long-term remission. While the use of biologicals is associated with increased incidence of pulmonary tuberculosis in IBD patients, immune suppression is not associated with widespread

MAP infections. Thus, the exact relationship between MAP and CD remains inconclusive.

Other microorganisms

Pathogenic bacteria, such as *Salmonella* and *Campylobacter*, as well as acute gastroenteritis have been implicated in IBD pathogenesis. Adherent-invasive *Escherichia coli* was associated with the ileal phenotype of CD (50,51). CD patients with NOD2 variants, which predispose to the CD ileitis phenotype, exhibit a reduced proinflammatory cytokine response to adherent-invasive *E coli* (52). Invasive strains of *Fusobacterium nucleatum* were discovered in actively inflamed IBD patients (53). Alternatively, increased use of refrigeration has allowed psychotrophic intracellular bacteria, such as *Listeria monocytogenes* and *Yersinia enterocolitica*, to thrive in modern societies. Exposure to these pathogenic organisms may increase the risk of developing IBD (42,43).

Dysbiosis

Dysbiosis, which refers to a condition of microbial imbalances in the intestine, is associated with CD (54). A recent case-control study focused on fecal microbiota of CD patients, their unaffected relatives and unrelated controls (55), and identified five bacterial species that characterized dysbiosis: a decrease in *Dialister invisus*, *Faecalibacterium prausnitzii* and *Bifidovacterium adolescentis*; and an increase in *Ruminococcus gnavus*. The unaffected relatives, in contrast, had fewer *Collinsella aerofaceins* and more *Ruminococcus torques* than the unrelated controls (55). The mechanisms by which these bacteria contribute to CD development requires further study; however, an increase in mucin-degrading bacterium (*R gnavus*) may predispose individuals to CD (55).

Urban versus rural environment

Multiple studies have investigated the association between urban areas and IBD, yielding inconsistent results. Several observational studies have shown that the incidence of both CD and UC was increased in densely populated areas (56-58). However, other studies have failed to find an association between urban areas and IBD (59-60), whereas one European study (40) found a protective association. These inconsistencies could be due to multiple definitions of 'urban', in addition ot poor study design (22). Studies of IBD in rural areas are sparse, which could be due to poor access to information in rural areas and/or the definitions of what constitutes a rural area.

MEDICATIONS

Nonsteroidal anti-inflammatory drugs

A prospective cohort study of more than 76,000 women, as part of the Nurses' Health Study (61), identified an increased absolute risk of both UC and CD in women who used nonsteroidal anti-inflammatory drugs (NSAIDs) at least 15 days per month. Additionally, a case-control study investigating the association between NSAIDs and IBD found a positive association in UC and CD (62). In a cohort of IBD patients in remission, NSAIDs were associated with a 15% to 30% rate of relapse within nine days of ingestion (63). In contrast, IBD patients in remission did not experience a relapse while on acetaminophen (63). However, a recent population-based study of triggers of symptomatic flares in IBD (64) found that NSAIDs did not increase the risk of IBD flares. NSAIDs increase intestinal permeability by inhibiting cyclo-oxygenase, which in turn reduces prostaglandin production (65). Reduced prostaglandin production has been implicated in IBD through the inhibition of tumour necrosis factor and the induction of anti-inflammatory cytokines (65).

Oral contraceptive pills

A meta-analysis suggested that the use of oral contraceptive pills (OCPs) was positively associated with UC and CD (66). The risk of CD was greater with prolonged exposure to OCPs, and women who discontinued OCPs were no longer at a significantly increased risk for

CD. A prospective cohort study (67) found that women who continued to take OCPs were at a threefold increased risk of developing a relapse of CD; this effect was amplified among women who were prescribed OCPs and smoked.

The mechanism by which OCPs increases the risk of IBD is unknown, but the effect may be promoted by estrogen and moderated by progesterone (68). Estrogen is an immune enhancer, specifically affecting humoral immunity and proliferation of macrophages (68). In contrast, progesterone acts as an immune suppressor (68).

Isotretinoin

Isotretinoin is a retinoid (ie, a vitamin A derivative), used to regulate epithelial cell growth and to treat severe acne and certain cancers. The United States Food and Drug Administration's Medwatch program reported several cases of IBD following the prescription of isotretinoin as an acne medication (69). However, results of case-control studies have been inconsistent. One study reported that isotretinoin was associated with UC, but not CD (70), whereas another found no relationship between isotretinoin and IBD (71). Retinoids are involved in the regulation of the intestinal mucosal immune response (72); however, the mechanism by which isotretinoin influences the development of IBD has yet to be elucidated.

Antibiotics

Colonization of the gut begins after birth through the introduction of bacteria by infant diet, hygiene level and medication exposure (73). Antibiotic exposure in childhood is hypothesized to disrupt the development of the body's natural tolerance to enteric bacteria, which may lead to IBD (74,75). Several studies have demonstrated a positive association between antibiotic use and the development of IBD (75,76). Additionally, exposure to antibiotics in the first year of life was associated with an increased risk of pediatric-onset CD (77). However, antibiotics are difficult to study because patients with undiagnosed IBD may be prescribed antibiotics to treat symptoms of IBD that are believed to be due to a gastrointestinal infection (76).

APPENDECTOMY

A meta-analysis found that appendectomy posed a significant risk of CD development (78). This risk, however, was primarily observed within the first year following appendectomy when incipient CD may lead to undue appendectomies (78,79). Five years following appendectomy, the risk of developing CD was no longer significant, which suggests that a biological association between appendectomy and the development of CD may not exist (78).

