Nonsteroidal Anti-Inflammatory Drug Use and Endometrial Cancer Risk in the NIH-AARP Diet and Health Study

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Abstract   Chronic inflammation may play an etiologic role in endometrial cancer. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammatory activity by inhibiting the proinflammatory cyclooxygenase enzymes and, therefore, may decrease cancer risk. However, few studies have examined the association between NSAID use and endometrial cancer. We conducted a prospective study among 72,524 women in the NIH-AARP Diet and Health Study. Women completed a questionnaire in 1996–1997 on lifestyle and health-related factors, including type and frequency of NSAID use within the past year, and were followed through 2003 by linkages to cancer registries and vital status databases. During 488,261 person-years of follow-up, there were 732 incident endometrial cancers. NSAID use, compared with non-use of NSAIDs, was not significantly associated with endometrial cancer risk [relative risk (RR), 0.90; 95% confidence interval (95% CI), 0.74–1.09]. Null associations were also observed by type of NSAID use [aspirin only: RR, 0.88; 95% CI, 0.70–1.11; nonaspirin NSAID (NA-NSAID) only: RR, 1.01; 95% CI, 0.79–1.29; both aspirin and NA-NSAIDs: RR, 0.85; 95% CI, 0.68–1.06]. Generally, results were not statistically significant by frequency of use for aspirin or NA-NSAIDs. Results did not change when women with a history of heart disease, hypertension, or diabetes were excluded to minimize the potential for confounding by indication. Overall, our data do not support an association between aspirin or NA-NSAID use and endometrial cancer risk.

Recent interest has focused on the role of chronic inflammation in the etiology of several cancers (1). Although many established risk factors for endometrial cancer, such as obesity, parity, oral contraceptive use, and unopposed estrogen use, have traditionally been viewed as acting via the estrogen and progesterone pathways, Modugno et al. (2) hypothesized that they also may influence endometrial cancer through their effects on inflammation. Cyclooxygenase (COX) is an enzyme for the rate-limiting step in the synthesis of prostaglandins, key mediators of the inflammatory process, and is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs; reviewed in refs. 3, 4). Increased COX expression has been observed in

endometrial tumors (5, 6). Thus, if chronic inflammation plays an etiologic role, NSAID use might be hypothesized to decrease endometrial cancer risk (2).

Few studies to date have described associations between NSAID use and endometrial cancer. Aspirin use was examined in one case-control (7) and one prospective study (8), which also examined associations with nonaspirin NSAIDs (NA-NSAIDs). Neither study observed a significant relationship between NSAID use and endometrial cancer risk overall. However, in each, aspirin use was associated with a reduction in endometrial cancer risk among obese women, and the authors proposed two explanations for the association (7, 8). First, obesity is associated with increased levels of inflammatory cytokines (9), and thus the anti-inflammatory effects of NSAIDs may have a greater health benefit among obese women. Second, COX-2 and aromatase levels are positively correlated (10), and therefore inhibition of COX-2 by NSAID use may reduce estrogen production through decreased aromatization of androgens in adipose tissue (11, 12). However, because obesity is a strong risk factor for endometrial cancer, it is possible that effect modification observed on a relative risk (RR) scale does not reflect meaningful differences on an absolute scale. Thus, it is important for studies to consider both relative and absolute measures of risk. Further, although all NSAIDs inhibit COX activity (4), there are important mechanistic differences by NSAID type. Aspirin is distinct from other NSAIDs because it permanently inactivates COX,

Table 1. Characteristics at study baseline of 72,524 women in the NIH-AARP Diet and Health Study by use of NSAIDs

