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Nonsteroidal Anti-inflammatory Drugs and Endometrial Carcinoma Mortality and Recurrence

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Abstract

Background: Recent data suggest that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with reductions in endometrial cancer risk, yet very few have examined whether their use is related to prognosis among endometrial cancer patients.
Methods: Study subjects comprised 4374 participants of the NRG Oncology/Gynecology Oncology Group 210 Study with endometrial carcinoma who completed a presurgical questionnaire that assessed history of regular prediagnostic NSAID use and endometrial cancer risk factors. Recurrences, vital status, and causes of death were obtained from medical records and cancer registries. Fine-Gray semiproportional hazards regression estimated adjusted subhazard ratios (HRs) and 95% confidence intervals (CIs) for associations of NSAID use with endometrial carcinoma–specific mortality and recurrence. Models were stratified by endometrial carcinoma type (ie, type I [endometrioid] vs type II [serous, clear cell, or carcinosarcoma]) and histology.
Results: Five hundred fifty endometrial carcinoma–specific deaths and 737 recurrences occurred during a median of five years of follow-up. NSAID use was associated with 66% (HR = 1.66, 95% CI = 1.21 to 2.30) increased endometrial carcinoma–specific mortality among women with type I cancers. Associations were statistically significant for former and current users, and strongest among former users who used NSAIDs for 10 years or longer (HR = 2.23, 95% CI = 1.19 to 4.18, two-sided $P_{trend} = .01$). NSAID use was not associated with recurrence or endometrial carcinoma–specific mortality among women with type II tumors.
Conclusions: In this study, use of NSAIDs was associated with increased endometrial carcinoma–specific mortality, especially in patients with type I tumors. Barring a clear biologic mechanism by which NSAIDs would increase the risk of cause-specific mortality, cautious interpretation is warranted.

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There is increasing evidence that chronic inflammation is involved in endometrial carcinogenesis and progression (1–3). Recent data suggest that inhibition of inflammation through nonsteroidal anti-inflammatory drug (NSAID) use is inversely associated with endometrial cancer risk (4,5), most likely through inhibition of cyclooxygenase (COX) enzymes.

Consistent data from several recent studies are highly suggestive of a therapeutic benefit for aspirin and other NSAIDs among colorectal cancer patients (6–11). Despite overlap in etiologic characteristics between cancers of the colorectum and endometrium (12,13) and an overexpression of COX-2 in endometrial cancers (14–16), no study has comprehensively examined whether NSAIDs improve prognosis among endometrial cancer patients. Here, we analyzed data from a large, prospective observational investigation of the association between different types of NSAIDs (ie, aspirin, nonaspirin NSAIDs, and COX-2 inhibitors) and endometrial carcinoma–specific survival and recurrence in the NRG Oncology/Gynecologic Oncology Group (GOG) 210 Study. Prior data in postmenopausal women suggest that NSAIDs reduce exposure to endogenous estrogens (17), which are important for endometrial proliferation (18,19). Therefore, our primary hypothesis was that use of NSAIDs would be associated with reduced carcinoma-specific mortality and recurrence among patients diagnosed with type I endometrial cancers, which are thought to be estrogen responsive. Secondarily, we hypothesized that associations would differ by individual endometrial cancer histology.

Methods

Study Population

The NRG Oncology/GOG 210 Study (Clinical Trials.gov Identifier: NCT00340808) was conducted from September 22, 2003, to December 1, 2011, at 62 US institutions. Eligible subjects included women with presurgical diagnoses of endometrial carcinoma or carcinosarcoma who were eligible for surgery and had not undergone prior retroperitoneal surgery or pelvic/abdominal radiation. Prior to surgery (hysterectomy, bilateral salpingo-oophorectomy, and lymph node sampling), consenting patients completed a self-administered questionnaire that collected demographic and epidemiologic information (20). On September 23, 2007, eligibility criteria in NRG Oncology/GOG 210 changed from unrestricted enrollment to poor prognosis tumors and cancers occurring among nonobese and nonwhite patients. Follow-up information on causes of death and recurrence were available through December 31, 2013.

Of 6124 women enrolled, 5492 (89.7%) completed questionnaires. We excluded women for the following reasons: incomplete surgical staging (n = 20), final diagnosis not endometrial carcinoma (n = 53), benign diagnoses (n = 6), diagnosis of a second primary (n = 2), misclassified pathologic diagnosis based on central pathology review (n = 49), inadequate material for pathology review (n = 22), protocol deviations (n = 17), and improper preprotocol treatment (n = 1). We excluded cases with missing grade (n = 23), mixed epithelial tumors (n = 556), mucinous tumors (n = 18), unusual histologic types (including squamous cell, undifferentiated, and dedifferentiated histologies; n = 111), missing stage (n = 5), and unknown NSAID use (n = 235), leaving 4374 patients for analysis. This study was approved by institutional review boards at the National Cancer Institute and participating study centers. All participants provided informed consent prior to participation.

Tumor Characteristics and Outcome Assessment

Endometrial tumors were classified as low-grade (grades 1 and 2) endometrioid carcinoma (n = 2657), high-grade (grade 3) endometrioid carcinoma (n = 582), serous carcinoma (n = 663), carcinosarcoma (n = 309), or clear cell carcinoma (n = 163). We further classified low- and high-grade endometrioid tumors as type I (n = 3239) and serous, clear cell, and carcinosarcomas as type II (n = 1135). Depth of myometrial invasion (negative, inner half, outer half, serosa), stage according to International Federation for Gynecology and Obstetrics 1988 criteria (21), pelvic and aortic lymph node involvement, peritoneal cytology results, and extra-uterine sites of metastasis were recorded. Diagnoses of high-grade endometrioid carcinoma, serous carcinoma, clear cell carcinoma, carcinosarcoma, and tumors involving the cervix or with non-nodal metastases were reviewed centrally. Information on recurrences, vital status, cause of death, date of events, and adjuvant treatment (none, chemotherapy, radiotherapy, chemotherapy + radiotherapy, or other therapy) were obtained from medical records, supplemented with cancer registry information. Recurrences were defined as evidence of a primary disease following complete response to therapy. Among the 4374 endometrial carcinoma patients enrolled in the GOG-210 Study, the median follow-up was 60 months after diagnosis (range = 1 day–118 months), from which 550 carcinoma-specific deaths and 737 recurrences were recorded.

