HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Int J Cancer. 2018 February 01; 142(3): 534–539. doi:10.1002/ijc.31062.

Migraine and invasive epithelial ovarian cancer risk in the Nurses' Health Study II and the Women's Health Study

Megan S. Rice[1,*], **Pamela M. Rist**[2,3,*], **Anke C. Winter**[4], **Tobias Kurth**[2,3,5,±], and **Shelley S. Tworoger**[3,6,±]

[1]Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[2]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA

[5]Institute of Public Health, Charité Universitätsmedizin, Berlin, Germany

[6]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Migraine is a common primary headache disorder, which predominantly impacts women. Recently, migraine has been hypothesized to be associated with hormonally related cancers; however the potential association between migraine and ovarian cancer has not been studied.

Therefore, we evaluated the association between migraine and invasive epithelial ovarian cancer risk in two prospective cohorts, the Nurses' Health Study II (NHSII) and the Women's Health Study (WHS). Our prospective analysis included 113,124 NHSII participants aged 25–42 at study baseline as well as 33,490 participants in the WHS who were 45 years or older at study entry. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (CIs) for the association between migraine and ovarian cancer risk in each cohort. In secondary analyses, we stratified by age and menopausal status. After adjusting for potential covariates, there was no statistically significant association between migraine and ovarian cancer risk in either the NHSII (HR=1.29, 95%CI: 0.96, 1.74) or the WHS (HR=0.60, 95%CI: 0.34, 1.06). In stratified analysis in the NHSII, there was a statistically significant positive association between migraine and ovarian cancer risk among women < 45 years of age (HR=1.76, 95%CI: 1.01, 3.07). We did not observe a clear association between migraine and ovarian cancer risk in two large prospective cohort studies.

Corresponding author: Megan S. Rice, Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital, 55 Fruit Street, Bartlett 9, Boston, MA 02116, Phone: 617.726.8502, mrice1@mgh.harvard.edu.

*contributed equally to the manuscript

±jointly directed the work

Introduction

Migraine is a common primary headache disorder that affects approximately one-fifth of women in the United States. With three times the prevalence in women compared to men,[1] migraine has been hypothesized to be related to circulating sex hormones, such as estrogen.[2] This is supported by observations that fluctuating estrogen levels may act as a trigger for migraine episodes, though studies of circulating hormones by migraine status have been mixed.[3–8]

Due to the hypothesized role of estrogen in the pathogenesis of migraine, a number of studies have assessed the potential associations between migraine and hormonally related cancers.[8–13] For example, early case-control studies observed that female migraineurs had a substantially lower risk of breast cancer;[10–12] however later cohort studies did not support a strong inverse association.[8,13] A recent cross-sectional study of over 40,000 Japanese nurses suggested a positive correlation between the prevalence of migraine and ovarian cancer.[14] However, to our knowledge, there have been no prospective evaluations of the potential association between migraine and ovarian cancer. Therefore, we aimed to examine the association between migraine and incident ovarian cancer in two large prospective cohort studies.

Methods

Nurses' Health Study II

Study population—The Nurses' Health Study II (NHS II) is an ongoing cohort study established in 1989 when 116,429 US nurses ages 25–42 years completed a baseline questionnaire. Every two years, information on reproductive variables, lifestyle factors, and disease outcomes was collected via questionnaires. Follow-up rates at each questionnaire cycle consistently have been 85–90%.

Migraine assessment—On the 1989 baseline questionnaire, participants were asked if they had physician-diagnosed migraine. This question was also included on the 1993 and 1995 follow-up questionnaires. Once a woman reported that she was a migraineur, she was considered a migraineur for all subsequent follow-up cycles.

Ovarian cancer assessment—In the NHSII, women indicated that they had been diagnosed with incident ovarian cancer on the biennial questionnaires. For each participant who reported a new ovarian cancer diagnosis, or diagnoses identified through death certificates, we requested medical records and pathology reports from the participant or next of kin. A gynaecologic pathologist, blinded to migraine status, reviewed the records to confirm the diagnosis and abstract information on the tumor, including invasiveness and histologic subtype. For a subset of 215 ovarian cancer cases, we compared the histologic type abstracted from the pathology report with a standardized review of pathology slides completed by a gynaecologic pathologist. As the concordance was 98 percent for invasiveness and 83 percent for histology, we used histologic type from the medical record for all cases.

