# Does Consuming the Recommend Daily Level of Fiber Prevent Crohn's Disease?

**See "A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis," by Ananthakrishnan AN, Khalili H, Konijeti GG, et al, on page 970.**

The inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gut that occur in genetically predisposed individuals exposed to environmental triggers.[1] The incidence of IBD continues to increase in the Western world; further, the incidence is rising in developing nations as these countries have become more industrialized.[2] Genetic revelations indicate that the pathogenesis of IBD is closely linked to the interplay between the intestinal immune system and microbiota.[3] Thus, environmental exposures that modulate the development of IBD are likely associated with a "Westernized" lifestyle that directly influences intestinal immunology and/or alters the composition of the microbiome.[4] However, identifying environmental risk factors, such as dietary factors, is particularly challenging for conditions like IBD that are multi-phenotypic, complex, genetic disorders with long diagnostic latency periods.[5]

Diet has long been considered a modulator of risk for IBD.[6] The evolving incidence of IBD has been correlated with important changes in dietary consumption patterns, such as increased refined sugars and fat, and reduced fiber. Observational studies of dietary risk factors have, in the past, yielded inconsistent results that question the relevance of diet in the pathogenesis of IBD.[7] However, many of these studies were limited by ascertainment and selection bias, residual confounding, misclassification, and multiple comparison errors.[5] Recall bias is a particularly influential limitation. Asking IBD patients to recall dietary behaviors years earlier is fraught with errors. Furthermore, the latency period before a formal diagnosis of IBD is lengthy in many patients.[8] During the latency period, individuals may alter behaviors that could be mistakenly recorded as an environmental risk factor. Differentiating a true association from a methodology-induced error requires a prospective cohort study that captures exposures before the onset of symptoms.[5]

The authors of "A Prospective Study of Long-term Intake of Dietary Fiber and Risk of Crohn's Disease and Ulcerative Colitis" in this edition of GASTROENTEROLOGY,[9] have designed a study that brings us closer to an answer to the fundamental question of whether high fiber consumption reduces the risk of developing Crohn's disease and/or ulcerative colitis. The authors used the Nurse's Health Study (NHS), which consists of 2 cohorts of >200,000 women ranging in age from 25 to 55 years who have been prospectively followed since as early as 1976. Questionnaires were administered before new diagnoses and repeated to measure exposures across time.

This prospective cohort study identified newly diagnosed women with Crohn's disease (n = 269) and ulcerative colitis (n = 338) after 3,317,425 person-years of follow-up. Food frequency questionnaires were captured before the diagnosis of IBD and were administered repeatedly to ensure that fiber consumption was measured as a cumulative average of intake rather than at a single point in time. After adjusting for relevant confounders (eg, smoking), the authors demonstrated that women who consistently consumed a high-fiber diet were at reduced risk of developing Crohn's disease, but an association was not observed for ulcerative colitis. The findings from this study raise several provocative questions that should guide clinical practice and future scientific direction.

## Why Was Long-term Fiber Consumption Associated With Crohn's Disease, But Not Ulcerative Colitis?

Most environmental risk factors differentially influence ulcerative colitis and Crohn's disease.[4] A systematic review demonstrated that diets enriched with fiber were associated with a reduced risk of developing Crohn's disease, whereas a high-fiber diet did not reduce the risk of ulcerative colitis.[10] The current study is consistent with this systematic review showing that the effect of total fiber intake was specific to Crohn's disease.[10] The biologic mechanism that explains the protective effect of a high-fiber diet is unknown; however, it may arise from alterations in the intestinal microbiome that affect Crohn's disease differently than ulcerative colitis.[11] Moreover, microbiota likely differentially influence different phenotypes (eg, Crohn's colitis vs ileitis) within Crohn's disease.[12] Thus, future studies should evaluate whether the effect of fiber is specific to a subtype of Crohn's disease (eg, by location or behavior).

## How Much Fiber Is Needed to Reduce the Risk of Developing Crohn's Disease?

The authors stratified the study population into 5 groups based on quintiles of the cumulative average of daily fiber consumption. Women who were classified in the highest long-term fiber consumption group had a 40% reduced risk of Crohn's disease compared with women in the lowest group. The fifth quintile cohort had a median

of 24 g/d fiber compared with only 12 g/d for the first quintile cohort. A dose–response effect was not consistently observed across the 5 quintiles. Unfortunately, the number of cases of Crohn's disease was insufficient for the current study to determine a threshold level effect. Thus, future studies should confirm the presence of a threshold effect and determine the optimal dose and duration of fiber that is required to reduce the risk of Crohn's disease.

## What Source of Fiber Had the Greatest Protective Effect for Crohn's Disease?

Fruit was associated with greatest risk reduction for Crohn's disease. The median intake of fiber from fruit in the highest quintile cohort was 6 g/d, which equates to 2 fruits (eg, banana or orange). In contrast, vegetables, cereals, whole grains, bran, and legumes were not significantly associated with protection from Crohn's disease. A systematic review also demonstrated that a diet high in fruit was negatively associated with Crohn's disease.[10] In contrast, this systematic review concluded that high vegetable intake reduced the risk of ulcerative colitis,[10] which was not observed in the current study.

