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Non-steroidal Anti-inflammatory Drugs and Endometrial Cancer Risk in the VITamins And Lifestyle (VITAL) Cohort

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Abstract

Background—Chronic inflammation may be an important factor in the initiation and promotion of endometrial cancer. Use of non-steroidal anti-inflammatory drugs (NSAIDs), however, has been inconsistently associated with endometrial cancer risk.

Methods—22,268 female residents of western Washington State, ages 50–76, completed a baseline questionnaire in 2000–2002 and reported on their use of individual NSAIDs over the past 10 years. Use was categorized as none, low (<4 days/week or <4years), and high (≥4 days/week and ≥4 years). Over 9 years of follow-up, 262 incident invasive endometrial cancers were identified. Multivariable proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results—Relative to non-use, high use of aspirin was inversely associated with endometrial cancer risk (HR 0.64, 95% CI: 0.41–1.01; *P* trend=0.03). Findings were stronger for regular-strength than low-dose aspirin. High use of non-aspirin NSAIDs (HR 1.15, 95% CI: 0.68–1.95), including ibuprofen (HR 1.29, 95% CI: 0.73–2.28), and naproxen (HR 1.08, 95% CI: 0.39–2.95) were not associated with risk. In subgroup analyses, findings for aspirin were strongest for cancers of endometrioid histology and were restricted to non-smokers.

Conclusions—This study provides additional evidence that use of aspirin, but not non-aspirin NSAIDs, may reduce the risk of endometrial cancer, especially in estrogen-mediated cases; however additional prospective studies with high-quality measurement of NSAID use are needed. Aspirin should continue to be examined as a potential agent for cancer chemoprevention.

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Conflict of Interest Statement
The authors declare that there are no conflicts of interest.

Keywords

Aspirin; Ibuprofen; Naproxen; NSAID; Endometrial Cancer

Introduction

Inflammation plays an important role in the development and progression of cancers at several anatomic sites [1], including the endometrium [2]. Recent findings from large prospective studies have shown that increases in blood markers of inflammation may be associated with increases in endometrial cancer risk [3–5]. It is estimated that cyxlooxygenase (COX)-2, which is responsible for the conversion of arachidonic acid (ω-6) to pro-inflammatory prostaglandins, is expressed in 35–92% of endometrial cancers [6–8]. There is also limited evidence that inhibition of COX-2 through the use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce estrogen synthesis [9, 10], a major driver of endometrial proliferation [11, 12].

The use of NSAIDs has been associated with reductions in endometrial cancer in some [13–16] but not all [17–22] epidemiologic studies. Findings from randomized trials have also been inconsistent [23, 24]. Recently, Rothwell et al. [24], reported a protective effect for uterine cancer (P=0.003) in a pooled analysis of 51 randomized trials of aspirin and cancer risk. Inferences from existing studies remain limited because randomized trials only examined aspirin use, some at low doses; most cohort studies only examined current, short-term use [15, 19, 20]; and no study to date has addressed individual types of commonly available non-aspirin formulations, which may have differing effects [25].

Here we give findings from our investigation of the association between long-term use of individual NSAIDs and endometrial cancer risk in a large, prospective study of women living western Washington State.

Methods

Study population

Participants were female members of the VITAL cohort, a prospective study designed to investigate the associations of dietary supplements and other behaviors, including over-the-counter medication use, with cancer risk. Detailed methods are given in White et al. [26]. Briefly, men and women, ages 50–76 years at baseline, who lived in the 13-county region of western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry were eligible to participate. Because this paper is limited to women, we describe here recruitment of women. Using names purchased from a commercial list, we mailed baseline questionnaires and post-card reminders two weeks later to 168,953 women between October 2000 and December 2002. Among these, 40,337 were returned and deemed eligible. We excluded participants with a positive or missing history of uterine (n=877), ovarian (n=25), or breast cancer (n=1,833) at baseline, participants who had a hysterectomy or were missing this datum (n=15,079), as well as incident diagnoses of *in situ* endometrial cancer (n=2) or endometrial cancers of mesenchymal origin or mixed tumor types (n=14). We additionally excluded 239 participants who were missing baseline NSAID data. After exclusions there were 22,268 women available for study. All participants gave informed consent and study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Data collection