Women's Health Study

Study population—The Women's Health Study (WHS) was a randomized, placebo-controlled trial of the effects of low dose aspirin and vitamin E on the primary prevention of cardiovascular disease and cancer among 39,876 US female health professionals aged 45 and older. Since the end of the trial in March 2004, participants have been followed on an observational basis. Twice during the first year and yearly thereafter, women completed a questionnaire asking about demographics, lifestyle information and disease outcomes.

Migraine assessment—At baseline, the women were asked, "Have you ever had migraine headaches?" Women who answered yes were classified as migraineurs. Previous validation studies in the WHS have demonstrated good agreement between self-reported migraine and the *International Classification of Headache Disorders* II.[15]

Ovarian cancer assessment—Women reported diagnoses of ovarian cancer on follow-up questionnaires. For all self-reported cases or cases identified through death certificates, we requested medical records and pathology reports from the participant or next-of-kin. An endpoints committee of physicians, blinded to migraine status, reviewed the records to confirm the diagnosis and abstract information on the tumor, including invasiveness and histologic subtype.

Statistical analysis—Participants accrued person-time from the return date of the baseline questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (except non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up (2013 in NHSII and 2014 in WHS). To ensure we do not exclude women who were diagnosed with ovarian cancer as a result of their bilateral oophorectomy, we use bilateral oophorectomy data from the questionnaire cycle prior to the two-year follow-up cycle when censoring. In NHSII, at baseline, we excluded women with cancer other than non-melanoma skin cancer (N=1050), bilateral oophorectomy (N=2225), or menopause due to pelvic irradiation (N=30). In WHS, at baseline, we excluded women missing information on migraine status (N=119), women with a history of cancer other than non-melanoma skin cancer (N=61), bilateral oophorectomy (N=6196), or menopause due to pelvic irradiation (N=10).

To control as finely as possible for confounding by age, calendar time and any possible two-way interactions between these two time scales, we stratified the analyses jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. The time scale for the analysis was then measured as months since the start of the current questionnaire cycle, which is equivalent to age in months. Cox regression with time-dependent covariates stratified by age and time period was used to estimate hazard ratios (HR) and 95% confidence intervals (CIs). In the multivariable model, we adjusted for body mass index (BMI), tubal ligation, hysterectomy, unilateral oophorectomy, parity, oral contraceptive use, family history of breast or ovarian cancer, smoking status, alcohol use, NSAID use, menopausal status, and type of postmenopausal hormone therapy (HT) use (estrogen only, estrogen and progesterone, and other HT). We used interaction terms and

stratified analyses to assess effect modification by age (<45, 45-<55, 55+) and menopausal status (premenopausal, postmenopausal, unknown).

We used Cox proportional hazards competing risk analysis, stratified by time period to allow for different associations by tumor histology (serous/poorly differentiated versus non-serous [endometrioid, mucinous, clear cell]).[16] The estimates for age, parity, tubal ligation, hysterectomy, and estrogen only HT use were allowed to vary by tumor histology based on prior analyses, whereas estimates for the remaining covariates were constrained to a single effect estimate across subtypes.[17] To test for heterogeneity by tumor subtype within cohort, we compared a model allowing the association for migraine to vary by subtype to a model that constrained the migraine estimates to be the same across subtypes. We considered a two-sided p-value of less than 0.05 to be statistically significant and used SAS version 9.4 (SAS Institute, Cary, NC) for all analyses. This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital.

