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Menopausal Hormone Therapy and Risk of Diverticulitis

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Abstract

INTRODUCTION: Diverticulitis is a significant cause of morbidity among older women, and little attention has been paid to understanding its etiology. We have shown that menopausal

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CONFLICTS OF INTEREST

Guarantors of the article: Lisa L. Strate, MD, MPH and Andrew T. Chan, MD, MPH.

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hormone therapy (MHT) is associated with the risk of inflammatory bowel disease. In this study, we prospectively examined the association between MHT and the risk of incident diverticulitis.

METHODS: We studied 65,367 postmenopausal women enrolled in the Nurses' Health Study who provided detailed information on hormone use and other medical and lifestyle factors biennially, and on diet every 4 years. Between 2008 and 2014, participants reported any episodes of diverticulitis that required antibiotics and the date of occurrence. We used Cox proportional hazards regression models to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS: Over 24 years encompassing 1,297,165 person-years of follow-up, we documented 5,425 incident cases of diverticulitis. We observed an increased risk of diverticulitis among both current (HR 1.28; 95% CI 1.18–1.39) and past (HR 1.35; 95% CI 1.25–1.45) MHT users compared to never users. The increased risk was observed among participants using estrogen only (HR 1.30; 95% CI 1.20–1.41) and those using combined estrogen and progesterone (HR 1.31; 95% CI 1.21–1.42) compared to nonusers. The risk did not increase with longer duration of use (*P*-trend = 0.76). The association between MHT and diverticulitis was not modified by age, body mass index, past oral contraceptive use, or fiber intake (all *P*-interaction >0.11).

CONCLUSIONS: Menopausal hormone therapy was associated with an increased risk of diverticulitis. Further studies are needed to understand the potential mechanisms that may underlie this association.

INTRODUCTION

Diverticulitis is one of the most common gastrointestinal indications for hospital admission in the United States (1–3), with more than $2 billion spent annually on inpatient management alone (4). It is also among the leading gastrointestinal diagnoses in the ambulatory care setting (4). Despite the impact of diverticulitis on patients and the healthcare system, its epidemiology and etiopathogenesis remain poorly understood (5). Recent studies have focused on identifying lifestyle risk factors (6), such as smoking (7,8), alcohol use (9), physical inactivity and obesity (10–13), use of nonsteroidal anti-inflammatory drugs (NSAIDs) (14), as well as dietary factors including a Western dietary pattern (15), fiber and red meat (16,17).

The incidence of diverticulitis increases with age, particularly among postmenopausal women (2,18–20). In addition, menopausal hormone therapy (MHT) is associated with an increased risk of inflammatory bowel disease (IBD), a gastrointestinal condition that may have some histological similarities to diverticulitis (21). These findings suggest a possible role for menopause and MHT in the development of diverticulitis. Only one prior study suggested that MHT may be associated with an increased risk of diverticular disease (17). However, that analysis had a number of important limitations. Therefore, we sought to prospectively examine the association between MHT and the risk of incident diverticulitis in an ongoing large prospective cohort of US postmenopausal women.

METHODS

Study population

We utilized the Nurses' Health Study, an ongoing cohort of 121,739 female registered nurses, aged 30–55 years at enrollment in 1976. Participants were mailed follow-up questionnaires every 2 years to provide data on lifestyle factors, medical history, and disease outcomes, and every 4 years to report dietary intake. The follow-up rates have been greater than 90%. The Institutional Review Boards of the Harvard T.H. Chan School of Public Health and Partners Healthcare approved the study protocol.

Assessment of menopausal hormone therapy

Menopausal hormone therapy was ascertained beginning in 1976 and every 2 years thereafter. On each biennial questionnaire, participants reported the number of months during the previous 2 years when prescription MHT was taken, whether MHT was currently being used, and the type of MHT preparation (estrogen, progestin, or combination of estrogen plus progestin).