	Any NSAID use*		NSAID type*		
	No (*n* = 10,729)	**Yes** (*n* = 60,436)	**Aspirin only** (*n* = 18,757)	**NA only** (*n* = 13,204)	**Aspirin + NA** (*n* = 28,475)
Mean age at baseline (SD), y	63.4 (5.2)	62.2 (5.5)	63.3 (5.3)	61.6 (5.5)	61.7 (5.5)
Race/ethnicity (%)					
White	88.8	92.8	92.8	92.0	93.3
Non-White	11.2	7.2	7.2	8.0	6.7
Education (%)					
<High school	6.2	4.1	4.6	4.0	3.7
High school	26.7	23.0	25.0	23.6	21.4
Post-High school	32.3	34.5	33.6	35.0	34.9
College graduate	32.2	36.2	34.5	35.1	37.8
Age at menarche (y) (%)					
≤12	46.6	47.6	46.2	49.7	47.5
13–14	43.1	43.1	44.3	41.2	43.3
≥15	10.0	9.0	9.3	8.8	9.0
Menopausal status (%)					
Premenopausal	3.5	6.6	4.0	8.1	7.5
Postmenopausal	96.0	93.0	95.6	91.4	92.1
Postmenopausal hormone use (%)					
Never use	61.8	49.7	58.4	47.1	45.3
E only, <10 y	5.5	6.0	5.7	6.0	6.1
E only, ≥10 y	0.6	0.8	0.9	0.8	0.7
E + P, <10 y	15.5	22.5	17.1	24.4	25.1
E + P, ≥10 y	4.9	7.4	5.7	7.7	8.4
Oral contraceptive use (%)					
Never or <1 y	65.6	57.6	64.0	54.7	54.7
1 to <10 y	25.0	30.9	26.3	33.0	33.0
≥10 y	8.9	10.9	9.1	11.7	11.8
Parity (%)					
No births	19.9	17.5	19.3	16.6	16.7
1	11.1	10.6	10.7	10.9	10.3
2	25.1	26.3	25.3	26.9	26.7
≥3	43.6	45.4	44.4	45.4	46.0
Smoking status (%)					
Never	46.9	43.7	45.1	43.2	42.9
Former	37.4	40.1	37.2	41.3	41.5
Current	13.2	13.7	15.2	13.3	12.9
BMI (kg/m^2) (%)					
<25	47.5	46.4	49.5	44.6	45.2
25 to <30	28.5	30.8	30.4	30.3	31.2
≥30	20.2	20.4	17.4	22.8	21.2
Self-reported:					
Heart disease (%)	8.1	6.9	8.7	4.6	6.7
Hypertension (%)	34.4	33.2	34.0	32.4	33.2
Diabetes (%)	7.5	5.8	6.0	6.1	5.5

NOTE: Missing data are not shown and were included in percentage calculations; therefore, percents may not sum to 100. Aspirin products were defined as generic aspirin, Bayer, Bufferin, Anacin, Ecotrin, or Excedrin. Nonaspirin products were defined as generic ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, or Fenoprofen, excluding Tylenol, acetaminophen, or any other pain relievers.

Abbreviations: E, estrogen; E + P, estrogen plus progestin; BMI, body mass index.

*Does not include 1,359 women excluded for reasons described in Materials and Methods.

whereas other NSAIDs reversibly inactivate COX (reviewed in refs. 13, 14).

Therefore, we sought to determine the associations, on both the relative and absolute scales, between endometrial cancer risk and aspirin and NA-NSAID use in the prospective NIH-AARP Diet and Health Study.

Materials and Methods

The NIH-AARP Diet and Health Study

The NIH-AARP Diet and Health Study was established in 1995–1996 when 3.5 million AARP members, ages 50 to 71 y, were sent a questionnaire to collect demographic, anthropometric, lifestyle, and health information (15). Questionnaires were mailed to AARP residents in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) that had high-quality cancer registries and substantial AARP membership. The baseline questionnaire was satisfactorily completed and returned by 566,402 members.

A second questionnaire was mailed in 1996–1997 to obtain additional information, including NSAID use. It was completed by 334,908 men and women, excluding individuals who died or moved out of the study area before their questionnaires were scanned. Our analysis additionally excluded individuals who used a proxy respondent for either the baseline ($n = 6,959$) or second ($n = 3,424$) questionnaire; were male ($n = 188,117$); or reported a diagnosis of cancer other than nonmelanoma skin cancer on either questionnaire ($n = 9,022$, including 617 endometrial cancers), a history of hysterectomy ($n = 51,515$) or unknown hysterectomy status ($n = 1,498$) on the baseline questionnaire, or menstrual periods that stopped due to surgery ($n = 1,063$) or radiation or chemotherapy ($n = 58$) on the baseline questionnaire. After further excluding women who developed nonepithelial endometrial cancer ($n = 51$) or had missing or inconsistent NSAID information ($n = 677$), there were 72,524 eligible women who had completed both questionnaires. The Special Studies Institutional Review Board of the National Cancer Institute approved the study, and all participants provided consent.