Results

Nurses' Health Study II

At baseline, 15 percent of NHSII women reported history of physician-diagnosed migraine (Table 1). These women were more likely to be current NSAID users as well as more likely to have undergone a tubal ligation or hysterectomy. In the age-adjusted model, there was a borderline statistically significant positive association between migraine and ovarian cancer risk; women with migraine were 34 percent more likely to develop ovarian cancer than women without migraine (95%CI: 1.00–1.80). This association was somewhat attenuated in the multivariable adjusted model (RR=1.29, 95%CI: 0.96–1.74). While the association was somewhat stronger for serous/poorly differentiated tumors (RR=1.52, 95%CI: 0.99–2.32) compared to non-serous tumors (RR=1.24, 95%CI: 0.76–2.02), this difference was not statistically significant (p-for-heterogeneity=0.54). In age-stratified analyses, there was a statistically significant positive association among women <45 years of age (RR=1.76, 95%CI: 1.01–3.07) whereas the association was weaker and not statistically significant for older women ($RR_{ages\ 45–55}$=1.18, 95%: 0.77–1.80 and $RR_{ages\ 55+}$=1.14, 95%: 0.59–2.07; p-for-heterogeneity=0.60). In analyses stratified by menopausal status, the association was strongest for premenopausal women (RR=1.46, 95%CI: 0.95–2.22), however this association was not statistically significant. Further, the associations were weaker and not statistically significant for postmenopausal women (RR=1.25, 95%CI: 0.74–2.10) as well as for women with unknown menopausal status (RR=0.77, 0.34, 1.73) (p-heterogeneity=0.64).

Women's Health Study

At baseline, 18 percent of WHS women reported a history of migraine. Women in WHS who reported migraine were more likely to be current NSAID users and to have undergone a tubal ligation or hysterectomy. Compared to the NHSII women, the WHS women were older and more likely to be postmenopausal.

In the age-adjusted model, women in the WHS who had ever experienced migraine were less likely to develop ovarian cancer than women who did not experience migraine (RR=0.58;

95% CI: 0.34, 1.00), with borderline statistical significance. A similar association, though not statistically significant, was seen after adjustment for additional covariates (RR=0.60; 95% CI: 0.34, 1.06). We observed non-statistically significant lower risk of both serous/poorly differentiated tumors (RR=0.60; 95% CI: 0.30, 1.16) and non-serous tumors (RR=0.56; 95% CI: 0.14, 2.14). We observed similar associations among women 45 to 55 years old (RR=0.51; 95% CI: 0.16, 1.64) as we did among women over 55 years of age (RR=0.62; 95%CI: 0.32, 1.23, p-heterogeneity=0.56). For our analyses stratified by menopausal status, we were unable to run separate analyses among women who were premenopausal or had unknown menopausal status due to the low number of events in these subgroups. Among postmenopausal women, those with migraine had a non-statistically significant lower risk of ovarian cancer compared to those without migraine (RR=0.55; 95% CI: 0.28, 1.07).

Discussion

Overall, we did not observe a statistically significant association between migraine and ovarian cancer risk in either of two large prospective cohorts. In the NHSII, migrainers had a borderline statistically significant elevated risk of ovarian cancer. In contrast, there was a borderline statistically significant inverse association between migraine status and ovarian cancer risk in WHS. In neither cohort did these associations differ statistically significantly by histology. In the NHSII, the positive association between migraine and ovarian cancer risk was statistically significant and strongest in women less than 45 years of age.

Prior studies have suggested that migraine may be hormonally driven given the observed sex-differences in migraine prevalence and changes in migraine frequency with changes in the menstrual cycle.[1,2] However, results from this study and prior prospective cohort studies on migraine and breast cancer risk do not support a strong link between migraine and hormonally related cancers.[8,13] However, we were unable to classify whether migraines reported by the women in these cohorts were hormonally sensitive; these types of migraines may be more relevant for hormonally-related chronic diseases. One potential limitation to these analyses may be the difference in age and menopausal status between the two included cohorts. NHSII is composed primarily of young, premenopausal women while the WHS is composed primarily of older, postmenopausal women. It is of interest that many ovarian cancer risk factors occur primarily in premenopause, however, we were underpowered to detect an association between migraine and ovarian cancer in this particular subgroup.[18] While some women may have had resolution of migraine symptoms later in follow-up, we were unable to further classify migraineurs by whether or not their symptoms resolved. Strengths of both of the cohorts included in this analysis include the large sample sizes, prospectively collected data on migraine as well as prospectively collected data on potential confounders, and medical record confirmation of incident ovarian cancer cases. The following limitations should also be considered when interpreting these results. Information on migraine, as well as covariate data, was self-reported. However, as all information was collected prior to diagnosis of ovarian cancer, any misclassification should be non-differential. Assessment of migraine differed slightly between the cohorts. However, the prevalence of migraine in the study populations is consistent between the two cohorts and with other population-based studies.[19–22] Lastly, the NHSII and WHS are predominantly

