

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Inflammatory Bowel Disease Findings From the Nurses' Health Study I and II



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G&H What are the Nurses' Health Study I and II?

AC Established in 1976, the Nurses' Health Study I is a prospective cohort of 121,700 female registered nurses aged 30 to 55 years residing in 11 states across the country who completed an initial mail-in health questionnaire. The Nurses' Health Study II, which began in 1989, is a parallel cohort of over 116,000 female registered nurses who were between the ages of 25 and 42 years at study enrollment. Every 2 years, women in both cohorts have returned follow-up questionnaires at a response rate of over 90% to update their information. Reports of diagnoses of chronic diseases have been confirmed via review of medical records. Together, these cohorts represent over 200,000 women who have been followed very closely for their diet, lifestyle, medication use, and diagnoses of chronic diseases, including Crohn's disease and ulcerative colitis.

G&H What are the demographics of the study participants, and how representative are they of the general US population?

AC Both cohorts represent a cross-section of the nursing profession at the time of their enrollment (1976 and 1989). Thus, the study populations include relatively more white and educated women than the general US population. However, in absolute terms, there is a reasonably large number of minority participants.

There has been a common misconception that these cohorts are thus not representative of the US population in terms of behavioral or lifestyle risk factors. However,

our studies have shown that these women are actually quite reflective of the overall population of US women in terms of risk factors such as body mass index, smoking, and physical activity. In addition, the age-appropriate incidence rates of chronic diseases, such as cancer, cardiovascular disease, and inflammatory bowel disease (IBD), are quite consistent with those of the general population.

G&H What are the strengths of the studies?

AC There are several key strengths. First, the size of the cohorts allows my colleagues and I to look prospectively at the association of diet, lifestyle, and other factors and the incidence of IBD. A large cohort is needed for such studies because IBD is actually a relatively rare disease. A cohort study is more useful than a case-control study, which enrolls patients with IBD and matches them to non-IBD controls. In the latter type of study, there is always a risk that the IBD patients might recall their lifestyle and diet differently than the non-IBD controls or that other factors involved in the selection of the non-IBD controls could influence the results.

Second, because the cohorts are comprised of nurses, the study participants are very engaged and educated about their health, so they are able to provide high-quality, detailed information about their lifestyle habits and medical conditions. Their motivation and willingness to complete multiple questionnaires have enabled us to sustain a response rate of over 90% over 3 decades. This high response rate is critical for collecting high-quality data regarding risk factors for Crohn's disease, ulcerative colitis, and other medical conditions.

Third, over the course of the studies, my colleagues and I have collected blood and urine specimens from the study participants. This has provided us with the opportunity to use genetic and biochemical markers to investigate the connection between certain lifestyle factors and the incidence of IBD.

G&H What are the limitations of these studies?

AC Although the Nurses' Health Study I and II were designed to prospectively examine the associations between diet, lifestyle habits, medications, and chronic diseases, it is important to keep in mind that these studies are not randomized, controlled trials. Thus, we are not able to definitively assign causality to our observed associations. However, a clinical trial of a lifestyle intervention or medication and the subsequent development of IBD will likely never be feasible. Thus, evidence from prospective cohort studies such as ours is probably the best source of data for understanding how environmental risk factors influence IBD risk.

G&H How do the Nurses' Health Study I and II compare with previous studies on IBD and risk factors?

AC As previously mentioned, an important aspect of these cohorts is the ability to prospectively examine the association of diet and lifestyle habits with the onset of IBD. In the past, most studies of lifestyle in relation to IBD have relied on surveying patients with the disease after they have been diagnosed. The problem with these studies is that patients are prone to recall bias; patients with IBD may have an inaccurate recollection of events prior to diagnosis that may be influenced by their disease status.

In addition, many prior studies are limited by relatively small numbers of individuals, which makes it difficult to detect associations or draw definitive conclusions.

G&H Specifically, what has been learned about IBD from these studies?

AC My colleagues and I have demonstrated several interesting findings linking environmental factors with the risk of IBD. First, we determined that there is geographic variation in the incidence of IBD in the United States that mirrors the variation that has been observed in other areas of the world, such as Europe. This finding has provided us with insight into the possibility that there are important environmental determinants in IBD risk, such as exposure to ultraviolet light. Ultraviolet light is also associated with vitamin D status, which we have also shown to be linked with the development of Crohn's disease. Second,

we have corroborated what has been seen in other studies with respect to smoking. We found that smoking is a risk factor for the development of Crohn's disease, but not ulcerative colitis. Third, we showed an association between the chronic use of nonsteroidal anti-inflammatory drugs, such as ibuprofen, and the risk of IBD. Fourth, similar to prior studies, we showed that oral contraceptive use is linked with the incidence of Crohn's disease, which may be due to alterations in sex steroid hormone levels. In contrast, menopausal hormone therapy has been linked with the onset of ulcerative colitis. Finally, we have found some interesting associations between the intake of fiber and certain types of anti-inflammatory fatty acids and the risk of IBD.

Together, these studies have provided insight into the importance of the environment on whether an individual might develop IBD. As such, these studies provide an important complement to the many studies that have been conducted and published over the past several years identifying genetic susceptibility factors for IBD. Although it is well known that there is a genetic basis to the development of IBD, there has been less focus on understanding whether there are lifestyle and environmental components in the development of the disease. These studies provide an opportunity for us to understand the likely reality that both genetics and environmental factors interact to predispose individuals to the development of IBD.

G&H Have there been any surprising findings?

AC I think it has been surprising that diet is not more strongly associated with the risk of IBD. Although we have uncovered several dietary associations, such as with fiber and fat intake, the linkages have not been as strong as we had previously suspected. In addition, overall dietary patterns or diet quality do not seem to be associated with IBD, as has been the case for other diseases, such as colorectal cancer. Thus, this is an important example that not everything we assume actually turns out to be true.

G&H Are there any take-home messages that clinicians can apply in clinical practice?

AC In general, some of the risk factors that we have identified for the onset of IBD may also turn out to be determinants of clinical outcomes among patients with established disease. For example, the association between low vitamin D intake and the risk of developing IBD may lead to consideration of whether vitamin D levels might be a predictor of clinical outcomes or whether supplementation may influence disease course. There are now clinical trials of vitamin D in patients with Crohn's disease, the results of which may ultimately influence clinical practice.

G&H Are there any other plans to confirm your findings via randomized, controlled trials?

AC In addition to the trials currently underway to examine the association between vitamin D and outcomes in patients with Crohn's disease, there are other efforts looking at dietary factors in relation to IBD. For example, the association between omega-3 fatty acids and outcomes is another area of significant interest. There are also trials of various fiber agents and IBD outcomes.

G&H Are you and your colleagues still actively following these cohorts for additional study?

AC Yes, we continue to collect data on diet and lifestyle from these cohorts and follow participants closely for the incidence of additional cases of IBD. We are continuing to study environmental factors, with a focus on understanding whether there are interactions between genetic susceptibility and lifestyle. I think that these studies will be very important going forward because although genetics plays an important role in IBD, it would be naive to think that genetic risk factors operate in isolation. It is likely that one's genetic background and exposure to certain environmental influences ultimately determine disease course.

In addition, we are trying to understand whether certain biomarkers can be used to help prospectively define patients with IBD. For example, we are measuring biomarkers in blood samples taken before the onset of disease to understand whether they are predictive of risk.

Dr Chan has no relevant conflicts of interest to disclose.

Suggested Reading

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