The baseline questionnaire included a detailed assessment of participants regular use of NSAIDs, defined as ≥1 day/week for ≥1 year, including frequency (days/week) and duration of use (years) in the past 10 years of low-dose aspirin, regular or extra-strength aspirin, ibuprofen, naproxen, and COX-2 inhibitors, celecoxib or rofecoxib. Use of each drug over the 10 years prior to baseline was categorized as none; low, <4 days/week or <4 years; and high, ≥4 days/week and ≥4 years. Additional variables included: 'total aspirin', defined as the maximum of 10-year use of low-dose or regular/extra-strength aspirin; 'non-aspirin NSAIDs', defined as the maximum of 10-year use of ibuprofen, naproxen, or celecoxib/rofecoxib; and 'any NSAIDs', defined as the maximum of 10-year use of any of the NSAIDs assessed. Each variable was categorized as none, low, and high use as for individual NSAIDs. Use of the analgesic acetaminophen was not analyzed as it has little anti-inflammatory capacity [27].

In addition to data on NSAID use, we collected information at baseline on endometrial cancer risk factors and indications/contraindications of NSAID use. Participants reported their demographic and health-related characteristics, including height and weight [from which body mass index (BMI, kg/m^2) was computed], education, family history of cancer, and medical history including detailed information on reproductive health. Participants who reported having had a heart attack, angina, angioplasty, or bypass surgery were considered to have a positive history of coronary artery disease. Participants also answered several questions regarding cigarette smoking behavior including the age at which they started smoking daily, whether they currently smoked as baseline, the number of cigarettes smoked each day, and the cumulative years of smoking. From these data, we computed pack-years of smoking and number of years since quitting.

Case ascertainment

Participants were followed for incident endometrial cancer diagnoses from baseline to December 31, 2010, with a median follow-up time of 9 years. Incident, primary, invasive endometrial cancers (ICD-O C54.1) were ascertained by linking the study cohort to the western Washington SEER cancer registry, which is maintained by the Fred Hutchinson Cancer Research Center. All incident cancer cases, except non-melanoma skin cancer, diagnosed within the 13-country region are reported to SEER along with stage, histologic subtype, and other tumor characteristics [28]. Cases were ascertained through all area hospitals, offices of pathologists, oncologists, and radiotherapists, and from state death certificates. Extensive quality-control procedures ensure that registry data are accurate and complete. Linkage to SEER is based on ranking of the agreement between characteristics common to VITAL and SEER including name, social security number, date of birth, etc.; matches with high concordance were made automatically, while visual inspection was performed for matches in which some, but not all criteria matched. 262 incident, primary, invasive endometrial cancer cases were diagnosed among eligible women between baseline and December 2010.

Follow-up for censoring

Excluding the 262 incident cases of endometrial cancer, participants were right-censored from the analysis at the earliest date of the following events: withdrawal from the study (n=9), death (n=1,394), emigration out of the SEER catchment region (n=1,469), or December 31, 2010, the most recent date of linkage to the SEER registry (n=19,134). Deaths that occurred in the cohort were ascertained by linkage to the Washington State death file, using procedures similar to the SEER linkage. The National Change of Address System and active follow-up by telephone calls and mailings were used to identify participants who moved out of the study region.

Statistical analyses

Age-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between participant characteristics and endometrial cancer risk. Multivariable-adjusted Cox proportional hazards models were used to estimate HR and 95% CI for associations between use of NSAIDs and endometrial cancer risk. Participants' ages were used as the time metric in regression models, with left-truncation at age at baseline. All reported *P* values are two-sided and *P* values for trend (*P* trend) were calculated by coding categorical NSAID variables as a single trend variable taking on values 0, 1, and 2 in Cox regression models. SAS v9.2 (Cary, NC) was used for all statistical analyses.

We selected potential confounders, *a priori*, for adjustment in multivariable models, including known or suspected risk factors for endometrial cancer. Our model included age (time variable); race (white/black/other); education (≤high school, some college, college graduate or advanced degree); body mass index (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2); pack-years of smoking (non-smokers and tertiles of smokers); alcohol consumption (drinks/day: non-drinkers, <1.0, 1.0–1.9, ≥2.0); physical activity (MET-hours/week: inactive and tertiles of activity); age at menarche (≤11, 12, 13, ≥14); age at menopause (≤44, 45–49, ≥50, premenopausal, perimenopausal); parity (nulliparous, 1–2, 3–4, ≥5); combined hormone therapy (never/former/current); estrogen-only hormone therapy (never/former/current); years of oral contraceptive use (0, 0.1–4, 5–9, ≥10); oophoerectomy (yes/no); family history of uterine cancer (yes/no); family history of ovarian cancer (yes/no); and history of diabetes (yes/no). To address the issue of confounding by indication, we further adjusted regression models for indications/contraindications of NSAID use, including (yes/no for each of the following): history of coronary artery disease; history of stroke; history of osteoarthritis/chronic joint pain; history of rheumatoid arthritis; history of migraine/chronic headaches; and history of ulcers. Regression analyses for any one NSAID exposure were further adjusted for use of other NSAIDs.

