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Hormone Therapy Increases Risk of Ulcerative Colitis but not Crohn's Disease

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Abstract

Background & Aims—Estrogen has been proposed to modulate gut inflammation through an effect on estrogen receptors found on gastrointestinal epithelial and immune cells. The role of postmenopausal hormone therapy on risk of Crohn's disease (CD) and ulcerative colitis (UC) is unclear.

Methods—We conducted a prospective cohort study of 108,844 postmenopausal US women (median age 54 years) enrolled in 1976 in the Nurses' Health Study without a prior history of CD or UC. Every 2 years, we have updated information on menopause status, postmenopausal hormone use, and other risk factors. Self-reported CD and UC diagnoses were confirmed through medical record review by two gastroenterologists who were blinded to exposure information. We

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HK - study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis.
LMH - study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

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used Cox proportional hazards models to calculate adjusted hazard ratios (HR) and 95% confidence intervals (CIs).

Results—Through 2008 with over 1.8 million person years of follow up, we documented 138 incident cases of CD and 138 of UC. Compared to women who never used hormones, the multivariate-adjusted HR for UC was 1.71 (95% CI, 1.07-2.74) among women who currently used hormones and 1.65 (95% CI, 1.03-2.66) among past users. The risk of UC appeared to increase with longer duration of hormone use ($P_{\text{trend}}=.04$) and decreased with time since discontinuation. There was no difference in risk according to the type of hormone therapy used (estrogen vs estrogen + progestin). In contrast, we did not observe an association between current use of hormones and risk of CD (multivariate-adjusted HR, 1.19 95% CI 0.78-1.82). The effect of hormones on risk of UC and CD was not modified by age, body mass index, or smoking.

Conclusion—In a large prospective cohort of women, postmenopausal hormone therapy was associated with an increased risk of UC but not CD. These findings indicate that pathways related to estrogens might mediate the pathogenesis of UC.

Keywords

Inflammatory Bowel Disease; IBD; predisposition; menopause

INTRODUCTION

Despite the success of genome-wide association studies^{1,2} in identifying more than 100 gene loci associated with Crohn's Disease (CD) and ulcerative colitis (UC), known collectively as inflammatory bowel diseases (IBD), the pathogenesis of these conditions remains largely unknown. Moreover, it is estimated that the risk contribution from these genetic predispositions is less than 25%³, highlighting the importance of the environment in the etiology of IBD.

The bimodal age distribution of UC and CD^{4,5} may be explained by differences in distribution of environmental factors between early and later life. Prior studies have demonstrated an association between exogenous hormones used for oral contraception and risk of IBD among younger, premenopausal women.⁶ However, it is unclear whether use of hormone therapy among older postmenopausal women is also associated with an increase in risk of UC or CD.

We therefore sought to examine the association between postmenopausal hormone therapy and risk of CD and UC in a large ongoing prospective study of U.S. women, the Nurses' Health Study (NHS). With more than 30 years of biennially updated data on lifestyle, diet, and medical diagnoses, this cohort offered us the unique opportunity to examine the association between hormone therapy and subsequent risk of UC and CD in the context of other risk factors among postmenopausal women.

METHODS

Study Population

The NHS is a prospective cohort that began in 1976 when 121,700 U.S. female registered nurses, ages 30 to 55 years, completed a mailed health questionnaire. Follow up questionnaires are mailed every two years to update health information. Because the NHS was not originally designed to evaluate the risk of IBD with hormone use, the current study represents a post hoc analysis of this prospective cohort. Follow-up for the current study was greater than 90%. The institutional review board at the Brigham and Women's Hospital approved this study. For the present analysis, we included the 22,044 women without a

history of CD, UC, or cancer (with the exception of non-melanoma skin cancer) who were postmenopausal at baseline. During follow up an additional 86,800 women who had been premenopausal at baseline were eligible to enter the analysis at the timepoint when they became postmenopausal and were without prevalent UC, CD, or cancer. Thus, through 2008, a total of 108,844 postmenopausal women contributed person-time to the analysis (Figure 1).

Assessment of Menopause Status, Hormone Use, and Other Covariates

On each questionnaire, menopausal status was determined by asking whether the participants' menstrual periods had ceased permanently and, if so, at what age and for what reason (ceasing naturally or after radiation therapy or surgery). If menopause was due to surgery, the subject was asked to report the number of ovaries removed. Self-reported type of menopause and age at time of menopause in this cohort were highly accurate compared to medical records.⁷

Women were defined as menopausal from the self-reported time of natural menopause or bilateral oophorectomy (surgical menopause). Women with indeterminable age at menopause were women who underwent hysterectomy without bilateral oophorectomy, women with incomplete availability of data on the extent of pelvic surgery, women with permanent cessation of menses due to radiation therapy, and women who did not report the age of onset of menopause. Consistent with prior analyses in this cohort, women with indeterminable age at menopause were considered menopausal when they reached the age at which natural menopause occurred in 90% of the women (54 years for smokers and 56 years for nonsmokers).^{8,9}

With each biennial questionnaire, participants reported the number of months during the past 2 years when prescription female hormones were taken, whether these hormones were taken currently, the hormone preparation (estrogen, progestin or a combination), and the route of use (oral, patch, or vaginal). We calculated the duration of use as well as time since discontinuation from sequential questionnaires, accounting for starting and stopping the medications over time.

