Published in final edited form as:

Gastroenterology. 2018 December ; 155(6): 1764–1775.e2. doi:10.1053/j.gastro.2018.08.029.

Identification of Menopausal and Reproductive Risk Factors for Microscopic Colitis – Results From the Nurses' Health Study

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- Hamed Khalili – Study concept and design, data acquisition, analysis and interpretation of data, drafting manuscript, critically revising manuscript

All authors have approved the final version of the manuscript, including the authorship list.

Potential Conflicts of Interest:

- Hamed Khalili receives consulting fees from Abbvie, Takeda, and Samsung Bioepis. Hamed Khalili also receives grant support from Takeda.
- Ashwin N. Ananthakrishnan served on the scientific advisory board of Abbvie, Takeda, Gilead, and Merck and had grant support from Pfizer Inc.
- Andrew T. Chan receives consulting fees from Janssen, Pfizer Inc., and Bayer Healthcare.
- The remaining authors have no conflicts to disclose.

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Abstract

Background and Aims—Microscopic colitis is a chronic inflammatory disorder of the colon primarily affecting postmenopausal women. However, the relationship between hormonal determinants, including reproductive and menopausal factors, and risk of microscopic colitis has yet to be characterized.

Methods—We collected data from 227,766 women who participated in the Nurses' Health Study (NHS) and NHSII without a baseline history of microscopic colitis. Reproductive and menopausal factors were assessed in 1988 in the NHS and 1989 in the NHSII, and updated biennially. Cases of microscopic colitis were confirmed through review of pathology records. We used Cox proportional hazards modeling to estimate hazard ratios (HRs) and 95% CIs.

Results—Through 2014 in NHS and 2015 in NHSII, we confirmed 275 incident cases of microscopic colitis over 5,147,282 person-years. Compared to never-use, current use of menopausal hormone therapy was associated with increased risk of microscopic colitis (multivariable-adjusted HR = 2.64; 95% CI 1.78 – 3.90). The risk increased with longer duration of use ($P_{\text{trend}} < 0.0001$) and diminished following discontinuation ($P_{\text{trend}} = 0.002$). The association did not differ according to disease subtype ($P_{\text{heterogeneity}} = 0.34$). Similarly, ever-use of oral contraceptives was associated with increased risk of microscopic colitis (multivariable-adjusted HR = 1.57; 95% CI 1.16 – 2.13). There were no associations between age of menarche, parity, age at first birth, age of menopause, or menopause type, and incident microscopic colitis.

Conclusions—In 2 large prospective cohort studies, we observed an association between exogenous hormone use and incident microscopic colitis. Further studies are needed to determine the mechanisms underlying these associations.

Graphical Abstract

Keywords

Parity; Age of Menopause; Collagenous Colitis; Lymphocytic Colitis

Introduction

Microscopic colitis is a chronic inflammatory disorder of the large intestine with a rising incidence.^{1, 2} Although the etiopathogenesis of the disease remains largely unknown, it is thought that it occurs as a result of inappropriate immune response to commensal bacteria or luminal antigens in genetically predisposed individuals.^{1, 3, 4} Prior epidemiologic findings have identified older age and female gender to be strongly associated with increased risk of microscopic colitis.^{1, 2, 5–13} Similarly, the disease incidence appears to be highest among postmenopausal women, suggesting that hormonal factors may play a critical role in development of microscopic colitis.^{1,12}

Reproductive and menopausal factors that lead to alterations in endogenous sex hormones have previously been linked to a number of immune-mediated disorders, such as rheumatoid arthritis and systemic lupus erythematosus, which have similar patterns of disease demographics (i.e., female predominance) to microscopic colitis.^{14–16} Additionally, exogenous use of hormones in the forms of oral contraceptives (OCPs) and menopausal hormone therapy (MHT) have previously been linked to the incidence and progression of other inflammatory bowel disorders.^{17–20} The role of estrogen in the pathogenesis of other inflammatory bowel diseases is thought to be related to the modification of gut barrier function and mucosal immunity,^{21–23} pathways critical in the pathogenesis of microscopic colitis.^{24–26} Nevertheless, the relationship between these hormonal factors and risk of microscopic colitis has not been well-established.

We therefore sought to examine the association between reproductive and menopausal factors and risk of microscopic colitis in two large prospective cohorts of US women, the Nurses' Health Study (NHS) and NHSII. With over 20 years of follow-up and detailed and updated information on lifestyle factors, these cohorts offered us the unique opportunity to examine the relationship of menopausal and reproductive factors with risk of microscopic colitis.

