Aspirin, NSAID, and Acetaminophen Use and the Risk of Endometrial Cancer

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Abstract

To date, no prospective studies have explored the relationship between the use of aspirin, other nonsteroidal anti-inflammatory medications (NSAID), and acetaminophen and endometrial adenocarcinoma. Of the 82,971 women enrolled in a prospective cohort study, 747 developed medical record–confirmed invasive endometrial cancer over a 24-year period. Use of aspirin was ascertained from 1980 to 2004, and for other NSAIDs and acetaminophen, from 1990 to 2004. Cox regression models calculated multivariate relative risks (MV RR), controlling for body mass index (BMI), postmenopausal hormone (PMH) use, and other endometrial cancer risk factors. Currency, duration, and quantity of aspirin were not associated with endometrial cancer risk overall [current use: MV RR, 1.03; 95% confidence interval (CI) 0.83–1.27; >10 years of use: MV RR, 1.01; 95% CI, 0.78–1.30; and cumulative average >7 tablets per week: (MV RR, 1.10; 95% CI, 0.84–1.44)]. However, stratified analyses showed that a lower risk of endometrial cancer among obese (BMI, $\geq$30 kg/m^2) women was seen with current aspirin use (MV RR, 0.66; 95% CI, 0.46–0.95). The greatest risk reduction for current aspirin users was seen in postmenopausal obese women who had never used PMH (MV RR, 0.43; 95% CI, 0.26–0.73). The use of other NSAIDs or acetaminophen was not associated with endometrial cancer. Our data suggest that use of aspirin or other NSAIDs does not play an important role in endometrial cancer risk overall. However, risk was significantly lower for current aspirin users who were obese or who were postmenopausal and had never used PMHs; these subgroup findings require further confirmation. [Cancer Res 2008;68(7):2507–13]

Introduction

Inflammation acts as an important mediator of human carcinogenesis. Conditions that cause chronic inflammation and tissue injury enhance cell proliferation, and the sustained growth of mutated cells may result in tumor development (1). However, inflammatory cells may also attenuate tumor growth (2). Clarifying the complex balance of various proinflammatory and anti-inflammatory cells and cytokines in different organs and their roles in the regulation of carcinogenesis is an active area of research (3).

Unique in its cyclical remodeling, the uterus provides a model in which repair of disrupted tissue occurs in premenstrual women on a monthly basis. Menstruation integrates and coordinates the endocrine and immune systems (4). At the end of the luteal phase, the modulation of estrogen and progesterone levels triggers a carefully orchestrated shift in immune mediators, growth factors, angiogenic factors, and cytokines that results in the breakdown of uterine tissue followed by wound healing. Although much research has focused on the roles of estrogen and progesterone in the development of endometrial cancer, little is known about the possible influence of inflammation (5).

Epidemiologic evidence assessing the association of aspirin, nonsteroidal anti-inflammatory medications (NSAID), and acetaminophen use on the risk of endometrial cancer is limited. One case control study in endometrial cancer showed no effect overall of aspirin consumption but a significantly decreased risk among obese women (6). In our analysis, we prospectively examined the influence of aspirin, other NSAIDs, and acetaminophen on the risk of endometrial cancer, using data from the Nurses' Health Study (NHS) cohort with 24 years of follow-up.

Materials and Methods

Study population and design. The NHS is a prospective cohort of 121,701 registered nurses who were between the ages of 30 and 55 years and living in 11 states in the United States when they completed an initial questionnaire on their medical history and life-style factors in 1976. Every 2 years, information has been obtained on risk factors and major medical events. Further details of the cohort have been reported previously (7). The follow-up rate through 2004, as a percentage of total possible person-years, was 95%. At least 98% of deaths have been ascertained by reports from family members and the U.S. Postal Service as well as by a search of the National Death Index. In our main analyses, we excluded participants who did not answer information about aspirin, NSAID, or acetaminophen use in each time period, those who died before 1980, those who had an unknown date of diagnosis, those with a reported diagnosis of endometrial cancer or any other cancer (with the exception of nonmelanoma skin cancer) before 1980, or those who had had a hysterectomy and were therefore not at risk for the development of endometrial cancer. A total of 7,049 women did not respond with information about aspirin consumption and therefore were excluded from analysis. A total of 82,971 women were included in the final study population. The Human Research Committee of the Brigham and Women's Hospital, Boston, MA, approved this analysis and protocol.

