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ORIGINAL PAPER

Migraine History, Nonsteroidal Anti-inflammatory Drug Use, and Risk of Postmenopausal Endometrial Cancer

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Abstract Endometrial cancer is primarily a hormonally mediated disease. As such, factors that mediate or reflect exposure to estrogens, or that mediate response to such exposure, may plausibly be associated with endometrial cancer risk. History of migraines, another hormonally mediated condition, has recently been associated with a reduced risk of hormone receptor-positive breast cancer; however, the relationship between migraines and endometrial cancer has not previously been explored. We evaluated the relationship between migraine history and endometrial cancer risk in postmenopausal women, considering also the potential impact of nonsteroidal anti-inflammatory drug (NSAID) use, given the relationship of NSAIDs to hormones and to migraine history. We identified 93,384 women participating in the Women's Health Initiative prospective cohort who had an intact uterus at the time of study entry. Using Cox proportional hazards regression, we assessed risk of endometrial cancer during study follow-up according to history of migraines and according to current NSAID use at the time of study entry, adjusting for age, study arm, race, and hormone therapy use. We also evaluated interaction in these associations by body mass index. Having a history of migraines was not associated with endometrial cancer risk [hazard ratio (HR)=0.91, 95 % confidence interval (CI)=0.75–1.11], regardless of body mass index (BMI) or NSAID use status. Similarly, current NSAID use was not associated with endometrial cancer risk (HR=1.01, 95 % CI=0.88–1.16), regardless of BMI. Migraine history and NSAID use do not appear to be associated with risk of endometrial cancer.

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Introduction

Exposure to estrogens is a central risk factor for endometrial cancer. Estrogen has a proliferative effect on the endometrium [1] and can also induce inflammatory changes in this tissue [2]. Estrogenic effects may explain observed associations with several established endometrial cancer risk factors, such as obesity and use of unopposed estrogen therapy [3–5]. Other factors directly mediating the effects of estrogens on the endometrium, or indirectly reflecting exposure to estrogens, may thus also be expected to be related to endometrial cancer risk.

One such factor that may reflect exposure to estrogens is migraine history. Migraines in women are often associated with declines in estrogen levels; in particular, migraines have been reported to fluctuate in frequency according to phase of the menstrual cycle in premenopausal women [6, 7], and are less frequent and severe in postmenopausal women [8]. Three recent studies have suggested that postmenopausal women with a history of migraines have a significantly lower risk of breast cancer than women with no such history, with associations largely limited to hormone receptor-positive disease [9–11]. Although the precise mechanisms underlying these associations are unclear, it is plausible that this association is hormonally mediated. As such, it is also possible that women with a history of migraines might experience a lower risk of other hormonally mediated cancers, including endometrial cancer. To our knowledge, however, no prior studies have explored this possible association.

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) may also plausibly be associated with endometrial cancer risk through hormonal mechanisms. Laboratory studies have demonstrated that NSAIDs suppress proliferation in endometrial cancer cell lines in a dose-dependent fashion [12], and prior observational studies have noted that postmenopausal women who are regular users of aspirin and non-aspirin NSAIDs have lower levels of estradiol than non-users [13]. Such hormonal differences in NSAID users have been suggested in some studies to contribute to a decreased risk of breast cancer [14–16]. However, of the studies that have assessed the association between NSAID use and endometrial cancer risk [17–23], most have reported no association [20–23]. The largely null findings of these prior studies may be a consequence of small numbers: five of seven studies included fewer than 500 endometrial cancer cases [17, 19, 21–23].

Thus, although biologically plausible, literature evaluating the association between migraine history and endometrial cancer risk is non-existent, and literature evaluating the association between NSAID use and risk of endometrial cancer is sparse and inconclusive. We used data from the Women's Health Initiative (WHI) to evaluate these related gaps in knowledge.