NSAID use

Women were asked whether they had taken aspirin products during the last 12 mo and, if they had, their usual frequency of use (<2 or

2–3 times per month; 1–2, 3–4, or 5–6 times per week; daily; or ≥2 times per day). They also were asked if they had taken other pain relievers, listed by their generic and brand names, during the past 12 mo, specifically excluding Tylenol, acetaminophen, and any other pain relievers. A single question asked about frequency of NA-NSAID use based on the same categories as aspirin NSAID use; the number of NA-NSAIDs used in the last year was not assessed.

Endometrial cancer

Incident cancers through 2003 were identified by probabilistic linkages with cancer registries in the original recruitment areas and three common states of relocation (Arizona, Nevada, and Texas). Fatal cancers were identified by linkages with mortality databases (Social Security vital status database, with cause of death from the National Death Index Plus file). The original cancer registries were certified by the North American Association of Central Cancer Registries as being 95% complete within 18 mo of the end of the diagnosis year, and a validation study found that our follow-up methods identify ~90% of cancers in the cohort (16). During 488,261 person-years of follow-up, there were 732 incident endometrial cancers, most of which were early-stage tumors (81% of tumors with known stage were localized).

Statistical analysis

Cox proportional hazards models were used to estimate RRs and 95% confidence intervals (95% CIs) with age as the time metric. Baseline age was used as a stratification variable to control for (potential) secular trends in endometrial cancer by birth cohort. Women entered analyses at the age they completed the second questionnaire and contributed person-time until they were diagnosed with endometrial cancer, moved out of the registry catchment area (self-reported or identified by the U.S. Postal Service), died, or reached the end of follow-up on December 31, 2003.

The reference group in all analyses was nonusers of NSAIDs, defined as women who had not taken aspirin or NA-NSAIDs in the year before the second study questionnaire. NSAID users were women who reported aspirin or NA-NSAID use (with or without a frequency of use), as well as those who skipped the yes/no use question but reported a frequency of use. The small proportion of women with inconsistent responses (i.e., report of nonuse with a frequency of use) was excluded.

NSAID use was examined overall and by type (nonuse, aspirin only, NA-NSAID only, both aspirin and NA-NSAIDs). For analyses of any NSAID use, results are presented for women with data on both aspirin and NA-NSAIDs ($n = 71,165$) to be consistent with the NSAID type

Table 2. Use of NSAIDs within the last year, overall and by type, and risk of endometrial cancer in the NIH-AARP Diet and Health Study

	Cases	Person-years	Age–adjusted RR (95% CI)	Multivariable RR (95% CI)*
NSAID use in the last year				
No	123	71,793	1.00 (reference)	1.00 (reference)
Yes	597	407,400	0.89 (0.73–1.08)	0.90 (0.74–1.09)
NSAID type				
Nonusers	123	71,793	1.00 (reference)	1.00 (reference)
Aspirin only	184	126,233	0.85 (0.68–1.07)	0.88 (0.70–1.11)
NA-NSAID only	149	88,816	1.05 (0.82–1.33)	1.01 (0.79–1.29)
Aspirin + NA-NSAID	264	192,351	0.85 (0.68–1.05)	0.85 (0.68–1.06)

*Adjusted for race (White, non-White), age at menarche (≤12, 13-14, ≥15 y), age at menopause (premenopausal, age at menopause: <45, 45-49, 50-54, ≥55 y, missing age at menopause/menopausal status), postmenopausal hormone use (never use, unopposed estrogen use: <10, ≥10 y, estrogen plus progestin: <10, ≥10 y, other/missing hormone use or duration), parity (nulliparous, 1, 2, 3 or more births), oral contraceptive use (never or <1 y 1 to <10, ≥10 y), smoking (never, former, current, missing), BMI (<25, 25 to <30, ≥30 kg/m², missing), physical activity (5 categories of exercise frequency over the past 12 mo), family history of breast cancer (yes, no, missing), personal history of diabetes (yes, no), heart disease (yes, no), and high blood pressure (yes, no, missing).

