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Environmental Factors and IBD: Elusive or non-existent?

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Abstract

Although abundant indirect evidence suggests that environmental factors contribute to the pathogenesis of inflammatory bowel disease (IBD), the search for specific etiological agents has been largely disappointing. Early life factors have been hypothesized to influence the risk of IBD; however, new data from the Nurses Health Study showed no associations between breastfeeding, gestational age, and birthweight and adult-onset IBD.

The quest for elucidating factors that contribute to the development of inflammatory bowel disease (IBD) remains elusive. Abundant indirect evidence suggests that environmental factors play a strong role in the pathogenesis of IBD. First, the rapidly increasing incidence of Crohn's disease and, to a lesser extent, ulcerative colitis in North America and Western Europe since the 1950's is more than can be explained by genetics alone. More recently, similar temporal trends have been observed in Eastern Europe and parts of Asia (1). Additional indirect evidence comes from studies of immigrants from low-incidence areas (i.e. South Asia) to high-incidence areas (i.e. Western Europe). IBD risk in immigrants, and particularly their children, is similar to (or even greater than) that of the Western Caucasian population, suggesting that factors attributable to the Western lifestyle or environment predispose to IBD(2). Finally, regional variation in IBD incidence provides additional support for the notion that environmental factors influence IBD pathogenesis (1).

How might environmental factors contribute to IBD pathogenesis? Significant preclinical evidence points towards a critical role of the commensal enteric microbiota as a key driver of host immunological responses that perpetuate intestinal inflammation in IBD. For example, IL-10 deficient mice and other animal models of IBD do not develop colitis unless exposed to, and colonized with, enteric microorganisms (3). Furthermore, colonization with different species of commensal bacterial results in different phenotypes of immune-mediated intestinal inflammation (4). One theory to explain how the gut microbiota contributes to chronic intestinal inflammation in IBD is the concept of dysbiosis. This suggests that a decrease in the ratio of protective/aggressive commensal bacteria may drive host inflammatory responses in the gut(5). Translational studies in humans provide support for the dysbiosis theory. IBD patients display a characteristic pattern of decreased complexity of

enteric bacteria manifested by decreased clostridial groups (including *F. prausnitzii*), and increased concentrations of proteobacteria (including *E. coli*) and Actinobacteria(6). Based on the dysbiosis theory, environmental factors may trigger IBD through altering the gut microbiota and its interaction with the host immune system.

What are the specific environmental factors that alter the microbiota and predispose to (or protect against) IBD? Is there a critical window in life during which these factors impact disease risk? To date, these questions remain largely unanswered. Environmental factors such as diet (including breast feeding) and the use of antimicrobial agents are well-known to influence the composition and function of the microbiota; however, such changes may only be temporary and their effects on IBD risk have not been reproducibly demonstrated. In adults, the microbiota is relatively resistant to long-term change. For example, Dethlefsen et al have demonstrated that ciprofloxacin temporarily decreases the taxonomic diversity in adults, but that the microbial composition returns to the pretreatment state within four weeks(7). However, it is possible that the effects of microbiota-related exposures on IBD risk take on greater importance when they occur during infancy. At birth, the intestinal tract is sterile. Bacterial colonization begins during vaginal delivery or with the first feeding and continues throughout infancy. Prior to weaning, the microbial diversity of the intestinal tract is relatively limited. Upon weaning, the microbiota begins to diversify and by adulthood contains greater than 15,000 species(8). Hence, as opposed to the relative stability of the microbiota in adults, the transitional state of the microbiota in infancy could represent a unique window of time during which environmental factors impacting gut colonization may influence IBD risk.

In this issue of *Inflammatory Bowel Diseases*, Khalili et al present epidemiological data on the effects of early life factors and the risk of IBD in adulthood. Using data from two large prospective cohort studies of U.S. women (Nurses Health Study I and Nurses Health Study II), they analyzed the associations between breastfeeding history, preterm birth (≥2 week preterm), and birth weight and the development of adult-onset IBD. In total, 146,681women comprising over 3,337,726 person-years of follow up were included in this analysis. All exposures and outcomes were assessed by self-report; however, the occurrence and type of IBD were confirmed by two independent gastroenterologists, blinded to exposure status, based on review of diagnostic tests and histopathology. Potential confounders including race, ethnicity, maternal smoking during pregnancy, maternal diabetes, smoking, use of oral contraceptives, and body mass index were measured using self-report, and adjusted for using Cox proportional hazards models.