Materials and Methods

The WHI is a large, longitudinal study of postmenopausal women comprised of multiple concurrent randomized clinical trials and an observational study. Details of the recruitment protocols and eligibility criteria used for the WHI have been published previously [24, 25]. Briefly, postmenopausal women between the ages of 50 and 79 years were enrolled from 40 clinical centers across the USA between October 1, 1993, and December 31, 1998. Women who had a medical condition associated with a predicted survival less than 3 years were excluded, as were women who were not likely to remain in the same geographic area for at least 3 years. Additional eligibility criteria pertaining to competing risks, likely adherence, and safety were imposed for women interested in participating in the WHI clinical trials (CT). Women not meeting these additional eligibility criteria for the CT, or who were not interested in the CT, were given the opportunity to enroll in the WHI observational study (OS). At the time of enrollment, all women provided written informed consent for participation. Human Subjects Review Committees at all participating institutions approved the WHI study protocol.

In total, 161,808 women enrolled in the WHI (N=93,676 in the OS; N=68,132 in the CT). For the present analysis, women who had a history of endometrial cancer (N=2,237) or hysterectomy at the time of study entry (N=65,535) were excluded. As a result of the latter criteria, all women participating in the unopposed estrogen hormone therapy (HT) CT were excluded: eligibility for the unopposed estrogen HT trial had been limited to women without an intact uterus at baseline [3]. We also excluded women for whom endometrial cancer history or hysterectomy status at study entry were unknown (N=150), and women without information on endometrial cancer diagnoses (N=478) or hysterectomy status (N=24) during study follow-up. Thus, the study population for this analysis included 93,384 women with an intact uterus.

Exposure Assessment

All WHI participants completed a series of self-administered questionnaires during baseline screening visits. These questionnaires ascertained detailed information on demographic and lifestyle factors, personal and family cancer history, and reproductive and medical history. Information on migraine history was assessed at this time by asking women to report if they had ever been told by a doctor that they had migraine headaches. Women were also asked to provide information on all prescription drugs and over-the-counter medications they were currently using at baseline. With respect to NSAIDs in particular, women were asked the following questions: "Do you take aspirin pills or powders, for

example, Anacin, Bufferin, BC? (This does not include aspirin-free drugs such as Tylenol or Advil.)"; "Do you take ibuprofen tablets or capsules, for example, Advil, Motrin, or Nuprin?"; "Do you take Naprosyn, Naproxen, Aleve, Indocin, Clinoril, Feldene, or other anti-inflammatory pain pills?" For each question in which a participant answered yes, information was collected on the product name, dosage, and duration of use. Medication data were verified by checking pill bottle labels and prescription records during the interview process. Based on these data, we defined baseline NSAID use as self-reported current use (defined as use of any NSAID for at least 2 weeks preceding the baseline interview) of aspirin, ibuprofen, and/or other prescription or over-the-counter nonsteroidal anti-inflammatory agents. Information on use of other prescription and over-the-counter migraine medications, including selective serotonin agonists, was also collected. Additionally, study staff collected information regarding lifetime use of postmenopausal hormone therapy (HT) through a structured in-person interview, and measured the height and weight of participants at baseline.

Follow-up and Outcome Ascertainment

Medical history, including diagnosis of endometrial cancer and hysterectomy since last contact, was updated on an annual (OS) or semi-annual (CT) basis via mailed or telephone-administered questionnaires. Endometrial cancer diagnoses reported by participants were verified locally by WHI physician adjudicator review of medical reports, and centrally by medical record review and cancer coding at the WHI Clinical Coordinating Center.

Statistical Analyses

Cox proportional hazards regression was used to assess the association between migraine history (yes, no) and endometrial cancer risk, both overall and within strata defined by NSAID use at baseline (yes, no) and body mass index (BMI) at baseline (<25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2). In separate regression models, we assessed the association between NSAID use at baseline (yes, no), duration of recent NSAID use (no use at baseline, current use for <3 years, current use for ≥3 years), and endometrial cancer risk. We also evaluated the association between NSAID use and endometrial cancer risk within strata defined by BMI (<25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2). Based on concerns that reported medication use may have been influenced by not yet diagnosed disease, we conducted sensitivity analyses excluding women diagnosed with endometrial cancer in the first year after study enrollment (N=104). We also conducted exploratory analyses to evaluate differences in associations with NSAID use and migraine history across age strata (50–59, 60–69, 70–79) and strata defined by race (white, non-white), and analyses distinguishing women reporting a migraine history who also self-reported use of migraine medications at the time of the baseline interview from other women with a migraine history. In all models, the time axis was defined as the time (in days) since randomization (CT) or study enrollment (OS). Women who reported on a follow-up questionnaire that they had undergone a hysterectomy since the time of their last follow-up were censored at the time of their hysterectomy (N=5,532). Proportional hazards assumptions were verified by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times and on the log of analysis time [26].