Table 3. Use of aspirin or NA-NSAIDs within the last year, overall and by frequency of use, and risk of endometrial cancer in the NIH-AARP Diet and Health Study

	Cases	Person-years	RR* (95% CI)
Aspirin use (any)			
No	123	71,793	1.00 (reference)
Yes	453	321,814	0.86 (0.71–1.06)
Frequency of aspirin use			
Nonuse	123	71,793	1.00 (reference)
<2 times/mo	135	104,342	0.83 (0.65–1.07)
2–3 times/mo	71	61,329	0.75 (0.56–1.00)
1–2 times/wk	53	35,534	0.94 (0.68–1.30)
3–4 times/wk	48	27,955	1.04 (0.74–1.46)
5–6 times/wk	24	12,886	1.07 (0.69–1.65)
Daily	108	65,979	0.91 (0.70–1.18)
≥2 times/d	14	13,454	0.55 (0.31–0.95)
			P-trend = *0.64*
NA-NSAID use (any)			
No	123	71,793	1.00 (reference)
Yes	417	284,122	0.90 (0.74–1.11)
Frequency of NA-NSAID use			
Nonuse	123	71,793	1.00 (reference)
<2 times/mo	123	96,554	0.86 (0.67–1.11)
2–3 times/mo	85	62,840	0.90 (0.68–1.19)
1–2 times/wk	49	35,947	0.91 (0.65–1.27)
3–4 times/wk	32	21,800	0.91 (0.62–1.36)
5–6 times/wk	17	10,782	0.92 (0.55–1.53)
Daily	53	24,247	1.17 (0.85–1.62)
≥2 times/d	57	31,122	0.97 (0.70–1.33)
			P-trend = *0.45*

NOTE: Some women were both aspirin and nonaspirin users.
*Adjusted for race, age at menarche, age at menopause, postmenopausal hormone use, parity, oral contraceptive use, smoking, BMI, physical activity, family history of breast cancer, personal history of diabetes, heart disease, and high blood pressure.

analyses; including the small number of additional women with information on one NSAID type only (*n* = 1,359) did not alter associations. Associations for aspirin and NA-NSAID use were also examined separately, overall, and by frequency of use. Analyses were stratified by obesity [body mass index (BMI) <30, ≥30 kg/m^2] to enable comparisons to previous studies. To minimize the potential for confounding by indication, we also assessed associations excluding women with a self-reported history of heart disease, hypertension, or diabetes at baseline.

Multivariable models included the following covariates based on *a priori* consideration of potential confounders: race, age at menarche, age at menopause, postmenopausal hormone use, parity, oral contraceptive use, smoking, BMI, physical activity, family history of breast cancer, and a personal history of heart disease, high blood pressure, or diabetes (see Table 2 for categories). For covariates with a small amount of missing data, women who did not report information were coded into the most frequently reported category. Additionally, the following variables were considered but not included in the final models because they did not meaningfully change results: education, age at

first birth, waist-to-hip ratio, body shape, alcohol consumption, multivitamin intake, total calories consumed, hours spent watching TV, amount of sleep, self-rated health, history of oophorectomy, history of other ovarian surgery, and a history of health conditions.

Proportional hazards were assessed using interaction terms with log exit age. The model assumptions seemed reasonable for all models (exposure interaction terms only, all *P* values ≥0.42; exposure and covariate interaction terms, all *P* values ≥0.12).

We calculated incidence rates, both crude and standardized to the age distribution of the entire study population, overall, by NSAID use, and by NSAID type. Rates were also stratified by obesity.

