

## Research Article

See Commentary on p. 1439

## Use of Nonsteroidal Anti-inflammatory Drugs and Risk of Ovarian and Endometrial Cancer: The Multiethnic Cohort

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### Abstract

**Background:** Chronic inflammation may play an etiologic role in ovarian and endometrial cancer, and it is hypothesized that nonsteroidal anti-inflammatory drugs (NSAID) decrease the risk of developing these malignancies. No prospective study with a large multiethnic population has explored this hypothesis.

**Methods:** We investigated whether NSAID use was associated with risks of ovarian and endometrial cancer in the Multiethnic Cohort Study. Medication use of at least twice a week for  $\geq 1$  month was assessed at baseline. Multivariable relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models.

**Results:** During 13.3 years of follow-up, 275 ovarian and 620 endometrial incident cases were identified among approximately 64,000 women included in this analysis (16.5% African Americans, 30.8% Japanese, 7.7% Native Hawaiians, 18.9% Latinas, and 26.0% whites). The RR (95% CI) for ovarian cancer associated with aspirin, non-aspirin NSAIDs, and acetaminophen were 0.87 (0.68–1.14), 0.97 (0.74–1.26), and 0.86 (0.67–1.12), respectively. The RR (95% CI) for endometrial cancer associated with aspirin, non-aspirin NSAIDs, and acetaminophen were 0.93 (0.79–1.10), 0.88 (0.74–1.05), and 0.96 (0.81–1.13), respectively. No heterogeneity across ethnic groups ( $P \geq 0.29$ ) or dose–response relation with increased duration of use ( $P_{\text{trend}} \geq 0.16$ ) was observed. The results did not differ by tumor histology.

**Conclusions:** We found no compelling evidence to support an association between the use of NSAIDs and risk of ovarian and endometrial cancers in a multiethnic population.

**Impact:** It is unlikely that NSAID is involved in the etiology of endometrial and ovarian cancer. *Cancer Epidemiol Biomarkers Prev*; 21(9): 1441–9. ©2012 AACR.

### Introduction

Chronic inflammation has been postulated to contribute to ovarian and endometrial carcinogenesis through various pathophysiologic pathways (1–3). Chronic inflammation, including elevations in cytokines, prostaglandins, and COX with concomitant oxidative stress, induces rapid cell division and DNA damage which increase the risk of malignancy (1).

Specific exposures, such as perineal talc use or medical conditions associated with inflammation, including endometriosis and pelvic inflammatory disease, have been reported to increase ovarian cancer risk (4–10). Elevated serum levels of C-reactive protein, a biologic marker of chronic systemic inflammation, have likewise been associated with increased risk of ovarian and endometrial cancers (11–13). These epidemiologic observations are supported by *in vitro* studies showing that aspirin and other analgesic drugs with anti-inflammatory properties inhibit tumor growth and induce apoptosis in ovarian and endometrial cancer cell lines (14–20).

Several epidemiologic studies have tested the hypothesis that nonsteroidal anti-inflammatory drugs (NSAID) reduce the risk of ovarian and endometrial cancers. Although there is a richer body of literature in this regard for ovarian cancer (21–37) than for endometrial cancer (24, 38–43), results supporting the chemopreventive potential of these agents are nonetheless contradictory

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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and inconclusive for both malignancies. The majority of published studies have been conducted in white women and only a few have been prospective in nature. On the basis of these considerations, we took advantage of existing data from the Multiethnic Cohort (MEC) Study, a large prospective study, to assess whether aspirin, non-aspirin NSAID, and acetaminophen use are associated with endometrial and ovarian cancer risk in a diverse population of women.