Methods

Study Population

The NHS consists of 121,706 female US nurses who have returned mailed health questionnaires biennially since 1976. The NHSII is a similar ongoing prospective cohort study of 116,684 female nurses that have returned biennial health questionnaires since 1989. For both cohorts, follow-up questionnaires have been returned with a greater than 85% response rate. As biopsies were not routinely taken for diagnosis of microscopic colitis until the late 1980s,¹ we restricted the follow-up of this study to 1988 through the 2014 questionnaire for NHS and to 1989 through the 2015 questionnaire for NHSII. At baseline, we excluded participants who reported a history of Crohn's disease, ulcerative colitis,

indeterminate colitis, cancer (except for non-melanoma skin cancer), or were lost to follow-up or died prior to the start of the study period (**Figure 1**). Additionally, for reproductive factor analyses, we excluded participants who had missing information on use of OCPs at baseline. Similarly, in analyses of menopausal factors, we excluded participants who did not provide information on menopause status and limited our analyses to postmenopausal women. This study was approved by the Partners Healthcare Institutional Review Board.

Assessment of Reproductive Factors

Age of menarche was queried at baseline for both NHS (1976) and NHSII (1989). Women in NHS reported OCP use from 1976 – 1984. OCP use was not queried after 1984, as the median age of the cohort was 47 and < 1% of participants had reported OCP use in 1982. In NHSII, OCP use was queried from 1989 – 2009, at which time nearly all participants were postmenopausal. Reported OCP use has been validated in NHSII in a study of 215 randomly-selected women that underwent interview of structured life events, with 99% agreement between questionnaire and interview response.²⁷

Women in NHS reported age at first child birth once in 1976. In NHSII, women reported age at first child birth biennially from 1989 – 2009. Number of children (parity) was queried biennially from 1976 – 1984 in NHS. Similarly, in NHSII, parity was queried from 1989 – 2009.

Assessment of Menopausal Factors

At baseline (1976 in NHS, 1989 in NHSII), women were asked if they were postmenopausal and whether or not they were taking MHT. Information on MHT use, duration of use, and time since cessation of MHT were updated biennially through follow-up. Missing values for duration of MHT use and time since cessation of MHT were present in 1% of ever-users and were set to the median values for each variable. Information on type of MHT use was also collected in the categories of oral conjugated estrogen, combined estrogen and progesterone, progesterone alone, estrogen and testosterone, and vaginal-only formulations.

Beginning in 1984 in NHS and 1989 in NHSII, participants were asked to provide information about their age at menopause and type of menopause (natural; surgical – hysterectomy without oophorectomy, hysterectomy with unilateral oophorectomy, hysterectomy with bilateral oophorectomy, oophorectomy alone; radiation/chemotherapy). Age at menopause and type of menopause were queried every two years through 2004 in NHS, at which time all women were older than 60 years and assumed to be postmenopausal. In NHSII every follow-up biennial questionnaire asked participants to update their menopausal status and type of menopause. To ensure that age of menopause is an accurate reflection of hormonal changes for women whose periods ceased due to hysterectomy without oophorectomy, age at menopause was calculated using a life-table based on date of surgery, MHT, and smoking status. Menopausal status has been validated in a subset of NHS participants, with reproducibility of menopause status of 98.8% between the 1978 and 1980 questionnaires.²⁸

Assessment of Covariates

Height, weight, and smoking status (current, past, never) were queried in the 1976 questionnaire for NHS and the 1989 questionnaire for NHSII. Weight and smoking status were updated biennially over the follow-up period. Body mass index (BMI) was calculated using height and weight. Self-reported weight was validated in 1990 through measurements of a subset of 140 NHS participants with high correlation ($r = 0.97$).²⁹

Beginning in 1990 and every 2 years since, the NHS questionnaire was expanded to include information on use of non-steroidal anti-inflammatory drugs (NSAIDs).^{30–32} Similarly, in NHSII, information on regular use of NSAIDs was collected at baseline (1989 questionnaire) and updated biennially through follow-up. Consistent with previous analyses, we defined regular use of NSAIDs as intake of two or more tablets per week.^{30–32} We also collected information on use of proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), statins, betablockers, angiotensin converting enzyme (ACE) inhibitors, and diuretics over follow-up as their prevalence increased in the US market.^{33–44} Beginning in 2000 in NHS and 2001 in NHSII, information regarding use of each of these medications was consistently collected and updated biennially.

Ascertainment of Microscopic Colitis

Diagnoses of microscopic colitis were initially ascertained through self-report on questionnaire and were subsequently validated by review of medical records. Participants have reported diagnoses of colitis via open-ended response on biennial surveys since 1976 in NHS and 1989 in NHSII. Since 1982 in NHS and 1991 in NHSII, diagnoses of inflammatory bowel diseases were specifically queried. Each reported diagnosis of inflammatory bowel disease has prompted (1) a supplementary questionnaire asking participants specifically for diagnoses of Crohn's disease, ulcerative colitis, or microscopic colitis and (2) a request to access medical records related to the diagnosis.