Several important sources of fiber were not studied, however: Fiber supplements were inadequately recorded in the NHS to assess their contribution. Furthermore, the authors were not able to separate soluble from insoluble fiber. Additionally, combination of fiber sources were not explored. Thus, future studies are necessary to tease out the exact source of fiber that maximizes the protective association with Crohn's disease.

## Is the Association Between Fiber Consumption and Crohn's Disease Owing to Reverse Causation?

Reverse causation means that the 'effect' leads to the 'cause' rather than the 'cause' leads to the 'effect.'[13] Reverse causation implies that developing Crohn's diseases causes a reduction in fiber consumption, rather than a high-fiber diet prevents Crohn's disease. For example, Crohn's disease patients with fibrostenotic ileal disease may reduce fiber consumption before their diagnosis because they recognize that high-fiber foods trigger abdominal pain. In the current study, reverse causation was addressed by evaluating cumulative exposure and including a 2–4-year lag period between the assessment of fiber consumption and the diagnosis of IBD. Further, the authors included a sensitivity analysis extending the lag period to 4–8 years, which did not affect the association for fiber from fruit and only modestly attenuated the association with total fiber. Thus, this study demonstrates that the effect of fiber temporally precedes the development of Crohn's disease.

## Can We Conclude That a High-Fiber Diet Will Protect All Individuals From Crohn's Disease?

Not yet. The NHS recruits highly educated women who are knowledgeable about health. Thus, extrapolating the findings to men and the average woman should be done cautiously. Even within the NHS, women consuming a higher fiber diet had different attributes compared with those with a low-fiber diet. For example, women in the highest quintile of cumulative fiber intake were more likely to never smoke, to have a body mass index $<30$ kg/m$^2$, and to regularly use aspirin. This group of women represents healthy women who likely have many other positive lifestyle and dietary behaviors; thus, fiber consumption may be a proxy for an unmeasured factor (ie, residual confounding) rather than being causally linked with Crohn's disease. Also, the average age of IBD diagnosis was in the 40s; thus, the findings may only be applicable for adult-onset IBD. Additionally, the sample size was small across the quintiles, which reduced the precision of the analysis and prevented meaningful assessment of effect modification. Consequently, a replication cohort with a more generalizable study population is necessary.

## How Should Clinicians Use the Information From This Study to Inform Their Clinical Practice?

The Institute of Medicine recommends that daily fiber consumption should be 14 g of fiber for every 1,000 calories.[14] Thus, the average adult women and man under the age of 50 should eat approximately 25 and 38 g/d of fiber, respectively.[14] Among the women recruited in the NHS, those in the highest fiber group consumed a median of 24 g/d of fiber. Thus, the majority of women were not following the daily recommended guidelines for fiber. The benefits of a high-fiber diet include regulation of bowel habits, weight loss, lowering cholesterol levels, and reducing the risk of diabetes.[15] The current study suggests that an added benefit to this recommendation is a 40% risk reduction in the incidence of Crohn's disease. Thus, despite the limitations of this study, gastroenterologists should educate society to follow current recommended guidelines of fiber consumption. Advocating for a high-fiber diet may ultimately reduce the incidence of Crohn's disease.

## Conclusion

Prospective cohort studies that collect validated environmental exposures and relevant confounders before the onset of symptoms and account for the time-varying nature of risk factors are necessary to clarify the role of the environment in the pathogenesis of IBD. Environmental risk factors for IBD are important to

discover because exposures can be modified to reduce the risk of developing IBD. The authors of "A Prospective Study of Long-term Intake of Dietary Fiber and Risk of Crohn's Disease and Ulcerative Colitis" in this edition of GASTROENTEROLOGY[9] have shown that a long-term diet that is enriched with fiber, particularly from fruit sources, was associated with a reduced risk of Crohn's disease. Although future studies are necessary for replication and more comprehensive exploration, physicians can use this study as added evidence to advocate for the consumption of the daily recommended fiber levels.

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***Conflicts of interest***
**The author discloses no conflicts.**


**0016-5085/$36.00**
**http://dx.doi.org/10.1053/j.gastro.2013.09.033**

# Lymphoma: The Bête Noire of the Long-term Use of Thiopurines in Adult and Elderly Patients With Inflammatory Bowel Disease

**See "Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study," by Khan N, Abbas AM, Lichtenstein GR, et al, on page 1007.**

In this issue of GASTROENTEROLOGY, Khan et al[1] report in a nationwide retrospective study a 4-fold increase in the risk of lymphoma in ulcerative colitis patients exposed to thiopurines. They confirm the extent and the reversibility of the risk reported previously in a prospective nationwide observational cohort,[2] and they additionally suggest that the risk gradually increases with duration of therapy.

Despite the increasing use of anti-tumor necrosis factor (TNF) agents, patients receiving thiopurines as monotherapy on a long-term basis still represent the vast majority of patients with inflammatory bowel disease (IBD) exposed to immunosuppressants in nationwide cohorts[3] and medico-administrative databases.[4] The main life-threatening risks attributable to the use of immunosuppressants are severe infections[5] and cancers,[6] for which the spectrum differs among immunosuppressant classes and some patient characteristics, such as age and gender. In