## Materials and Methods

### Study population

The MEC is a prospective cohort study established to investigate the association of lifestyle and genetic factors with chronic disease. Details of the study design, recruitment, response rates, and baseline characteristics of the MEC have been previously published (44). Briefly, the cohort consists of 215,251 men and women between the ages of 45 and 75 years selected from 5 racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites. Potential participants were identified through drivers' license files from the Department of Motor Vehicles, voter registration lists, and Health Care Financing Administration data files primarily from Los Angeles County, California, and the state of Hawaii. During the period of 1993 to 1996, participants completed a 26-page baseline questionnaire that included items on demographic and lifestyle factors, physical activity, tobacco smoking history, diet, anthropometric measures, personal history of medical conditions, and family history of cancer, as well as reproductive history and hormone use (women only). The institutional review boards at the University of Hawaii (Honolulu, HI) and the University of Southern California (Los Angeles, CA) have approved the study protocol.

### NSAID use assessment

The use of pain medication in the cohort was assessed at baseline by means of the question, "Have you ever taken any of the following medications at least 2 times a week (for 1 month or longer)?" Queries for specific medications included the 3 categories of pain medication— aspirin, other NSAIDs (ibuprofen, naproxen, indomethacin, or others), and acetaminophen. The respondent could specify never, former, or current use. If a participant responded affirmatively about use of a medication, she was asked to classify the duration of use as 1 year or less, 2–3 years, 4–5 years, 6–10 years, or 11 years or more.

### Exclusion criteria

The MEC included more than 118,000 women at baseline. However, we excluded women if they did not belong to one of the 5 major ethnic groups listed above ( $n = 8,050$ ), if they had invalid dietary data as a marker of quality for the questionnaire ( $n = 4,611$ ), if they were diagnosed with

ovarian, endometrial, cervical, or breast cancer before the date of the baseline questionnaire because their cancer treatment may affect their subsequent risk of ovarian or endometrial cancer ( $n = 8,426$ ), if they had missing menopausal status ( $n = 8,750$ ), or if they did not answer the questions about use of aspirin, non-aspirin NSAIDs, or acetaminophen ( $n = 8,287$ ). In addition, women who reported a bilateral oophorectomy ( $n = 11,907$ ) and were missing ovarian cancer covariate data (i.e., age at menarche, oral contraceptive use, menopausal hormone use, and parity;  $n = 4,000$ ) were excluded in the ovarian cancer analysis; and women with hysterectomy ( $n = 12,530$ ) and missing endometrial cancer covariate data [i.e., body mass index (BMI), smoking status, age at menarche, oral contraceptive use, menopausal hormone use, and parity;  $n = 3,386$ ] were excluded in the endometrial cancer analysis. After all exclusions, 64,387 women were available for the ovarian cancer analysis and 64,828 women were available for the endometrial cancer analysis.

### Follow-up and case identification

Participants' follow-up time began at the completion of the baseline questionnaire and continued to one of the following endpoints: (i) diagnosis of endometrial or ovarian cancer, (ii) death, or (iii) end of follow-up (December 31, 2007, for Los Angeles and December 31, 2008, for Hawaii). All incident cases of ovarian cancer [International Classification of Diseases for Oncology (ICD-O-3) code C56.9 8010-8580] or endometrial [(ICD-O-3) code C54] were identified through record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry; these cancer registries are part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Deaths within the cohort were determined through annual linkage to state death certificate files in California and Hawaii and periodically to the National Death Index. The follow-up rate in the cohort is 95%; National Death Index information was available for the remaining 5% of the cohort. Cohort participants were followed for an average of 13.3 years. A total of 275 women with incident epithelial ovarian cancer and 620 women with incident endometrial cancer were identified during the follow-up period. In the ovarian cancer analysis, non-epithelial ovarian cancer cases ( $n = 22$ ) were censored at the corresponding dates of diagnosis. In the endometrial cancer analysis, uterine sarcomas ( $n = 66$ ) were censored at the corresponding dates of diagnosis.