Results

Study population description

The mean age at baseline was 62.4 years among this primarily Caucasian (>90%) population. Almost half the women reported use of aspirin (26%) or NA-NSAIDs (19%) only, whereas 40% reported using both and 15% reported using neither in the last year. Most women reported using aspirin or NA-NSAIDs less than weekly (51% and 56%, respectively), with about a quarter reporting weekly and daily use of aspirin (24% and 25%, respectively) or NA-NSAIDs (24% and 20%, respectively). The frequencies of aspirin and NA-NSAID use were positively correlated (ρ = 0.72) and were similar for exclusive and nonexclusive users (e.g., the proportion using aspirin two or more times a day was 4.3% among aspirin-only users and 4.1% among users of both aspirin and NA-NSAIDs).

The average 6.7 years of follow-up per woman was similar across NSAID use category (nonuse, aspirin only, NA-NSAID only, both aspirin and NA-NSAID). The majority of women were parous, and among parous women, most had three or more children (Table 1). Nonusers of NSAIDs within the last year were slightly less likely than NSAID users to be White or have education beyond the high school level. Nonusers and users of NSAIDs had similar mean ages at baseline and menarche, smoking status, BMI, and history of hypertension. Despite a similar mean age at baseline, nonusers of NSAIDs were less likely than NSAID users to use postmenopausal hormones or oral contraceptives. There was heterogeneity among NSAID users, with aspirin-only users less likely than users of NA-NSAIDs only or both aspirin and NA-NSAIDs to use postmenopausal hormones and oral contraceptives and more likely to report a history of heart disease.

Multivariable results

Age- and multivariable-adjusted (Table 2) results were similar. NSAID use was not statistically significantly associated with endometrial cancer risk (RR, 0.90; 95% CI, 0.74–1.09). A null association was observed for use of aspirin only, nonaspirin only, and both aspirin and NA-NSAIDs. Results remained similar in analyses restricted to women with complete covariate information.

Any aspirin use was not significantly associated with endometrial cancer risk (RR, 0.86; 95% CI, 0.71–1.06, Table 3). Users of aspirin two or more times per day had a lower risk of endometrial cancer than nonusers of NSAIDs (RR, 0.55; 95% CI, 0.31–0.95). However, there were only 14 endometrial cancers among these most frequent users, and there was no significant trend by frequency of use (*P* = 0.64). NA-NSAID use was not significantly associated with endometrial cancer risk overall (RR, 0.90; 95% CI, 0.74–1.11) or by frequency of use (*P*-trend = 0.45).

In analyses stratified by obesity, NSAID use (overall, by type, and by frequency) was not associated with endometrial
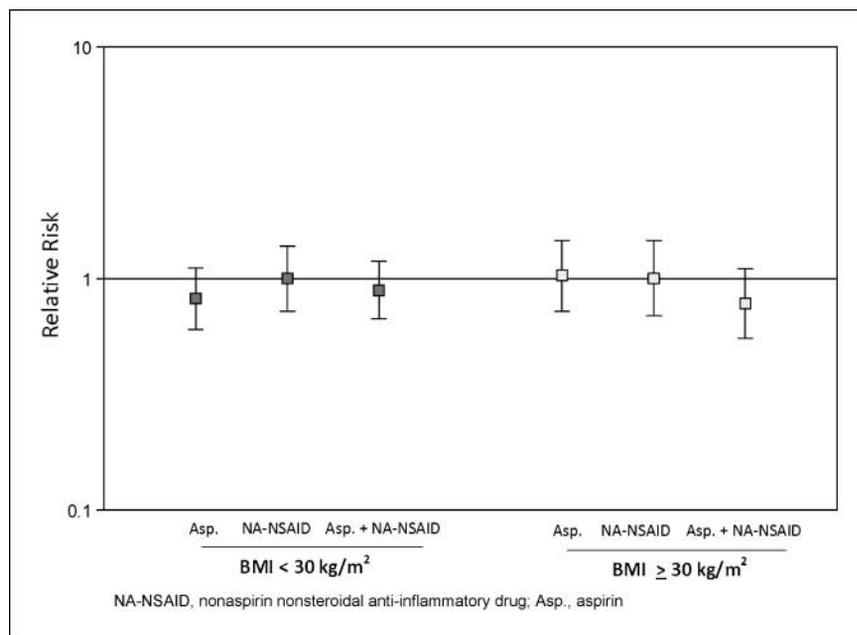
Fig. 1. Type of nonsteriodal anti-inflammatory drug (aspirin only, NA-NSAID only, both aspirin and NA-NSAIDs) and endometrial cancer risk by body mass index (BMI).

