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

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Abstract

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

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associated with an 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 an 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—Based on 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

Introduction

Rosacea is a chronic, progressive inflammatory cutaneous disorder affecting approximately 16 million people in the United States, characterized by various cutaneous signs on cheeks, chin, nose and central forehead, such as flushing, erythema, telangiectasia, oedema, 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 two predominant types of inflammatory bowel disease (IBD), are chronic relapsing inflammatory disorders of the gastrointestinal tract, which arise in genetically susceptible individuals as a consequence of a dysregulated inflammatory response to intestinal microbes.[7,8] While 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, based on 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 y, 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 was considered informed consent.

Assessment of main exposure (Supplementary Table 1)

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 five categories (0, <1, 1–2, 3–4, ≥5 years).

Assessment of main outcomes (Supplementary Table 1)

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 two gastroenterologists blinded to exposure information. Data were extracted on diagnostic tests, histopathology, anatomic location of disease, and disease behavior. Using standardized criteria,[19,20] a diagnosis of UC was confirmed based on a typical clinical presentation ≥4 weeks along with one or more characteristic changes on endoscopy, surgery, or radiology study consistent with UC. A diagnosis of CD was confirmed based on typical clinical history for ≥4 weeks along with at least one characteristic change on endoscopy, surgery, or radiology demonstrating small bowel involvement, or an endoscopic or surgical pathological 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 due to 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 for was 78%.[18] Previous study in this cohort showed that the incidence rate is largely consistent with other US 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 of 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 at 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, UC, death from any cause, the last questionnaire response, or June of 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 of 2011, whichever came first. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of CD and UC respectively, using Cox proportional hazards models, stratified by 2-year interval. Multivariate models were adjusted *a priori* for age, body mass index, alcohol consumption, physical activity, physical examination, multi-vitamin use, smoking status, oral contraceptive use, menopausal status and post-menopausal hormone use, use of non-steroidal anti-inflammatory drugs (NSAIDs), personal history of other common autoimmune diseases, as well as use of antibiotics for treatment of rosacea (or acne) (Supplementary Data). We used updated covariates information, whenever available. For the analysis of rosacea as the main exposure, we additionally adjusted for use of tetracycline and isotretinoin. For the analysis of tetracycline as the main exposure, we additionally adjusted for history of rosacea and use of the other medication. An indicator was created for the missing data of each covariate as appropriate.

We calculated the duration time of rosacea from the diagnosis to the date of diagnosis of IBD, death, or June of 2011, whichever came first. Based on the median duration time, we examined the categories of rosacea duration time and risk of IBD. Linear trend test was applied to evaluate the trend in incidence of IBD by rosacea duration time.

We conducted several sets of sensitivity, secondary, and interaction analyses for the association between rosacea, tetracycline use and risk of IBD (Supplementary Data).

Analyses were carried out by using SAS (version 9.2; SAS Institute Inc, Cary, NC). All *P* values were 2-tailed with the significance level set at $P < 0.05$.

Results

Among 96,314 women, 6,584 (6.8%) had been diagnosed with rosacea, with a median (interquartile range) duration time of 7 (6.5) years. Of them, 1,127 had rosacea diagnosed before 1991. Women with rosacea were older and more likely to be post-menopausal, but less likely to be current smokers or oral contraceptive users. Rosacea cases tended to be Whites and reported more physical examinations. Rosacea cases also were more likely to report diagnosis of severe teenage acne and use of tetracycline, isotretinoin, or antibiotics for treatment of acne or rosacea (Table 1).

During the follow-up (1991–2011), we identified 149 cases with CD and 215 cases with UC. Personal history of rosacea was significantly associated with an elevated risk of subsequent CD (HR=2.20, 95% CI=1.15–4.18), even after multivariate adjustment. However, we did not observe a significant association between rosacea and risk of UC (HR=0.94, 95% CI=0.45–1.95) (Table 2). For the 11 rosacea cases that developed incident CD, all were

diagnosed before age 50 years and half were diagnosed before age 45 years. Incident CD cases with a history of rosacea had a higher diagnosis age of CD than those in the non-rosacea group (Supplementary Table 2). The association between rosacea and risk of CD appeared stronger among rosacea which lasted for at least 7 years (HR=3.07, 95% CI=1.31–7.21) than those that lasted for less than 7 years (HR=1.86, 95% CI=0.75–4.60) (P_{trend}=0.01).