### Statistical analysis

The use of aspirin, non-aspirin NSAID, and acetaminophen was coded as never or ever (past or current). We also created 4 categories for duration of use: never,  $\leq 1$  year, 2–5 years, or  $\geq 6$  years. Women who reported using analgesic medication but did not indicate the number of years of use were treated as missing duration (2.3% for

aspirin, 3.8% for non-aspirin NSAID, and 4.2% for acetaminophen). An NSAID user was defined as a user of aspirin and/or non-aspirin NSAIDs. Relative risks (RR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models. Age (in days) was the underlying time variable in the Cox regression, starting with a participant's age at entry to one of the endpoints. For ovarian cancer, Cox models were adjusted for the following variables: race/ethnicity (African-American, Native Hawaiian, Japanese, Latina, and white) as a strata variable, age at cohort entry (continuous), age at menarche ( $\leq 12$ , 13–14,  $\geq 15$ ), oral contraceptive use (never,  $\geq 1$  month use), menopausal hormone use (never, past, current estrogen, current estrogen-progestin), and parity (nulliparous, 1, 2–3,  $\geq 4$  children). For endometrial cancer, Cox models were adjusted for race/ethnicity as a strata variable, age at cohort entry (continuous), BMI in  $\text{kg}/\text{m}^2$  (continuous), smoking status (never, past, current), age at menarche ( $\leq 12$ , 13–14,  $\geq 15$ ), oral contraceptive use (never,  $\geq 1$  month use), menopausal hormone use (never, past, current estrogen, current estrogen-progestin), and parity (nulliparous, 1, 2–3,  $\geq 4$  children). Further adjustment for duration of use for both oral contraceptive and menopausal hormone did not change the results, thus they were not included in the final model. The proportional hazards assumption was tested by examining the Kaplan–Meier curves and by assessing the Schoenfeld residuals; no major violations were observed. Linear trend tests were conducted by treating the categorical variable of interest as a continuous term (0, 1, 2, 3) in the model. The likelihood ratio test was used to assess statistical interactions between drug use and ethnicity or other risk factors with the risk for ovarian or endometrial cancers. Interaction models compared a model with main effects only to a saturated model containing main effects and appropriate interaction terms. To compare our results with those of Viswanathan and colleagues (40), who reported that current use of aspirin was associated with a reduced risk of endometrial cancer among obese women, we further divided the ever use of analgesics into past or current in the interaction analysis. Secondary analyses were conducted to investigate the association of analgesics with the risk of major ovarian cancer subtypes (serous, non-serous) and endometrial cancer histologic subtypes (type I, including endometrioid adenocarcinoma, tubular papillary adenocarcinoma, adenocarcinoma with squamous metaplasia, mucinous adenocarcinoma, adenocarcinoma not otherwise specified; and type II, including serous, clear cell, squamous cell, adenosquamous, small cell carcinoma, mixed cell adenocarcinoma). In the subgroup analyses, duration of use was recategorized as never,  $\leq 5$  years, or  $\geq 6$  years because of the limited number of cases. All statistical analyses were conducted in SAS version 9.2 (SAS Institute Inc.). All *P* values were 2-sided.

**Table 1.** Baseline characteristics and prevalence of ovarian and endometrial cancer risk factors by NSAID use among women in the Multiethnic Cohort Study, 1993–2008

Characteristics	NSAID		<i>P</i> <sup>b</sup>
	Nonusers	Ever-users	
Number of women	31,938	32,890	
Age at cohort entry, mean	58.3	58.8	
BMI ( $\text{kg}/\text{m}^2$ ), mean	25.2	27.2	<0.0001
Race/ethnicity, %			
African American	33.8	66.2	<0.0001
Japanese American	67.0	33.0	
Latina	38.9	61.1	
Native Hawaiian	54.1	45.9	
White	44.1	55.9	
Menopausal status, %			
Premenopausal	54.7	45.3	<0.0001
Postmenopausal	47.9	52.1	
BMI ( $\text{kg}/\text{m}^2$ ), %			
<25	57.2	42.8	<0.0001
25–<30	45.4	54.6	
30+	36.1	63.9	
Age at menarche (y), %			
$\leq 12$	48.8	51.2	0.004
13–14	50.1	49.9	
$\geq 15$	48.6	51.4	
Parity, %			
Nulliparous	52.4	47.6	<0.0001
Parous	48.8	51.2	
Menopausal hormone use, <sup>a</sup> %			
Never	50.4	49.6	<0.0001
Past	41.9	58.1	
Current estrogen	45.9	54.1	
Current estrogen-progestin	49.1	50.9	
Ever used oral contraceptive, %			
Never	50.6	49.4	<0.0001
Ever	47.7	52.3	
Smoking status			
Never	53.3	46.7	<0.0001
Past	45.0	55.0	
Current	42.3	57.7	