The authors found no association between having been breastfed and the risk of UC (aHR 1.03, 95% CI 0.81–1.32) or CD (aHR 0.99, 95% CI 0.76–1.30). When duration of breastfeeding was evaluated, no statistical trends were observed. They also found no significant association between preterm birth or birthweight and the risk of UC or CD. For preterm birth, the aHRs were 0.69 (95% CI, 0.37–1.29) for CD and 0.82 (95% CI, 0.46–1.43) for UC. For low birthweight, the aHRs were 1.29 (95% CI, 0.79–2.11) for CD and 0.91 (95% CI, 0.55 1.49) for UC. Similarly, associations between high birthweight status and CD and UC were not statistically significant.

Important strengths of this study include the relatively large sample size and length of follow-up of the base cohorts, and the rigorous validation of all study outcomes. Additionally, the authors were able to adjust for a number of potential "later-life" confounders, such as smoking. The prospective design is another strength of this study; however, readers should be cautioned that, unlike a traditional cohort study in which exposures are assessed at the onset of the study, the Nurses Health Studies recruited adult subjects and the assessment of early life exposures was performed retrospectively. To address this, the authors attempted to validate a portion of these self-reported exposures against the subjects' mothers' report (breastfeeding and preterm delivery) or birth certificate (birthweight) and found modest correlations. Although a mother's recollection of breastfeeding or gestational age decades earlier may not be a perfect gold standard, it is unlikely that misclassification of exposure status introduced significant recall bias, particularly as exposure status was assessed prior to the development of IBD.

It is also important to note that, despite the large number of women included in the cohort, the number of actual outcomes of IBD were fairly small (248 cases of CD and 304 cases of UC) owing to the low incidence of these conditions. Therefore, this study was not adequately powered to detect modest associations between early life factors and IBD. Additionally, the number of outcomes limited the precision of the risk estimates provided, particularly for some of the categorical exposures, as illustrated by the wide confidence intervals. This may have also contributed to the authors' decision to analyze preterm status as ≤ 38 weeks, rather than using the more clinically relevant categories of late preterm (34–37 weeks), moderate preterm (29–33 weeks), and very preterm (≤ 28 weeks). An additional study limitation is that the Nurses Health Studies did not collect data on early life antibiotic use and route of delivery, and hence the authors were not able to evaluate the effects of these potentially confounding factors. Finally, the inclusion of female health professionals in the cohort may limit the generalizability of these findings to other populations. However, the age-specific incidence of CD and UC in this cohort is similar to that of other U.S. studies, as is the prevalence of other risk factors. Readers should keep in mind the numerous advantages of a cohort study comprised of health professionals, including greater accuracy of self-report and high follow-up rates.

The negative association between breastfeeding and IBD observed in the present study by Khalili et al is somewhat surprising, given the biological plausibility of the hypothesis and the results of a recent meta-analysis which demonstrated a possible protective effect for breast milk in the development of early onset IBD (Crohn's disease OR 0.64, 95% CI 0.38–1.07; ulcerative colitis OR 0.72, 95% CI 0.51–1.02)(9). There are three possible explanations for this seemingly contradictory data. First, this may be interpreted as evidence that pediatric and adult-onset IBD represent distinct phenotypes with distinct environmental risk factors. Second, it is worth considering that these discrepant data may be due to chance and uncertainty. The lower bounds of the 95% confidence intervals in the present study are 0.76 for Crohn's disease and 0.81 for UC, indicating that the present study cannot exclude a mild to moderate protective effective of breastfeeding. Finally, the possible protective effect of breastfeeding in the meta-analysis might be due to multiple sources of bias in prior studies, including recall bias, confounding, misclassification of IBD outcomes, and publication bias (failure to publish negative studies). Khalili et al are to be congratulated on

conducting a well designed study which minimizes many sources of bias and appropriately acknowledges the others, and for publishing their negative results.

Over the last decade we have witnessed groundbreaking advances in our understanding of the genetic basis of IBD. Yet, despite the overwhelming indirect evidence suggesting the role of the environment, the search for specific causal or protective factors has been largely disappointing. In the future, IBD epidemiology will need to overcome a number of methodological challenges discussed above, including the difficulty in measuring both exposures and outcomes, along with the daunting task of recruiting and following sufficient numbers of subjects for long enough time periods given the rarity of these diseases. Key components to the design of future studies must include the following: 1) accurate measurement of biologically plausible exposures and exposure periods (i.e. exposures that affect the microbiota during infancy) specified at the time of study onset 2) simultaneous collection of DNA to facilitate studies of gene-environment interactions, and 3) sufficient sample size and follow-up time to assess IBD outcomes, along with careful validation and phenotyping of these outcomes. Emphasis should be placed on modifiable risk factors (either protective or causative) in order to maximize the impact on population health and prevention.

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