Ascertainment of aspirin and NSAID use. Aspirin use has been assessed biennially since 1980, with the exception of 1986. Data have been collected and participants have been classified by the status (never, past, and current) and quantity of aspirin use (tablets per week), and duration of use as a continuous variable in years; duration of use was calculated in each cycle among current aspirin users. Current users of aspirin included participants reporting at least 1 tablet per week or 1 d per week of use for the previous 2 y. Beginning in 1984, the frequency of current use (1 d/wk, 1–3 d/wk, 4–5 d/wk, 6+ d/wk, and unknown) was queried. In this analysis, data were carried forward one questionnaire cycle for all aspirin variables in the event of missing data. Those not reporting aspirin use in 1980 were not

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Table 1. Age-standardized prevalence of potential endometrial cancer risk factors by aspirin use among women in the Nurses' Health Study, 1990

Characteristics	Aspirin nonuser	Past aspirin user	Current aspirin user
Age* (y; SD)	55.4 (7.4)	55.1 (7.2)	55.9 (7.2)
Height* (in inches; SD)	64.3 (3.5)	64.4 (3.4)	64.4 (3.6)
BMI* (kg/m^2; SD)	25.4 (5.0)	25.8 (5.0)	25.7 (4.9)
Age at menarche* (y; SD)	12.6 (1.4)	12.5 (1.4)	12.6 (1.4)
Nulliparous (%)	5.4	5.4	5.6
Age at birth of first child* (y; SD)	25.1 (3.5)	24.9 (3.4)	24.9 (3.4)
Oral contraceptive use (% ever)	44	51	49
Postmenopausal (%)	65	66	65
Age at menopause* (y; SD)	49.2 (3.9)	49.4 (3.7)	49.4 (3.8)
PMH use (% ever) †	42	47	47
History of diabetes (%)	4	4	4
History of hypertension (%)	24	28	29
Ever smoked (%)	57	58	56
Current smoker (%)	20	18	18

NOTE: BMI, weight in kg/height in m^2. Directly standardized to the age distribution of the entire population in 1990.
*Mean values.
† Among postmenopausal women only.

included in the analysis in 1980 but were allowed to enter the analysis if they reported use in a subsequent time period. To better estimate long-term intake, the cumulative average number of days per week and the cumulative average number of tablets per week were calculated for everyone classified as a past or current aspirin user, as the average of the current and all previous cycles. For a particular respondent, if the aspirin status was missing, or she was classified as a current user with unknown quantity, she was not included in the cumulative average. Starting in 1992, questionnaires asked participants to convert intake of four baby aspirin to one adult standard (325 mg) dose as has been previously described (8).

Participants were also asked whether they were currently taking nonsteroidal analgesics other than aspirin (Indocin, Tolectin, Clinoril, or ibuprofen) or acetaminophen regularly since 1990. NSAID use was determined once in 1980, then again in 1990, but no information from 1982 to 1988 is available. In 1990, 1992, 1998, 2000, and 2002, we asked for the frequency of use of nonaspirin NSAIDs or acetaminophen using questions identical to those for aspirin. In 1994 and 1996, we assessed regular use of nonaspirin NSAIDs and acetaminophen (more than or equal to twice per week); the last reported frequency was assigned to regular users in these follow-up cycles. Information on NSAID and acetaminophen use before 1990 was not queried.

In 1990, a short questionnaire was sent to 100 participants who reported taking 1 to 6 aspirins per week (90% response) and 100 women who reported taking ≥7 aspirins per week (92% response) on the 1980, 1982, and 1984 questionnaires. The major reasons for use among women taking 1 to 6 or ≥7 aspirins per week were headache (32% and 18%, respectively), arthritis and other musculoskeletal pain (30% and 50%), a combination of headache and musculoskeletal pain (16% and 15%), prevention of cardiovascular disease (9% and 8%), and other reasons (13% and 9%; ref. 8).

Endometrial cancer cases. Participants were asked to report any diagnosis of endometrial cancer; we requested permission to obtain medical records and pathology reports to verify diagnosis and establish an exact diagnosis date. A study physician, blinded to exposure information, confirmed the diagnosis, histologic type, presence of invasion, and stage. After accounting for all exclusions >24 y of follow-up, 747 cases of invasive adenocarcinoma defined by the International Federation of Gynecology and Obstetrics (FIGO) as stage IB to IVA were included in the analyses.

Covariate data. Information on most potential confounders, including menopausal status, postmenopausal hormone use (PMH), weight, diabetes, smoking, and hypertension, was collected on the baseline questionnaire and in 2-y updates. Information on parity and oral contraceptive use was collected through 1982 when the youngest woman was 36, and <500 women reported current use of oral contraceptives.