All analyses were adjusted for age at randomization/enrollment (10-year intervals) and study component (CT, OS) through stratification of the baseline hazards. To further account for potential confounding by age, we also adjusted for age as a continuous term. In addition to these variables, we evaluated confounding by the following variables as categorized in Table 1: race/ethnicity, education, BMI, parity, oral contraceptive use, age at menopause, age at menarche, use of unopposed estrogen HT, use of combined estrogen–progestin HT, physical activity, smoking history, alcohol consumption, and consumption of regular coffee. Data on all potential confounders was based on information provided at the study baseline questionnaire; additionally, women who were assigned to the intervention arm of the combined estrogen–progestin HT study arm were considered current users of combined estrogen–progestin HT regardless of HT use self-reported on the baseline questionnaire. Of those potential confounders evaluated, only race/ethnicity, BMI, use of unopposed estrogen HT, and use of combined estrogen–progestin HT changed multivariate-adjusted risk estimates by at least 10 % and were included in our final analytic model. All analyses were performed using STATA SE version 11.0 (College Station, TX, USA).

Results

Characteristics of the study population are presented in Table 1 according to exposure status. Compared to women who reported no history of a clinical diagnosis of migraines, women with physician-diagnosed migraines were slightly younger at study entry, were more likely to have used oral contraceptives, and more likely to have used combined estrogen–progestin HT. Compared to women who were not NSAID users at study entry, women who used NSAIDs were more likely to be obese and more likely to have used combined estrogen–progestin HT.

Table 1 Study population characteristics according to migraine history and NSAID use

	History of migraine[a]		NSAID use at baseline[b]	
	No (*N*=79,400)	Yes (*N*=8,598)	No (*N*=77,266)	Yes (*N*=16,118)
	N (%)	*N* (%)	*N* (%)	*N* (%)
Age at enrollment, years (SD)	63.3 (7.2)	61.5 (7.1)	63.0 (7.2)	63.1 (7.1)
Race/ethnicity				
Non-Hispanic White	67,007 (85)	7,577 (88)	65,123 (85)	14,051 (87)
African American	5,660 (7)	393 (5)	5,289 (7)	1,114 (7)
Hispanic/Latina	2,851 (4)	332 (4)	2,948 (4)	540 (3)
Asian/Pacific Islander	2,491 (3)	154 (2)	2,534 (3)	172 (1)
Other	1,177 (1)	130 (2)	1,174 (2)	202 (1)
Missing	214	12	198	39
Education				
High school/GED or less	16,146 (20)	1,518 (18)	15,437 (20)	3,488 (22)
Vocational/training school	7,379 (9)	744 (9)	7,050 (9)	1,574 (10)
Some college/associates degree	20,564 (26)	2,394 (28)	20,055 (26)	4,326 (27)
College graduate	34,718 (44)	3,895 (46)	34,159 (45)	6,626 (41)
Missing	593	47	565	104
Body mass index (kg/m^2)				
<25	29,986 (38)	3,443 (40)	30,576 (40)	4,643 (29)
25.0–29.9	26,840 (34)	2,834 (33)	26,369 (34)	5,280 (33)
≥30.0	21,808 (28)	2,250 (26)	19,605 (26)	6,050 (38)
Missing	766	71	716	145
Parity				
Nulliparous	10,331 (13)	1,056 (12)	10,004 (13)	2,003 (13)
1	6,912 (9)	837 (10)	6,861 (9)	1,331 (8)
2	19,833 (25)	2,326 (27)	19,454 (25)	3,926 (25)
≥3	41,927 (53)	4,342 (50)	40,453 (53)	8,763 (55)
Missing	397	37	494	95
Oral contraceptive use				
Never used	46,390 (58)	4,411 (51)	45,061 (58)	8,749 (54)
<5 years of use	17,554 (22)	2,393 (28)	17,393 (23)	3,876 (24)
5–9 years of use	7,586 (10)	928 (11)	7,334 (9)	1,717 (11)
≥10 years of use	7,845 (10)	865 (10)	7,459 (10)	1,766 (11)
Missing	25	1	19	10
Age at menopause (years)				
<45	7,541 (10)	817 (10)	7,068 (10)	1,588 (10)
45–54	56,517 (73)	6,250 (74)	53,475 (73)	11,202 (73)
≥55	13,476 (17)	1,360 (16)	12,870 (18)	2,601 (17)
Missing	1,866	171	3,853	727
Age at menarche (years)				
<12	16,482 (21)	1,906 (22)	15,757 (20)	3,625 (23)
12–13	43,941 (55)	4,673 (55)	42,708 (56)	8,831 (55)
≥14	18,776 (24)	1,998 (23)	18,492 (24)	3,605 (22)
Missing	201	21	309	57
Unopposed estrogen hormone therapy use at baseline				
Never used	70,361 (89)	7,470 (87)	68,613 (89)	13,911 (86)
Former use	7,350 (9)	885 (10)	6,962 (9)	1,833 (11)
Current use	1,661 (2)	242 (3)	1,664 (2)	369 (2)
Missing	28	1	27	5