Ascertainment of diverticulitis

In 2008 and 2012, participants were asked whether they ever had a diagnosis of diverticulitis requiring antibiotic therapy or hospitalization. If yes, participants were asked the year of each episode dating back to 1990. In 2014, participants were asked the same question, but restricted to the previous 2 years. In a review of 107 medical records from women reporting incident diverticulitis in 2008, self-report was confirmed in 88% of cases, through review of medical records. We confirmed the self-report of diverticulitis by a combination of factors presented in the medical records, such as imaging (e.g., computed tomography scan) and/or clinical notes (e.g., hospitalization or need for antibiotics) and/or need for surgery.

Assessment of other exposures

Participants were asked about age at menarche (in 1976), parity (from 1976 to 1996), oral contraceptive (OC) use (from 1976 to 1984), menopausal status, age at menopause, and type of menopause (from 1976 to 2004, after which all subjects were postmenopausal). Weight, smoking status, physical activity, history of recent physical examination, aspirin or other NSAID use, and history of cancer were assessed in 1976 and updated every 2 years thereafter. We determined body mass index (BMI) from measurements of height provided by participants in 1976 and from measurements of weight updated every 2 years. Dietary information was first obtained in 1980 using a semiquantitative food frequency questionnaire and every 4 years thereafter. Based on this information, we calculated Alternative Healthy Eating Index–2010 scores, as a measure of overall diet quality (22). Cigarette and alcohol use, dietary intake, physical activity, and menopausal status in this cohort have been validated previously. We used cumulative measures of covariates when appropriate.

Statistical analysis

We restricted the analysis to participants who returned the 2008, 2012, or 2014 questionnaires (n = 71,110). Women who reported a diagnosis of diverticulitis or its complications (n = 1,853), gastrointestinal cancer (n = 290), or IBD (n = 463) at or prior to baseline in 1990 were excluded from the analysis. In addition, we excluded study participants who reported diverticulitis prior to menopause (n = 113) and those who at baseline had missing information on our outcome of interest (n = 479). After these exclusions, there were 45,977 women in our baseline study population. Participants that had not undergone menopause or did not provide information on hormone use at baseline (n = 22,048) were excluded from entry at baseline, but were able to enter the analysis when they became menopausal and/or reported data on hormone use, provided they did not report diverticulitis prior to that date. Overall, 65,367 participants contributed to the final analysis. For each participant, person-time was calculated from the moment of inclusion in the study until the date of incident diverticulitis, death, loss to follow-up, or the end of follow-up (June 2014), whichever came first. We censored women who reported a new diagnosis of gastrointestinal cancer or IBD at the date of diagnosis. We updated and used the most recent information for all exposures.

Cox proportional hazards models were applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). To control for confounding by age, calendar time, and any possible 2-way interactions between these 2 timescales, we stratified the analysis jointly by age in years at the start of follow-up and calendar time of the current questionnaire cycle. Proportional hazards assumption was tested by including the product term between exposure variable and age and testing significance using the Wald test. No deviation from the proportional hazards assumption was detected.

Consistent with prior studies on risk factors for diverticulitis (6,11–16,23), we chose *a priori* the following potential confounding variables to include in our multivariable model: age at menarche, age at menopause, time since menopause, parity, OC use, type of menopause, vigorous physical activity, alcohol intake, smoking, regular use of aspirin or other NSAIDs, BMI, caloric intake, dietary fiber and red meat intake, and Alternative Healthy Eating Index score. We tested the hypothesis of whether current or past MHT use was associated with the risk of diverticulitis in the overall cohort. We also performed several sensitivity analyses, such as (i) the association of MHT with the risk of diverticulitis restricting follow-up from 2008 to 2014 to ensure that cases were ascertained prospectively, (ii) the association of MHT with diverticulitis in the subgroup of participants who reported having ever undergone endoscopy, and (iii) the association of MHT with diverticulitis that required surgery. Tests for interaction were performed by including the cross-product term between ever hormone use and the stratified variable into the model, and testing the statistical significance using the Wald test. We tested for linear trends across categories by assigning the median value for the sample to each category and modeling this as a continuous variable.