NSAIDS and Covariate Assessment

A standard risk factor questionnaire administered prior to surgery included a detailed assessment of participants' "regular" use, defined as one or more per week for one or more years (or more than 50 pills during any one-year period) of aspirin, nonaspirin NSAIDs (including ibuprofen, naproxen, indomethacin, piroxicam, and sulindac), and cyclooxygenase-2 (COX-2) inhibitors. For each NSAID type, we collected information on duration of regular use (<1, 1–4.99, 5–9.99, and ≥10 years) and recency of regular use (former, current) relative to the date the questionnaire was completed. We created combination exposure variables of recency and duration based on cross-tabulations. A summary variable, "any NSAIDs," was also created. If a patient responded that she was a regular user of aspirin, nonaspirin NSAIDs, or COX-2 inhibitors, she was considered an ever user of "any NSAIDs." If a woman reported use of multiple NSAIDS, the longest duration of the three medications was recorded as the duration of "any NSAID" use. Likewise, if a woman reported current use of any of the three medications, her status was recorded as current. NSAID data were available in 4374 patients. Frequency distributions of epidemiologic factors and tumor characteristics were similar between the 235 women with unknown NSAID use and nonusers or users of any NSAIDs (data not shown).

Information on demographic characteristics (age, race, annual income, education) and established endometrial carcinoma risk factors, including anthropometric measures, reproductive and menstrual characteristics, exogenous hormone use, smoking status, and medical conditions, was also collected by the questionnaire.

Statistical Analysis

Distributions of epidemiologic and tumor characteristics by any NSAID use and by individual NSAIDs were compared using

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chi-square tests. In order to test our primary hypothesis that NSAID use was inversely associated with endometrial carcinoma–specific mortality and recurrence, we used the Fine and Gray semiproportional model of competing risks (22), using time since enrollment as the time metric, to estimate subhazard ratios (HRs) and 95% confidence intervals (CIs) between NSAIDs and risk of endometrial carcinoma outcomes. In analyses treating endometrial carcinoma–specific death as the outcome, deaths from other causes were treated as competing risks. In the recurrence analyses, deaths from all causes were treated as competing events. Recurrence and cancer-specific mortality were considered exclusive events in regression models (a woman could have both events provided that recurrence preceded death). The proportionality of the subhazards were assessed by evaluating the Wald *P* value for an interaction term, including NSAID use and calendar time (23).

For each individual NSAID, we constructed minimally adjusted competing risk models that included age at diagnosis (continuous) and stage (I, II, III, IV). Clinical, demographic, lifestyle, and reproductive characteristics were explored as confounders and retained when inclusion of the factor changed estimates in the minimally adjusted model by more than 10% or when the model fit was statistically significantly improved as assessed by the likelihood ratio (LR) test. Final models were adjusted for age (time variable), stage, ethnicity, education, income, body mass index (kg/m^2, BMI), and menopausal hormone therapy. Tests for linear trend (P_{trend}) were evaluated by generating orthogonal polynomial contrasts corresponding to the levels of NSAID variables (24). We repeated the analyses stratified by tumor histologic subtype. To test our secondary hypothesis that associations differed by histology, a $P_{heterogeneity}$ value was calculated by including an interaction term in regression models between NSAID exposure variables and histologic subtype.

We tested for formal interactions between use of NSAIDs and endometrial carcinoma–specific mortality and recurrence and enrollment periods (2003–2007 vs 2007–2011) by including a multiplicative interaction term between NSAID variables and a binary variable indicating the enrollment period. Because no differences by time period were observed, results are given here using data from the entire cohort. The competing risk models were conducted using STATA software (version 11, STATA Corp., College Station, TX) while all other analyses were performed using SAS (version 9.3, SAS Institute, Cary, NC). All *P* values were two-sided, and a *P* value of less than .05 was considered statistically significant; for perspective, 44 comparisons were made to address our primary hypothesis.

Results

Descriptive characteristics of GOG-210 participants stratified on NSAID use are given in Table 1. Compared with NSAID nonusers, NSAID users were more likely to be older, African American, heavier, and smokers. NSAID users were also more likely to be multiparous, users of menopausal hormone therapy and/or tamoxifen, and to have a history of diabetes. NSAID use was not clearly associated with any tumor characteristic, including stage, histology, myometrial invasion, lymph node involvement, peritoneal cytology, or peritoneal biopsy result. With few exceptions, directions of associations between the uses of individual NSAID groups (ie, aspirin, nonaspirin NSAIDs, and COX-2 inhibitors) were consistent with the summary variable.

Given the strong association between subtype and prognosis, we analyzed the relation between NSAID use and endometrial carcinoma–specific mortality stratified by cancer subtypes (ie, types I and II). Relative to nonuse, any NSAID use was associated with a 66% (HR = 1.66, 95% CI = 1.21 to 2.30) increased risk of endometrial carcinoma–specific mortality among women diagnosed with type I tumors (Table 2). The increased risk was of similar magnitude for both former and current users and was statistically significant with 10 or more years of use. When recency and duration data were combined, the strongest association was among former users who used NSAIDs for 10 or more years (HR = 2.23, 95% CI = 1.19 to 4.18, P_{trend} = .01). Associations for uses of individual NSAID classes (ie, aspirin, nonaspirin NSAIDs, and COX-2 inhibitors) were similar to the summary measure although statistically nonsignificant (Supplementary Table 1, available online). There was no clear association between NSAID use and endometrial carcinoma–specific mortality among women diagnosed with type II tumors. However, among former users, women who used NSAIDs for 10 or more years had approximately twofold increased risk (HR = 1.92, 95% CI = 1.20 to 3.08, P_{trend} = .004) of endometrial carcinoma–specific mortality relative to nonusers (Table 2). Results did not change when patients were stratified on their stages at diagnosis (not shown).

When cancers were further stratified by individual histologies (Table 3), NSAID use was associated with higher endometrial carcinoma–specific mortality for women diagnosed with low-grade (HR = 2.18, 95% CI = 1.33 to 3.58) and high-grade endometrioid tumors (HR = 1.65, 95% CI = 1.03 to 2.62), as well as carcinosarcomas (HR = 1.54, 95% CI = 1.00 to 2.38). Associations were elevated in former and current users, but only increased with increased duration of use for carcinosarcomas. There were no associations between NSAID use and endometrial carcinoma–specific mortality among patients with serous or clear cell histologies.