On each biennial questionnaire, women were also asked about pertinent lifestyle factors, including body weight, smoking status, and oral contraceptive use. Participants' self-report of body weight, height, use of NSAIDs, and oral contraceptives have been previously validated.^{10,11} In 1978, women were asked whether in the past year they have had a physical examination by a physician and for what reason: "screening" or "diagnostic". This information was asked again in 1988 and has been updated biennially thereafter. Similarly starting in 1988 and in every questionnaire since then, women were asked whether they have had flexible sigmoidoscopy/colonoscopy and for what reason: "screening" or "symptoms". In 1992, women were also asked their latitude of residence at age 30, which we have previously shown to be associated with risk of UC and CD.¹² In 1992, we inquired if women had ever had an appendectomy.

Outcome Ascertainment

We have previously detailed our methods for confirming self-reported cases of CD and UC.¹² In brief, since 1976, participants have reported diagnoses of UC or CD through an open-ended response on biennial surveys. In addition, we have specifically queried participants about diagnoses of UC since 1982 and CD since 1992. Specifically in the 1982 questionnaire, women were asked whether they were diagnosed with UC and if yes, the year of diagnosis (< 1965, 1965-1969, 1970-1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983). Similarly in 1992, women were asked whether they were diagnosed with CD before

1976, 1976-1980, 1981-1984, 1985-1989, or 1990. When a diagnosis was reported on any biennial questionnaire, a supplementary questionnaire and related medical records were requested and reviewed by two gastroenterologists blinded to exposure information. We excluded participants who subsequently denied the diagnosis on the supplementary questionnaire or permission to review their records. Data were extracted on diagnostic tests, histopathology, anatomic location of disease, and disease behavior. Using standardized criteria¹³⁻¹⁶, UC diagnosis was based on a typical clinical presentation > 4 weeks and endoscopic or surgical pathological specimen consistent with UC (e.g. evidence of chronicity). CD diagnosis was based on a typical clinical history for > 4 weeks and endoscopy or radiologic evaluation demonstrating small bowel findings, or surgical findings consistent with CD combined with pathology suggesting transmural inflammation or granuloma contributed to a diagnosis of CD. Disagreements were resolved through consensus. Among those women whom we received adequate medical records, the case confirmation rate for IBD was 78%.¹² Women for whom we did not confirm CD or UC were included in the analyses as non-cases. After excluding all cases of CD and UC at the baseline questionnaire and among premenopausal women, we included 138 incident cases of CD and 138 cases of UC among postmenopausal women (Supplementary Material). These incidence rates are largely consistent with those reported by other U.S. populations.^{4,12,17}

Statistical Analysis

Consistent with prior studies^{9,18}, person-time for each participant was calculated from the date of return of their first questionnaire at which they reached menopause to the date of the diagnosis of UC or CD, date of last questionnaire, death from any cause, or June 1, 2008, whichever came first. To calculate adjusted hazard ratios (HR) and 95% confidence interval (CIs), we used Cox proportional hazards modeling adjusting for covariates selected *a priori* based on their previously demonstrated associations in our cohort.^{12,19,20} Consistent with prior analyses²¹, we included variables for age, use of postmenopausal hormones, use of NSAIDs, and smoking as time-varying covariates prior to each two-year interval to account for changes in these exposures over time. We adjusted for age at menarche, menopause type, oral contraceptive use (prior to menopause), and latitude of residence at age 30 based upon their baseline values since these exposures would not be expected to change over follow-up. Consistent with prior analyses^{12,22}, we also used baseline BMI to minimize the effect of disease status on body weight. For any covariates in which data were missing from a questionnaire interval, the values from the most recent non-missing questionnaire were used. We also examined the association between hormone use and risk of UC or CD within strata of age, BMI, and smoking and evaluated for potential interaction using cross-classified categories of these covariates and hormone use. We tested the significance of these interactions by using the log likelihood ratio test comparing the model with these cross-classified categories with a model that included the covariate as an independent variable. We used SAS version 9.1.3 (Cary, NC) for these analyses. All *P*-values were 2-sided and < 0.05 was considered statistically significant.