Finally, we also considered the possibility that the association of MHT with diverticulitis may be mediated, at least partially, by diverticulosis, defined as any diverticular disease that did not result in bleeding and that did not require antibiotics, hospitalization, or surgery. Hence, we conducted a multivariable logistic regression to estimate the risk of diverticulosis

among ever MHT users in a cross-sectional analysis of 61,839 participants answering the 2012 questionnaire, which specifically ascertained diverticulitis as well as diverticulosis. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Over the 24 years, encompassing 1,297,165 person-years of follow-up, we documented 5,425 incident cases of diverticulitis. At the midpoint of the study, ever hormone users were more likely to have undergone surgical or radiological menopause, become menopausal earlier, and used more NSAIDs and OCs compared to those who never received MHT. The remaining characteristics at the study midpoint did not differ substantially among never, past, or current hormone users (Table 1).

We observed an increased risk of diverticulitis among women who had ever used MHT (Table 2). After adjusting for lifestyle and dietary risk factors, compared to women who never received MHT, the multivariate HRs for diverticulitis were 1.28 (95% CI 1.18–1.39) among current users and 1.35 (95% CI 1.25–1.45) among past users. This association was observed for estrogen only (multivariate HR 1.30; 95% CI 1.20–1.41) and combined estrogen plus progesterone (multivariate HR 1.31; 95% CI 1.21–1.42) (see Table, Supplementary Digital Content 1, http://links.lww.com/AJG/A9). The risk of diverticulitis did not vary with the duration of MHT (Table 3). Furthermore, the risk associated with ever use of MHT was only slightly attenuated 10 years after discontinuation of MHT (Table 4; *P*-trend = 0.32).

In stratified analyses, the association of hormone use with the risk of diverticulitis was not modified by categories of age, dietary fiber intake, BMI, and past OC use (all *P*-interaction >0.11; Table 5). However, whereas the risk of diverticulitis appeared increased in both strata of smoking (never vs ever), the increase in risk of diverticulitis associated with MHT appeared more pronounced among those who never smoked (HR 1.42; 95% CI 1.27–1.58) than ever smokers (HR 1.25; 95% CI 1.14–1.37; Table 5).

When we restricted our analysis to participants at risk for developing diverticulitis from 2008 to 2014 (n = 55,118), we observed a similar association between current and past MHT use and risk of diverticulitis (HR 1.47; 95% CI 1.17–1.83 and HR 1.53; 95% CI 1.31–1.79, respectively, when compared to never use) (see Table, Supplementary Digital Content 2, http://links.lww.com/AJG/A10). In participants who had undergone flexible sigmoidoscopy, colonoscopy, or virtual colonoscopy, current and past MHT use was associated with the increased risk of diverticulitis (HR 1.22; 95% CI 1.06–1.40 and HR 1.21; 95% CI 1.06–1.37, respectively, compared to never users). Likewise, current and past MHT use was significantly associated with diverticulitis that required surgery (HR 1.35; 95% CI 1.07–1.71 and HR 1.41; 95% CI 1.15–1.74, respectively, compared to never users). Because some data suggest that cardiovascular diseases may also be a risk factor for diverticulitis, we further adjusted for it in the multivariable model, and the results were not substantially altered: HR 1.32 (95% CI 1.23–1.41) when comparing ever MHT users with never users. Finally, in a cross-sectional analysis of participants who returned the 2012 questionnaire, we observed a

significant association between ever MHT use and uncomplicated diverticulosis (OR 1.31; 95% CI 1.23–1.39).

DISCUSSION

In this large prospective cohort study, we observed an association between MHT and increased risk of diverticulitis after adjusting for other known or suspected risk factors for diverticulitis. The risk was increased for both estrogen and estrogen plus progesterone users. We found MHT use was also associated with an increase in the risk of diverticulitis that required surgical treatment.