NOTE: Percentages shown are horizontal percentages.

<sup>a</sup>Among postmenopausal women only.

<sup>b</sup>Significance tested using  $\chi^2$  or using the 2-tailed Student *t* test, as appropriate.

## Results

More than half of cohort participants were NSAID users (Table 1). NSAID users were slightly older than

**Table 2.** Association between aspirin, non-aspirin NSAIDs, acetaminophen and risk of ovarian cancer in the Multiethnic Cohort Study 1993–2008

Exposure	White		African American		Native Hawaiian		Japanese		Latina		All women		
	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	P <sub>het</sub> <sup>b</sup>
<b>NSAID use</b>													
Never	28	1.00	19	1.00	13	1.00	66	1.00	21	1.00	147	1.00	
Ever	41	1.16 (0.72–1.89)	22	0.60 (0.32–1.11)	12	1.09 (0.50–2.41)	24	0.76 (0.47–1.21)	29	0.86 (0.49–1.52)	128	0.87 (0.68–1.11)	0.51
<b>Aspirin use</b>													
Never	41	1.00	27	1.00	17	1.00	72	1.00	30	1.00	187	1.00	
Ever	28	0.94 (0.58–1.53)	14	0.64 (0.34–1.23)	8	1.04 (0.45–2.42)	18	0.87 (0.52–1.46)	20	0.99 (0.56–1.75)	88	0.87 (0.68–1.14)	0.76
<b>Duration of aspirin use</b>													
Never	41	1.00	27	1.00	17	1.00	72	1.00	30	1.00	187	1.00	
≤1 y	8	1.34 (0.63–2.86)	4	0.65 (0.23–1.85)	2	1.05 (0.24–4.57)	6	1.17 (0.51–2.68)	6	0.95 (0.39–2.28)	26	1.02 (0.67–1.54)	
2–5 y	4	0.48 (0.17–1.35)	6	0.94 (0.39–2.29)	3	1.39 (0.41–4.76)	4	0.63 (0.23–1.73)	8	1.46 (0.67–3.18)	25	0.87 (0.57–1.33)	
≥6 y	15	1.07 (0.59–1.93)	2	0.28 (0.07–1.17)	3	0.99 (0.29–3.37)	7	0.86 (0.39–1.86)	3	0.45 (0.14–1.49)	30	0.76 (0.52–1.13)	0.87
P <sub>trend</sub>		0.81		0.10		0.84		0.50		0.44		0.16	
<b>Non-aspirin NSAID use</b>													
Never	42	1.00	25	1.00	16	1.00	77	1.00	28	1.00	188	1.00	
Ever	27	1.25 (0.77–2.04)	16	0.68 (0.36–1.28)	9	1.35 (0.59–3.11)	13	0.81 (0.45–1.46)	22	0.96 (0.54–1.68)	87	0.97 (0.74–1.26)	0.65
<b>Duration of non-aspirin NSAID use</b>													
Never	42	1.00	25	1.00	16	1.00	77	1.00	28	1.00	188	1.00	
≤1 y	9	1.16 (0.56–2.39)	7	0.74 (0.32–1.72)	5	1.73 (0.63–4.76)	6	0.87 (0.38–1.99)	12	1.23 (0.62–2.43)	39	1.08 (0.76–1.54)	
2–5 y	10	1.29 (0.64–2.58)	2	0.24 (0.06–1.02)	2	0.88 (0.20–3.92)	4	0.74 (0.27–2.02)	9	1.24 (0.58–2.65)	27	0.89 (0.59–1.34)	
≥6 y	6	1.60 (0.68–3.79)	2	0.65 (0.15–2.74)	0	—	2	0.91 (0.22–3.71)	0	—	10	0.80 (0.42–1.52)	0.45
P <sub>trend</sub>		0.23		0.07		0.61		0.56		0.67		0.48	
<b>Acetaminophen use</b>													
Never	49	1.00	24	1.00	18	1.00	74	1.00	27	1.00	192	1.00	
Ever	20	0.94 (0.55–1.58)	17	0.93 (0.50–1.74)	7	0.65 (0.27–1.56)	16	0.67 (0.39–1.14)	23	1.16 (0.66–2.03)	83	0.86 (0.67–1.12)	0.89
<b>Duration of acetaminophen use</b>													
Never	49	1.00	24	1.00	18	1.00	74	1.00	27	1.00	192	1.00	
≤1 y	1	0.21 (0.03–1.54)	2	0.36 (0.09–1.54)	4	1.39 (0.47–4.13)	2	0.37 (0.09–1.51)	6	0.92 (0.38–2.24)	15	0.59 (0.35–1.00)	
2–5 y	6	0.89 (0.38–2.08)	5	0.85 (0.32–2.25)	0	—	5	0.78 (0.32–1.93)	11	1.90 (0.93–3.85)	27	0.96 (0.64–1.45)	
≥6 y	11	1.44 (0.75–2.78)	6	1.35 (0.55–3.30)	2	0.53 (0.12–2.32)	8	0.85 (0.41–1.76)	4	0.91 (0.32–2.62)	31	1.04 (0.71–1.52)	0.82
P <sub>trend</sub>		0.52		0.81		0.20		0.43		0.43		0.89	