We hypothesized *a priori* that the association between NSAID use and endometrial cancer may be modified by smoking, BMI, and use of combined hormone therapy, factors which are associated with inflammation [29–31]. Therefore, we performed stratified analyses by smoking status (never vs. ever), BMI (<30 vs. ≥30), and use of combined hormone therapy (never/former vs. current). *P* values for multiplicative interaction (*P* interaction) were calculated by including a cross-product term between dichotomous variables for NSAID exposure (use/non-use) and the effect modifier in the unstratified multivariable models.

We additionally performed a subgroup analysis examining the association between NSAID use and endometrial cancer risk, restricting incident cancers to those of endometrioid subtypes (n=227), which are thought to be estrogen responsive [32]. We hypothesized that NSAIDs would more strongly reduce the risk of this histology. Diagnoses of clear cell and serous cell subtypes were right-censored at their respective dates of diagnosis.

Results

In this cohort, female NSAID users tended to be older, smoke more, and consume alcohol and red meat in greater amounts [33]. NSAID users were also more likely to have a history of coronary heart disease, diabetes, hypertension, and arthritis [33]. Age-adjusted associations between participant characteristics and endometrial cancer risk are given in Table 1. Findings were generally consistent with the literature: increasing age, body size, age at menopause, and positive family histories of uterine or ovarian cancers were associated with increased risks of endometrial cancer; whereas smoking, increasing alcohol consumption, physical activity, age at menarche, parity, and increasing duration of

combined hormone therapy or oral contraceptive use were associated with reduced risks of endometrial cancer. Reflective of the change in clinical practice after unopposed estrogens were found to increase endometrial cancer risk, few women in VITAL were taking unopposed estrogens at baseline. Inconsistent with the literature, a history of diabetes and current use of unopposed estrogens at baseline were not associated with increased risks of endometrial cancer (however, increased duration of estrogen therapy was suggestive of a positive association).

Table 2 gives associations between NSAID use and endometrial cancer risk. Relative to non-use, high 10-year use of aspirin was associated with a linear reduction in endometrial cancer risk (HR 0.64, 95% CI: 0.41–1.01; *P* trend=0.03). Relative to non-use, any use of aspirin ≥1 day/week and ≥1 year was associated with a 28% reduction in endometrial cancer risk (HR 0.72, 95% CI: 0.53–0.98; data not shown). The finding for 10-year use was driven by use of regular-strength (high vs. non-use: HR 0.53, 95% CI: 0.27–1.04; *P* trend=0.06) rather than low-dose aspirin (high vs. non-use: HR 1.00, 95% CI: 0.62–1.62; *P* trend=0.65), although neither finding reached statistical significance. Use of non-aspirin NSAIDs considered as a class or individually was not associated with endometrial cancer risk. In a sensitivity analysis examining the association between use of NSAIDs and endometrial cancers of endometrioid histologies (n=227), we found the association for high 10-year aspirin use to be strengthened (HR 0.60, 95% CI: 0.37–0.97; *P* trend=0.01), driven by a stronger, linear inverse association between regular-strength aspirin use and endometrial cancer of endometrioid histology (HR 0.46, 95% CI: 0.21–0.99; *P*-trend=0.02) (data not shown). The associations between other NSAIDs were not appreciably changed when the analysis was restricted to endometrioid histologies.