Prior data examining the association between MHT and diverticulitis are scant. In a study primarily focused on dietary factors, ever use of MHT was included as a potential confounder and was significantly associated with the risk of diverticulitis (RR 1.29; 95% CI 1.09–1.54) (17), comparable to our findings. However, detailed information on MHT, such as type or duration of use, was not available in this study, and MHT use was assessed at one time point and analyzed as a fixed covariate. The prospective, biennial assessment of MHT in our study, on the other hand, enabled us to extend these preliminary findings in several important ways. We were able to account for changes in MHT use over time, distinguish between current and past use, assess duration of use, and perform a number of sensitivity analyses. Even though the effect estimate observed in our study was modest, if our findings are corroborated by other future studies, diverticulitis may be an additional potential adverse effect that should be weighed carefully by prescribers and patients considering MHT (24).

Our results have biological plausibility. Previous studies, including an analysis in the Nurses' Health Study, have shown that MHT is associated with the increased risk for a number of inflammatory diseases, including IBD (21,25). The presence of chronic inflammation in asymptomatic patients with diverticula even in areas not involved by the condition, a Crohn-like inflammation in patients with diverticulitis, the cyclical nature of symptoms/exacerbations, and other clinical or histological similarities suggest that diverticulitis and IBD may share some similar biological mechanisms involving intestinal inflammation and the gut microbiota (26–34). While diverticulitis is most commonly thought to be associated with microperforation due to either ischemic or traumatic damage from fecalith obstruction (35,36), this theory is not proved, and growing data suggest that microbiota may also play a significant role in the onset of diverticulitis (32–34,37). Indeed, the influence of other risk factors for diverticulitis such as diet, physical activity and obesity may, in part, be mediated by alterations in the gut microbiota (5,12,38). Some Authors have speculated that local quantitative and qualitative changes in gut microbes could potentially induce inflammatory and/or neuromuscular changes (39). This hypothesis is corroborated by a recent study that suggests that microbiota and metabolome changes are related to inflammation and gut neuromotor dysfunction, potentially resulting in diverticular disease establishment and/or consolidation (31). Estrogen has a number of effects on the gut microbiome (40–44), as well as colonic mucosa, including increasing intestinal permeability (45,46), all factors that may predispose to diverticulitis. Similar factors may also be responsible for the gender differences observed in immune-mediated diseases (47–50). However, at present the association between the microbiota and diverticulitis is inconclusive,

and we cannot ascertain whether altered microbiota may be the cause or the effect. Future studies therefore may serve to explore potential mechanisms that underlie the association between altered microbiota and diverticulitis.

We observed that the increase in the risk of diverticulitis was consistent among women with a prior colonoscopy, indicating that ascertainment bias did not play a significant role in our findings. We did observe that the association of MHT with risk persisted even after discontinuation of MHT. It is possible that MHT displays a so-called legacy effect, a memory of a treatment that produces effects long after cessation (51,52), or that the association is partly mediated through the development of diverticulosis. In support of this hypothesis, we found a significant positive association between MHT and uncomplicated diverticulosis at a cross-sectional analysis of our cohort. These mechanisms may also explain, at least in part, why we did not observe a dose-related effect. Even though much of this evidence is still preliminary, taken together it suggests that MHT may have both long- and short-term effects on the onset of diverticulitis. Further understanding of such mechanisms could potentially lead to elucidation of new targets for interventions that may modulate disease incidence and/or activity.

Our study has several strengths. First, the prospective study design allowed the acquisition of detailed information on many important potential confounders independently of disease status, thus minimizing the potential for recall and selection bias. Second, our analysis included 65,367 women with 5,425 incident cases, allowing a more comprehensive analysis of the association. Third, our endpoint, which was ascertained via questionnaire and validated in a subset of our population through medical record review by physicians blinded to the exposure information, represents the broad clinical spectrum of diverticulitis cases. This contrasts with prior studies that often relied on administrative data which are prone to misclassification and/or were limited to severe cases managed in the inpatient setting (2,19,20). Fourth, we modeled MHT using time-varying exposures to account for changes in hormone use over time and minimize exposure misclassification. Finally, participants in our study are nurses, increasing the validity of self-reported medical and risk factor information and minimizing potential confounding associated with variability in access to care.