White, potentially limiting generalizability. In summary, we did not observe a clear association between migraine and ovarian cancer risk in two large prospective cohort studies.

Acknowledgments

We would like to thank the participants of the Nurses' Health Study II and Women's Health Study for their continuing contributions. We thank the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Funding support: This study was supported by research grants from the National Institutes of Health, P01 CA87969, UM1 CA176726, R01 CA047988, R01 HL043851, R01 HL080467, RC1 HL099355, and UM1 CA182913. Dr. Rist is funded by K01 HL128791 and Dr. Rice received support from T32 CA09001.

References

1. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. Neurol Clin. 2009; 27(2):321–334. [PubMed: 19289218]
2. Brandes JL. The influence of estrogen on migraine: a systematic review. JAMA. 2006; 295(15): 1824–1830. [PubMed: 16622144]
3. Epstein MT, Hockaday JM, Hockaday TD. Migraine and reporoductive hormones throughout the menstrual cycle. Lancet. 1975; 1(7906):543–548. [PubMed: 47017]
4. Murialdo G, Martignoni E, De Maria A, et al. Changes in the dopaminergic control of prolactin secretion and in ovarian steroids in migraine. Cephalalgia : an international journal of headache. 1986; 6(1):43–49. [PubMed: 3698093]
5. Nagel-Leiby S, Welch KM, Grunfeld S, D'Andrea G. Ovarian steroid levels in migraine with and without aura. Cephalalgia : an international journal of headache. 1990; 10(3):147–152. [PubMed: 2245460]
6. de Lourdes Figuerola M, Levin G, Leston J, Barontini M. Plasma met-enkephalin and catecholamine changes during the menstrual cycle and pain episode in menstrual migraine. Functional neurology. 1997; 12(2):69–75. [PubMed: 9238340]
7. Patacchioli FR, Monnazzi P, Simeoni S, et al. Salivary cortisol, dehydroepiandrosterone-sulphate (DHEA-S) and testosterone in women with chronic migraine. The journal of headache and pain. 2006; 7(2):90–94. [PubMed: 16575505]
8. Winter AC, Rice MS, Fortner RT, Eliassen AH, Kurth T, Tamimi RM. Migraine and breast cancer risk: a prospective cohort study and meta-analysis. J Natl Cancer Inst. 2015; 107(1):381. [PubMed: 25505231]
9. Shi M, DeRoo LA, Sandler DP, Weinberg CR. Migraine and possible etiologic heterogeneity for hormone-receptor-negative breast cancer. Sci Rep. 2015; 5:14943. [PubMed: 26456840]
10. Li CI, Mathes RW, Malone KE, et al. Relationship between migraine history and breast cancer risk among premenopausal and postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2009; 18(7):2030–2034. [PubMed: 19589913]
11. Li CI, Mathes RW, Bluhm EC, et al. Migraine history and breast cancer risk among postmenopausal women. J Clin Oncol. 2010; 28(6):1005–1010. [PubMed: 20100960]
12. Mathes RW, Malone KE, Daling JR, et al. Migraine in postmenopausal women and the risk of invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17(11):3116–3122. [PubMed: 18990752]
13. Winter AC, Rexrode KM, Lee IM, Buring JE, Tamimi RM, Kurth T. Migraine and subsequent risk of breast cancer: a prospective cohort study. Cancer Causes Control. 2013; 24(1):81–89. [PubMed: 23143336]
14. Nagai K, Hayashi K, Yasui T, et al. Disease history and risk of comorbidity in women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey. BMJ Open. 2015; 5(3):e006360.