Medical records were reviewed by two gastroenterologists blinded to patient exposures. Clinical, endoscopic, and histopathology findings were extracted, and cases of microscopic colitis were confirmed based on review of histopathology records. Information on type of microscopic colitis, lymphocytic colitis or collagenous colitis, was also obtained. Participants who declined medical record review were not counted as cases of microscopic colitis, as the diagnosis could not be confirmed.

We confirmed 275 incident cases through follow-up. Of these, 262 cases had enough reported histologic detail to discriminate between subtypes of collagenous colitis ($n=133$) and lymphocytic colitis ($n=129$).

Statistical Analysis

For analysis of reproductive factors and risk of microscopic colitis, participants accrued person-time of follow-up from return of the 1988 questionnaire for NHS or 1989 questionnaire for NHSII through the first of the following events: date of diagnosis of microscopic colitis, diagnosis of Crohn's disease or ulcerative colitis, death, last returned questionnaire, or end of follow-up (2014 for NHS and 2015 for NHSII). For analysis of

menopausal factors and risk of microscopic colitis, person-time was calculated from the date of return of their first questionnaire at which they reached menopause to diagnosis of microscopic colitis, inflammatory bowel disease, death, last returned questionnaire, or end of follow-up, whichever came first. We used Cox proportional hazards modeling with time-varying exposure and covariate data to estimate the hazard ratios (HR) and 95% confidence intervals (CI). All models were stratified by age (months) and study period (2-year intervals) as defined by each questionnaire cycle. Ordinal categories of reproductive and menopausal factors were used to evaluate for significance of linear trends.

To further account for secular trends in use of MHT with the 2003 publication of the seminal paper demonstrating no benefit for MHT in the primary prevention of cardiovascular disease,⁴⁵ we assessed the association between MHT use and risk of microscopic colitis before and after 2004 in our cohorts. We also evaluated the association between MHT use and risk of microscopic colitis according to strata defined by cohort, BMI, NSAID use, OCP use, age at menopause, and smoking status, and evaluated for potential interactions using cross-classified categories of these risk factors and MHT use. We used log-likelihood ratio tests, comparing models with cross-classified categories with models that included these factors as independent variables, to test the significance of interactions. We tested the proportional hazards assumption by examining the interaction between age and OCP and MHT use and observed no evidence for violation of this assumption ($p = 0.13$). A two-sided P -value < 0.05 was considered statistically significant. All analyses were done using SAS 9.4 (Cary, NC).

Results

Characteristics of participants in the NHS and NHSII

The mean age of participants in NHS at the start of the study (1988 questionnaire) was 54.8 years (range 41.5 – 69.0 years), and at the end of the study (2014 questionnaire) was 76.9 years (range 65.5 – 93.3 years). The mean age of participants in NHSII at the start of the study (1989 questionnaire) was 34.8 years (range 24.8 – 44.3 years), and at the end of the study (2015 questionnaire) was 59.1 years (range 48.6 – 69.2 years). The characteristics of women at the midpoint of the study (1998 questionnaire for NHS and 1999 questionnaire for NHSII) are presented in **Table 1**. The mean age of participants in NHS at the midpoint of the study was 64.3 years, with approximately 94% of women having reached menopause. The mean age of participants in NHSII at the midpoint of the study was 44.7 years, with approximately 25% of women having reached menopause. Overall, in pooled cohorts 34% of women were past smokers, and nearly 10% were current smokers (**Table 1**). The mean BMI of all participants at the midpoint of the study was 26.7 kg/m².

Among 227,766 women, we documented 275 incident cases of microscopic colitis over 26 years encompassing 5,147,282 person-years. Of these, 239 cases occurred in postmenopausal women. The overall incidence rate of microscopic colitis in the cohorts was 5.3 cases/100,000 person-years. The incidence increased with age and peaked at 12 cases / 100,000 person-years in women aged 70–79 years. Over the entire study period, the mean age at diagnosis of microscopic colitis was 65.4 (SD 9.9) years.

Menopausal hormone therapy and risk of incident microscopic colitis

In our pooled analyses (NHS + NHSII), amongst postmenopausal women, both past and current MHT use were associated with increased risk of microscopic colitis ($P_{\text{trend}} < 0.0001$; **Figure 2**). As compared to never-users, the multivariable-adjusted HRs for microscopic colitis were 1.95 (95% CI 1.37 – 2.78) amongst past users and 2.64 (95% CI 1.78 – 3.90) amongst current users, after adjusting for cohort, age, age at menopause, menopause type, age of menarche, OCP use, smoking, and BMI. The risk of microscopic colitis increased with longer duration of MHT use ($P_{\text{linear trend}} < 0.0001$; **Figure 2**). Compared to never-users, the multivariable-adjusted HRs of microscopic colitis were 1.43 (95% CI 0.85 – 2.40) amongst women with 2 years of use, 1.97 (95% CI 1.17 – 3.29) amongst women with 2.1 – 4 years of use, 1.54 (95% CI 0.95 – 2.49) amongst women with 4.1 – 8 years of use, 2.69 (95% CI 1.81 – 4.01) amongst women with 8.1 – 16 years of use, and 4.12 (95% CI 2.60 – 6.52) amongst women with > 16 years of use (**Supplementary Table 1**).