<sup>a</sup>RRs were adjusted for age, age at menarche, oral contraceptive use, menopausal hormone use, and parity. Further adjusted for race/ethnicity as a strata variable for all women combined.

<sup>b</sup>P<sub>heterogeneity</sub> across the 5 racial/ethnic groups.

**Table 3.** Association between aspirin, non-aspirin NSAIDs, acetaminophen and risk of endometrial cancer in the Multiethnic Cohort Study, 1993–2008

Exposure	White		African American		Native Hawaiian		Japanese		Latina		All women	
	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)	No. of cases	RR <sup>a</sup> (95% CI)
<b>NSAID use</b>												
Never	80	1.00	35	1.00	41	1.00	116	1.00	33	1.00	305	1.00
Ever	111	1.01 (0.75–1.35)	54	0.71 (0.46–1.09)	28	0.67 (0.41–1.09)	51	0.84 (0.60–1.17)	71	1.28 (0.84–1.94)	315	0.91 (0.77–1.07)
<b>Aspirin use</b>												
Never	106	1.00	48	1.00	51	1.00	133	1.00	63	1.00	401	1.00
Ever	85	1.06 (0.79–1.41)	41	0.96 (0.63–1.46)	18	0.70 (0.41–1.21)	34	0.84 (0.58–1.23)	41	0.92 (0.62–1.37)	219	0.93 (0.79–1.10)
<b>Duration of aspirin use</b>												
Never	106	1.00	48	1.00	51	1.00	133	1.00	63	1.00	401	1.00
≤1 y	17	1.09 (0.65–1.82)	9	0.68 (0.33–1.39)	5	0.76 (0.30–1.91)	10	1.00 (0.52–1.90)	8	0.56 (0.27–1.16)	49	0.82 (0.61–1.11)
2–5 y	16	0.73 (0.43–1.25)	16	1.30 (0.74–2.30)	6	0.81 (0.35–1.91)	12	0.97 (0.54–1.76)	13	1.11 (0.61–2.02)	63	0.96 (0.73–1.25)
≥6 y	48	1.23 (0.87–1.73)	12	0.92 (0.49–1.74)	7	0.71 (0.32–1.58)	11	0.68 (0.37–1.26)	13	0.92 (0.50–1.67)	91	0.98 (0.78–1.23)
<i>P</i> <sub>trend</sub>		0.48		0.88		0.34		0.29		0.82		0.72
<b>Non-aspirin NSAID use</b>												
Never	119	1.00	49	1.00	54	1.00	140	1.00	55	1.00	417	1.00
Ever	72	1.02 (0.76–1.38)	40	0.80 (0.52–1.22)	15	0.56 (0.31–0.99)	27	0.79 (0.52–1.20)	49	1.07 (0.73–1.58)	203	0.88 (0.74–1.05)
<b>Duration of non-aspirin NSAID use</b>												
Never	119	1.00	49	1.00	54	1.00	140	1.00	55	1.00	417	1.00