Table 1 (continued)

	History of migraine[a]		NSAID use at baseline[b]	
	No *N* (%)	Yes *N* (%)	No *N* (%)	Yes *N* (%)
Estrogen–progestin hormone therapy use at baseline[c]				
Never used	43,907 (55)	4,126 (48)	42,813 (55)	8,010 (50)
Former use	6,438 (8)	876 (10)	6,244 (8)	1,480 (9)
Current use	29,026 (37)	3,588 (42)	28,173 (36)	6,626 (41)
Missing	29	8	36	2
Physical activity at study baseline (MET-hours per week)				
No activity	11,434 (14)	1,351 (16)	10,432 (14)	2,579 (17)
0.1–5.0	17,310 (22)	1,896 (22)	15,922 (22)	3,585 (23)
5.1–11.5	16,697 (21)	1,798 (21)	15,576 (21)	3,186 (21)
11.6–21.2	16,841 (21)	1,823 (21)	15,785 (21)	3,114 (20)
≥21.3	16,936 (21)	1,704 (20)	16,040 (22)	2,886 (19)
Missing	182	26	3,511	768
Smoking history at study baseline				
Never smoked	39,502 (50)	4,350 (51)	38,942 (51)	7,561 (48)
Former smoker	33,498 (43)	3,625 (43)	32,001 (42)	7,265 (46)
Current smoker	5,460 (7)	508 (6)	5,332 (7)	1,080 (7)
Missing	940	115	991	212
Alcohol consumption at baseline				
Non-drinker	8,045 (10)	789 (9)	7,889 (10)	1,499 (9)
Former drinker	13,039 (17)	1,679 (20)	12,623 (16)	2,967 (19)
Current drinker:				
<7 drinks per week	47,303 (59)	5,274 (62)	46,295 (61)	9,505 (59)
≥7 drinks per week	10,548 (13)	807 (9)	9,912 (13)	2,037 (13)
Missing	465	49	547	110
Coffee consumption at baseline				
Not a regular coffee drinker	31,397 (40)	3,506 (41)	30,769 (40)	6,072 (38)
1 cup per day	12,039 (15)	1,336 (16)	11,619 (15)	2,390 (15)
2 cups per day	15,781 (20)	1,633 (19)	15,233 (20)	3,210 (20)
≥3 cups per day	19,443 (25)	2,051 (24)	18,857 (25)	4,291 (27)
Missing	740	72	788	155

[a] Excludes 5,386 women with missing data on migraine history. Women were classified as having a history of migraines if they self-reported having been told by a doctor that they had migraine headaches

[b] NSAID use at baseline defined on the basis of self-reported use of aspirin or non-aspirin NSAIDs in the 2 weeks prior to baseline interview