15. Schurks M, Buring JE, Kurth T. Agreement of self-reported migraine with ICHD-II criteria in the Women's Health Study. Cephalalgia. 2009; 29(10):1086–1090. [PubMed: 19735535]
16. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics. 1995; 51(2):524–532. [PubMed: 7662841]
17. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. American journal of epidemiology. 2010; 171(1):45–53. [PubMed: 19910378]
18. Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016; 34(24):2888–2898. [PubMed: 27325851]
19. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. JAMA. 2006; 296(3):283–291. [PubMed: 16849661]
20. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. BMJ. 2016; 353:i2610. [PubMed: 27247281]
21. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology. 1999; 53(3):537–542. [PubMed: 10449117]
22. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001; 41(7):646–657. [PubMed: 11554952]

Novelty and impact

While migraine has been hypothesized to be associated with hormonally related cancers, the potential association between migraine and ovarian cancer has not previously been studied. In this analysis in two large prospective cohorts, we did not observe statistically significant associations between migraine and ovarian cancer risk in either cohort.

Table 1

Participant characteristics in the Nurses' Health Study II (NHSII) and the Women's Health Study (WHS) by migraine status at baseline (NHSII=1989, WHS=1993–1996).

	NHSII (1989)		WHS (1993–1996)	
	No migraine (N=96,138, 85%)	**Migraine (N=16,986, 15%)**	**No migraine (N=27,476, 82%)**	**Migraine (N=6014, 18%)**
Mean (SD)				
Age	34.6 (4.7)	35.5 (4.5)	54.6 (7.1)	53.3 (6.4)
BMI (kg/m^2)	24.0 (4.9)	24.6 (5.3)	25.9 (5.0)	26.1 (5.1)
Percent				
Family history of breast or ovarian cancer	7.2	7.6	8.2	8.4
Oral contraceptive use (NHS)				
Never	17.3	13.7	--	--
<1 year	12.7	14.1	--	--
1–<5 years	38.4	39.6	--	--
5–<10 years	23.6	24.1	--	--
10+ years	8.0	8.4	--	--
Oral contraceptive use (WHS)				
Never	--	--	31.6	26.2
<0.5 year	--	--	9.2	10.7
0.5–2 years	--	--	19.2	23.1
3–4 years	--	--	14.7	14.8
5+ years	--	--	25.3	25.2
Parity				
Nulliparous	29.5	25.5	12.9	12.2
1 child	19.1	18.9	9.0	9.6
2 children	32.9	35.2	29.6	29.9
3 children	14.3	15.6	24.1	24.8
4+ children	4.3	4.8	24.4	23.5
Alcohol use				
None	37.0	39.5	43.7	46.3
0.1–<5 grams/day	42.6	43.4	31.7	33.8
5+ grams/day	20.4	17.2	24.6	19.9
Smoking status				
Never	66.0	62.4	50.6	53.9
Past	21.0	22.8	36.3	34.0
Current	13.0	14.9	13.1	12.1
NSAID use				
Never	75.2	57.4	89.0	84.3

	NHSII (1989)		WHS (1993–1996)	
	No migraine (N=96,138, 85%)	**Migraine (N=16,986, 15%)**	**No migraine (N=27,476, 82%)**	**Migraine (N=6014, 18%)**
Past	--	--	--	--
Current	24.8	42.6	11.0	15.7
Tubal ligation	15.0	19.4	16.8	17.9
Hysterectomy	3.0	6.6	20.8	25.5
Unilateral oophorectomy	0.7	1.6	5.4	6.5
Menopausal status				
Premenopausal	99.0	98.7	32.3	34.1
Postmenopausal	0.4	0.5	47.0	39.2
Unknown	0.6	0.8	20.5	26.5
HT use *				
E ever use	4.7	9.6	11.2	13.9
E+P ever use	40.2	39.8	18.6	18.1
Other HT ever use	15.5	20.5	13.6	15.6