≤1 y	32	1.28 (0.86–1.90)	10	0.55 (0.28–1.08)	8	0.78 (0.37–1.66)	12	0.82 (0.45–1.48)	21	1.08 (0.65–1.78)	83	0.93 (0.73–1.18)
2–5 y	22	0.81 (0.51–1.28)	23	1.30 (0.78–2.16)	5	0.62 (0.25–1.56)	12	1.04 (0.57–1.88)	15	1.00 (0.56–1.78)	77	0.93 (0.73–1.21)
≥6 y	13	1.09 (0.61–1.93)	4	0.53 (0.19–1.49)	0	—	3	0.60 (0.19–1.89)	7	1.41 (0.64–3.12)	27	0.80 (0.54–1.18)
<i>P</i> <sub>trend</sub>		0.87		0.76		0.02		0.49		0.57		0.25
<b>Acetaminophen use</b>												
Never	124	1.00	50	1.00	47	1.00	127	1.00	59	1.00	407	1.00
Ever	67	1.11 (0.82–1.50)	39	0.98 (0.64–1.50)	22	0.67 (0.40–1.12)	40	0.90 (0.63–1.29)	45	1.04 (0.71–1.54)	213	0.96 (0.81–1.13)
<b>Duration of acetaminophen use</b>												
Never	124	1.00	50	1.00	47	1.00	127	1.00	59	1.00	407	1.00
≤1 y	9	0.65 (0.33–1.27)	14	1.20 (0.66–2.18)	6	0.79 (0.33–1.85)	11	1.14 (0.62–2.11)	10	0.73 (0.37–1.42)	50	0.88 (0.66–1.19)
2–5 y	29	1.65 (1.10–2.48)	15	1.15 (0.64–2.06)	6	0.78 (0.33–1.84)	10	0.85 (0.45–1.62)	19	1.50 (0.90–2.52)	79	1.24 (0.97–1.58)
≥6 y	24	1.03 (0.66–1.60)	4	0.42 (0.15–1.17)	6	0.48 (0.20–1.13)	17	0.94 (0.56–1.56)	8	0.80 (0.38–1.68)	59	0.80 (0.61–1.06)
<i>P</i> <sub>trend</sub>		0.32		0.35		0.09		0.72		0.81		0.55

<sup>a</sup>RRs were adjusted for age, BMI, smoking status, age at menarche, oral contraceptive use, menopausal hormone use, and parity. Further adjusted for race/ethnicity as a strata variable for all women combined.

<sup>b</sup>*P*<sub>heterogeneity</sub> across the 5 racial/ethnic groups.

nonusers. African-American and Latina women were more likely to use NSAIDs than white, Japanese-American, or Native Hawaiian women. Postmenopausal, heavy, and parous women tended to use NSAIDs more than premenopausal, lean, and nulliparous women. Oral contraceptive and menopausal hormone users and tobacco smokers also reported a higher prevalence of NSAID use.