We also acknowledge several limitations. First, as an observational study, we cannot rule out the possibility of unmeasured residual confounding or noncausal association. However, we adjusted for many known potential confounding factors, and multivariate adjustment did not significantly alter our age-adjusted ezinment of diverticulitis was based on self-reported and recalled information. However, the validity of self-reported diverticulitis has been confirmed in this cohort. Third, we cannot completely rule out secular effects due to a decrease in the use of MHT and an increase in the incidence of diverticulitis over time. However, in our analysis we have accounted for different periods of time. Fourth, based on our available data, we could not finely distinguish between symptomatic uncomplicated diverticular disease and asymptomatic diverticulosis. However, we could observe the association of MHT with other, more common clinically significant manifestations of the disease, namely diverticulitis requiring antibiotics, hospitalization, or surgery. Finally, although the homogeneity of healthcare access and socioeconomic status of our population helps minimize confounding and enhances internal validity, the results may not be generalizable to other populations.

However, the overall prevalence of diverticulitis and other risk factors in our population is consistent with that of the broader population of US women (5,53,54).

In conclusion, in this prospective cohort study, we observed that MHT is associated with an increased risk of diverticulitis. This potential adverse effect of MHT should be considered by prescribers and patients considering MHT particularly those at increased risk for diverticulitis. Additional studies are needed to better understand the potential mechanisms underlying this association. Further understanding of these mechanisms could inform new targets for prevention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS KNOWN

- Menopausal hormone therapy has been associated with IBD.
- No study has evaluated the association between MHT and diverticulitis.

WHAT IS NEW HERE

- Menopausal hormone therapy is associated with increased risk of diverticulitis.
- Diverticulitis might be added to the list of potential adverse effects that should be weighed carefully by prescribers and patients considering MHT.
- These results could help to shed light on the biological mechanisms underlying the development of diverticulitis.
- Further understanding of these mechanisms could inform new targets for prevention and treatment.

Table 1.

Characteristics of postmenopausal women in the Nurses' Health Study according to hormone use at the midpoint[a] of follow-up

	Never user (n = 14,305)	Current user (n = 29,263)	Past user (n = 16,308)
Age, yr[b]	65.5 (6.8)	63.4 (6.4)	66.3 (6.7)
Whites, %	97.2	97.8	97.2
Age at menarche, yr	12.5(1.5)	12.5(1.4)	12.5(1.4)
Age at first birth, yr	29.7(17.9)	30.0 (18.9)	29.7 (18.4)
Age at menopause, yr	50.8 (3.6)	49.4 (4.7)	49.4 (4.6)
Natural menopause, %	75.0	48.7	59.0
Past use of OC, %	45.7	59.0	54.4
Parity			
No children, %	6.5	7.7	7.5
One child, %	6.5	6.6	6.8
Two children, %	26.4	29.8	28.0
Three or more children, %	60.6	56.0	57.7
BMI, kg/m^2			
<22.5, %	17.5	21.8	19.0
22.5–24.9, %	19.5	24.1	22.3
25.0–27.4, %	20.7	21.6	21.0
27.5–29.9, %	14.2	13.0	14.3
30.0–34.9, %	17.5	14.0	15.4
≥35, %	10.5	5.5	8.1
Alcohol, g/d	5(9)	5(9)	5(9)
Past smoker, %	43.0	47.6	46.3
Current smoker, %	10.3	6.8	9.4
Aspirin use, %	40.5	43.02	42.0
Other NSAID use, %	23.3	29.0	27.3
Total energy intake, kcal/d	1,745 (553)	1,742 (528)	1,744 (545)
Protein intake, g/d	73 (10)	74 (10)	74 (10)
Fiber intake, g/d	18(5)	18(4)	18(4)
Alternate Healthy Eating Index score	45 (9)	46 (9)	46 (9)
Cardiovascular diseases, %	7.92	8.96	9.18

Values are means (SD) or percentages and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding.

BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; OC, oral contraceptive.

[a] In the year 2000.

[b] Value is not age-adjusted.

Table 2.

Current or past hormone use and risk of diverticulitis

	Never hormone use	Current hormone use	Past hormone use
No. of cases	1,102	1,673	2,650
Person-years	342,572	430,068	524,524
Age-adjusted, HR (95% CI)	Reference	1.29 (1.19–1.39)	1.38 (1.28–1.48)
Multivariate,[a] HR (95% CI)	Reference	1.28 (1.18–1.39)	1.35 (1.25–1.45)

CI, confidence interval; HR, hazard ratio.

