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A Prospective Study of Long-term Intake of Dietary Fiber and Risk of Crohn's Disease and Ulcerative Colitis

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BACKGROUND & AIMS: Increased intake of dietary fiber has been proposed to reduce the risk of inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]). However, few prospective studies have examined associations between long-term intake of dietary fiber and risk of incident CD or UC. **METHODS:** We collected and analyzed data from 170,776 women, followed up over 26 years, who participated in the Nurses' Health Study, followed up for 3,317,425 person-years. Dietary information was prospectively ascertained via administration of a validated semiquantitative food frequency questionnaire every 4 years. Self-reported CD and UC were confirmed through review of medical records. Cox proportional hazards models, adjusting for potential confounders, were used to calculate hazard ratios (HRs). **RESULTS:** We confirmed 269 incident cases of CD (incidence, 8/100,000 person-years) and 338 cases of UC (incidence, 10/100,000 person-years). Compared with the lowest quintile of energy-adjusted cumulative average intake of dietary fiber, intake of the highest quintile (median of 24.3 g/day) was associated with a 40% reduction in risk of CD (multivariate HR for CD, 0.59; 95% confidence interval, 0.39–0.90). This apparent reduction appeared to be greatest for fiber derived from fruits; fiber from cereals, whole grains, or legumes did not modify risk. In contrast, neither total intake of dietary fiber (multivariate HR, 0.82; 95% confidence interval, 0.58–1.17) nor intake of fiber from specific sources appeared to be significantly associated with risk of UC. **CONCLUSIONS: Based on data from the Nurses' Health Study, long-term intake of dietary fiber, particularly from fruit, is associated with lower risk of CD but not UC. Further studies are needed to determine the mechanisms that mediate this association.**

Keywords: Population-Based Study; Diet; Fruits; Vegetables.

To date, 163 distinct genetic polymorphisms associated with risk of either Crohn's disease (CD) or ulcerative colitis (UC) have been identified, with many loci involved in regulation of the innate or adaptive immune response to the gut microbiome or maintenance of the intestinal epithelial barrier.[1,2] The external environment may also influence disease development by modification of the gut immune response, altering the composition of the microbiome, or disruption of epithelial barrier integrity. Secular changes in the external environment, such as the westernization of lifestyle, may explain observed temporal and geographic variations in incidence and distribution of disease as well as changes seen with migration.[3,4]

Diet has been long purported to modify risk of CD or UC.[5,6] However, the role of specific dietary components in the etiopathogenesis of inflammatory bowel disease (IBD) remains unclear, with studies variably implicating carbohydrates, proteins, fats, and dietary fiber.[5–11] Among these food groups, a role for dietary fiber in the predisposition to IBD appears to have particularly compelling biologic plausibility. For example, fermentable fiber is metabolized by intestinal bacteria to short-chain fatty acids, which inhibit nuclear factor $\kappa\beta$ and transcription of proinflammatory mediators.[12] In addition, fiber plays a vital role in the maintenance of intestinal barrier function.[13]

Previous investigation of the association between dietary fiber and risk of CD or UC has been limited for several reasons. First, retrospective ascertainment of preillness diet is subject both to recall bias and the alteration of dietary patterns related to symptoms of the disease preceding formal diagnosis.[11] Second, studies of specific dietary macronutrients require cohorts of sufficient size to examine individual associations as well as the influence of different sources of dietary fiber in the context of consumption of other foods in a typical diet. Third, prior studies have been limited to the pediatric IBD population[11] or have assessed diet at a single time point,[5,6] thus inadequately capturing the expected variation in long-term dietary patterns that occur over adult life.

To address these limitations, we performed a prospective study using 2 large, well-characterized cohorts of women, with validated outcomes and periodic assessments of diet across the adult life span, to examine the association between long-term intake of dietary fiber and risk of

Abbreviations used in this paper: AhR, aryl hydrocarbon receptor; CD, Crohn's disease; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; UC, ulcerative colitis.

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incident CD and UC. Furthermore, we examined the effect of fiber intake from different sources to shed light on the specific mechanisms through which dietary fiber intake may modulate risk of disease.

Patients and Methods

Study Population

Our study included participants from the Nurses' Health Study (NHS) I and II. The NHS I is a prospective cohort of 121,700 female registered nurses between the ages of 30 and 55 years at recruitment in 1976. The NHS II includes 116,686 female registered nurses between the ages of 25 and 42 years at enrollment in 1989. Both cohorts are followed up with detailed biennial questionnaires ascertaining environmental exposures and health outcomes with a follow-up rate of approximately 90%. The present study included women who completed a detailed semiquantitative dietary food frequency questionnaire (FFQ) in 1984 in NHS I and in 1991 in NHS II. Women who died before the first dietary questionnaire, had a diagnosis of cancer (except nonmelanoma skin cancer), or received a diagnosis of IBD before the baseline diet questionnaire were excluded. The study was approved by the institutional review board of Partners Healthcare.