Over the course of study follow-up (median 12.5 years), 1,337 women in the sample eligible for this study were diagnosed with endometrial cancer. Overall, after adjusting for age and study arm, having a clinical history of migraines was not associated with endometrial cancer risk [hazard ratio (HR)= 0.96, 95 % confidence interval (CI)=0.79–1.16]; further adjustment for BMI, race/ethnicity, and hormone therapy use had little impact (HR=0.91, 95 % CI=0.75–1.11) (Fig. 1). There was no significant difference in the association with migraine history when distinguishing migraineurs who did versus did not self-report use of migraine medications other than NSAIDs at baseline (p=0.34). There was no change to results when excluding women diagnosed within the first year of study follow-up (results not shown). Although we observed no statistically significant interaction by BMI or by NSAID use (p interaction=0.19 and 0.14, respectively), there was a suggestion of lower endometrial cancer risk associated with migraine history restricted to women who were of normal weight (i.e., BMI 18.5–24.9 kg/m^2) (HR=0.75, 95 % CI=0.52–1.08) and in women who were NSAID users at study baseline (HR=0.68, 95 % CI=0.43–1.07).

With respect to NSAID use, there was a modest increased risk of endometrial cancer in women who reported current NSAID use at the baseline interview compared with those who

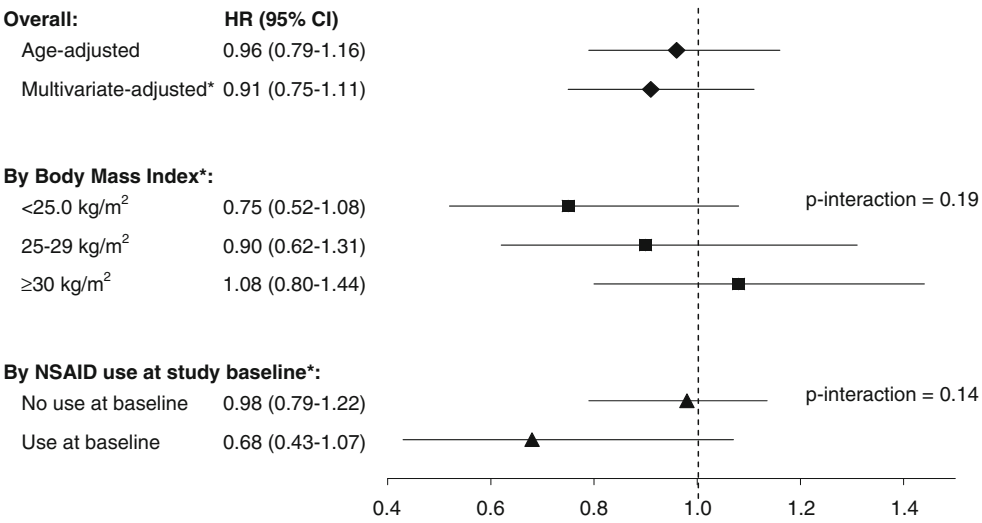

Fig. 1 Migraine history and endometrial cancer risk. Hazard ratios adjusted for age at study entry, study arm, body mass index, race/ethnicity, use of unopposed estrogen hormone therapy, and use of combined estrogen–progestin hormone therapy. Women were classified as having a history of migraines if they self-reported having been told by a doctor that they had migraine headaches

reported no such use (HR=1.17, 95 % CI=1.02–1.34); however, this association was no longer evident after multivariate adjustment (HR=1.01, 95 % CI=0.88–1.16) (Table 2). Exclusion of cases diagnosed within the first year of study follow-up had little impact on point estimates (age-adjusted HR=1.19, 95 % CI=1.03–1.36 and multivariate-adjusted HR=1.03, 95 % CI=0.89–1.18). Associations were similar when we restricted the exposed category to women who reported use of aspirin (results not shown). There was no difference in the association with NSAID use according to duration of recent use (Table 2). Similarly, there was no difference in the association with NSAID use according to BMI (Table 3).

Discussion

Although migraines and endometrial cancer are both largely hormonally related diseases, and although NSAIDs have been suggested to counter the inflammatory effect of estrogens on the endometrium, the results from this large cohort analysis indicate that neither migraine history nor NSAID use are associated with risk of endometrial cancer in postmenopausal women.