Table 2 shows the associations between any NSAIDs, aspirin, non-aspirin NSAIDs, acetaminophen, and risk of ovarian cancer. We did not observe associations between any NSAIDs, aspirin, non-aspirin NSAIDs, or acetaminophen use with the risk of ovarian cancer in whites, African Americans, Native Hawaiians, Japanese Americans, or Latinas. The tests of heterogeneity of risk across the 5 racial/ethnic groups were not statistically significant ( $P \geq 0.45$ ). Risk did not vary significantly by duration of use for any of the medications under study ( $P_{\text{trend}} \geq 0.07$ ). The lack of association of NSAID use with the risk of ovarian cancer was consistent between serous and non-serous subtypes (Supplementary Table S1). To address the effect of latent disease on analgesic intake, we lagged exposure time by 2 years; the results were similar. Mutual adjustment for all 3 drugs in the model and using never-users of any of the 3 drugs as the reference category also produced similar results (data not shown).

The associations of any NSAIDs, aspirin, non-aspirin NSAIDs, and acetaminophen use with the risk for endometrial cancer are shown in Table 3. No significant relation was observed between endometrial can-

cer and either aspirin or acetaminophen use separately within each racial/ethnic group, nor was there evidence for decreasing risk with increasing duration of use ( $P_{\text{trend}} \geq 0.09$ ). In Native Hawaiians, non-aspirin NSAID use was associated with a reduced risk of endometrial cancer (RR, 0.56; 95% CI, 0.31–0.99), which may have been due to chance given for the many comparisons in the table, and especially as no significant heterogeneity of the analgesic–endometrial cancer association across the 5 racial/ethnic groups was found ( $P \geq 0.16$ ). In all women combined, none of the analgesic drugs was associated with endometrial cancer risk. Additional analyses using a 2-year lag, mutual adjustment for the 3 drugs in the same model and using never-users of any of the 3 drugs as the reference group produced similar results (data not shown). Furthermore, results for type I and II tumors did not vary substantially (Supplementary Table S2).

We examined the potential modifying effects of BMI and menopausal hormone use on the analgesic–endometrial cancer association (Table 4). There was no notable difference in the association of aspirin and non-aspirin NSAID use with endometrial cancer risk in obese or nonobese women ( $P_{\text{interaction}} \geq 0.71$ ) or in postmenopausal women who never used or ever used menopausal hormones ( $P_{\text{interaction}} \geq 0.10$ ). Although there was some variation in the direction and size of associations between acetaminophen use and endometrial cancer according to menopausal hormone use ( $P_{\text{interaction}} = 0.03$ ), none of the associations was statistically significant.

**Table 4.** Association between use of aspirin, non-aspirin NSAIDs, and acetaminophen and risk of endometrial cancer stratified by BMI and menopausal hormone use

Exposure	BMI <30 kg/m <sup>2</sup>		BMI ≥30 kg/m <sup>2</sup>		Never use hormone <sup>a</sup>		Ever use hormone <sup>a</sup>	
	No. of cases	RR <sup>b</sup> (95% CI)	No. of cases	RR <sup>b</sup> (95% CI)	No. of cases	RR <sup>b</sup> (95% CI)	No. of cases	RR <sup>b</sup> (95% CI)
Aspirin use								
Never	254	1.00	147	1.00	135	1.00	165	1.00
Past	53	0.89 (0.66–1.21)	48	0.92 (0.66–1.28)	48	1.15 (0.82–1.61)	35	0.74 (0.51–1.07)
Current	65	0.96 (0.73–1.27)	53	1.09 (0.79–1.49)	46	1.12 (0.80–1.58)	49	0.88 (0.64–1.22)
Non-aspirin NSAID use								
Never	270	1.00	147	1.00	157	1.00	156	1.00
Past	54	0.86 (0.64–1.15)	48	0.78 (0.56–1.08)	45	0.97 (0.69–1.36)	43	0.87 (0.61–1.22)
Current	48	1.05 (0.77–1.43)	53	1.05 (0.77–1.45)	27	0.81 (0.53–1.22)	50	1.25 (0.90–1.74)
Acetaminophen use								
Never	261	1.00	146	1.00	141	1.00	172	1.00
Past	59	1.00 (0.75–1.33)	51	0.95 (0.69–1.30)	47	1.21 (0.86–1.69)	36	0.73 (0.51–1.06)
Current	52	1.00 (0.74–1.35)	51	1.03 (0.75–1.42)	41	1.20 (0.84–1.71)	41	0.84 (0.60–1.19)