RESULTS

Through 2008, we documented 138 incident cases of CD and 138 cases of UC among 108,844 postmenopausal women who contributed 1,892,027 person years of follow up. Compared to never users, current postmenopausal hormone users had lower body-mass index (BMI) and age at menopause, were less likely to be current smokers or have natural menopause, and were more likely to have ever used oral contraceptives (Table 1). In addition, compared to past users, current hormone users were younger, had a lower BMI, were more likely to have used oral contraceptives, and were less likely to have undergone a natural menopause.

Compared to never users, past and current hormone users had a statistically significant higher age-adjusted risk of developing UC (Table 2). The risk estimates were not significantly altered after adjusting for known and potential risk factors for UC including BMI, smoking, latitude of residence at age 30, NSAIDs use, oral contraceptive use, age at menopause, age at menarche, menopause type, and parity. Compared to women who never used hormones, the multivariate-adjusted HRs for UC was 1.71 (95% CI, 1.07-2.74) among women who currently used hormones and 1.65 (95% CI, 1.03-2.66) among past users. The effect did not appear to vary according to the type of hormone preparation in subgroup analyses. Compared to never use of any hormones, the multivariate HRs for UC were 1.55 (95% CI, 0.94-2.56) for past or current use of estrogen-only and 1.62 (95% CI, 0.98-2.67) for combined estrogen and progestogen preparations.

In contrast to UC, we did not observe an association between hormone use and risk of CD. Compared to women who never used hormones, the multivariate-adjusted HRs for CD was 1.19 (95% CI, 0.78-1.82) among women who currently used hormones and 0.72 (95% CI, 0.44-1.17) among past users. There was no increase in risk of CD associated with past or current use of either estrogen-only (multivariate HR 1.18, 95% CI, 0.74-1.89) or estrogen and progestogen preparations (multivariate HR 0.87, 95% CI, 0.52-1.46).

The risk of UC appeared to increase according to the duration of hormone use, although both short-term and long-term use was associated with risk (Table 3). Compared to never users, the multivariate-adjusted HR of UC was 1.61 (95% CI, 1.01-2.56) for women with 1-5 years of use, 1.78 (95% CI, 1.03-3.05) for 6-10 years of use, and 1.80 (95% CI, 1.02-3.15) for greater than 10 years of use ($P_{\text{linear trend}} = 0.04$). We did not observe any significant association between postmenopausal hormone use and risk of CD, even among women who used for greater than 10 years (HR 1.28, 95% CI, 0.76-2.14).

We also considered time since discontinuation of hormone use in relation to risk of UC (Table 4). Although risk persisted for women who discontinued hormone use within 5 years, women who stopped use more than 5 years in the past had an attenuated risk of developing UC (multivariate-adjusted HR 1.39, 95% CI 0.78-2.49). There was no significant association between discontinuation of hormone use and risk of CD.

We considered the possibility that the associations we observed with UC may be due to differential health-seeking behaviors among women who use hormones (e.g. women who seek more regular medical follow-up may be more likely to receive a formal diagnosis of UC). Thus, we examined the association between hormone use and risk of developing pan-ulcerative colitis, which generally represents a more severe form of the disease for which diagnosis is less likely to vary according to differential evaluation for bowel symptoms. Compared to never users, the multivariate-adjusted HRs for pan-ulcerative colitis were 2.23 (95% CI, 1.05-4.74) among past users and 2.07 (95% CI, 1.00-4.32) among current users. In addition, we performed sensitivity analysis limiting the study population to women who reported an annual physical examination in each questionnaire cycle. Among such women, compared to never users of hormones, past and current users had a multivariate-adjusted HR of 2.19 (95% CI, 1.22 to 3.94) for UC. Similarly, among women who reported having undergone colon cancer screening with colonoscopy or sigmoidoscopy over follow up, current and past hormone use was associated with a multivariate-adjusted HR of 1.66 (95% CI, 1.03-2.69). To exclude the possibility that our associations may be due to a greater likelihood of surgical menopause among women with UC, we limited our analyses to women with natural menopause. Among such women, compared to never use, the multivariate-adjusted HR of UC was 1.72 (95% CI, 1.07-2.77) for ever use of hormones.

Because age, smoking and BMI may influence the association of postmenopausal hormones with risk of UC or CD, we examined hormone use according to strata defined by these variables (Tables 5 and 6). The effect of hormone use was not significantly modified by age, BMI, or smoking (All $P_{\text{interaction}} > 0.20$). Finally, as oral contraceptive use has previously been shown to be associated with risk of CD and UC, we assessed hormone use according to strata of oral contraceptive use. There was no effect modification by oral contraceptive on the effect on hormone use in risk of UC and CD (all $P_{\text{interaction}} > 0.30$).