To our knowledge, this study represents the first evaluation of the relationship between migraine history and endometrial cancer risk. Previous studies have reported a lower risk of breast cancer in women with a history of migraines [9–11]. The most recent of these studies, also conducted in the WHI [11], reported an overall HR for the association between migraine history and breast cancer risk (HR=0.89, 95 % CI=0.80–0.98) that was more modest than previous reports of a 26 % to 33 % lower risk in women with a history of migraines [9, 10] but similar in magnitude to the non-significant HR with endometrial risk reported here (HR=0.91, 95 % CI=0.75–1.11). The mechanisms underlying the observed relationship between migraines and breast cancer risk are unclear; however, it is plausible that this association in breast cancer is hormonally mediated, especially given that migraine history is most strongly, if not exclusively, associated with lower risk of hormone

Table 2 Association between nonsteroidal anti-inflammatory drug (NSAID) use and endometrial cancer risk[a]

	Person-time at risk, in years (%)	Cases *N* (%)	HR[b]	(95 % CI)	HR[c]	(95 % CI)
NSAID use at baseline						
No	857,040.8 (83)	1,078 (81)	1.00	(ref)	1.00	(ref)
Yes	177,062.5 (17)	259 (19)	1.17	(1.02–1.34)	1.01	(0.88–1.16)
Duration of NSAID use at baseline						
No use	857,040.8 (83)	1,078 (81)	1.00	(ref)	1.00	(ref)
<3 years	99,148.1 (10)	145 (11)	1.16	(0.98–1.38)	1.02	(0.86–1.22)
≥3 years	77,914.5 (8)	114 (9)	1.17	(0.97–1.42)	1.00	(0.82–1.22)

[a] NSAID use at baseline defined on the basis of self-reported use of aspirin or non-aspirin NSAIDs in the 2 weeks prior to baseline interview; duration of NSAID use was queried only from those reporting current NSAID use at baseline

[b] Adjusted for age at study entry and study arm

[c] Adjusted for age at study entry, study arm, body mass index, race/ethnicity, use of unopposed estrogen hormone therapy, and use of combined estrogen-progestin hormone therapy

Table 3 Association between NSAID use and endometrial cancer risk by BMI

		NSAID use at baseline	Person-time at risk, in years (%)	Cases *N* (%)	HR[a]	(95 % CI)	*p* interaction
BMI (kg/m^2):	<25.0	No	343,662.4 (87)	347 (84)	1.00	(ref)	0.15
		Yes	51,925.6 (13)	65 (16)	1.13	(0.87–1.48)	
	25.0–29.9	No	293,469.2 (83)	308 (83)	1.00	(ref)	
		Yes	58,318.1 (17)	64 (17)	1.00	(0.77–1.32)	
	≥30.0	No	211,797.6 (76)	417 (77)	1.00	(ref)	
		Yes	65,201.5 (24)	126 (23)	0.96	(0.78–1.16)	

[a] NSAID use at baseline defined on the basis of self-reported use of aspirin or non-aspirin NSAIDs in the 2 weeks prior to baseline interview

[b] Adjusted for age at study entry, study arm, race/ethnicity, use of unopposed estrogen hormone therapy, and use of combined estrogen–progestin hormone therapy

receptor-positive breast cancer [9–11]. It is plausible that the more modest association with migraine history reported by Li et al. in their analysis of breast cancer risk in the WHI [11], and the null association with endometrial cancer risk in WHI reported here, reflect limitations of the assessment of migraine history in this population. In particular, reliance on self-report of a clinical diagnosis of migraines likely means that migraine history is underreported for women who experience headaches meeting clinical criteria for migraines but who have never been formally diagnosed. Such underreporting could be expected to result in a conservative bias towards the null.

Previous studies have reported a link between migraines and exposure fluctuations in levels of endogenous and exogenous estrogens. Migraines in women are often associated with declines in estrogen levels and have been reported to fluctuate in frequency across phases of the menstrual cycle [6, 7]. In particular, the majority of migraineurs report more frequent migraines around the time of the menstrual cycle when estrogen levels are declining or are at their lowest level [27], and the prevalence of migraines is notably lower among older women who are likely to have undergone menopause [28]. Despite this hormonal association, and despite the established hormonal basis for endometrial cancer, we did not observe an association between migraine history and endometrial cancer risk in postmenopausal women overall. We did, however, observe a non-statistically significant lower risk of endometrial cancer associated with migraine history in postmenopausal women with a BMI <25.0 kg/m^2 and in those who were NSAID users.