Amongst ever-MHT users, we also examined the influence of time since discontinuation of MHT on risk of microscopic colitis (**Figure 2**) and observed decreased risk with longer time since discontinuation ($P_{\text{linear trend}} = 0.002$). Compared to current users, the multivariable-adjusted HRs of microscopic colitis were 0.91 (95% CI 0.61 – 1.35) amongst women that discontinued MHT 4 years prior, 0.76 (95% CI 0.52 – 1.13) amongst women that discontinued MHT 4.1 – 8 years prior, and 0.53 (95% CI 0.33 – 0.84) amongst women that discontinued MHT > 8 years prior.

Overall, although we observed a similar positive association between MHT and risk of microscopic colitis in both cohorts, the effect estimates were significantly stronger for NHS compared to NHSII ($P_{\text{interaction}} = 0.01$). As the primary difference between the two cohorts is the age of participants, we explored whether the observed differences were related to the older age of women in NHS, who had reached the peak age of diagnosis of microscopic colitis^{1, 7–10, 12, 39, 46–48} by the end of the study period. Amongst postmenopausal participants 60 years old, current use of MHT, compared to never use, was associated with a multivariable-adjusted HR of microscopic colitis of 3.61 (95% CI 2.22 – 5.87), an estimate similar to that observed in NHS. In contrast, amongst postmenopausal participants < 60 years old, compared to never use, current use of MHT was associated with a multivariable-adjusted HR of microscopic colitis of 1.36 (95% CI 0.68 – 2.75; $P_{\text{interaction}} = 0.007$), similar to our estimate from NHSII.

We also examined the association between type of hormone preparation and risk of microscopic colitis. In pooled analysis, compared to never-use, the multivariable-adjusted HRs of microscopic colitis were 2.33 (95% CI 1.54 – 3.52) for ever-use of estrogen-only MHT, 2.12 (95% CI 1.43 – 3.12) for combined estrogen and progestin preparations, and 1.42 (95% CI 0.34 – 5.89) for progestin-only MHT. Similarly, we evaluated the association between MHT and risk of microscopic colitis according to disease subtype and observed no significant heterogeneity ($P_{\text{heterogeneity}} = 0.34$). As compared to never-MHT users, the multivariable-adjusted HRs of collagenous colitis and lymphocytic colitis were 2.96 (95% CI 1.72 – 5.11) and 2.41 (95% CI 1.34 – 4.36), respectively, amongst current users.

In an analysis restricted to follow-up after 2000, when medications previously shown to be associated with risk of microscopic colitis were consistently ascertained, we observed a significant association between MHT use and risk of microscopic colitis. Compared to never users, the multivariable-adjusted HR of microscopic colitis was 2.60 (95% CI 1.67 – 4.04) amongst current users of MHT after further adjusting our models for use of NSAIDs, SSRIs, PPIs, beta blockers, statins, ACE inhibitors, and diuretics. In this analysis, SSRIs (HR 1.68; 95% CI 1.15 – 2.46) and NSAIDs (HR 1.96; 95% CI 1.46 – 2.62) were also independently associated with risk of microscopic colitis while the association between PPI use and risk of microscopic colitis did not reach statistical significance (HR = 1.25, 95% CI 0.89–1.77).

We considered the possibility that the associations we observed with microscopic colitis may be due to differential health-seeking behaviors amongst women who use MHT (i.e., women who seek more regular medical follow-up may be more likely to receive a formal diagnosis of microscopic colitis). Thus, we performed a sensitivity analysis limiting the study population to women who reported an annual physical examination in every questionnaire cycle and found similar results. Compared to never users, the multivariable-adjusted HR of microscopic colitis among current MHT users was 2.63 (95% CI 1.51 – 4.58). We also performed a sensitivity analysis limiting the study population to women who reported a screening colonoscopy at least once during the follow-up period and found a consistent association between current MHT use and risk of microscopic colitis (HR 2.12; 95% CI 1.40 – 3.20).

We also examined the association between MHT and risk of microscopic colitis before and after 2004 to examine whether changes in the patterns of prescription of these medications altered our associations. Compared to never users, the multivariable-adjusted HRs of microscopic colitis amongst current users of MHT were 2.01 (95% CI 1.00 – 4.04) prior to 2004 (follow up from 1988 to 2004), and 2.88 (95% CI 1.80 – 4.60) after 2004 (follow up from 2004 – 2015). Lastly, we explored the possibility that the association between MHT use and risk of microscopic colitis may be modified by age at menopause, BMI, OCP use, NSAID use, or smoking and did not observe any evidence for effect modification (all $P_{\text{interaction}} = 0.13$; **Supplementary Table 2**).