Further secondary and sensitivity analyses did not change the association for CD materially (Supplementary Table 3). The HRs (95% CIs) were 2.19 (1.15–4.18) (additionally adjusting for severe teenage acne), 2.45 (1.28–4.69) (excluding those reporting severe teenage acne), 2.43 (1.22–4.84) (excluding those using tetracycline or isotretinoin, or antibiotics for acne or rosacea), 2.19 (1.15–4.17) (additionally adjusting for depressive systems and UV index), 2.36 (1.24–4.51) (excluding those with other major autoimmune diseases), 2.06 (0.98–4.34) (excluding cases identified in the first follow-up period), and 2.04 (1.04–4.00) (restricting to Whites), respectively. For the analysis restricting follow-up to 1991–2005, we found even stronger association of rosacea with risk of CD (HR=2.56, 95% CI=1.21–5.44). We did not find significant interactions between rosacea and smoking for CD (P_{int}=0.56) or UC (P_{int}=0.52).

For the analysis of tetracycline use for rosacea treatment, we identified 126 cases of CD and 185 cases of UC during the follow-up (1993–2011). Tetracycline use was associated with an 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 towards elevated risk of CD and UC with increasing duration of tetracycline use (P_{trend}=0.02 for CD and 0.009 for UC) (Table 3). Distribution of the diagnosis age of incident IBD cases according to tetracycline ever use is shown in Supplementary Table 4. The secondary analyses excluding all participants that reported a history of rosacea or acne and the lag analysis did not change the results materially (data not shown). We did not observe significant statistical interactions between tetracycline use and smoking (P_{int}=0.28 for CD and 0.45 for UC), or between tetracycline use and rosacea (P_{int}=0.77 for CD and 0.27 for UC).

Discussion

In our study, women with a history of rosacea had a statistically significantly elevated risk of CD. Ever use of tetracycline use at baseline was also shown to be associated with an increased risk of both CD and UC during the follow-up. To our knowledge, our study is the first to reveal such an association between rosacea and risk of incident CD and the first prospective study to reveal an association between tetracycline use and risk of incident IBD.

Inflammation may be a potential link between rosacea and CD. Genetic studies have indicated immune response-related genetic predisposition potentially shared by rosacea and IBD. Although little evidence is available on the genetic basis of rosacea, a recent genome-wide association study found that variants in three major histocompatibility complex (MHC) class II protein-coding genes (*HLA-DRB1*03:01*, *HLA-DQB1*02:01* and *HLA-DQA1*05:01*) were associated with rosacea.[21] Recent fine mapping of MHC regions in IBD also suggested a primary role for *HLA-DBR1*03:01*.[22] In addition to genetic predisposition,

UV radiation and lifestyle factors may be associated with rosacea, which requires large prospective studies to confirm.[1,2,23,24] The associations may not be explained by acne, major medications, and physical examination. We only showed an association for CD but not for UC. This suggests that the positive association with CD is not likely due to a diagnosis bias owing to increased medical care among individuals with rosacea.

We did not observe an increased risk of incident UC associated with rosacea, similar with our previous study that showed an association between psoriasis and risk of CD only.[9] One recent meta-analysis also showed that exposure to antibiotics may increase the risk of incident CD but not UC[25]. CD and UC have distinct features, which may partly explain the difference in their association with rosacea. CD and UC display varied cytokine profiles.[7,8] The genetic disposition of CD and UC may also be different. For example, whereas the contribution of class I and class II HLA variants to disease risk is relatively equivalent in CD, HLA class II variation has a more important role in UC.[22] As case reports have reported rosacea and UC as comorbidities[10], further study is warranted to elucidate the mechanisms underlying the observed differential associations for CD and UC.