Associations between NSAID use and endometrial carcinoma recurrence, stratified by cancer subtype, are given in Table 4. Unlike mortality, any NSAID use was not associated with recurrence from type I endometrial carcinoma (HR = 1.16, 95% CI = 0.92 to 1.47). Although NSAID use was also generally not associated with recurrence among women with type II tumors, we did observe an increased recurrence risk among former users who used NSAIDs 10 or more years (HR = 1.81, 95% CI = 1.19 to 2.74, P_{trend} = .004); however, there was no association with increased duration among current users (P_{trend} = .60). Point estimates were again similar when individual NSAIDs were considered (Supplementary Table 2, available online).

When recurrence models were stratified by individual tumor histologies (Table 5), any NSAID use was associated with a 54% (HR = 1.54, 95% CI = 1.03 to 2.32) increased risk of recurrence among women with high-grade endometrioid tumors and a statistically nonsignificant 47% (HR = 1.47, 95% CI = 0.97 to 2.23) increased risk of recurrence among women with carcinosarcomas. For each, neither association strengthened with increased duration of use.

Discussion

In this prospective study of women with endometrial carcinoma, we observed that NSAID use was associated with increased risks of carcinoma-specific mortality and, to a lesser extent, recurrence, especially among women diagnosed with endometrioid histology. NSAIDs bind to and inhibit COX

Table 1. Descriptive characteristics of participants in the NRG Oncology/GOG 210 Study according to NSAID use (n = 4374)

Baseline characteristics	Any NSAIDs: Nonuser (n = 1653) No. (%)*	Any NSAIDs: User (n = 2721) No. (%)*	P†
Age at diagnosis, y			<.001
<55	409 (24.7)	506 (18.6)	
55–59	359 (21.7)	476 (17.5)	
60–64	306 (18.5)	491 (18.0)	
65–69	239 (14.5)	454 (16.7)	
≥70	340 (20.6)	794 (29.2)	
Race			<.001
White	1410 (85.3)	2267 (83.3)	
Black	152 (9.2)	352 (12.9)	
Other	76 (4.6)	83 (3.1)	
Education			.05
<High school	164 (9.9)	334 (12.3)	
High school	504 (30.5)	843 (31.0)	
Some college	458 (27.7)	751 (27.6)	
≥College graduate	517 (31.3)	769 (28.3)	
Income			.005
<$20 000	321 (19.4)	631 (23.2)	
$20 000–$39 999	342 (20.7)	600 (22.1)	
$40 000–$69 999	389 (23.5)	604 (22.2)	
≥$70 000	409 (24.7)	573 (21.1)	
Body mass index, kg/m^2			<.001
<18.5	22 (1.3)	9 (0.3)	
18.5–24.9	406 (24.6)	454 (16.7)	
25.0–29.9	350 (21.2)	567 (20.8)	
30.0–34.9	313 (18.9)	544 (20.0)	
35.0–39.9	212 (12.8)	403 (14.8)	
≥40.0	240 (14.5)	541 (19.9)	
Smoking status			.001
Never	1128 (68.2)	1719 (63.2)	
Former	380 (23.0)	774 (28.4)	
Current	110 (6.7)	171 (6.3)	
Menopausal status			.05
Premenopausal	172 (10.4)	224 (8.2)	
Postmenopausal	1443 (87.3)	2433 (89.4)	
Age at menarche, y			.42
≤11	333 (20.1)	588 (21.6)	
12	465 (28.1)	792 (29.1)	
13	447 (27.0)	688 (25.3)	
≥14	363 (22.0)	567 (20.8)	
Parity			.02
Nulliparous	331 (20.0)	469 (17.2)	
1–2	682 (41.3)	1089 (40.0)	
≥3	584 (35.3)	1077 (39.6)	
Oral contraceptive use			.65
Never	709 (42.9)	1128 (41.5)	
Ever	898 (54.3)	1515 (55.7)	
Menopausal hormone use			<.001
Never	1236 (74.8)	1809 (66.5)	
Estrogen only	95 (5.7)	226 (8.3)	
Progestin only	74 (4.5)	108 (4.0)	
Estrogen + progestin	235 (14.2)	548 (20.1)	
Tamoxifen use			<.001
Never	1587 (96.0)	2487 (91.4)	
Ever	59 (3.6)	134 (4.9)	
History of diabetes			<.001
Never	1336 (80.8)	1938 (71.2)	
Ever	254 (15.4)	650 (23.9)	
Clinical characteristics			
Histologic subtype			.58
Low-grade endometrioid	1016 (61.5)	1641 (60.3)	
High-grade endometrioid	230 (13.9)	352 (12.9)	
Serous	235 (14.2)	428 (15.7)	
Carcinosarcoma	113 (6.8)	196 (7.2)	
Clear cell	59 (3.6)	104 (3.8)	
Stage			.90
I	1195 (72.3)	1990 (73.1)	
II	116 (7.0)	190 (7.0)	
III	265 (16.0)	425 (15.6)	
IV	77 (4.7)	116 (4.3)	
Myometrial invasion			.97
Negative	418 (26.1)	684 (25.9)	
Inner half	758 (47.4)	1273 (48.1)	
Outer half	386 (24.1)	628 (23.7)	
Serosa	37 (2.3)	60 (2.3)	
Pelvic lymph node involvement‡			.27
No	1340 (87.6)	2246 (88.8)	
Yes	189 (12.4)	284 (11.2)	
Aortic lymph node involvement‡			.93
No	1362 (88.1)	2290 (89.8)	
Yes	101 (6.9)	166 (7.0)	
Peritoneal cytology‡			.09
Negative	1352 (88.1)	2290 (89.8)	
Positive	182 (11.9)	259 (10.2)	
Peritoneal biopsy‡			.55
Negative	667 (93.4)	1146 (94.1)	
Positive	47 (6.6)	72 (5.9)	
Adjuvant treatment			.83
None	959 (58.0)	1537 (56.5)	
Chemotherapy	223 (13.5)	364 (13.4)	
Radiotherapy	258 (15.6)	456 (16.8)	
Chemotherapy and radiotherapy	200 (12.1)	342 (12.6)	
Other	13 (0.8)	22 (0.8)	