cancer risk among nonobese or obese women (Fig. 1, results by NSAID type; other data not shown). Among aspirin users of two or more times per day, point estimates were lower among obese women (RR, 0.49; 95% CI, 0.21–1.13) than among nonobese women (RR, 0.65; 95% CI, 0.31–1.36). However, there were few cases among the aspirin users of two or more times per day ($n = 6$ among obese women and $n = 8$ among nonobese women).

When women with a history of heart disease, hypertension, or diabetes were excluded from the study population, associations for any NSAID use and NSAID type seemed to be consistent with the primary analyses (Fig. 2). In another sensitivity analysis, the reference group was expanded to include infrequent (less than monthly) users; results remained similar to the main findings.

Incidence rates

The crude incidence rate of endometrial cancer was 17 per 10,000 person-years among nonusers of NSAIDs and 15 per 10,000 person-years among NSAID users. There was slight variation by NSAID type, with an endometrial cancer rate per 10,000 person-years of 15 among aspirin-only users, 17 among NA-NSAID-only users, and 14 among both aspirin and NA-NSAID users. The crude and age-standardized rates were similar (data not shown).

Nonobese (BMI <30 kg/m^2) women had a much lower rate of endometrial cancer compared with obese (BMI ≥30 kg/m^2) women (11 versus 29 per 10,000 person-years, respectively). Nonusers of NSAIDs had rates of 12 and 36 per 10,000 person-years among nonobese and obese women, respectively, whereas NSAID users had rates of 11 and 28 per 10,000 person-years
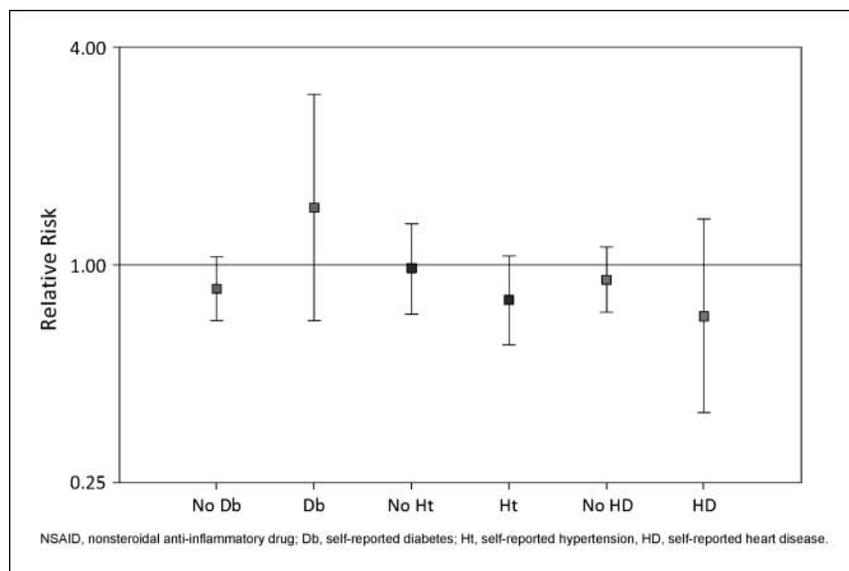

Fig. 2. Ever use of NSAIDs and endometrial cancer risk by self-reported history of diabetes, hypertension, and heart disease.

among nonobese and obese women, respectively. Similarly, among aspirin-only users, nonobese and obese women had crude rates of 10 and 36 per 10,000 person-years, respectively. The crude rate was 2.3 times higher among obese NSAID users and 3 times higher among obese aspirin-only users than the crude rate among nonobese nonusers.