Few studies are available on tetracycline use and IBD risk. One retrospective cohort study found that tetracycline use may be associated with CD but not with UC.[16] Our prospective study adds to the literature that tetracycline ever use at baseline may be associated with both CD and UC, adjusting for history of rosacea and acne and other confounders. Therefore, disease itself or increased medical surveillance may not explain our findings. However, the mechanisms underlying the associations are still unclear.

Rosacea and acne are chronic inflammatory skin conditions that share an inflammatory pathogenesis. However, rosacea and acne are clinically and etiologically quite distinct.[7] For example, *Propionibacterium acnes* is connected with acne but not found to be involved in pathogenesis of rosacea. Studies on the association between acne, rosacea, and risk of incident cancer also yielded distinct findings[6,26]. Our sensitivity analyses adjusting for history of severe teenage acne or excluding those with severe teenage acne did not change the associations between rosacea and risk of CD appreciably.

Our study was strengthened by the systemic follow-up, confirmed IBD diagnosis by medical record review, and detailed information on potential confounders. Our study has limitations. First, there may be etiologic heterogeneities underlying different types of rosacea[2,27] but we were not able to examine the associations by rosacea subtypes.

Second, our study has retrospective feature for the analysis of rosacea as the main exposure. Information on personal history of rosacea was self-reported in 2005, which may introduce recall bias. We therefore conducted analyses to examine the potential reverse-causation bias. Moreover, because the participants were health professionals, a high validity of the rosacea self-report was expected. Information on rosacea was not updated after 2005. As some non-cases of rosacea may get rosacea during the follow-up of 2005 to 2011, this may have brought in misclassification and led to a conservative effect estimate of the association between rosacea and risk of IBD.

Third, we did not have information on other therapies for rosacea other than major medications, and were not able to evaluate the possible effects of treatment such as radiotherapy. However, no known association has been revealed for radiotherapy and risk of IBD.

Fourth, information on ever use of tetracycline and duration of use was only asked once in 1993 and not updated, which may inevitably lead to misclassification for tetracycline use during the follow-up (1993–2011). There was no clear information about the temporal relationship between tetracycline use and diagnosis of rosacea, although we guarantee the prospective design on tetracycline ever use and risk of incident IBD. We do not have information on exact timing of tetracycline use or the use after 1993.

Fifth, because of the modest case numbers in the exposed group, statistical power was limited. For the analysis on the association between rosacea and risk of IBD, the modest case number in the rosacea group precluded from detailed subgroup analyses. Previous studies have also examined use of tetracycline and isotretinoin risk of IBD, but the results were inconsistent.[14,15,17] However, we do not have enough statistical power to examine the association between use of isotretinoin use and risk of IBD in our study.

Sixth, it would be interesting to examine whether a bi-directional relationship between rosacea and IBD exists. Because we did not seek to confirm prevalent IBD cases diagnosed before the cohort initiation given the prospective design of NHS II, we did not examine IBD as the exposure. Although age less than 30 years (particularly 20–29 years) represents a peak period of IBD incidence, our cohort was able to capture the majority of incident IBD cases[18,28]. There is also no clear biological rationale that the mechanisms supporting an association between rosacea and risk of IBD would differ for IBD diagnosed at different ages. Nevertheless, we acknowledge that generalization of our findings to IBD cases at younger age of onset should be cautious.

Seventh, an epidemiologic study cannot rule out the possibly of unmeasured or imperfectly measured confounders. Whether the association of CD with rosacea and tetracycline use may still be partly attributable to each other remains unclear.