In contrast, appendicitis has been consistently shown to protect against the development of UC in meta-analyses (80-82). Children who experience appendicitis before 10 years of age were at decreased risk of UC (83,84). The mechanism by which appendicitis protects against UC is not clear; however, the appendix may have a physiological role in antigen sampling and regulating the immunological response to intestinal microflora (82,85).

NUTRITION

Diet

The realtionship between diet and IBD has been studied extensively (86); however, the findings should be interpreted with caution because patients may change their diet before diagnosis to reduce disease symptoms. Studies have found that a high intake of dietary fibre, including fruits and vegetables, protects against IBD (87,88). A case-control study found that CD was associated with the intake of total fats (89). The same study demonstrated a negative relationship between carbohydrate consumption and IBD. Consumption of sugars and/or sweeteners and fats were associated with an increased risk of CD in Asian and North American populations (89,90). Similar associations were found between UC and monounsaturated and polyunsaturated fat consumption (91).

Recent prospective studies have provided new insights into the association between diet and IBD development. One hundred twenty-

six cases of UC were diagnosed in a cohort of more than 200,000 healthy adults who were followed for a median of four years. Food frequency questionnaires were administered before the diagnosis of UC. Individuals with the highest consumption of linoleic acid, which is present in red meat, oil and certain margarines, were at increased risk of developing UC (92). Another prospective cohort study involving more than 65,000 healthy middle-age women followed for a median of 4.5 years identified 77 new cases of IBD. Dietary questionnaires were completed at baseline. The results suggested that consumption of animal protein – including meat and fish, but not eggs or dairy – significantly increased the risk of IBD development (93). Ananthakrishnan et al (94) used the Nurses' Health Study to demonstrate that high-fibre intake, recorded before the diagnosis of IBD, was associated with a significant 30% risk reduction of CD. In contrast, dietary intake did not influence the development of UC (94). These studies, however, were limited by small sample sizes, which reduced the power to explore these relationships in greater detail.

Breastfeeding

Breastfeeding, which protects infants against many immune diseases, may also reduce the risk of IBD development (95). Breastfeeding helps develop oral tolerance to microflora and food antigens, which may prevent IBD (42,95). Lactoferrin, which is present in breast milk, but is absent in formula, may have anti-inflammatory characteristics (42,96). Several studies support a protective association between breastfeeding and IBD (95,97), others have found breastfeeding to be a risk factor (34,98), whereas some fail to find an association (99-101). A meta-analysis reported that breastfeeding reduced the risk of developing IBD (95). A second meta-analysis evaluating only pediatric-onset IBD demonstrated a significant protective effect for early-onset IBD (101). However, significance was lost when pooled studies were stratified according to CD and UC (101).

GEOGRAPHICAL RISK FACTORS

The prevalence of IBD has been considered in the context of a north-south gradient, with higher prevalence reported in countries with northern latitudes (6,102). For example, studies using geographical information systems demonstrate a north-south gradient in France for CD, but not for UC (103,104). However, a study published from the Nurses' Health Study (105) found that for both CD and UC, women who were diagnosed after 30 years of age had a significantly lower risk of living in a southern state than a northern state. One potential explanation is differences in exposure to ultraviolet light, resulting in relative vitamin D deficiencies in northern countries (106). The Nurses' Health Study found that women in the top two quartiles of plasma levels of vitamin D (ie, calcifediol) had significantly lower risk of developing CD compared with women in the lowest quartile (107). Activated vitamin D (ie, calcitriol) can modulate the innate immune system (108). Sunlight exposure with subsequent increased vitamin D levels, may be involved in downregulating a T-helper 1 proinflammatory response (106).

AMBIENT AIR POLLUTION

Children and young adults living in areas with high sulfur dioxide (an industrial-based pollutant) concentrations were at an increased risk of developing UC (109). Furthermore, children and young adults living in areas of high nitrogen dioxide (a known traffic-related pollutant) concentrations were at increased risk for CD (109). Paradoxically, nitrogen dioxide was negatively associated with the onset of CD in middle-age adults (109). This finding highlights that environmental exposures may have age-specific effects. Another study demonstrated that hospitalizations for IBD flares were more frequent in counties with higher concentrations of ambient air pollutants (110). Air pollution has also been implicated in triggering appendicitis (111) and nonspecific abdominal pain (112). The mechanism by which air pollution influences the development of IBD is unknown; however, animals fed urban air particles experienced a proinflammatory response and alterations in gut microflora (112). Future studies are necessary to validate these findings and to determine the biological plausibility of the effect of air pollution on IBD.

STRESS

Stress may play a role in IBD pathogenesis but is, however, more likely to modulate rather than initiate disease activity (113). Both chronic and acute stress can alter immune function and, in turn, may influence the natural course of IBD (114). Results from observational studies (114,115) are inconsistent. One prospective study found that CD patients with poor perceived stress and coping strategies were more likely to experience an early relapse of their disease (116). Animal models also suggest that chronic stress may exacerbate IBD by promoting damage to the intestinal mucosa and increasing intestinal permeability, which reduces the efficacy of the intestinal barrier against invading organisms (117,118).

SUMMARY

Several environmental factors have been associated with IBD, such as smoking, hygiene, microorganisms, OCPs, NSAIDs, antibiotics, appendectomy, diet, breastfeeding, vitamin D, stress and ambient air pollution. However, a clear mechanism by which these environmental risk factors interact to cause IBD has not been elucidated. Furthermore, most risk factors have not been consistently demonstrated across studies. The significant heterogeneity among studies may be due to methodological challenges associated with studying environmental risk factors in IBD. The next generation of environmental health studies should explore environmental risk factors in the context of genetic susceptibility and IBD phenotypes. Therefore, continued research is necessary to better identify and understand the mechanisms of environmental determinants of IBD.

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