In sensitivity analyses, we adjusted our models for additional putative risk factors that may be associated with risk of IBD based on prior literature. Specifically, we have previously shown that a predicted vitamin D score derived from age, latitude of residence, body mass index, physical activity, and dietary intake of vitamin D, is associated with risk of IBD.²⁰ Thus, we limited analyses to follow-up after 1986 after which we began collecting detailed information on each of these factors. Compared to never users of hormones, the multivariate-adjusted HRs for current hormone use were 1.20 (95% CI 0.78-1.86) for CD and 1.64 (95% CI 0.99-2.69) for UC after additionally adjusting for predictors of vitamin D status.

DISCUSSION

In this large prospective cohort of women, postmenopausal hormone use was associated with an increased risk of UC. These results were consistent even after accounting for known and possible risk factors for UC, including smoking and BMI. Our results largely agree with prior work that has observed an association between oral contraceptive agents that contain estrogen and progestins on risk of UC among premenopausal women.⁶ However, data specifically relating the use of exogenous hormones in postmenopausal women are sparse. A case-control study²³ using the United Kingdom General Practice Research Database assessed the relationship between a number of risk factors, including hormone use and incidence of IBD and found a positive statistically significant association with CD but not UC. However, the study was limited by a small number of cases (7 for UC and 12 for CD) among hormone users, short follow up (mean 2.2 years), and inability to account for other potential confounders including BMI and other reproductive factors.

In contrast with prior studies of oral contraceptives in premenopausal women, we did not observe an effect of postmenopausal hormones on risk of CD. This may be explained by differences in the dosage and formulation of hormones in oral contraceptives as compared with postmenopausal hormone therapy. Alternatively, the effect of exogenous hormones may differ according to a woman's age or endogenous hormonal milieu (e.g. the high estrogen environment of premenopause or estrogen-depleted state of postmenopause).

Although our understanding of the pathogenesis of UC and CD remains incomplete, the discovery of distinct genetic susceptibility loci for both diseases points to potential diverging biological pathways that may be differentially influenced by exogenous hormones.^{3,24} Most notably, genome-wide association studies have identified a number of distinct UC candidate genes (e.g. *HNF4A*, *LAMB1*, *CDH1* and *GNAI2*) primarily involved in regulation of intestinal barrier function. Recent observations that estrogen compounds modify colonic barrier function^{25,26} may therefore explain the unique association between hormone use and UC in our study. In addition, UC and CD have immunologically distinct gastrointestinal mucosal cytokine profiles, with mucosal inflammation in CD primarily mediated by Th1-related cytokines and UC mediated by Th2-related cytokines.²⁷⁻³⁰ Estrogen has been implicated in the etiology and progression of other Th2-mediated diseases such as rheumatoid arthritis and systemic lupus erythematosus,^{8,31} through enhancing cell proliferation and the humoral immune system. Of note, Kane et al.³² previously observed

that postmenopausal hormones were associated with a decreased risk of flare among patients with established IBD. The seemingly contrary association of hormones with an increased risk of incident disease in our study but lower risk of flare observed by Kane et al. may be due to the pleiotropic functions of estrogen/progestins or differences in the effects of hormones within various milieus (i.e. healthy mucosa vs. subacute inflammation).

Our study has several notable strengths. First, our prospective study design avoids the potential recall and selection biases of retrospective, case-control studies, which collect data on lifestyle and medications after diagnosis of CD or UC. Second, the availability of detailed and validated information on BMI, prior oral contraceptive use, smoking, and other important reproductive and menopausal factors allowed us to control for a number of potential confounding factors that may have influenced our observed associations. Third, we confirmed all cases of CD and UC through medical record review, a significant advantage over studies that rely on self-report or discharge codes, which may not accurately reflect true diagnoses. Fourth, in our analysis, we collected information on menopause status and hormone use every two years and used time-varying exposures in our Cox models. Thus, we were able to include women in our analysis as they became postmenopausal and account for changes in hormone use over several years of follow-up, minimizing the possibility of exposure misclassification.