*Numbers may not sum to total because of missing data.
†P value from two-sided $\chi 2$ test among women with nonmissing data for the included variables.
‡Among patients for whom the procedure was performed.

enzymes, resulting in decreased synthesis of prostaglandins and eicosanoids, among which several are associated with angiogenesis and tumor growth in endometrial tumors (1). In vitro experimental studies have shown that inhibition of COX enzymes results in decreases in prostaglandin E_2, aromatase, and estrogen synthesis (25,26), which is particularly relevant because of the strong role that unopposed estrogens play in driving endometrial proliferation (18,19). Experimental findings are further supported by positive correlations between expressions of COX-2 and aromatase in endometrial cancer tissue (16) and inverse associations between NSAID use and blood estrogen

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Table 2 Multivariable subhazard ratios and 95% confidence intervals for endometrial carcinoma–specific mortality according to NSAID use, stratified by type I and II in the NRG Oncology/GOG 210 Study (n = 4374)

	Type I endometrial carcinoma (n = 3239)		Type II endometrial carcinoma (n = 1135)		
Any NSAID use	Deaths No. (%)*	HR (95% CI)†	Deaths No. (%)*	HR (95% CI)†	$P_{heterogeneity}$‡
Regular use					.01
Nonuser	55 (4.4)	1.00 (reference)	127 (31.2)	1.00 (reference)	
User	153 (7.7)	1.66 (1.21 to 2.30)	215 (29.5)	1.02 (0.81 to 1.28)	
Recency					.05
Nonuser	55 (4.4)	1.00 (reference)	127 (31.2)	1.00 (reference)	
Former	54 (8.1)	1.65 (1.11 to 2.46)	86 (34.7)	1.23 (0.93 to 1.64)	
Current	75 (6.8)	1.58 (1.10 to 2.27)	107 (26.5)	0.94 (0.71 to 1.23)	
Duration, y					.01
Nonuser	55 (4.4)	1.00 (reference)	127 (31.2)	1.00 (reference)	
0.1–4.9	62 (8.0)	1.69 (1.16 to 2.46)	70 (26.7)	0.87 (0.65 to 1.17)	
5–9.9	15 (5.2)	1.29 (0.73 to 2.26)	38 (33.0)	1.18 (0.82 to 1.72)	
≥10	46 (7.3)	1.65 (1.10 to 2.48)	68 (31.9)	1.21 (0.87 to 1.66)	
P_{trend}§		.06		.11	
Recency and duration, y					.18
Nonuser	55 (4.4)	1.00 (reference)	127 (31.2)	1.00 (reference)	
Former					
<10	33 (7.8)	1.41 (0.89 to 2.24)	45 (31.0)	1.02 (0.72 to 1.44)	
≥10	13 (8.0)	2.23 (1.19 to 4.18)	27 (45.0)	1.92 (1.20 to 3.08)	
P_{trend}§		.01		.004	
Current, y					
<10	34 (6.2)	1.74 (1.13 to 2.69)	55 (26.8)	0.89 (0.65 to 1.25)	
≥10	27 (6.5)	1.46 (0.89 to 2.39)	36 (25.7)	0.88 (0.59 to 1.32)	
P_{trend}§		.16		.53	

*Row percentage. CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs.

†Hazard ratios from Fine and Gray semiproportional competing risk model adjusted for age (continuous), stage (I, II, III, IV), ethnicity (white, black, other), education (less than high school, high school/GED, some college/technical school, college graduate), income (<$20 000, $20 000–$39 999, $40 000–$69 999, ≥$70 000 per year), body mass index (<18.5, <25, 25–29.99, 30–34.99, 35–39.99, ≥40 kg/m^2), menopausal hormone therapy (none, estrogen only, progestin only, estrogen plus progestin).

‡$P_{heterogeneity}$ values based on a two-sided Wald test in the regression model corresponding to an interaction term between tumor type (I and II) and the corresponding NSAID variable.

§P_{trend} values were calculated using two-sided orthogonal polynomial contrasts.

concentrations (17). Indeed, given these mechanisms of action, we know of little reason why NSAID use would be associated with increased risks of death or recurrence among endometrial cancer patients. Recent data has suggested that endometrial cancers are immunogenic, resulting in important therapeutic and prognostic implications (especially related to the response to PD-1/PD-L1 [ie, checkpoint] inhibitors) (27). It is plausible that the anti-inflammatory effects of NSAIDs could modify the immune environment of endometrial cancer through differential cytokine recruitment that could negatively affect mortality.

Several prospective cohort studies (4,28–32) and randomized controlled trials of aspirin (33–35) have examined associations between NSAID use and endometrial cancer risk, with inconsistent results. A 2013 meta-analysis of aspirin reported that its use was associated with a 13% reduction in risk (relative risk [RR] = 0.87, 95% CI = 0.79 to 0.96) (5). Two recent studies not included in the meta-analysis published conflicting results: Use of aspirin (HR = 0.64, 95% CI = 0.41 to 1.01, P_{trend} = .03) but not nonaspirin NSAIDs was inversely associated with endometrial cancer risk in the Vitamins and Lifestyle cohort, which included 262 cases (4), whereas no association was reported for either medication in the Women's Health Initiative Study, which included 774 cases (28). Among randomized trials, no association with endometrial cancer risk was reported in the Women's Health Study of 100 mg aspirin given every second day (HR = 1.00, 95% CI = 0.83 to 1.20) (33,34). In contrast, a pooled analysis of 51 randomized trials of aspirin for heart disease prevention reported reduced uterine cancer incidence among women assigned to aspirin (P = .003) (35), although the analysis relied heavily upon small numbers of women and incident cases.