* Postmenopausal only

Table 2

Hazard ratios (HR) and 95% confidence intervals (CIs) for the association between migraine and invasive ovarian cancer risk, by cohort and histology

	NHSII			WHS		
	Cases	**Model 1 HR (95%CI)**	**Model 2 HR (95%CI)**	**Cases**	**Model 1 HR (95%CI)**	**Model 2 HR (95%CI)**
All invasive	236	1.34 (1.00, 1.80)	1.29 (0.96, 1.74)	205	0.58 (0.34, 1.00)	0.60 (0.34, 1.06)
Serous and poorly differentiated	108	1.57 (1.03, 2.40)	1.52 (0.99, 2.33)	143	0.58 (0.31, 1.09)	0.60 (0.30, 1.16)
Non-serous (endometrial, clear cell, mucinous)	92	1.27 (0.79, 2.06)	1.24 (0.76, 2.02)	52	0.51 (0.16, 1.66)	0.56 (0.14, 2.14)

Model 1: Adjusted for age (continuous) and time period

Model 2: Further adjusted for BMI (continuous), family history of breast or ovarian cancer (yes, no), parity (0, 1,2, 3, 4+), oc use (NHSII: never, <1, 1–5, 5–9,10+ years; WHS: never, <0.5 year, 0.5–2 years, 3–4 years, 5+years), smoking (never, past, current), alcohol (none, 0–5, 5+ g/day), NSAID use (never, past, current), menopausal status (premenopausal, postmenopausal, unknown), postmenopausal hormone therapy (ever estrogen only HT use, ever estrogen plus progestin HT use, ever other HT use), tubal ligation (yes, no), unilateral oophorectomy (NHSII: yes, no, unknown; WHS: yes, no), hysterectomy (NHSII: yes, no, unknown; WHS: yes, no)

p-for-heterogeneity by histologic subtype in NHSII=0.54

p-for-heterogeneity by histologic subtype in WHS=0.90

Table 3

Hazard ratios (HR) and 95% confidence intervals (CIs) for the association between migraine and invasive ovarian cancer risk, by selected factors

	NHSII				WHS			
	Cases	**Model 1 HR (95%CI)**	**Model 2 HR (95%CI)**	**p-het**	**Cases**	**Model 1 HR (95%CI)**	**Model 2 HR (95%CI)**	**p-het**
Age								
<45	65	1.71 (0.99, 2.95)	1.76 (1.01, 3.07)	0.60	--	--	--	0.56
45–<55	121	1.23 (0.81, 1.86)	1.18 (0.77, 1.80)		35	0.56 (0.20, 1.55)	0.51 * (0.16, 1.64)	
55+	50	1.16 (0.61, 2.22)	1.14 (0.59, 2.20)		170	0.59 (0.31, 1.11)	0.62 (0.32, 1.23)	
Menopausal status								
Premenopausal	119	1.57 (1.04, 2.36)	1.46 (0.95, 2.22)	0.64	18	--	--	--
Postmenopausal	79	1.31 (0.78, 2.18)	1.25 (0.74, 2.10)		169	0.54 (0.28, 1.01)	0.55 (0.28, 1.07)	
Unknown	38	0.86 (0.39,1.90)	0.77 (0.34, 1.73)		18	--	--	

Model 1: Adjusted for age (continuous)

Model 2: Adjusted for age (continuous), BMI (continuous), family history of breast or ovarian cancer (yes, no), parity (0, 1,2, 3, 4+), oral contraceptive use (NHSII: never, <1, 1–5, 5–9,10+ years; WHS: never, <0.5 year, 0.5–2 years, 3–4 years, 5+years), smoking (never, past, current), alcohol (none, 0–5, 5+ g/day), NSAID use (never, past, current), menopausal status (premenopausal/unknown, postmenopausal), postmenopausal hormone therapy (ever estrogen only HT use, ever estrogen plus progestin HT use, ever other HT use), tubal ligation (yes, no), unilateral oophorectomy (yes, no, unknown), hysterectomy (yes, no, unknown)

* not adjusted for unilateral oophorectomy and HT use due to small sample size