We acknowledge several limitations. First, it is possible that our observed associations are related to differences in the likelihood of receiving a formal diagnosis of UC due to differential health-seeking behaviors among hormone users. However, our long-term follow-up over 32 years minimizes the likelihood that true cases of UC would remain undiagnosed, particularly among health professionals with high knowledge about health and less variability in access to care. Moreover, the influence of hormones on risk of UC did not vary according to extent of anatomic involvement and we also did not observe any association of hormones with CD. Taken together, these findings suggest that differences in the diagnostic evaluation of symptoms are unlikely to account for our results. Second, our cohort may not be representative of the overall US population. However, as we have previously reported,¹² our age-specific incidence of CD and UC are largely similar to rates from other U.S. populations. In addition, previous studies have shown that the prevalence of risk factors, such as smoking and BMI, in our cohort are consistent with those of the broader population of U.S. women.^{33,34} Third, despite greater than 90% follow up over 32 years and participants' health literacy as nurses, it is possible that some cases of UC and CD were not reported. However, such misclassification of the outcome would tend to attenuate our risk estimates towards the null. Fourth, based upon our strict inclusion criteria, we excluded a substantial number of women with IBD from our analyses. In addition, we were not able to obtain medical records for all participants who reported the diagnoses of CD or UC. However as we have previously shown,¹⁹ the characteristics of these individuals were similar to those of women from whom we were able to obtain medical records. In our primary analyses, we included these women as non-cases but also obtained similar risk estimates when we excluded these individuals or censored them at the time of report of IBD. Lastly, our study is observational and we do not have information about all known or suspected risk factors, such as family history of IBD. It is conceivable that family history of IBD could confound our associations if this knowledge influenced an individual's decision to use hormones. Based upon previously described methods³⁵, we estimate that an unmeasured confounder that could account for our observed risk estimates for hormone use and UC would need to have a prevalence of at least 20% with a HR greater than 4.0.

In this large prospective cohort of women, postmenopausal hormone use was associated with an increased risk of UC, but not CD. Whether these associations with disease incidence have meaning for the safety of postmenopausal hormones in patients with existing UC or

CD is unclear and merits further study. Because there are already many cogent reasons for women to minimize their use of postmenopausal hormones given their potential for adverse effects, our results have more mechanistic than clinical implications.³⁶ These findings provide novel insights into unique biological pathways related to estrogens that mediate the pathogenesis of UC. Further understanding of such mechanisms could eventually lead to elucidation of new targets for interventions that may modulate disease incidence or activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nature genetics*. Mar; 2011 43(3): 246–252. [PubMed: 21297633]
2. Franke A, McGovern DP, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nature genetics*. Dec; 2010 42(12):1118–1125. [PubMed: 21102463]
3. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. Nov; 2009 361(21):2066–2078. [PubMed: 19923578]
4. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis*. Mar; 2007 13(3):254–261. [PubMed: 17206702]
5. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther*. Jan; 2002 16(1):51–60. [PubMed: 11856078]
6. Cornish JA, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol*. Sep; 2008 103(9): 2394–2400. [PubMed: 18684177]
7. Colditz GA, Stampfer MJ, Willett WC, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol*. Aug; 1987 126(2):319–325. [PubMed: 3605058]
8. Gonzalez DA, Diaz BB, Rodriguez Perez Mdel C, Hernandez AG, Chico BN, de Leon AC. Sex hormones and autoimmunity. *Immunol Lett*. Sep; 2010 133(1):6–13. [PubMed: 20637236]
9. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med*. Apr; 2008 168(8):861–866. [PubMed: 18443262]
10. Hunter DJ, Manson JE, Colditz GA, et al. Reproducibility of oral contraceptive histories and validity of hormone composition reported in a cohort of US women. *Contraception*. Dec; 1997 56(6):373–378. [PubMed: 9494771]
11. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. *Int J Obes Relat Metab Disord*. Aug; 1995 19(8):570–572. [PubMed: 7489028]
12. Khalili H, Huang ES, Ananthakrishnan AN, et al. Geographical variation and incidence of inflammatory bowel disease among US women. *Gut*. Jan 11.2012