In conclusion, our data from a large, well-maintained, cohort study suggest a possible association between personal history of rosacea and an increased risk of CD, which may not be entirely explained by increased medical surveillance or medication use. We provide evidence further supporting that rosacea may represent a systemic disorder beyond a skin condition. We also found an association between ever use of tetracycline at baseline and risk of subsequent both CD and UC during the follow-up. Further efforts are warranted to examine the risk of IBD by the status and duration of tetracycline use, taking into consideration of the continuous or intermittent use during the follow-up for a comprehensive pharcoepidemiologic assessment. Our epidemiologic study cannot prove cause and effect. Further prospective studies with large sample size are warranted to replicate our findings and to examine the underlying etiological mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
CD	Crohn's disease
HR	Hazard ratio
IBD	inflammatory bowel disease
NHS II	Nurses' Health Study II
NSAIDs	non-steroidal anti-inflammatory drugs
UC	ulcerative colitis

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Table 1

Age-adjusted baseline characteristics of women according to history of rosacea (1991)

Characteristics[†]	Rosacea	
	No (*n*=95,187)	Yes (*n*=1,127)
Age (SD)	36.2 (4.7)	37.6 (4.1)
Caucasian, %	92.8	96.7
Body mass index, kg/m^2 (SD)	24.6 (5.3)	25.0 (5.9)
Alcohol consumption, g/wk (SD)	3.1 (6.1)	2.9 (5.3)
Physical activity, metabolic equivalent hours/week (SD)	116.7 (292.1)	92.3 (259.1)
Multi-vitamin use, %	45.8	46.1
Current smoker, %	11.6	8.9
Current oral contraceptive use, %	10.5	9.7
Postmenopausal women, %	7.5	8.4
Non-steroidal anti-inflammatory drug use, ≥2 tablets/wk, %	19.1	19.7
Physical examination, %	89.7	92.6
History of severe teenage acne, %	8.1	13.0
Antibiotics use for treatment of acne or rosacea[*], %	6.9	41.1
Tetracycline use[*], %	44.7	72.1
Isotretinoin use[*], %	1.7	4.5
History of other common autoimmune diseases[#], %	1.7	4.0

[†]Variables other than age are age-adjusted.

[*]Information on ever use of tetracycline/isotretinoin was collected in 1993. Use of antibiotics was collected in 2005.

[#]Including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and multiple sclerosis.

Table 2

Personal history of rosacea and risk of incident IBD (1991–2011)

	Person-years	Cases	Age-adjusted HR	Multivariable-adjusted HR†
Crohn's disease				
No rosacea	1,786,216	138	Ref (1.00)	Ref (1.00)
Rosacea	70,371	11	2.20 (1.18–4.09)	2.20 (1.15–4.18)
Ulcerative colitis				
No rosacea	1,786,216	207	Ref (1.00)	Ref (1.00)
Rosacea	70,371	8	1.05 (0.51–2.13)	0.94 (0.45–1.95)

†Adjusted for age, BMI, alcohol consumption, physical activity, physical examination, multi-vitamin use, smoking, oral contraceptive use, menopausal status and menopausal hormone therapy, use of NSAIDs and use of medications including tetracycline, isotretinoin and antibiotics.

Table 3

Use of tetracycline and risk of incident IBD (1993–2011)

	Person-years	Cases	Age-adjusted HR	Multivariable-adjusted HR†
Crohn's disease				
No use	855,072	56	Ref (1.00)	Ref (1.00)
Use	699,316	70	1.54 (1.09–2.19)	1.56 (1.09–2.24)
<1 year	536,245	55	1.58 (1.09–2.30)	1.55 (1.06–2.26)
≥1 year	163,071	15	1.42 (0.80–2.51)	1.61 (0.88–2.95)
P for trend			0.04	0.02
Ulcerative colitis				
No use	863,344	88	Ref (1.00)	Ref (1.00)
Use	706,182	97	1.34 (1.01–1.79)	1.34 (1.00–1.80)
<1 year	541,556	69	1.25 (0.91–1.71)	1.24 (0.90–1.71)
≥1 year	164,626	28	1.66 (1.08–2.53)	1.77 (1.12–2.80)
P for trend			0.01	0.009

†Adjusted for age, BMI, alcohol consumption, physical activity, physical examination, multi-vitamin use, smoking, oral contraceptive use, menopausal status and menopausal hormone therapy, use of NSAIDs, personal history of rosacea, common autoimmune diseases, use of antibiotics and isotretinoin use.