NSAID use has also been hypothesized to influence endometrial cancer risk through hormonal pathways [13]. Estrogens can have an adverse inflammatory effect on the endometrium; such chronic inflammation may contribute to cancer risk by inducing rapid cell division and DNA damage [2]. Laboratory studies have demonstrated that NSAIDs suppress proliferation in endometrial cancer cell lines in a dose-dependent fashion [12], and NSAID use has been associated with lower estrogen levels [13] and a reduced risk of several other cancers, including breast cancer, in repeated observational studies [16, 28–30]. However, randomized clinical trials have generally noted no association between aspirin use and cancer risk [31–34] with the exception of possible associations with reduced lung and colorectal cancer risk [31, 34–36]. Prior observational studies investigating the association between NSAID use and endometrial cancer risk have yielded largely null results. In the most recent investigation, Bosetti et al. reported a non-significant 35 % lower risk of endometrial cancer (OR=0.65, 95 % CI=0.37–1.11) in women who reported ever using aspirin and noted no difference in this association according to the duration of use (OR=0.66, 95 % CI=0.34–1.30 for <5 years of use and OR=0.68, 95 % CI=0.29–1.63 for ≥5 years of use) [22]. Most other studies have reported null associations [17, 18, 20, 21, 23], although some studies have suggested a reduced risk of endometrial cancer associated with ever-use of NSAIDs when restricted to women with a BMI ≥30 kg/m^2 [17, 18]. We did not find any association with NSAID use, regardless of BMI.

The results presented here should be interpreted in the context of study limitations. With respect to our measurement of migraine history, as described above, reliance on self-report of a clinical diagnosis likely led to underreporting of migraines: an estimated 27 % to 59 % of migraine sufferers are never clinically diagnosed [37–39]. Misclassification of migraine history is also possible in instances where women were clinically diagnosed with migraines during study follow-up, as this exposure was ascertained only at the time of the baseline interview. However, given that 75 % of migraineurs experience onset of the disease before age 35 [40], new-onset cases in this population would be rare. Misclassification and underreporting are likely non-differential, but could have resulted in attenuation of the association with migraine history. It is also possible that our observed associations might differ had our study population included premenopausal women, among whom migraines are more common. Additionally, because information on the severity and frequency of migraine history was not collected, we were unable to evaluate associations between

these factors and endometrial cancer risk. Thus, although we observed no association between migraine history and endometrial cancer risk, we cannot rule out the possibility that severe and/or frequent migraines may be associated with risk; however, we did not find evidence of significant differences in the association with migraine history for migraineurs who did versus did not report use of migraine medications other than NSAIDs. We also cannot rule out the possibility that our study was underpowered to detect a true but very modest association between migraine history and endometrial cancer. Given the overall sample size, number of incident cases, and prevalence of migraine history in this cohort, we had 80 % power to detect an HR of 0.78, although we observed an HR of only 0.91 in our multivariate-adjusted analyses. With respect to our measurement of NSAID use, we limited our investigation to current NSAID use as reported on the baseline questionnaire. Information on history of NSAID use prior to study entry was not collected, precluding us from looking at associations with ever use of NSAIDs or patterns of lifetime use. We did, however, assess associations across limited categories of duration of current NSAID use reported at baseline and found no association. Lastly, WHI participants are volunteers and, thus, may not be representative of the general population of postmenopausal women.

There are several important strengths in this analysis, including the prospective design, collection of detailed data on endometrial cancer risk factors, centralized adjudication of endometrial cancer diagnoses, and large overall sample size. The largest prior study of NSAID use in relation to endometrial cancer risk included 747 women with incident endometrial cancer [18], compared to the 1,337 women with incident disease included here.

In summary, our findings suggest that history of migraines is not associated with endometrial cancer risk and are consistent with previous reports that NSAID use is not associated with risk of endometrial cancer in postmenopausal women.

Conflict of Interest The authors declare that they have no conflicts of interest.

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