<sup>a</sup>Among postmenopausal women only.

<sup>b</sup>RRs were adjusted for race/ethnicity (as a strata variable) and when appropriate were adjusted for age, BMI, smoking status, age at menarche, oral contraceptive use, menopausal hormone use, and parity.

## Discussion

In this large multiethnic prospective study, we found no significant association of ovarian cancer and endometrial cancer risk with the use of aspirin, non-aspirin NSAID, or acetaminophen. There was no evidence of heterogeneity in these risk associations across racial/ethnic groups, nor was there evidence for decreasing risk with increasing duration of use.

Results of several epidemiologic studies of NSAID use and risk of ovarian cancer are inconsistent. Some investigators have reported significant inverse associations of ovarian cancer risk with the use of aspirin/non-aspirin NSAID (24, 32–34, 36, 37) or acetaminophen (27, 31), but more investigators have found no risk association with aspirin/non-aspirin NSAID use (21–23, 25–27, 29–31) or acetaminophen use (23, 29, 32, 33, 37), and results from one study suggested an increased risk of ovarian cancer associated with long-term use of aspirin and acetaminophen (28). The only randomized trial that investigated aspirin use in relation to cancer risk found no association between low-dose aspirin taken every other day for an average of 10 years and ovarian cancer (45).

Lack of consistent findings in the published studies could reflect heterogeneity across study design, geographic locations, and/or potential biases due to selection of subjects, misclassification of exposures, and unmeasured confounders. A meta-analysis of 10 ovarian cancer studies published between 1998 and 2004 found no evidence for an association of ovarian cancer risk with either aspirin or non-aspirin NSAID use (46). This lack of evidence suggests that neither study design (cohort vs. case-control) nor method used to elicit analgesic use (questionnaire/interview vs. medication database) influenced the study results. Since the publication of the meta-analysis, 7 more studies [5 case-control (refs. 28, 30, 33, 36, 37) and 2 cohort (refs. 23, 24)] have been published. Results from the 2 cohort studies are inconsistent (23, 24), with the study with a much larger number of cases and longer follow-up found no association with aspirin, NSAID, or acetaminophen (23). The case-control studies are more likely to report protective effects of NSAIDs (33, 36, 37), but this may also reflect biases inherent in case-control design. Our null findings in the MEC are consistent with the majority of published data.

Six of 7 studies exploring the association of NSAID use with endometrial cancer risk have found no overall association (24, 38–41, 43). Results from the Nurses' Health Study cohort suggest that BMI and menopausal hormone

use may modify the association of aspirin with endometrial cancer risk (40), but this finding was not replicated within the MEC, nor was it in agreement with results from other studies (24, 38, 41–43).

The strengths of our study include its prospective design, multiethnic population, exclusion of prevalent cancer cases at baseline, and the ability to control for potential confounding factors. The main limitation of this study is that our analyses were based on exposures collected at baseline and we did not consider changes in exposure during follow-up. Furthermore, self-reported NSAID use is susceptible to misclassification error, which may have biased the results toward the null. We had no information on reasons for NSAID use and we had not collected frequency of use and dosage, thus we could not distinguish consistent from sporadic users. Finally, we had limited power in the interaction analysis.

In summary, our cohort data, combined with existing epidemiologic literature, do not support the hypothesis that NSAID use plays a role in the chemoprevention of ovarian or endometrial cancers.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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