Table 3 gives associations between total, low-dose, and regular-strength aspirin use and endometrial cancer risk, stratified on smoking status (never vs. ever), combined hormone replacement therapy (never/former vs. current), and BMI (<30 vs. ≥30). The inverse association we observed for aspirin and endometrial cancer appeared to be restricted to never smokers (HR 0.55, 95% CI: 0.37–0.82) versus ever smokers (HR 1.25, 95% CI: 0.77–2.04; *P* interaction=0.04), and possibly to current (HR 0.49, 95% CI: 0.22–1.10) rather than never or former users of combined HRT at baseline (HR 0.98, 95% CI: 0.66–1.45; *P* interaction=0.10). For each comparison, the associations tended to be stronger for regular-strength rather than low-dose aspirin, although all comparisons by dose were statistically non-significant due to small numbers. There was no evident heterogeneity in the association between aspirin and endometrial cancer risk by participants' obesity status.

Discussion

In this large, prospective cohort study of women living in western Washington State, regular, long-term use of aspirin was associated with a reduction in endometrial cancer risk, particularly of endometrioid histology and among non-smokers. Use of ibuprofen and naproxen were not associated with risk.

There is increasing evidence that inflammation and the COX pathway are involved in endometrial carcinogenesis. In response to cytokines, growth factors, and oncogenes, the COX-2 enzyme converts arachidonic acid to prostaglandins, among which several are associated with angiogenesis and tumor growth in endometrial cancers [2]. *In vitro* experimental studies have shown increases in COX expression to result in increases of prostaglandin E_2, aromatase, and estrogen synthesis [9, 34], which is important because unopposed estrogens are hypothesized to be the primary drivers behind endometrial proliferation [11, 12]. *In vitro* findings are further supported by positive correlations between expressions of COX-2 and aromatase in human endometrial cancer tissue [8], and a

recent finding from the Nurses' Health Study that use of NSAIDs is associated with reduced blood concentration of estrogen among postmenopausal women [10]. COX-2 is also strongly expressed in early tumors of *in vivo* models of endometrial cancer, suggesting that it plays a role in cancer initiation and progression [2, 35]. Although the NSAIDs under study are all known to bind to COX-2, we found that only the use of aspirin, and not ibuprofen or naproxen, was associated with reduced risks of endometrial cancer. One possible explanation for this difference in association is that unlike non-aspirin NSAIDs, aspirin binds irreversibly to COX-2 [36]. It is unclear, however, whether this would translate into greater anti-cancer properties. The stronger, linear reductions in risk observed between aspirin use and endometrial cancer of endometrioid histology, which are highly estrogen-sensitive [32], support, albeit indirectly, *in vitro* findings suggesting an association between inflammation and estrogen synthesis.

Among five case-control studies [13, 14, 16–18], four prospective cohort studies [15, 19–21], a randomized controlled trial [23], and a pooled analysis of randomized controlled trials [24] which have examined the association between aspirin use and endometrial cancer risk, our findings are supported by two case-control studies, one cohort study, and the pooled analysis of trials. In a recent paper, Neill et al. [16], reported results from a population-based case-control study of Australian women and a meta-analysis of epidemiologic studies. In the case-control analysis, ever use of aspirin (OR 0.78, 95% CI: 0.62–0.97) and increasing frequency of use (≥2/week vs. never use: OR 0.54, 95% CI: 0.38–0.78; P trend<0.0001) were associated with reductions in endometrial cancer risk. In their meta-analysis, aspirin was found to reduce endometrial cancer risk by 13% (RR 0.87, 95% CI: 0.79–0.96) [16]. Similarly, Fortuny et al. [14], found that ever use of aspirin was associated with a 30% reduction (OR 0.7, 95% CI: 0.4–1.0) in endometrial cancer risk in a population-based case-control study of women in New Jersey. In the NIH-AARP Diet and Health cohort, Danforth et al. [19], observed a strong reduction in endometrial cancer risk among very high users of aspirin (≥2/day vs. non-use: RR 0.55, 95% CI: 0.31–0.95). The remaining observational studies observed no overall reduction in endometrial cancer risk [13, 15, 17, 18, 20, 21]. Authors of the Multiethnic Cohort study were recently the first to examine the association between NSAIDs and endometrial cancer histologies; they observed no association overall and no differences by histologic subtype [21]. In contrast, in the Australian case-control study (mentioned above), Neill et al. [16], reported similar reductions in risk regardless of endometrial cancer histology. Among randomized trials, no effect on uterine cancer was reported in the Women's Health Study trial of 100mg aspirin given every other day for an average of 10 years (RR 1.22, 95% CI: 0.94–1.58). In contrast to the Women's Health Study and similar to our finding, Rothwell et al. [24], recently reported a protective effect of aspirin contrasted against a placebo on uterine cancer incidence (P=0.003) in a pooled analysis of 51 randomized trials of aspirin and cancer incidence. However, in both cases the uterine cancer endpoints may have included some cervical cancers and cancers of mesenchymal origin.