13. Loftus EV Jr, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gastroenterology*. Jun; 1998 114(6):1161-1168. [PubMed: 9609752]
14. Loftus EV Jr, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gut*. Mar; 2000 46(3):336-343. [PubMed: 10673294]
15. Fonager K, Sorensen HT, Rasmussen SN, Moller-Petersen J, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. *Scand J Gastroenterol*. Feb; 1996 31(2):154-159. [PubMed: 8658038]
16. Moum B, Vatn MH, Ekbom A, et al. Incidence of inflammatory bowel disease in southeastern Norway: evaluation of methods after 1 year of registration. Southeastern Norway IBD Study Group of Gastroenterologists. *Digestion*. 1995; 56(5):377-381. [PubMed: 8549880]
17. Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996-2002. *Am J Gastroenterol*. Aug; 2008 103(8):1998-2006. [PubMed: 18796097]
18. Baik CS, Strauss GM, Speizer FE, Feskanich D. Reproductive factors, hormone use, and risk for lung cancer in postmenopausal women, the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*. Oct; 2010 19(10):2525-2533. [PubMed: 20739629]
19. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med*. Mar 6; 2012 156(5):350-359. [PubMed: 22393130]
20. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology*. Mar; 2012 142(3):482-489. [PubMed: 22155183]
21. Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum*. Apr; 2007 56(4):1251-1262. [PubMed: 17393454]
22. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. *The New England journal of medicine*. Dec 23; 2004 351(26):2694-2703. [PubMed: 15616204]
23. Garcia Rodriguez LA, Gonzalez-Perez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther*. Aug 15; 2005 22(4):309-315. [PubMed: 16097997]
24. Lees CW, Barrett JC, Parkes M, Satsangi J. New IBD genetics: common pathways with other diseases. *Gut*. Dec; 2011 60(12):1739-1753. [PubMed: 21300624]
25. Braniste V, Jouault A, Gaultier E, et al. Impact of oral bisphenol A at reference doses on intestinal barrier function and sex differences after perinatal exposure in rats. *Proc Natl Acad Sci U S A*. Jan 5; 2010 107(1):448-453. [PubMed: 20018722]
26. Looijer-van Langen M, Hotte N, Dieleman LA, Albert E, Mulder C, Madsen KL. Estrogen receptor-beta signaling modulates epithelial barrier function. *Am J Physiol Gastrointest Liver Physiol*. Apr; 2011 300(4):G621-626. [PubMed: 21252046]
27. Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J Clin Invest*. May; 2004 113(10):1490-1497. [PubMed: 15146247]
28. Fuss IJ, Neurath M, Boirivant M, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol*. Aug 1; 1996 157(3):1261-1270. [PubMed: 8757634]
29. Heller F, Florian P, Bojarski C, et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology*. Aug; 2005 129(2):550-564. [PubMed: 16083712]
30. Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology*. Apr; 1997 112(4):1169-1178. [PubMed: 9098000]

31. Cutolo M, Capellino S, Straub RH. Oestrogens in rheumatic diseases: friend or foe? *Rheumatology* (Oxford). Jun; 2008 47(Suppl 3):iii2–5. [PubMed: 18504280]
32. Kane SV, Reddy D. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. *Am J Gastroenterol*. May; 2008 103(5):1193–1196. [PubMed: 18177456]
33. Sarna L, Bialous SA, Jun HJ, Wewers ME, Cooley ME, Feskanich D. Smoking trends in the Nurses' Health Study (1976-2003). *Nurs Res*. Nov-Dec;2008 57(6):374–382. [PubMed: 19018212]
34. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *Bmj*. 2008; 337:a1440. [PubMed: 18796495]
35. Walker M. *Observation and Inference: An Introduction to the Methods of Epidemiology*: Epidemiology Resources. 1991
36. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *The New England journal of medicine*. Aug 7; 2003 349(6):523–534. [PubMed: 12904517]

Figure 1. Flow of eligible participants in the study

Table 1
Characteristics of Postmenopausal Women in the Nurses' Health Study According to
Hormone Use at the Midpoint of Follow-up*

	Hormone Use		
	Never	Past	Current
Age, mean years (SD)	61.2 (5.7)	63.6 (5.6)	59.7 (6.1)
Race (non-white), %	5.5	5.7	4.5
Geographic latitude at age 30, %			
Northern	39	34	29
Middle	41	42	41
Southern	7	12	17
Missing/foreign	13	12	13
Age at menopause, mean years (SD)	50.6 (9.9)	46.5 (7.9)	47.8 (10.4)
Body-mass index, %			
< 20 kg/m ²	10	10	13
20-24.9 kg/m ²	54	58	64
25-29.9 kg/m ²	25	23	18
30 kg/m ²	11	9	5
Smoking, %			
Never	43	41	45
Past	39	42	43
Current	18	17	12
Age at menarche, %			
10 years	5	6	5
11 years	16	17	16
12 years	27	27	27
13 years	31	29	31
14 years	21	21	21
Ever used oral contraceptives, %	36	44	47
Regular use of NSAIDs [§] , %	17	23	25
Parity, %			
0	5	7	6
1	7	7	7
2	23	25	26
3	65	61	61
Menopause type, %			
Natural	76	54	46
Surgical/radiation	24	46	54
History of appendectomy, %	24	32	33

* Characteristics based upon data from the 1992 follow up questionnaire. At this time point, 69,039 women were postmenopausal, with 24,816 never users of hormones, 16,143 past users of hormones, and 28,080 current users of hormones. Values are means (SD) or percentages and are standardized to the age distribution of the study population.

[§]Regular use is defined as ≥ 2 tablets/week.