Other menopausal factors and risk of incident microscopic colitis

Age at menopause and type of menopause were not independently associated with risk of microscopic colitis amongst postmenopausal women (**Table 2**). As compared to postmenopausal women with natural menopause, women with surgical or radiation-induced menopause had a multivariable-adjusted HR of microscopic colitis of 0.80 (95% CI 0.60 – 1.05). Similarly, compared to women who experienced menopause at 49 – 52.9 years of age, the multivariable-adjusted HRs of microscopic colitis were 1.23 (95% CI 0.80 – 1.90) amongst women with menopause < 44 years, 1.25 (95% CI 0.80 – 1.93) amongst women with menopause 44 – 46.9 years, 0.81 (95% CI 0.49 – 1.31) amongst women with menopause 47 – 48.9 years, and 1.09 (95% CI 0.77 – 1.54) amongst women with menopause ≥ 53 years ($P_{\text{trend}} = 0.49$) in pooled cohorts.

Reproductive factors and risk of incident microscopic colitis

In pooled analysis of NHS and NHSII, compared with never-use we observed a statistically significant increase in risk of microscopic colitis with ever use of OCPs (age-adjusted HR = 1.83; 95% CI 1.36 – 2.47; **Table 3**). The estimate did not alter substantially after adjusting for additional covariates, including age at menarche, parity, menopausal status and MHT use, cohort, BMI, and smoking (multivariable-adjusted HR = 1.57; 95% CI 1.16 – 2.13). Age at menarche, parity, and age at first birth were not independently associated with risk of microscopic colitis (**Table 3**).

We performed an analysis restricting follow-up to after 2000, when medications associated with risk of microscopic colitis were consistently available and observed no significant change in the association between OCP use and risk of microscopic colitis. Compared to never users of OCPs, the multivariable-adjusted HR of microscopic colitis was 1.56 (95% CI 1.11 – 2.19) amongst ever users after further adjusting our models for use of NSAIDs, SSRIs, PPIs, beta blockers, statins, ACE inhibitors, and diuretics.

Discussion

In two large prospective cohorts of US women, we demonstrate that exogenous hormone use in the form of OCPs and MHT is associated with increased risk of incident microscopic colitis. Although the association between MHT and risk of microscopic colitis appeared to be significantly stronger among older women (> 60 years), we did not see any evidence for effect modification by smoking, BMI, or NSAID use. Lastly, the associations appear to be stronger with estrogen-containing MHT and similar for both subtypes of microscopic colitis.

Consistent with our study, one prior retrospective case-control study of 131 patients with a known diagnosis of microscopic colitis demonstrated that prevalence of OCP use was higher among cases compared to controls.⁴⁹ In contrast to our findings, the study found an inverse association between MHT exposure and risk of microscopic colitis.⁴⁹ However, this study had two notable limitations. First, while controls were selected from a population-based study in Malmo with prospectively collected data on reproductive and menopausal factors, the cases were recruited from a hospital database with all patients having had the diagnosis for at least 3 years. This may have introduced selection and recall biases inherent to retrospective case-control studies. Second, controls in this study were recruited in the early 1990s while the cases were selected in the mid-2000s, which may have also introduced biases in estimating exposure prevalence in cases and controls as a result of secular changes in patterns of hormone use over time.⁴⁹ In contrast, in our study, detailed reproductive and menopausal factors were collected and updated over follow-up time allowing us to account for changes in exposure information over time. In addition, we were able to account for all known and potential confounders of the association between exogenous hormone use and risk of microscopic colitis.

Our observation that the association between MHT and risk of microscopic colitis is stronger in NHS compared to NHSII is likely related to significantly older age of the participants in NHS. Specifically, the median age of women in NHS at the end of follow-up was 76 years compared to 59 years in NHSII. Since the peak age of diagnosis of

microscopic colitis in most studies is reported to be in the sixth and seventh decade of life, 1, 7–10, 12, 39, 46–48 there were significantly fewer cases of microscopic colitis in NHSII (n = 105; pooled incidence rate = 4 cases/100,000 person-years) compared to NHS (n = 170; pooled incidence rate = 7 cases/100,000 person-years). Additionally, consistent with secular trends, the prevalence of MHT use was significantly lower in NHSII (13.4% among postmenopausal women) compared to NHS (24.7%).