NSAIDs have been shown to play a chemopreventive and therapeutic role in colorectal cancer across the continuum of tumorigenesis from polyp (36), to invasive disease (28,37), metastasis (38,39), and mortality (6–11,40–42); yet to our knowledge only two limited studies have examined the potential impact of NSAIDs on endometrial cancer outcomes (43,44). In a retrospective medical record linkage study of 282 type II endometrial cancers (n = 158 deaths), investigators correlated aspirin use with carcinoma-specific mortality in a secondary analysis (43). Relative to nonuse, aspirin use was associated with a reduced risk of death (HR = 0.60, 95% CI = 0.36 to 0.99) (43). This year, Matsuo et al. (44) examined the relation between use of low-dose (ie, ≤100 mg) aspirin and endometrial cancer–specific mortality (n = 127) and recurrence (n = 226) in 1687 patients accrued in California and Japan. Use vs nonuse of low-dose aspirin was associated with reduced risks of each (recurrence: HR = 0.46, 95% CI = 0.25 to 0.86; disease-specific mortality: HR = 0.23, 95% CI = 0.08 to 0.64) (44). Our findings for aspirin (which included both low- and regular-strength formulations) contrasted strongly from those previously reported (43,44). Similar to our findings, Matsuo et al. reported use of "other NSAIDs" to be associated with increased risks of recurrence (HR = 1.92, 95% CI = 1.18

Table 3 Multivariable subhazard ratios and 95% confidence intervals for endometrial carcinoma–specific mortality according to NSAID use, stratified by histologic subtype in the NRG Oncology/GOG 210 Study (n = 4374)

	Type I endometrial carcinoma				Type II endometrial carcinoma						
	Low-grade endometrioid (n = 2657)		High-grade endometrioid (n = 582)		Serous (n = 663)		Carcinosarcoma (n = 309)		Clear cell (n = 163)		
Any NSAID use	Deaths No. (%)*	HR (95% CI)†	Deaths No. (%)*	HR (95% CI)†	Deaths No. (%)*	HR (95% CI)†	Deaths No. (%)*	HR (95% CI)†	Deaths No. (%)*	HR (95% CI)†	$P_{heterogeneity}$‡
Regular use											.02
Nonuser	21 (2.1)	1.00 (reference)	34 (14.8)	1.00 (reference)	75 (31.9)	1.00 (reference)	38 (33.6)	1.00 (reference)	14 (23.7)	1.00 (reference)	
User	75 (4.6)	2.18 (1.33 to 3.58)	78 (22.2)	1.65 (1.03 to 2.62)	121 (28.3)	0.95 (0.70 to 1.30)	74 (37.8)	1.54 (1.00 to 2.38)	20 (19.2)	0.73 (0.28 to 1.93)	
Recency											.03
Nonuser	21 (2.1)	1.00 (reference)	34 (14.8)	1.00 (reference)	75 (31.9)	1.00 (reference)	38 (33.6)	1.00 (reference)	14 (23.7)	1.00 (reference)	
Former	28 (5.2)	2.30 (1.29 to 4.12)	26 (20.6)	1.41 (0.78 to 2.52)	47 (33.3)	1.12 (0.76 to 1.65)	27 (39.7)	1.92 (1.12 to 3.28)	12 (30.8)	0.86 (0.29 to 2.51)	
Current	32 (3.5)	1.78 (1.01 to 3.15)	43 (22.8)	1.83 (1.12 to 2.98)	61 (25.8)	0.93 (0.65 to 1.33)	39 (34.8)	1.36 (0.84 to 2.20)	7 (12.7)	0.57 (0.16 to 2.01)	
Duration, y											
Nonuser	21 (2.1)	1.00 (reference)	34 (14.8)	1.00 (reference)	75 (31.9)	1.00 (reference)	38 (33.6)	1.00 (reference)	14 (23.7)	1.00 (reference)	.12
0.1–4.9	31 (4.9)	2.23 (1.26 to 3.94)	31 (22.1)	1.57 (0.92 to 2.68)	44 (27.7)	0.81 (0.55 to 1.21)	18 (30.5)	1.32 (0.73 to 2.36)	8 (18.2)	0.52 (0.18 to 1.50)	
5–9.9	8 (3.3)	1.85 (0.83 to 4.13)	7 (14.9)	1.05 (0.44 to 2.49)	20 (28.6)	1.13 (0.69 to 1.84)	11 (37.9)	1.44 (0.67 to 3.07)	7 (43.7)	1.52 (0.25 to 6.53)	
≥10	21 (4.0)	2.12 (1.13 to 3.98)	25 (23.4)	1.80 (1.03 to 3.14)	35 (29.2)	1.12 (0.71 to 1.77)	29 (42.6)	1.89 (1.10 to 3.25)	4 (16.0)	0.89 (0.16 to 5.01)	
P_{trend}§		.03		.13		.37		.05		.76	

*Row percentage. CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs.

†Hazard ratios from Fine and Gray semiproportional competing risk model adjusted for age (continuous), stage (I, II, III, IV), ethnicity (white, black, other), education (less than high school, high school/GED, some college/technical school, college graduate), income (<$20 000, $20 000–$39 999, $40 000–$69 999, ≥$70 000 per year), body mass index (<18.5, <25, 25–29.99, 30–34.99, 35–39.99, ≥40 kg/m^2), menopausal hormone therapy (none, estrogen only, progestin only, estrogen plus progestin).

‡$P_{heterogeneity}$ values based on a two-sided Wald test in regression models corresponding to an interaction term between tumor histology and the corresponding NSAID variable.

§P_{trend} values were calculated using two-sided orthogonal polynomial contrasts.

Table 4 Multivariable subhazard ratios and 95% confidence intervals for endometrial carcinoma recurrence according to NSAID use, stratified by type I and II in the NRG Oncology/GOG 210 Study (n = 4374)