Our finding of no associations between long-term use of non-aspirin NSAIDs, individually or in sum, are consistent with the literature. Although none have examined the use of these medications individually, authors of one case-control [14] and four prospective cohort studies [15, 19–21] have investigated the use of non-aspirin NSAIDs as a group with endometrial cancer. Similar to our findings, none reported an association. Lastly, a recent report from the Women's Health Initiative examining NSAID use as a group found no association with endometrial cancer [22]. In that study, only current use was assessed.

In subgroup analyses, we observed effect-modification by smoking status, and no statistically significant interaction by BMI or HRT use. To our knowledge, this is the first study to examine effect-modification by smoking. Because aspirin is metabolized by some

of the same enzymes which are responsible for the metabolism of polycyclic aromatic hydrocarbons (PAH) found in cigarette smoke, it is possible that our finding represents a biological phenomenon [37–39]. However, our finding that the inverse association between aspirin and endometrial cancer risk was restricted to never smokers is complicated by the well-established risk reduction for endometrial cancer among smokers. Thus, these findings clearly warrant replication in larger samples that will allow for a more detailed analysis of this initially detected interaction.

Whereas we observed an inverse association between aspirin and endometrial cancer risk overall, two studies [13, 15] and a meta-analysis [16] reported inverse associations between aspirin use and endometrial cancer risk restricted to obese women only. Moysich et al. [13], reported that use of aspirin ≥1 day/week for ≥6 months was associated with a 50% reduction in endometrial cancer risk (OR 0.50, 95% CI: 0.27–0.92) among obese women (BMI>30) and no association among overweight (25≤BMI≤30; OR 1.21, 95% CI: 0.65–2.23) or normal-weight (18.5 ≤BMI<25; OR 1.61, 95% CI: 0.71–1.90) women. In an analysis of the prospective Nurses' Health Study, including 82,971 women and 747 incident cases identified over >24 years of follow-up, Viswanathan et al. [15], reported that relative to non-use, current use of aspirin was associated with a 44% reduction (RR 0.66, 95% CI: 0.36–0.95) in endometrial cancer risk among obese (BMI≥30) women, and a statistically significant increase in risk among non-obese women (1.41, 95% CI: 1.05–1.89; *P* interaction=0.009). In their meta-analysis, Neill et al. [16], found that aspirin was inversely associated with endometrial cancer only among obese women (BMI≥30, RR 0.72, 95% CI: 0.58–0.90; BMI<30, RR 1.08, 95% CI: 0.82–1.43). Similar to our findings, several others observed no differences by BMI [14, 17–21]. Authors of the Nurses' Health Study additionally reported a reduction in endometrial cancer among never users of post-menopausal hormones (RR 0.64, 95% CI: 0.45–0.91) and increases in risk among ever users (RR 1.34, 95% CI: 0.94–1.89; *P* interaction=0.046) [15]. No study, including this one, has replicated the latter finding.

The major strengths of the VITAL study include: 1) its prospective nature and near-complete follow-up of participants; 2) collection of long-term use of individual NSAIDs; and 3) our strong ability to statistically control for the potential confounding effects of indications/contraindications of NSAID use. The chief limitation of this study is that we did not collect data on the number of NSAID pills taken per day, or dose of individual non-aspirin NSAIDs. Such measurement error could potentially explain a null finding for non-aspirin NSAIDs, but findings for aspirin would be in spite of such error. An additional limitation is that we did not prospectively update participants' post-baseline NSAID exposures, further contributing to measurement error. Lastly, a relatively small percentage of women were high users of non-aspirin NSAIDs. It is therefore possible that analyses of the uses of these medications lacked statistical power.

In this large, prospective study of women living in western Washington State, we provide added evidence that long-term, regular use of aspirin is associated with reductions in endometrial cancer risk; particularly for endometrioid tumors and among non-smokers. Given the inconsistent nature of studies which have examined NSAIDs and endometrial cancer thus far, additional prospective studies with high-quality measurement of NSAID use are needed before a public health recommendation could be made. Nevertheless, given the evidence that aspirin reduces the risk of colorectal cancer [40, 41] and possibly other cancers [24, 42, 43], our findings add support of aspirin for cancer chemoprevention.