Dietary Assessment

Intake of dietary fiber and other nutrients was assessed using validated, self-administered, semiquantitative FFQs administered in 1984, 1986, 1990, 1994, 1998, 2002, and 2006 in NHS I and 1991, 1995, 1999, 2003, and 2007 in NHS II. The 1984 FFQ included a total of 121 items, which was expanded to 136 items in 1986 and subsequent years.[14–16] For each food item, a commonly used portion size was specified and participants were asked how often they consumed the food on average over the past year. Nutrient intake was calculated by multiplying the frequency of consumption of each food item by the nutrient content based on tables provided by the Department of Agriculture. Total dietary fiber was calculated based on the method of the Association of Official Analytic Chemists. Nutrient intake was adjusted for total energy intake by the residual method. Fiber supplements were not assessed until 1994 but were taken by less than 6% of women. The 1984 FFQ also contained 15 questions on fruit consumption comprising 20 fruits and 28 questions on vegetable consumption, with similar patterns repeated on subsequent questionnaires through 2002.[14–16] Prior studies have shown the validity of the FFQ. The correlation between total dietary fiber intake measured by the FFQ and weighted records was 0.61.[17] Fiber intake from various sources correlated well with weighed portions for white bread (0.71), cold cereal (0.79), apples (0.80), bananas (0.79), tomatoes (0.73), and broccoli (0.69).[18]

Ascertainment of CD and UC

Details about the confirmation of CD and UC have been described in previous reports.[19–25] In brief, 2735 women from NHS I since 1976 and 2541 women from NHS II since 1989 self-reported a diagnosis of CD or UC on a biennial questionnaire through 2010 in NHS I and 2009 in NHS II. Self-report was followed by a detailed supplementary questionnaire inviting further information on IBD type, date of diagnosis, disease behavior, and history of treatment, as well as requesting permission to obtain medical records from the treating physician. Among the 3415 women who were still alive, did not have a diagnosis of IBD before the start date of the study, and could be contacted, 1549 subsequently denied the diagnosis based on this more detailed description of the diseases. Among the remaining 1866 patients, permission to view medical records was obtained from 1532. Medical records were reviewed by 2 board-certified gastroenterologists blinded to the exposure status. A diagnosis of CD or UC was confirmed based on accepted clinical criteria comprising typical symptoms of 4 weeks or longer and confirmatory endoscopic, surgical, histologic, and radiographic findings.[26,27] Disagreements between the 2 reviewers occurred infrequently and were resolved through consensus. Among those with sufficient medical records, a diagnosis of chronic colitis was rejected in 312 women and a diagnosis of non-IBD chronic colitis was made in 192. After excluding cases with missing information on date of diagnosis (n = 17) or dietary fiber (n = 53), our final cohort for analysis included 269 incident cases of CD and 338 cases of UC.

Covariates

Detailed information on cigarette smoking,[21] menopausal status,[22] use of oral contraceptives,[23] use of postmenopausal hormones,[22] use of aspirin, use of nonsteroidal anti-inflammatory drugs (NSAIDs),[19] and weight was collected every 2 years. Smoking, use of oral contraceptives, and use of postmenopausal hormones were modeled as time-varying covariates based on biennially updated estimates. Consistent with prior analysis, to avoid modification of weight by disease symptoms, body mass index (in kilograms per square meter) was modeled according to the baseline diet questionnaire (1984 for NHS I, 1989 for NHS II). Covariates were selected for inclusion a priori based on prior or suspected association with CD or UC based on the literature and prior data from our cohorts.[19–23]

Statistical Analysis

Participants contributed follow-up time from the date of return of the baseline FFQ (1984 in NHS I, 1991 in NHS II) to the date of diagnosis of CD or UC, death, or the return of the last questionnaire, whichever came first. A Cox proportional hazards model adjusting for potential confounders was used to estimate the multivariate hazard ratios (HRs) and 95% confidence intervals (CIs). Our main exposure, dietary fiber intake, was modeled as a cumulative average of intake through the questionnaire preceding the diagnosis and was stratified into quintiles, consistent with prior analyses using these cohorts.[14] Cumulative average intake provides the most stable estimate of adult diet in studies involving repeated measurements.[28] Tests for linear trend were conducted using the median value for each quintile as a continuous variable in the regression models. Because we observed no significant heterogeneity for the association of dietary fiber intake with CD or UC separately in NHS I and NHS II ($P > .30$), the cohorts were pooled for the final analysis, adjusting for cohort. To account for the potential modification of diet by development of symptoms before the formal diagnosis of disease, we conducted a lag analysis in which we used exposure information derived at least 2 questionnaire cycles before a follow-up interval. We performed formal tests for interaction between fiber intake and other potential risk factors by introducing a cross-product interaction term in the multivariate model. All models satisfied the proportionality of hazards assumption. We used SAS software 9.1 for all analyses (SAS