Table 2
Postmenopausal Hormone Use and Risk of Ulcerative Colitis and Crohn's Disease
(1976-2008)*

	Hormone use		
	Never	Past	Current
Person-years of follow-up	647,896	599,319	644,812
Ulcerative Colitis			
No. of cases	31	47	60
Age-adjusted HR (95% CI)	1.00	1.62 (1.01-2.59)	1.64 (1.05-2.56)
Multivariate-adjusted HR (95% CI) [§]	1.00	1.65 (1.03-2.66)	1.71 (1.07-2.74)
Crohn's Disease			
No. of cases	43	31	64
Age-adjusted HR (95% CI)	1.00	0.78 (0.48-1.26)	1.27 (0.86-1.89)
Multivariate-adjusted HR (95% CI) [§]	1.00	0.72 (0.44-1.17)	1.19 (0.78-1.82)

* Abbreviations: Confidence Interval (CI), Hazard Ratio (HR). Postmenopausal hormone use, age, smoking, and regular use of NSAIDs, were entered as time-varying exposures over follow-up. Age at menopause, body-mass index, use of oral contraceptives, age at menarche, menopause type, and geographic latitude at age 30 were entered as time invariant exposures.

[§] Models adjusted for age (months), age at menopause (yrs), smoking (never, past, current), body-mass index (< 20, 20-24.9, 25-29.9, ≥ 30 kg/m²), oral contraceptive use (never, ever), regular use of NSAIDs (< 2 tablets/wk, ≥ 2 tablets/wk), parity (0, 1, 2, ≥ 3), geographic latitude at age 30 (south, middle, northern, foreign/missing), age at menarche (10, 11, 12, 13, ≥ 14), history of appendectomy (no, yes), and menopause type (natural, surgical/radiation).

Table 3
Duration of Postmenopausal Hormone Use and Risk of Ulcerative Colitis and Crohn's Disease (1976-2008)^{*}

	Years of hormone use				P _{trend} [†]
	0	1-5	6-10	>10	
Person-years of follow-up	647,896	564,090	308,884	371,157	
Ulcerative Colitis					
No. of cases	31	46	28	33	
Age-adjusted HR (95% CI)	1.00	1.61 (1.01-2.55)	1.68 (0.99-2.83)	1.63 (0.98-2.72)	0.06
Multivariate-adjusted HR (95% CI) [§]	1.00	1.61 (1.01-2.56)	1.78 (1.03-3.05)	1.80 (1.02-3.15)	0.04
Crohn's Disease					
No. of cases	43	39	19	37	
Age-adjusted HR (95% CI)	1.00	0.98 (0.63-1.52)	0.83 (0.48-1.45)	1.40 (0.88-2.22)	0.25
Multivariate-adjusted HR (95% CI) [§]	1.00	0.93 (0.59-1.45)	0.79 (0.45-1.39)	1.28 (0.76-2.14)	0.49

^{*} Abbreviations: Confidence Interval (CI), Hazard Ratio (HR). Postmenopausal hormone use, age, smoking, and regular use of NSAIDs, were entered as time-varying exposures over follow-up. Age at menopause, body-mass index, use of oral contraceptives, age at menarche, menopause type, and geographic latitude at age 30 were entered as time invariant exposures.

[§] Models adjusted for age (months), age at menopause (yrs), smoking (never, past, current), body-mass index (< 20, 20-24.9, 25-29.9, ≥ 30 kg/m²), oral contraceptive use (never, ever), regular use of NSAIDs (< 2 tablets/wk, 2 tablets/wk), parity (0, 1, 2, 3), geographic latitude at age 30 (south, middle, northern, foreign/missing), parity (0, 1, 2, 3), age at menarche (10, 11, 12, 13, 14), history of appendectomy (no, yes), and menopause type (natural, surgical/radiation).

[†] Linear trend estimated by entering duration of use as a continuous variable in the model.

Table 4
Time Since Discontinuation of Postmenopausal Hormone Use and Risk of Ulcerative Colitis and Crohn's Disease (1976-2008)*

	Years since discontinuation			
	Never	> 5	1-5	Current
Person-years of follow-up	647,896	231,162	288,413	644,812
Ulcerative Colitis				
No. of cases	31	16	26	60
Age-adjusted HR (95% CI)	1.00	1.35 (0.76-2.39)	2.06 (1.14-3.73)	1.65 (1.05-2.57)
Multivariate-adjusted HR (95% CI) [§]	1.00	1.39 (0.78-2.49)	2.06 (1.14-3.75)	1.72 (1.07-2.75)
Crohn's Disease				
No. of cases	43	14	16	64
Age-adjusted HR (95% CI)	1.00	0.77 (0.43-1.39)	0.65 (0.30-1.41)	1.27 (0.85-1.89)
Multivariate-adjusted HR (95% CI) [§]	1.00	0.70 (0.38-1.27)	0.61 (0.28-1.32)	1.20 (0.78-1.83)

* Abbreviations: Confidence Interval (CI), Hazard Ratio (HR). Postmenopausal hormone use, age, smoking, and regular use of NSAIDs, were entered as time-varying exposures over follow-up. Age at menopause, body-mass index, use of oral contraceptives, age at menarche, menopause type, and geographic latitude at age 30 were entered as time invariant exposures.