Our findings are biologically plausible. Exogenous estrogen has been linked to the development and progression of systemic lupus erythematosus, Crohn's disease, and ulcerative colitis.^{17, 18, 20, 50, 51} The hypothesized role of estrogen in other inflammatory bowel diseases is through modification of colonic epithelial permeability and mucosal immunity.^{22, 23} In animal models, estrogen receptors have been shown to modulate the permeability of tight junctions in the large intestine.^{21, 22} Interestingly, epithelial barrier function has been shown to be impaired in microscopic colitis, leading to an inflammatory response to fecal microbiota that improves with diversion of the fecal stream.^{24–26} Furthermore, estrogen receptors are found on immune cells, including lymphocytes, where they may regulate immune response to gut flora.^{52, 53} Estrogen exposure through OCPs or MHT may thus lead to changes in mucosal immunity, heightening the abnormal inflammatory response to commensal bacteria seen in microscopic colitis. Further research is required to elucidate the specific mechanisms of exogenous estrogen in development of microscopic colitis.

Our study has several strengths. We leveraged two large cohorts of US women with questionnaires that were specifically focused on collecting detailed and updated information on reproductive and menopausal factors, allowing for accurate temporal characterization of these exposures in relation to incident microscopic colitis. Survey response rates were > 85% in these cohorts⁵⁴ and ability to adjust for numerous confounders through time-varying covariates minimized bias. All microscopic colitis cases were confirmed by review of medical records, minimizing the possibility of outcome misclassification inherent in registry-based analyses that rely on ICD codes for case confirmation. Lastly, the incidence of microscopic colitis, and specific subtypes of collagenous and lymphocytic colitis, in our cohorts are similar to figures reported in other population-based studies.⁴⁷ Additionally, the prevalence of MHT and OCP use in our cohorts mirror that in the general U.S. population,^{55–57} which further support the generalizability of our findings.

Though a large, nationwide, prospective cohort study of US women, our study did have some limitations. The vast majority of participants in the cohorts were white, possibly limiting the generalizability of the study. However, there have been no studies that demonstrate a difference in risk factors for microscopic colitis based on race. As the study was conducted through questionnaire, we relied on participants' self-report to identify women with a possible diagnosis of microscopic colitis. Thus, some cases of microscopic colitis may not have been identified due to either under-reporting or undiagnosed disease. However, our participants were nurses, enhancing the accuracy of self-reported medical history and minimizing differences due to access to health care. We have also previously demonstrated that the incidence rate of microscopic colitis in our cohorts is similar to those reported in other population-based studies.⁴⁷ Lastly, consistent with prescribing patterns of

hormone therapy, the rate of progestin-only hormone therapy was low in our cohorts (1.3%), which may have limited our ability to identify an association between this type of hormone therapy and risk of microscopic colitis.

In summary, this is the first prospective cohort study demonstrating an association between exogenous hormone use in the form of OCPs and MHT and risk of incident microscopic colitis. Because there are many cogent reasons for women to minimize use of MHT, particularly later in life when it could be associated with cardiovascular adverse effects, ^{45, 58, 59} our results may have more mechanistic than clinical implications. In particular, our findings add to the body of literature that biological pathways related to sex hormones, particularly estrogen, play a critical role in the pathogenesis of chronic inflammatory disorders of the gastrointestinal tract. Future studies are required to elucidate the mechanistic basis of these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support:

- This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health [F32 DK115134 to KEB; K23 DK099681 to HK; K24 DK098311 to ATC; and P30 DK043351 to the Center for the Study of Inflammatory Bowel Disease at Massachusetts General Hospital].
- This work was also supported by a career development award from the Crohn's and Colitis Foundation Senior Research Award, and a Stuart and Suzanne Steele MGH Research Scholars Award to ATC; and a career development award from the Crohn's and Colitis Foundation to PL.
- The Nurses' Health Study and Nurses' Health Study II are supported by the National Cancer Institute at the National Institutes of Health [UM1 CA186107 and UM1 CA176726, respectively].

Abbreviations:

ACE	Angiotensin Converting Enzyme
BMI	Body Mass Index
CI	Confidence Interval
HR	Hazard Ratio
MHT	Menopausal Hormone Therapy
NHS	Nurses' Health Study
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCP	Oral Contraceptive
PPI	Proton Pump Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

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Figure 1:
Flow chart of eligible participants in the study

Figure 2:
Menopausal hormone therapy (MHT) and risk of microscopic colitis

Table 1:

Characteristics of participants in the Nurses' Health Study (NHS) and NHSII at midpoint of study ¹