	Type I endometrial carcinoma (n = 3239)		Type II endometrial carcinoma (n = 1135)		
Any NSAID use	Recurrences No. (%)*	HR (95% CI)†	Recurrences No. (%)*	HR (95% CI)†	$P_{heterogeneity}$‡
Regular use					.28
Nonuser	117 (9.4)	1.00 (reference)	148 (36.4)	1.00 (reference)	
User	224 (11.2)	1.16 (0.92 to 1.47)	248 (34.1)	1.01 (0.82 to 1.25)	
Recency					.61
Nonuser	117 (9.4)	1.00 (reference)	148 (36.4)	1.00 (reference)	
Former	78 (11.7)	1.19 (0.88 to 1.60)	102 (41.1)	1.25 (0.96 to 1.62)	
Current	110 (9.9)	1.03 (0.79 to 1.35)	123 (30.5)	0.93 (0.72 to 1.20)	
Duration, y					.14
Nonuser	117 (9.4)	1.00 (reference)	148 (36.4)	1.00 (reference)	
0.1–4.9	93 (12.0)	1.22 (0.93 to 1.62)	84 (32.1)	0.93 (0.71 to 1.23)	
5–9.9	25 (8.7)	0.94 (0.60 to 1.47)	41 (35.6)	1.13 (0.79 to 1.63)	
≥10	65 (10.3)	1.03 (0.75 to 1.41)	75 (35.2)	1.10 (0.82 to 1.47)	
P_{trend}§		.69		.32	
Recency and duration, y					.19
Nonuser	117 (9.4)	1.00 (reference)	148 (36.4)	1.00 (reference)	
Former					
<10	49 (11.6)	1.13 (0.80 to 1.60)	55 (37.9)	1.10 (0.80 to 1.51)	
≥10	15 (9.3)	0.94 (0.55 to 1.64)	30 (50.0)	1.81 (1.19 to 2.74)	
P_{trend}§		.92		.004	
Current, y					
<10	57 (10.5)	1.16 (0.84 to 1.60)	64 (31.2)	0.94 (0.69 to 1.29)	
≥10	37 (8.8)	0.83 (0.59 to 1.28)	42 (30.0)	0.88 (0.61 to 1.26)	
P_{trend}§		.42		.60	

*Row percentage. CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs.

†Hazard ratios from Fine and Gray semiproportional competing risk model adjusted for age (continuous), stage (I, II, III, IV), ethnicity (white, black, other), education (less than high school, high school/GED, some college/technical school, college graduate), income (<$20 000, $20 000–$39 999, $40 000–$69 999, ≥$70 000 per year), body mass index (<18.5, <25, 25–29.99, 30–34.99, 35–39.99, ≥40 kg/m^2), menopausal hormone therapy (none, estrogen only, progestin only, estrogen plus progestin).

‡$P_{heterogeneity}$ values based on a two-sided Wald test in the regression model corresponding to an interaction term between tumor type (I and II) and the corresponding NSAID variable.

§P_{trend} values were calculated using two-sided orthogonal polynomial contrasts.

to 3.13) (44); however, associations with disease-specific mortality were not reported (44).

When recency and duration of NSAID use were considered together in relation to endometrial carcinoma death, the associations were linear only among former users. We have no ready explanation for why this might be. Implied from this finding may be that past use of NSAIDs is associated with the development of more aggressive tumors, independent of their putative role on endometrial carcinoma risk; however, our data on stage at diagnosis and other endometrial carcinoma characteristics argues against this hypothesis. While it remains possible that NSAID use affects molecular markers of an aggressive phenotype (such as *COX-2* expression) early in tumorigenesis, such data were not available for examination in this study. There are limited data to support a role of NSAIDs in inducing or promoting growth in benign endometrial tissues in women undergoing hysterectomy. NSAIDs have been associated with loss of *PTEN* expression (45) and insulin receptor expression (46), possibly indicating aggressive molecular features.

In histology-stratified models, we observed similar patterns of increased risk between NSAID use and carcinoma-specific mortality among women with low-grade endometrioid, high-grade endometrioid, or carcinosarcomas. The behavior of uterine carcinosarcomas, which demonstrate malignant epithelial and stromal components, is thought to be driven by the epithelial component of the tumor (47–50). Similarities in outcomes associated with NSAID use could reflect a shared biology between endometrioid tumors and carcinosarcomas, a hypothesis reinforced by overlap in etiologic factors for these histologic subtypes, including obesity, parity, and cigarette smoking (51–53).

This study has several strengths aside from its prospective design and length of follow-up. With 3239 type I and 1135 type II endometrial carcinoma patients, it is well powered to detect relatively small associations. Given this large sample size, we were able to examine associations with mortality and recurrence stratified on cancer histology. The study is further strengthened by its strong measurement of (and control for) potential confounding factors, including endometrial carcinoma risk factors and tumor characteristics. Lastly, although not ideal, measurement of NSAIDs included type (aspirin, nonaspirin, COX-2 inhibitors) as well as recency and duration.

There are also limitations that should be considered. Reported NSAID use was not validated, and data on the frequency and dose of NSAIDs were not collected, possibly contributing to nondifferential measurement errors. Given the prospective nature of the study, these errors would not explain the increased risks we report; however, they may explain relatively flat associations for duration of use. We were further limited in our ability to assess the potential for several indications of NSAID use (eg, prevalent cardiovascular disease, arthritis) to confound associations. Cardiovascular disease, a strong

Table 5 Multivariable subhazard ratios and 95% confidence intervals for endometrial recurrence according to NSAID use, stratified by histologic subtype in the NRG Oncology/GOG 210 Study (n = 4374)

	Type I endometrial carcinoma				Type II endometrial carcinoma						
	Low-grade endometrioid (n = 2657)		High-grade endometrioid (n = 582)		Serous (n = 663)		Carcinosarcoma (n = 309)		Clear cell (n = 163)		
Any NSAID use	Recurrences No. (%)*	HR (95% CI)†	Recurrences No. (%)*	HR (95% CI)†	Recurrences No. (%)*	HR (95% CI)†	Recurrences No. (%)*	HR (95% CI)†	Recurrences No. (%)*	HR (95% CI)†	$P_{heterogeneity}$‡
Regular use											.06
Nonuser	76 (7.5)	1.00 (reference)	41 (17.8)	1.00 (reference)	94 (40.0)	1.00 (reference)	38 (33.6)	1.00 (reference)	16 (27.1)	1.00 (reference)	
User	132 (8.0)	1.00 (0.74 to 1.35)	92 (26.1)	1.54 (1.03 to 2.32)	149 (34.8)	0.91 (0.69 to 1.19)	77 (39.3)	1.47 (0.97 to 2.23)	22 (21.1)	0.60 (0.29 to 1.26)	
Recency											
Nonuser	76 (7.5)	1.00 (reference)	41 (17.8)	1.00 (reference)	94 (40.0)	1.00 (reference)	38 (33.6)	1.00 (reference)	16 (27.1)	1.00 (reference)	.15
Former	47 (8.7)	1.08 (0.74 to 1.57)	31 (24.6)	1.42 (0.86 to 2.34)	57 (40.4)	1.08 (0.76 to 1.52)	32 (47.1)	2.13 (1.28 to 3.55)	13 (33.3)	0.78 (0.34 to 1.80)	
Current	63 (6.8)	0.87 (0.62 to 1.23)	47 (24.9)	1.46 (0.93 to 2.29)	75 (31.8)	0.86 (0.62 to 1.18)	40 (35.7)	1.33 (0.81 to 2.16)	8 (14.5)	0.44 (0.18 to 1.08)	
Duration, y											
Nonuser	76 (7.5)	1.00 (reference)	41 (17.8)	1.00 (reference)	94 (40.0)	1.00 (reference)	38 (33.6)	1.00 (reference)	16 (27.1)	1.00 (reference)	.20
0.1–4.9	54 (8.5)	1.05 (0.74 to 1.50)	39 (27.9)	1.66 (1.03 to 2.67)	56 (35.2)	0.90 (0.63 to 1.29)	19 (32.2)	1.37 (0.75 to 2.52)	9 (20.4)	0.53 (0.24 to 1.19)	
5–9.9	16 (6.7)	0.87 (0.51 to 1.50)	9 (19.1)	1.09 (0.49 to 2.44)	23 (32.9)	0.91 (0.55 to 1.48)	11 (37.9)	1.48 (0.72 to 3.05)	7 (43.7)	1.23 (0.36 to 4.15)	
≥10	40 (7.6)	0.97 (0.65 to 1.45)	25 (23.4)	1.30 (0.76 to 2.22)	44 (36.7)	1.02 (0.70 to 1.49)	27 (39.7)	1.55 (0.90 to 2.68)	4 (16.0)	0.51 (0.15 to 1.74)	
P_{trend}§		.69		.69		.66		.13		.50	