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Research Highlights

- Existing studies of NSAIDs and endometrial cancer risk are inconsistent
- In this cohort study, aspirin linearly reduced endometrial cancer risk
- Individual non-aspirin NSAIDs were not associated with risk

Table 1

Association between baseline characteristics of VITAL study participants and endometrial cancer, n=22,268.

Characteristic	Endometrial Cancer		
	Case, *n*=262 n (%)	Non-case, *n*=22,006 n (%)	Age-adjusted HR (95% CI)
Age, years			
<55	58 (22.14)	6,399 (29.08)	
55–59	61 (23.28)	5,409 (24.58)	
60–65	47 (17.94)	3,635 (16.52)	
65–69	46 (17.56)	2,956 (13.43)	
≥70	50 (19.08)	3,607 (16.39)	
Race			
White	248 (95.75)	20,047 (92.89)	1.00 (reference)
Black	4 (1.54)	239 (1.11)	1.38 (0.51–3.70)
Other race	7 (2.70)	1,295 (6.00)	0.44 (0.21–0.94)
Education			
≤ High school graduate	45 (17.44)	4,504 (20.88)	1.00 (reference)
Some college	113 (43.80)	8,364 (38.78)	1.44 (1.02–2.04)
≥ College graduate	100 (38.76)	8,700 (40.34)	1.27 (0.88–1.81)
Body mass index, kg/m^2			
<25.0	69 (28.28)	9,063 (43.95)	1.00 (reference)
25.0–29.9	73 (29.92)	6,695 (32.47)	1.41 (1.02–1.96)
30.0–34.9	48 (19.67)	2,939 (14.25)	2.17 (1.50–3.13)
≥35.0	54 (22.13)	1,923 (9.33)	3.91 (2.73–5.59)
P trend			<0.0001
Smoking status			
Never	175 (67.05)	12,396 (56.53)	1.00 (reference)
Former (≥10y since quitting)	65 (4.62)	6,541 (29.89)	0.71 (0.39–1.27)
Recent (<10y since quitting)	12 (4.62)	1,226 (5.60)	0.70 (0.52–0.93)
Current	8 (3.08)	1,723 (7.87)	0.35 (0.17–0.71)
Smoking, pack-years			
Non-smoker	175 (67.05)	12,396 (56.68)	1.00 (reference)
<7.5	33 (12.64)	3,606 (16.49)	0.65 (0.44–0.94)
7.5–25.0	27 (10.34)	3,004 (13.74)	0.64 (0.43–0.96)
≥25.0	26 (9.96)	2,865 (13.10)	0.66 (0.43–0.99)
P trend			<0.01
Alcohol, drinks/day			
Non-drinker	95 (37.25)	7,180 (33.59)	1.00 (reference)
<1.0	127 (49.80)	10,650 (49.83)	0.91 (0.70–1.19)
1–1.9	21 (8.24)	2,109 (9.87)	0.75 (0.47–1.21)
≥2.0	12 (4.71)	1,435 (6.71)	0.63 (0.35–1.16)
P trend			0.08