		NHS (n=100,955)	NHSII (n=108,812)	All Participants (N=209,767)
Age (years), mean (SD)		64.3 (7.1)	44.7 (4.6)	54.2 (11.5)
Body Mass Index, mean (SD)		26.8 (5.4)	26.6 (6.3)	26.7 (5.9)
Smoking Status, %				
	Never	46.8	65.2	56.3
	Past	42.8	25.2	33.7
	Current	10.4	9.6	10.0
White, %		96.9	95.8	96.3
Non-White, %		3.1	4.2	3.7
Age of Menarche, %				
	11	22.3	24.5	23.4
	12	27.1	30.4	28.8
	13	30.6	27.3	28.9
	14	20.0	17.8	18.9
Ever Oral Contraceptive Use, %		45.0	86.6	66.6
Number of Children, %				
	0	6.7	19.1	13.1
	1	7.3	14.6	11.1
	2	27.6	38.6	33.3
	3	58.4	27.7	42.5
Age at First Birth²				
	< 22 years	11.7	13.6	12.6
	22 and < 25 years	45.1	22.0	34.0
	25 and < 29 years	31.0	34.4	32.7
	29 years	12.2	30.0	20.7
Post-Menopause, %		94.4	24.6	58.2
Ever MHT Use³		66.2	66.0	66.2
Age of Menopause³				
	< 44	9.2	26.5	13.0
	44 – 46.9	8.6	14.5	9.9
	47 – 48.9	10.4	11.2	10.6
	49 – 52.9	52.0	47.6	51.0
	53	19.8	0.2	15.5

	NHS (n=100,955)	NHSII (n=108,812)	All Participants (N=209,767)
Regular NSAID⁴ use	32.2	48.3	40.8
Diabetes, %	5.8	1.9	3.8

¹ Data derived from midpoint of study: 1998 questionnaire for NHS I and 1999 questionnaire for NHSII

² Amongst parous women

³ Amongst postmenopausal women

⁴ Non-steroidal anti-inflammatory drug

Table 2:

Age and type of menopause and risk of microscopic colitis amongst postmenopausal women in the Nurses' Health Studies

	No. of cases	No. of person-years	Age-adjusted hazard ratio [95% CI]	Multivariable-adjusted hazard ratio [95% CI] ^I
NHS				
< 44	22	209,942	1.59 (0.99 – 2.56)	1.56 (0.96 – 2.53)
44 – 46.9	20	194,149	1.55 (0.95 – 2.53)	1.40 (0.85 – 2.29)
47 – 48.9	14	231,582	0.89 (0.51 – 1.58)	0.79 (0.44 – 1.39)
49 – 52.9	81	1,154,069	(reference)	(reference)
> 53	33	426,219	0.98 (0.65 – 1.47)	0.95 (0.63 – 1.44)
<i>P-trend</i>			0.027	0.059
NHSII				
< 44	5	118,321	0.77 (0.30 – 2.02)	0.67 (0.25 – 1.79)
44 – 46.9	5	66,272	0.96 (0.37 – 2.49)	0.92 (0.35 – 2.41)
47 – 48.9	5	62,981	0.91 (0.35 – 2.36)	0.88 (0.34 – 2.27)
49 – 52.9	38	591,656	(reference)	(reference)
> 53	16	71,251	1.39 (0.73 – 2.61)	1.45 (0.75 – 2.78)
<i>P-trend</i>			0.296	0.193
NHS + NHSII Pooled				
< 44	27	328,263	1.33 (0.87 – 2.04)	1.23 (0.80 – 1.90)
44 – 46.9	25	260,421	1.37 (0.89 – 2.11)	1.25 (0.80 – 1.93)
47 – 48.9	19	294,563	0.89 (0.55 – 1.45)	0.81 (0.49 – 1.31)
49 – 52.9	119	1,745,725	(reference)	(reference)
> 53	49	497,470	1.07 (0.76 – 1.50)	1.09 (0.77 – 1.54)
<i>P-trend</i>			0.189	0.494
NHS				
Natural	101	1,215,973	(reference)	(reference)
Surgical/Radiation	69	999,988	0.88 (0.64 – 1.19)	0.72 (0.52 – 1.00)
NHSII				
Natural	43	462,283	(reference)	(reference)
Surgical/Radiation	26	448,198	0.99 (0.59 – 1.64)	1.06 (0.62 – 1.80)
NHS + NHSII Pooled				
Natural	144	1,678,256	(reference)	(reference)
Surgical/Radiation	95	1,448,185	0.90 (0.69 – 1.17)	0.80 (0.60 – 1.05)

^I Adjusted for age (months), cohort (NHS, NHSII), body mass index (<20, 20–24.9, 25–29.9, 30), smoking (never, past, current), age of menarche (years), oral contraceptive use (never, ever), age of menopause (<44, 44–46.9, 47–48.9, 49–52.9, 53), and menopause type (natural, surgical/radiation).