[a]Adjusted for age, vigorous activity, alcohol intake, smoking, aspirin use, other nonsteroidal anti-inflammatory drug use, body mass index and calorie intake, age at menarche, parity, age at menopause, time since menopause, type of menopause, past use of oral contraceptives, dietary intake of fiber and red meat, and Alternative Healthy Eating Index score.

Table 3.

Duration of hormone use and risk of diverticulitis

	Never hormone use	1–5 yr	6–10 yr	>10 yr
No. of cases	1,102	1,472	1,055	1,796
Person-years	342,572	355,609	246,414	352,569
Age-adjusted, HR (95% CI)	Reference	1.34 (1.24–1.45)	1.29 (1.19–1.41)	1.36 (1.26–1.47)
Multivariate,[a] HR (95% CI)	Reference	1.33 (1.23–1.44)	1.29 (1.18–1.41)	1.33 (1.22–1.44)

CI, confidence interval; HR, hazard ratio.

[a]Adjusted for age, vigorous activity, alcohol intake, smoking, aspirin use, other nonsteroidal anti-inflammatory drug use, body mass index and calorie intake, age at menarche, parity, age at menopause, time since menopause, type of menopause, past use of oral contraceptives, dietary intake of fiber and red meat, and Alternative Healthy Eating Index score.

Table 4.

Time since discontinuation of hormone use and risk of diverticulitis[a]

	Never hormone use	1–5 yr	6–10 yr	>10 yr
No. of cases	1,102	1,048	694	629
Person-years	342,572	208,250	146,051	118,808
Age-adjusted, HR (95% CI)	Ref	1.36 (1.25–1.49)	1.36 (1.23–1.50)	1.35 (1.22–1.49)
Multivariate,[b] HR (95% CI)	Ref	1.36 (1.24–1.49)	1.35 (1.22–1.49)	1.30 (1.17–1.44)

CI, confidence interval; HR, hazard ratio.

[a]Only among past users.

[b]Adjusted for age, vigorous activity, alcohol intake, smoking, aspirin use, other nonsteroidal anti-inflammatory drug use, body mass index and calorie intake, age at menarche, parity, age at menopause, time since menopause, type of menopause, past use of oral contraceptives, dietary intake of fiber and red meat, and Alternative Healthy Eating Index score.

Table 5.

Stratified analysis

	No. of cases	Never hormone use	Ever hormone use[a]	*P*-interaction
Age ≤70 yr	3,454	Reference	1.29 (1.19–1.41)	0.36
Age >70 yr	1,971	Reference	1.37 (1.22–1.54)	
Ever smoker	3,129	Reference	1.25 (1.14–1.37)	0.04
Never smoker	2,267	Reference	1.42 (1.27–1.58)	
BMI <25	2,109	Reference	1.37 (1.22–1.54)	0.36
BMI ≥25	3,315	Reference	1.27 (1.17–1.39)	
Natural menopause	2,860	Reference	1.36 (1.25–1.48)	0.33
Surgery/radiation	2,565	Reference	1.24 (1.10–1.40)	
Ever OC use	2,526	Reference	1.40 (1.26–1.55)	0.16
Never OC use	2,899	Reference	1.26 (1.15–1.38)	
Fiber intake, <18 g/d	2,478	Reference	1.28 (1.17–1.41)	0.11
Fiber intake, >18 g/d	2,947	Reference	1.38 (1.24–1.53)	

BMI, body mass index; OC, oral contraceptive.

[a]HR (95% confidence interval) for age, vigorous activity, alcohol intake, smoking, aspirin use, other nonsteroidal anti-inflammatory drug use, BMI and calorie intake, age at menarche, parity, age at menopause, time since menopause, type of menopause, past use of OCs, dietary intake of fiber and red meat, and Alternative Healthy Eating Index score. The strata variable is omitted from the multivariable model.