*Row percentage. CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs.

†Hazard ratios from Fine and Gray semiproportional competing risk model adjusted for age (continuous), stage (I, II, III, IV), ethnicity (white, black, other), education (less than high school, high school/GED, some college/technical school, college graduate), income (<$20 000, $20 000–$39 999, $40 000–$69 999, ≥$70 000 per year), body mass index (<18.5, <25, 25–29.99, 30–34.99, 35–39.99, ≥40 kg/m^2), menopausal hormone therapy (none, estrogen only, progestin only, estrogen plus progestin).

‡$P_{heterogeneity}$ values based on a two-sided Wald test in regression models corresponding to an interaction term between tumor histology and the corresponding NSAID variable.

§P_{trend} values were calculated using two-sided orthogonal polynomial contrasts.

correlate of aspirin use, is among the most common causes of all-cause mortality among women with endometrial cancer (54). Yet it and other indications for NSAID use have not been identified as risk factors for endometrial carcinoma–specific mortality. Additionally, because of the relatively small numbers of events among NSAID users in histology-stratified models, we were unable to jointly examine associations with recency and duration of NSAIDs. As with all observational analyses, it remains possible that the associations reported here reflect, at least to some degree, confounding from unmeasured or insufficiently measured factors. Lastly, due to the number of comparisons made, the play of chance cannot be ruled out.

In this large, prospective study of women diagnosed with endometrial carcinoma, NSAID use was not associated with reductions in carcinoma-specific mortality or recurrence. Rather, increases in risk of each outcome were observed, especially among patients diagnosed with endometrioid histologies. Barring a clear biologic mechanism by which NSAIDs would worsen prognosis, our findings necessitate a cautious interpretation.

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References

1. Wallace AE, Gibson DA, Saunders PT, et al. Inflammatory events in endometrial adenocarcinoma. *J Endocrinol*. 2010;206(2):141–157.
2. Dossus L, Becker S, Rinaldi S, et al. Tumor necrosis factor (TNF)-alpha, soluble TNF receptors and endometrial cancer risk: The EPIC study. *Int J Cancer*. 2011;129(8):2032–2037.
3. Dossus L, Rinaldi S, Becker S, et al. Obesity, inflammatory markers, and endometrial cancer risk: A prospective case-control study. *Endocr Relat Cancer*. 2010;17(4):1007–1019.
4. Brasky TM, Moysich KB, Cohn DE, et al. Non-steroidal anti-inflammatory drugs and endometrial cancer risk in the VITamins And Lifestyle (VITAL) cohort. *Gynecol Oncol*. 2013;128(1):113–119.
5. Neill AS, Nagle CM, Protani MM, et al. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: A case-control study, systematic review and meta-analysis. *Int J Cancer*. 2013;132(5):1146–1155.
6. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med*. 2012;367(17):1596–606.
7. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA*. 2009;302(6):649–658.
8. Ng K, Meyerhardt JA, Chan AT, et al. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. *J Natl Cancer Inst*. 2015;107(1):345.
9. Nishihara R, Lochhead P, Kuchiba A, et al. Aspirin use and risk of colorectal cancer according to BRAF mutation status. *JAMA*. 2013;309(24):2563–2571.
10. Coghill AE, Newcomb PA, Campbell PT, et al. Prediagnostic non-steroidal anti-inflammatory drug use and survival after diagnosis of colorectal cancer. *Gut*. 2011;60(4):491–498.
11. Coghill AE, Newcomb PA, Chia VM, et al. Pre-diagnostic NSAID use but not hormone therapy is associated with improved colorectal cancer survival in women. *Br J Cancer*. 2011;104(5):763–768.
12. Karageorgi S, Hankinson SE, Kraft P, et al. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. *Int J Cancer*. 2010;126(1):208–216.
13. Zervoudakis A, Strickler HD, Park Y, et al. Reproductive history and risk of colorectal cancer in postmenopausal women. *J Natl Cancer Inst*. 2011;103(10):826–834.
14. Kilic G, Gurates B, Garon J, et al. Expression of cyclooxygenase-2 in endometrial adenocarcinoma. *Eur J Gynaecol Oncol*. 2005;26(3):271–274.
15. Keser SH, Gul AE, Barisik NO, et al. The relationship of COX-2 expression with estrogen receptor, progesterone receptor and prognostic parameters in endometrial carcinomas. *J Obstet Gynaecol Res*. 2010;36(3):560–566.
16. Fowler JM, Ramirez N, Cohn DE, et al. Correlation of cyclooxygenase-2 (COX-2) and aromatase expression in human endometrial cancer: Tissue microarray analysis. *Am J Obstet Gynecol*. 2005;192(4):1262–1271; discussion 1271–1273.
17. Gates MA, Tworoger SS, Eliassen AH, et al. Analgesic use and sex steroid hormone concentrations in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(4):1033–1041.
18. Allen NE, Key TJ, Dossus L, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer*. 2008;15(2):485–497.
19. Henderson BE, Ross RK, Pike MC, et al. Endogenous hormones as a major factor in human cancer. *Cancer Res*. 1982;42(8):3232–3239.
20. Brinton LA, Felix AS, McMeekin DS, et al. Etiologic heterogeneity in endometrial cancer: Evidence from a Gynecologic Oncology Group trial. *Gynecol Oncol*. 2013;129(2):277–284.
21. Zaino RJ. FIGO staging of endometrial adenocarcinoma: A critical review and proposal. *Int J Gynecol Pathol*. 2009;28(1):1–9.
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:13.
23. Zhou B, Fine J, Laird G. Goodness-of-fit test for proportional subdistribution hazards model. *Stat Med*. 2013;32(22):3804–3811.
24. Vittinghoff E, Glidden D, Shiboski SC, et al. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. 2nd ed. New York: Springer; 2012.
25. Brueggemeier RW, Diaz-Cruz ES, Li PK, et al. Translational studies on aromatase, cyclooxygenases, and enzyme inhibitors in breast cancer. *J Steroid Biochem Mol Biol*. 2005;95(1–5):129–136.
26. Ebert AD, Bartley J, David M. Aromatase inhibitors and cyclooxygenase-2 (COX-2) inhibitors in endometriosis: New questions—old answers? *Eur J Obstet Gynecol Reprod Biol*. 2005;122(2):144–150.
27. Howitt BE, Shukla SA, Sholl LM, et al. Association of polymerase E-mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. *JAMA Oncol*. 2015;1(9):1319–1323.
28. Brasky TM, Liu J, White E, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: Results from the Women's Health Initiative. *Int J Cancer*. 2014;135(8):1869–1883.
29. Danforth KN, Gierach GL, Brinton LA, et al. Nonsteroidal anti-inflammatory drug use and endometrial cancer risk in the NIH-AARP Diet and Health Study. *Cancer Prev Res (Phila)*. 2009;2(5):466–472.

