Rosacea, Use of Tetracycline, and Risk of Incident Inflammatory Bowel Disease in Women

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Q6 **BACKGROUND & AIMS:** **Rosacea is an inflammatory skin disease. Case reports have shown rosacea as a comorbidity of inflammatory bowel disease (IBD), but no epidemiologic studies have examined rosacea and risk of subsequent IBD. The association between tetracycline use and risk of IBD was assessed but produced limited findings. We examined the association between rosacea, use of tetracycline, and risk of incident Crohn's disease (CD) and ulcerative colitis (UC).**

METHODS: **We analyzed data from 96,314 participants in the Nurses' Health Study II (1991–2011). Information on IBD was confirmed by medical review. Participants were asked in 2005 about their lifetime histories of clinician-diagnosed rosacea and year of diagnosis. Information on ever use of tetracycline was collected in 1993.**

RESULTS: **During 1,856,587 person-years (1991–2011), we identified 149 cases of CD and 215 cases of UC. Rosacea was not associated with risk of UC. In contrast, rosacea was significantly associated with increased risk of subsequent CD (hazard ratio [HR], 2.20; 95% confidence interval [CI], 1.15–4.18), which appeared particularly stronger for a longer duration after a diagnosis of rosacea (P_{trend} = .01). Tetracycline use was associated with increased risk of CD (HR, 1.56; 95% CI, 1.09–2.24) and UC (HR, 1.34; 95% CI, 1.00–1.80); there was a trend toward increased risk with increased duration of use (both P_{trend} < .05) (1993–2011).**

CONCLUSIONS: **On the basis of an analysis of data from the Nurses' Health Study II, ever use of tetracycline at baseline is associated with an increased risk of CD and UC. Personal history of rosacea is associated with an increased risk of only CD.**

Keywords: Dermatologic; Side Effect; NHS; Population; Antibiotic.

Rosacea is a chronic, progressive inflammatory cutaneous disorder affecting approximately 16 million people in the United States; it is characterized by various cutaneous signs on cheeks, chin, nose, and central forehead such as flushing, erythema, telangiectasia, edema, papules, pustules, ocular lesions, and rhinophyma.[1,2] Dysfunction in the innate and (or) adaptive immune response, dysregulation in the vascular and nervous system, and its interplay with the inflammatory response have been implicated in the development of rosacea.[1,2] This not only indicates a complicated basis for initiation and aggravation of rosacea but also raises the possibility that rosacea may be an end-organ response in a systemic disorder. Case-control studies have linked rosacea to several major chronic diseases such as cardiovascular disease.[3–5] Recently we found significant association between rosacea and risk of incident basal cell carcinoma and thyroid cancer in a cohort study.[6]

Crohn's disease (CD) and ulcerative colitis (UC), the 2 predominant types of inflammatory bowel disease (IBD), are chronic relapsing inflammatory disorders of the gastrointestinal tract that arise in genetically susceptible individuals as a consequence of a dysregulated

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Abbreviations used in this paper: BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; NHS II, Nurses' Health Study II; NSAID, nonsteroidal anti-inflammatory drug; UC, ulcerative colitis.

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inflammatory response to intestinal microbes.[7,8] Although IBD may have skin manifestations, the association between skin inflammatory disorders such as psoriasis and risk of subsequent IBD has also been reported.[9] Anecdotal evidence and case reports in clinical settings have reported rosacea as a comorbidity of IBD.[10–13] However, there are no direct data on the link between rosacea and subsequent development of incident IBD. Epidemiologic studies have examined medications commonly prescribed for the treatment of rosacea and acne and risk of IBD.[14–17] However, consistent findings have been limited. We examined the association between personal history of rosacea, ever use of tetracycline at baseline for rosacea treatment, and risk of incident CD and UC during the follow-up, on the basis of the Nurses' Health Study II (NHS II).

Materials and Methods

Study Population

The NHS II began in 1989 when 116,430 U.S. female nurses aged 25–42 years completed a baseline questionnaire on medical history and lifestyle practices. Biennially, participants received a questionnaire, and a response rate exceeding 90% has been achieved in the follow-up. The study was approved by the Human Research Committee at Brigham and Women's Hospital (Boston, MA). Participants' completion and return of the questionnaire were considered informed consent.

Assessment of Main Exposure

In 2005, NHS II participants responded to a question on whether they had clinician-diagnosed rosacea and, if so, the diagnosis year (before 1991, 1991–1994, 1995–1998, 1999–2002, or 2003–2005). We collected information on the ever use of medications including tetracycline and oral isotretinoin in 1993 and antibiotics for acne or rosacea in 2005. Information on duration of use of these medications was collected in 5 categories (0, <1, 1–2, 3–4, ≥5 years) (Supplementary Table 1).

Assessment of Main Outcomes

We have previously detailed our methods for confirming cases of CD and UC.[18] Briefly, since 1989, participants have reported newly diagnosed CD or UC biennially. In addition, we have specifically queried participants about diagnoses of both UC and CD since 1993. We excluded subjects who subsequently denied the diagnosis of CD or UC on the supplemental questionnaire or denied permission for medical record review. Among those from whom we requested medical records, 93% were obtained with adequate information for review. The medical records were independently reviewed by 2 gastroenterologists blinded to exposure information. Data were extracted on diagnostic tests, histopathology, anatomic location of disease, and disease behavior (Supplementary Table 1). By using standardized criteria,[19,20] a diagnosis of UC was confirmed on the basis of a typical clinical presentation ≥4 weeks along with 1 or more characteristic changes on endoscopy, surgery, or radiology study consistent with UC. A diagnosis of CD was confirmed on the basis of typical clinical history for ≥4 weeks along with at least 1 characteristic change on endoscopy, surgery, or radiology demonstrating small bowel involvement or an endoscopic or surgical pathologic specimen consistent with CD in combination with pathology suggesting transmural inflammation or granulomatous disease. Disagreements were resolved through consensus. Suitable with the prospective follow-up for incident cases, we did not seek to confirm cases diagnosed before the cohort onset because of the limitations of obtaining medical records associated with diagnoses that were made far in the past and excluded these participants from all analyses of incident IBD. The overall case confirmation rate of the medical records reviewed was 78%.[18] Previous study in this cohort showed that the incidence rate is largely consistent with other U.S. population-based cohorts.[18]

Statistical Analysis

For the analysis of the association between rosacea and subsequent IBD, participants who provided information on personal history of rosacea served as the base population. After exclusions for missing date of birth and self-reported diagnosis of IBD at baseline, a total of 96,314 remained in the analysis. Person-years of follow-up were calculated from the return date of the 1991 questionnaire to the date of diagnosis of CD or UC, death, the last questionnaire response, or end of follow-up (June 2011), whichever came first. We assigned a date of diagnosis of rosacea according to the midpoint of the time interval in which she reported being diagnosed with rosacea in the 2005 questionnaire. In our analysis, we assigned rosacea status according to the presence or absence of the reported rosacea (as assigned by the time intervals reported in the 2005 questionnaire) before the diagnosis of CD or UC, death from any cause, the last questionnaire response, or June 2011, whichever came first. For the analysis of tetracycline, we confined to the 81,739 women who provided complete information on both medications in 1993 and calculated person-years of follow-up from the return date of the 1993 questionnaire to the date of diagnosis of CD or UC, death, or June 2011, whichever came first. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of CD and UC, respectively, by using Cox proportional hazards models, stratified by 2-year interval. Multivariate models were adjusted *a priori* for age, body mass index (BMI), alcohol consumption, physical activity, physical examination, multivitamin use, smoking status, oral contraceptive use,