Discussion

In this large, prospective study, we did not observe significant associations between ever use of NSAIDs in the past year and endometrial cancer risk overall or by NSAID type. Aspirin use twice or more per day was inversely associated with endometrial cancer, but the trend across frequency categories was not significant and there were few cases among these aspirin users. There was no significant reduction in endometrial cancer risk among daily aspirin users or the most frequent NA-NSAID users. Thus, given the inconsistency of results by NSAID frequency and type, it seems possible that the single significant association among frequent aspirin users may be a spurious finding.

Two other studies did not observe significant overall associations between NSAID use and endometrial cancer. In a hospital-based case-control study (7), duration, frequency, and lifetime or regular use of aspirin were not associated with endometrial cancer risk. In the prospective Nurses' Health Study (8), null associations were observed for recency, duration, dosage, and frequency of aspirin use, as well as frequency of NA-NSAID use. However, aspirin use was inversely associated with endometrial cancer among obese women in both studies (7, 8). In the hospital-based case-control study (7), use of aspirin seven or more times per week (*n* = 23 cases and 16 controls) was associated with a reduced endometrial cancer risk among obese women (RR, 0.40; 95% CI, 0.18–0.92), with similar associations for long-duration (over 10 years: RR, 0.46) or cumulative (over 10 tablet-years: RR, 0.49) aspirin use. In the Nurses' Health Study (8), current use of aspirin was inversely associated with endometrial cancer among obese women (RR, 0.66; 95% CI, 0.46–0.95; *n* = 48 and 125 cases among never and current users, respectively) and positively associated among nonobese women (RR, 1.41; 95% CI, 1.05–1.89; *n* = 71 and 261 cases among never and current users, respectively).

It is possible that the significant results stratified by obesity were driven by small differences on the absolute scale. Using data presented in the Nurses' Health Study paper (Table 3 of ref. 8) to calculate crude endometrial cancer rates, never and current aspirin users had similar rates among both obese (12 and 10 per 10,000 person-years, respectively) and nonobese (3 and 4 per 10,000 person-years, respectively) women. Obese aspirin users had a 3.3 times higher rate than nonobese nonaspirin users in the Nurses' Health Study, similar to our findings.

In 2001, NSAIDs accounted for 30 billion over-the-counter and 70 million prescription sales (4). The prevalence of NSAID use in epidemiologic studies reflects the way it was assessed, and the three epidemiologic studies to date have used different methods: use within the last year (our study), regularly updated information (Nurses' Health Study; ref. 8), or retrospective recall of NSAID use before illness, with "regular" use defined as use of at least once a week for 6 months (hospital case-control study; ref. 7). Despite different ways of defining NSAID use, all three studies found an overall null association and do not provide evidence of a strong association between NSAID use and endometrial cancer risk.

A limitation of our study is that we did not have information on dose or duration, and our results reflect an unknown average dose and duration. However, the primary results from two previous studies with this information (7, 8) were consistent with our study results. We also did not update exposure information during follow-up and were unable to separately examine nonprescription and prescription NA-NSAIDs.

We did not collect information on the reason for NSAID use. The most common reason for use of nonprescription NSAIDs is relief of pain (4). To reduce the influence of reverse causation, we excluded the first year of follow-up among all participants to ensure the prospective nature of our exposure. As expected, given the large number of early-stage tumors in our study, results remained similar to the main analyses. We also were concerned about aspirin use taken for cardiovascular health benefits because inflammation is a key factor in cardiovascular health (17), and thus aspirin use for secondary prevention of cardiovascular disease might obscure a protective association with endometrial cancer risk. In analyses restricted to individuals without a self-reported history of heart disease, hypertension, or diabetes, results were generally similar to the main analyses.

Our study had several strengths. The NIH-AARP Diet and Health Study is a large, prospective study with detailed information on NSAID type and frequency of use. We had data on numerous potential confounders, including other health conditions, and could adjust for and stratify by key variables. We also were able to calculate both absolute and RR measures to describe the relationship between NSAID use, BMI, and endometrial cancer.

In conclusion, our results, in conjunction with the existing epidemiologic literature, do not suggest a strong association between aspirin or NA-NSAID use and endometrial cancer risk. Because relatively few studies exist on this topic, future studies will be needed to confirm this finding, ideally with the ability to examine NSAID type, frequency, dose, and duration.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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