Characteristic	Endometrial Cancer		
	Case, *n*=262 n (%)	Non-case, *n*=22,006 n (%)	Age-adjusted HR (95% CI)
Physical activity, MET-hours/wk			
Inactive	39 (15.12)	3,079 (14.17)	1.00 (reference)
<3.7	83 (32.17)	6,263 (28.82)	1.03 (0.71–1.51)
3.7–11.4	75 (29.07)	6,142 (28.27)	0.94 (0.64–1.39)
≥11.4	61 (23.64)	6,245 (28.74)	0.75 (0.50–1.13)
P trend			0.08
Reproductive Health			
Age at menarche, years			
≤11	56 (21.46)	3,699 (16.89)	1.00 (reference)
12	81 (31.03)	6,507 (29.70)	0.83 (0.59–1.16)
13	73 (27.97)	6,648 (30.35)	0.72 (0.51–1.02)
≥14	51 (19.54)	5,053 (23.07)	0.65 (0.45–0.96)
P trend			0.02
Age at menopause, years			
≤44	18 (7.23)	2,647 (12.29)	1.00 (reference)
45–49	58 (23.29)	5,646 (26.22)	1.55 (0.91–2.63)
≥50	144 (57.83)	10,848 (50.37)	1.89 (1.16–3.09)
Premenopausal	11 (4.42)	1,333 (6.19)	1.61 (0.73–3.52)
Perimenopausal	18 (7.23)	1,062 (4.93)	3.29 (1.66–6.54)
Parity			
Nulliparous	49 (19.68)	3,106 (15.23)	1.00 (reference)
1–2	109 (43.78)	9,267 (45.43)	0.72 (0.51–1.00)
3–4	78 (31.33)	6,527 (32.00)	0.65 (0.45–0.94)
≥5	13 (5.22)	1,499 (7.35)	0.45 (0.24–0.84)
P trend			<0.01
Combined hormone therapy			
Never	146 (67.59)	10,596 (57.39)	1.00 (reference)
Former	28 (12.96)	1,878 (10.17)	0.99 (0.66–1.48)
Current	42 (19.44)	5,988 (32.43)	0.50 (0.35–0.70)
Years of combined hormone therapy			
Never	151 (60.40)	10,725 (51.56)	1.00 (reference)
1–4	39 (15.60)	3,492 (16.79)	0.83 (0.58–1.18)
5–9	28 (11.20)	3,114 (14.97)	0.61 (0.40–0.91)
≥10	32 (12.80)	3,471 (16.69)	0.56 (0.38–0.83)
P trend			<0.001
Estrogen-only hormone therapy			
Never	193 (89.35)	16,543 (89.61)	1.00 (reference)
Former	17 (7.87)	1,319 (7.14)	1.01 (0.61–1.66)
Current	6 (2.78)	600 (3.25)	0.84 (0.37–1.89)
Years of estrogen-only hormone therapy			

Characteristic	Endometrial Cancer		
	Case, *n*=262 n (%)	Non-case, *n*=22,006 n (%)	Age-adjusted HR (95% CI)
Never	204 (89.08)	17,271 (89.47)	1.00 (reference)
1–4	5 (2.18)	615 (3.19)	0.69 (0.28–1.66)
5–9	12 (5.24)	918 (4.76)	1.02 (0.57–1.83)
≥10	8 (3.49)	499 (2.59)	1.21 (0.59–2.45)
P trend			0.78
Years of oral contraceptive use			
Never	103 (39.62)	5,739 (26.36)	1.00 (reference)
≤4	93 (35.77)	8,229 (37.79)	0.62 (0.46–0.85)
5–9	39 (15.00)	4,007 (18.40)	0.54 (0.36–0.80)
≥10	25 (9.62)	3,798 (17.44)	0.36 (0.23–0.57)
P trend			<0.0001
Oophoerectomy			
No	249 (95.04)	21,144 (96.08)	1.00 (reference)
Yes	13 (4.96)	862 (3.92)	1.28 (0.73–2.23)
Family and Medical History			
Family history of uterine cancer			
No	234 (91.05)	20,702 (94.88)	1.00 (reference)
Yes	23 (8.95)	1,116 (5.12)	1.81 (1.18–2.78)
Family history of ovarian cancer			
No	243 (94.19)	21,089 (96.65)	1.00 (reference)
Yes	15 (5.81)	731 (3.35)	1.78 (1.06–3.00)
History of diabetes			
No	248 (94.66)	20,883 (94.90)	1.00 (reference)
Yes	14 (5.34)	1,123 (5.10)	1.06 (0.62–1.81)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval

Table 2

Association between non-steroidal anti-inflammatory drug use and endometrial cancer risk in the VITAL study, n=22,268.