[§] Models adjusted for age (months), age at menopause (yrs), smoking (never, past, current), body-mass index (< 20, 20-24.9, 25-29.9, ≥ 30 kg/m²), oral contraceptive use (never, ever), regular use of NSAIDs (< 2 tablets/wk, ≥ 2 tablets/wk), parity (0, 1, 2, ≥ 3), geographic latitude at age 30 (south, middle, northern, foreign/missing), parity (0, 1, 2, ≥ 3), age at menarche (10, 11, 12, 13, ≥ 14), history of appendectomy (no, yes), and menopause type (natural, surgical/radiation).

Table 5
Postmenopausal Hormone Use and Risk of Ulcerative Colitis According to Strata of Age, Smoking and Body-mass Index*

	Never	Ever	P _{interaction}
Age 60 years [¶]			0.47
No. of Cases / Person-years	14/234,878	51/604,177	
Age-adjusted HR, 95% CI	1.00	1.40 (0.77-2.54)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.35 (0.74-2.49)	
Age > 60 years			
No. of Cases / Person-years	17/413,018	56/639,954	
Age-adjusted HR, 95% CI	1.00	1.86 (1.07-3.24)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.75 (1.00-3.08)	
Never smoking			0.73
No. of Cases / Person-years	12/281,318	37/540,233	
Age-adjusted HR, 95% CI	1.00	1.53 (0.78-2.97)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.68 (0.83-3.40)	
Past / current smoking			
No. of Cases / person-years	19/366,431	70/703,169	
Age-adjusted HR, 95% CI	1.00	1.68 (1.00-2.83)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.77 (1.03-3.04)	
Body-mass index < 25 kg/m²			0.40
No. of Cases / person-years	21/417,363	76/923,280	
Age-adjusted HR, 95% CI	1.00	1.49 (0.91-2.44)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.45 (0.87-2.42)	
Body-mass index ≥ 25 kg/m²			
No. of Cases / Person-years	10/230,534	31/320,852	
Age-adjusted HR, 95% CI	1.00	2.01 (0.97-4.14)	
Multivariate-adjusted HR, 95% CI [†]	1.00	2.26 (1.06-4.82)	

* Abbreviations: Hazard Ratio (HR), Confidence Interval (CI). Strata variable refers to specific predictor used for stratification.

[¶]Age at the midpoint of follow up in 1992.

[†]Adjusted for same variables as Table 4 with the strata variable omitted.

Table 6
Postmenopausal Hormone Use and Risk of Crohn's Disease According to Strata of Age, Smoking and Body-mass Index *

	Never	Ever	P _{interaction}
Age 60 years [¶]			0.21
No. of Cases / Person-years	15/234,878	52/604,177	
Age-adjusted HR, 95% CI	1.00	1.35 (0.76-2.42)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.29 (0.71-2.34)	
Age > 60 years			
No. of Cases / Person-years	28/413,018	43/639,954	
Age-adjusted HR, 95% CI	1.00	0.87 (0.54-1.42)	
Multivariate-adjusted HR, 95% CI [†]	1.00	0.88 (0.53-1.46)	
Never smoking			0.31
No. of Cases / Person-years	17/281,318	28/540,233	
Age-adjusted HR, 95% CI	1.00	0.78 (0.42-1.45)	
Multivariate-adjusted HR, 95% CI [†]	1.00	0.71 (0.37-1.38)	
Past/current smoking			
No. of Cases / Person-years	26/366,431	67/703,169	
Age-adjusted HR, 95% CI	1.00	1.24 (0.78-1.97)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.10 (0.67-1.79)	
Body-mass index < 25 kg/m²			0.89
No. of Cases / Person-years	30/417,363	76/923,280	
Age-adjusted HR, 95% CI	1.00	1.06 (0.69-1.63)	
Multivariate-adjusted HR, 95% CI [†]	1.00	0.92 (0.59-1.46)	
Body-mass index ≥ 25 kg/m²			
No. of Cases / Person-years	13/230,534	21/320,852	
Age-adjusted HR, 95% CI	1.00	0.95 (0.46-1.95)	
Multivariate-adjusted HR, 95% CI [†]	1.00	1.04 (0.48-2.27)	

* Abbreviations: Hazard Ratio (HR), Confidence Interval (CI). Strata variable refers to specific predictor used for stratification.

[¶]Age at the midpoint of follow up in 1992.

[†]Adjusted for same variables as Table 4 with the strata variable omitted.