Table 3:

Reproductive factors and risk of microscopic colitis amongst women in the Nurses' Health Study (NHS) and NHSII

		No. of cases	No. of person-years	Age-adjusted hazard ratio [95% CI]	Multivariable-adjusted hazard ratio [95% CI] ^I
OCP Use	NHS				
	Never	61	1,331,484	(reference)	(reference)
	Ever	109	1,120,604	1.76 (1.27 – 2.45)	1.48 (1.06 – 2.07)
	NHSII				
	Never	7	367,492	(reference)	(reference)
	Ever	98	2,327,702	2.08 (0.96 – 4.47)	1.84 (0.85 – 4.00)
	NHS + NHSII Pooled				
	Never	68	1,698,976	(reference)	(reference)
	Ever	207	3,448,306	1.83 (1.36 – 2.47)	1.57 (1.16 – 2.13)
Age at Menarche	NHS				
	11	41	547,108	1.02 (0.67 – 1.56)	1.04 (0.68 – 1.59)
	12	46	664,777	(reference)	(reference)
	13	49	751,829	0.92 (0.61 – 1.38)	0.90 (0.60 – 1.35)
	14	34	488,374	1.04 (0.67 – 1.63)	1.00 (0.64 – 1.56)
	NHSII				
	11	24	659,110	0.75 (0.45 – 1.25)	0.79 (0.47 – 1.31)
	12	39	818,834	(reference)	(reference)
	13	25	736,381	0.71 (0.43 – 1.17)	0.68 (0.41 – 1.12)
	14	17	480,869	0.78 (0.44 – 1.38)	0.74 (0.42 – 1.31)
	NHS + NHSII Pooled				
	11	65	1,206,218	0.91 (0.65 – 1.25)	0.93 (0.67 – 1.28)
	12	85	1,483,612	(reference)	(reference)
	13	74	1,488,210	0.83 (0.61 – 1.13)	0.81 (0.59 – 1.10)
	14	51	969,243	0.93 (0.66 – 1.32)	0.88 (0.62 – 1.25)
Parity	NHS				
	0	9	163,206	(reference)	(reference)
	1	5	178,875	0.50 (0.17 – 1.49)	0.51 (0.17 – 1.52)
	2	52	681,285	1.24 (0.61 – 2.51)	1.18 (0.58 – 2.42)
	3	104	1,428,722	1.28 (0.65 – 2.54)	1.28 (0.65 – 2.55)
	NHSII				
	0	15	560,001	(reference)	(reference)
	1	9	416,404	0.78 (0.34 – 1.79)	0.73 (0.32 – 1.67)
	2	50	1,018,426	1.62 (0.91 – 2.89)	1.59 (0.88 – 2.84)
	3	31	700,363	1.48 (0.79 – 2.75)	1.52 (0.81 – 2.83)
	NHS + NHSII Pooled				
	0	24	723,207	(reference)	(reference)

		No. of cases	No. of person-years	Age-adjusted hazard ratio [95% CI]	Multivariable-adjusted hazard ratio [95% CI] ¹
	1	14	595,297	0.65 (0.34 – 1.26)	0.64 (0.33 – 1.24)
	2	102	1,699,711	1.42 (0.91 – 2.23)	1.43 (0.91 – 2.24)
	3	135	2 129 085	1.40 (0.89 – 2.19)	1.48 (0.94 – 2.32)
NHS					
	22 years	18	270,139	0.82 (0.49 – 1.38)	0.81 (0.48 – 1.35)
	22 and < 25 years	80	1,036,062	(reference)	(reference)
	25 and < 29 years	47	707,400	0.92 (0.64 – 1.32)	0.94 (0.65 – 1.35)
	29 years	16	275,281	0.89 (0.52 – 1.52)	0.92 (0.53 – 1.58)
NHSII					
	22 years	15	294,192	1.11 (0.57 – 2.16)	1.03 (0.53 – 2.00)
	22 and < 25 years	21	481,080	(reference)	(reference)
	25 and < 29 years	26	745,735	0.96 (0.54 – 1.72)	0.95 (0.53 – 1.69)
	29 years	28	614,996	1.19 (0.67 – 2.11)	1.16 (0.65 – 2.06)
NHS + NHSII Pooled					
	22 years	33	564,332	0.93 (0.63 – 1.38)	0.87 (0.58 – 1.29)
	22 and < 25 years	101	1,517,141	(reference)	(reference)
	25 and < 29 years	73	1,453,135	0.92 (0.68 – 1.25)	0.93 (0.68 – 1.26)
	29 years	44	890,277	1.03 (0.71 – 1.50)	1.03 (0.71 – 1.49)

¹ Adjusted for age (months), cohort (NHS, NHSII), body mass index (<20, 20–24.9, 25–29.9, ≥30), smoking (never, past, current), age of menarche (11, 12, 13, 14), parity (0, 1, 2, ≥3 children), oral contraceptive use (never, ever), menopausal status and MHT use (pre-menopausal, postmenopausal never-user, postmenopausal past-user, postmenopausal current-user).

² Amongst parous women. Adjusted for age (months), cohort (NHS, NHSII), body mass index (<20, 20–24.9, 25–29.9, ≥30), smoking (never, past, current), age of menarche (11, 12, 13, 14), oral contraceptive use (never, ever), menopausal status and MHT use (pre-menopausal, postmenopausal never-user, postmenopausal past-user, postmenopausal current-user).