NSAID	Non-use	Low (<4d/wk or <4y)	High (≥4d/wk and ≥4y)	*P* trend
Total NSAIDs				
Cases/Non-cases	110 / 8,844	81 / 6,845	47 / 4,055	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	0.94 (0.71–1.25)	0.89 (0.63–1.25)	0.48
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	0.95 (0.69–1.29)	0.83 (0.56–1.22)	0.35
Aspirin				
Cases/Non-cases	166 / 12,936	50 / 4,682	32 / 2,936	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	0.76 (0.54–1.05)	0.74 (0.50–1.10)	0.06
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	0.77 (0.54–1.09)	0.64 (0.41–1.01)	0.03
Low-dose aspirin				
Cases/Non-cases	195 / 15,842	35 / 3,298	24 / 1,820	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	0.77 (0.52–1.13)	1.00 (0.65–1.56)	0.56
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	0.81 (0.54–1.21)	1.00 (0.62–1.62)	0.65
Regular-strength aspirin				
Cases/Non-cases	214 / 17,423	25 / 2,476	14 / 1,521	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	0.84 (0.55–1.29)	0.66 (0.37–1.19)	0.12
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	0.85 (0.55–1.32)	0.53 (0.27–1.04)	0.06
Non-aspirin				
Cases/Non-cases	164 / 14,002	65 / 5,387	21 / 1,535	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	1.11 (0.83–1.50)	1.27 (0.80–2.01)	0.25
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	1.16 (0.84–1.60)	1.15 (0.68–1.95)	0.40
Ibuprofen				
Cases/Non-cases	178 / 15,541	55 / 4,447	18 / 1,232	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	1.27 (0.82–1.73)	1.50 (0.92–1.73)	0.04
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	1.31 (0.94–1.83)	1.29 (0.73–2.28)	0.12
Naproxen				
Cases/Non-cases	243 / 19,685	13 / 1,695	5 / 329	
Age & NSAID-adjusted HR (95% CI)	1.00 (reference)	0.54 (0.29–1.01)	1.26 (0.51–3.08)	0.30
Multivariable-adjusted HR (95% CI)[a]	1.00 (reference)	0.54 (0.28–1.04)	1.08 (0.39–2.95)	0.23

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval

[a]Adjusted for age (time variable), race, education, body mass index, pack-years of smoking, alcohol consumption, physical activity, age at menarche, age at menopause, parity, combined hormone therapy, estrogen-only hormone therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, history of coronary artery disease, history of stroke, history of osteoarthritis/chronic joint pain, history of rheumatoid arthritis, history of migraine/chronic headaches, history of ulcers, and other NSAIDs.

Table 3

Association between aspirin use and endometrial cancer risk, stratified by smoking status, body mass index, and combined hormone replacement therapy.

	Multivariable-adjusted HR (95% CI)[a]	
NSAID	**Non-user**	**Ever Use (≥1d/wk and ≥1y)**
Any Aspirin		
Never smoker	1.00 (reference)	0.55 (0.37–0.82)
Ever smoker	1.00 (reference)	1.25 (0.77–2.04)
		P interaction = 0.04
Low-dose aspirin		
Never smoker	1.00 (reference)	0.73 (0.48–1.13)
Ever smoker	1.00 (reference)	1.30 (0.77–2.20)
		P interaction = 0.18
Regular-strength aspirin		
Never smoker	1.00 (reference)	0.64 (0.40–1.05)
Ever smoker	1.00 (reference)	0.92 (0.50–1.71)
		P interaction = 0.51
Any Aspirin[b]		
Never/former HRT	1.00 (reference)	0.98 (0.66–1.45)
Current HRT user	1.00 (reference)	0.49 (0.22–1.10)
		P interaction = 0.10
Low-dose aspirin[b]		
Never/former HRT	1.00 (reference)	1.25 (0.83–1.88)
Current HRT user	1.00 (reference)	0.57 (0.23–1.43)
		P interaction = 0.09
Regular-strength aspirin[b]		
Never/former HRT	1.00 (reference)	0.84 (0.52–1.37)
Current HRT user	1.00 (reference)	0.52 (0.18–1.53)
		P interaction = 0.36
Any Aspirin		
BMI <30	1.00 (reference)	0.73 (0.48–1.10)
BMI ≥30	1.00 (reference)	0.67 (0.41–1.09)
		P interaction = 0.40
Low-dose aspirin		
BMI <30	1.00 (reference)	0.90 (0.57–1.40)
BMI ≥30	1.00 (reference)	0.92 (0.54–1.58)
		P interaction = 0.71
Regular-strength aspirin		
BMI <30	1.00 (reference)	0.74 (0.44–1.24)
BMI ≥30	1.00 (reference)	0.60 (0.31–1.15)
		P interaction = 0.42

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; HRT, combined hormone replacement therapy

[a]Adjusted for age (time variable), race, education, body mass index, pack-years of smoking, alcohol consumption, physical activity, age at menarche, age at menopause, parity, combined hormone therapy, estrogen-only hormone therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, history of coronary artery disease, history of stroke, history of osteoarthritis/chronic joint pain, history of rheumatoid arthritis, history of migraine/chronic headaches, history of ulcers, and other NSAIDs

[b]Among post-menopausal women only