30. Prizment AE, Folsom AR, Anderson KE. Nonsteroidal anti-inflammatory drugs and risk for ovarian and endometrial cancers in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19(2):435–442.
31. Viswanathan AN, Feskanich D, Schernhammer ES, et al. Aspirin, NSAID, and acetaminophen use and the risk of endometrial cancer. *Cancer Res*. 2008; 68(7):2507–2513.
32. Setiawan VW, Matsuno RK, Lurie G, et al. Use of nonsteroidal anti-inflammatory drugs and risk of ovarian and endometrial cancer: The multiethnic cohort. *Cancer Epidemiol Biomarkers Prev*. 2012;21(9):1441–1449.
33. Cook NR, Lee IM, Zhang SM, et al. Alternate-day, low-dose aspirin and cancer risk: Long-term observational follow-up of a randomized trial. *Ann Intern Med*. 2013;159(2):77–85.
34. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: The Women's Health Study: A randomized controlled trial. *JAMA*. 2005;294(1):47–55.
35. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet*. 2012; 379(9826):1602–1612.
36. Cole BF, Logan RF, Halabi S, et al. Aspirin for the chemoprevention of colorectal adenomas: Meta-analysis of the randomized trials. *J Natl Cancer Inst*. 2009; 101(4):256–266.
37. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010;376(9754):1741–1750.
38. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol*. 2012;13(5): 518–527.
39. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: A study of incident cancers during randomised controlled trials. *Lancet*. 2012;379(9826):1591–1601.
40. Li P, Wu H, Zhang H, et al. Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: A meta-analysis. *Gut*. 2015; 64(9):1419–1425.
41. Ye XF, Wang J, Shi WT, et al. Relationship between aspirin use after diagnosis of colorectal cancer and patient survival: A meta-analysis of observational studies. *Br J Cancer*. 2014;111(11):2172–2179.
42. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: An analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011;378(9809):2081–2087.
43. Nevadunsky NS, Van Arsdale A, Strickler HD, et al. Association between statin use and endometrial cancer survival. *Obstet Gynecol*. 2015;126(1): 144–150.
44. Matsuo K, Cahoon SS, Yoshihara K, et al. Association of low-dose aspirin and survival of women with endometrial cancer. *Obstet Gynecol*. 2016;128(1): 127–137.
45. Yang HP, Meeker A, Guido R, et al. PTEN expression in benign human endometrial tissue and cancer in relation to endometrial cancer risk factors. *Cancer Causes Control*. 2015;26(12):1729–1736.
46. Merritt MA, Strickler HD, Einstein MH, et al. Insulin/IGF axis in human endometrium and associations with cancer risk factors. *Cancer Causes Control*. 2016;27(6):737–748.
47. Silverberg SG, Major FJ, Blessing JA, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. *Int J Gynecol Pathol*. 1990;9(1):1–19.
48. Sreenan JJ, Hart WR. Carcinosarcomas of the female genital tract. A pathologic study of 29 metastatic tumors: Further evidence for the dominant role of the epithelial component and the conversion theory of histogenesis. *Am J Surg Pathol*. 1995;19(6):666–674.
49. Nordal RR, Kristensen GB, Stenwig AE, et al. An evaluation of prognostic factors in uterine carcinosarcoma. *Gynecol Oncol*. 1997;67(3):316–321.
50. McCluggage WG. Malignant biphasic uterine tumours: Carcinosarcomas or metaplastic carcinomas? *J Clin Pathol*. 2002;55(5):321–325.
51. Felix AS, Cook LS, Gaudet MM, et al. The etiology of uterine sarcomas: A pooled analysis of the epidemiology of endometrial cancer consortium. *Br J Cancer*. 2013;108(3):727–734.
52. Zelmanowicz A, Hildesheim A, Sherman ME, et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. *Gynecol Oncol*. 1998;69(3):253–257.
53. Bland AE, Stone R, Heuser C, et al. A clinical and biological comparison between malignant mixed mullerian tumors and grade 3 endometrioid endometrial carcinomas. *Int J Gynecol Cancer*. 2009;19(2):261–265.
54. Ward KK, Shah NR, Saenz CC, et al. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol*. 2012; 126(2):176–179.