Body mass index (BMI; weight in kilograms/height in m^2) was calculated from height determined in 1976 and from the updated report of current weight. Weight from the prior questionnaire cycle was brought forward if it was missing. Measurements of waist and hip were queried in 1986 and used to calculate a waist-hip ratio variable. In a validation study among 140 NHS members in 1986, self-reported waist, hip, and weight measures correlated highly with standardized measures as confirmed by a technician (weight, r = 0.97; hip, r = 0.84; waist circumference, r = 0.89; ref. 9).

A woman was classified as postmenopausal from the time she returned a questionnaire reporting natural menopause (women reporting a hysterectomy were excluded from subsequent follow-up). Self-report of menopausal status has also been shown to be valid in this cohort (10). Information on PMH use was collected from 1976 through 1994. In 1976, users of PMHs reported their total duration of use; all users were classified in 1976 as using unopposed estrogen. From 1978 to 1994, women were asked whether they were currently using PMH and the type by brand name; these were categorized into estrogen only, progesterone only, or combination estrogen and progesterone. In addition to the current use and type, in 1980, dose information was added. In 1982, route of administration as well as dose and daily or cyclical Premarin information was collected. Starting in 1988, information on progesterone dose and pattern of hormone use (oral or patch) was obtained.

Statistical analysis. Follow-up began with the date of return of the 1980 questionnaire and continued until the date of diagnosis of endometrial cancer, the date of death, the date of report of other cancer, hysterectomy, or end of follow-up (June 1, 2004), whichever came first. Person-time, equal to the number of months between the return of successive questionnaires, was allocated for each variable on the basis of the updated exposure/covariate status at the beginning of each 2-y interval. Age standardization of baseline characteristics was performed; removing the effects of age variation facilitates comparisons of demographic rates across different populations.

The primary analysis included only invasive adenocarcinoma (FIGO stage IB-IVA) and used incidence rates with person-years of follow-up in the denominator. Incidence rates were calculated by dividing the number of events by the number of person-years of follow-up. We used relative risk (RR) as the measure of association; RR was defined as the incidence rate of endometrial cancer among participants who reported use of aspirin divided by the incidence rate among participants without such a report. Age-adjusted rates were calculated with 5-y age categories.

Cox proportional hazard regression was used to calculate multivariate (MV) RRs and their 95% confidence intervals (CI); age was used as a continuous variable in these models. Tests for linear trend were calculated using the median values of each exposure category. Multivariate Cox proportional hazards models included all potential risk factors for endometrial cancer, including BMI, age at menopause, age at menarche, pack-years of smoking, duration of oral contraceptive use, duration of PMH use, parity, hypertension, and diabetes (see footnote to Tables for categories). Additional analyses included BMI and age at menopause as continuous rather than categorical variables, waist-hip ratio, family history of endometrial cancer, physical activity, intrauterine device use, height, type of PMH used (estrogen only or estrogen with progesterone), age at birth of first child, and BMI at age 18 years. Adjustment for these factors did not significantly alter our RRs, and we therefore did not include them in our final model. We also evaluated the use of analgesics at the time of diagnosis (of either invasive or preinvasive disease) to assess whether use varied by stage at diagnosis. Noninvasive cases were analyzed separately. A separate analysis mutually adjusted for aspirin and NSAID use in the same model with other covariates. We conducted stratified analyses based on prior evidence that the effect of aspirin may vary by BMI (6). Given their role as important endometrial cancer risk factors, we also wanted to determine whether the influence of aspirin use varied by PMH use, oral contraceptive use, parity, menopausal, or smoking status. We used the Wald statistic and the likelihood ratio test to assess statistical significance. All P values are two-sided ($P = 0.05$).

Results

A total of 747 incident cases of invasive endometrial adenocarcinoma were identified between 1980 and 2004. Characteristics of the population in 1990 are shown in Table 1. Of those diagnosed with endometrial cancer, a total of 98 were premenopausal and 645 were postmenopausal; 268 had a BMI of ≥30 and 286 had ever used PMH. Factors were generally similar across categories of aspirin status. There were slightly more women who reported oral contraceptive or PMH use among women who had ever used aspirin. Aspirin users had a slightly higher prevalence of hypertension.

In age-adjusted analyses, the RR for past aspirin use was 1.22 (95% CI, 0.98–1.52; Table 2) and for current aspirin users was 1.07 (95% CI, 0.87–1.32), and the association was only slightly attenuated after adjustment for important covariates, including BMI and PMH use (MV RR for past users, 1.12; 95% CI, 0.89–1.42; MV RR for current users, 1.03; 95% CI 0.83–1.27; Table 2). When analyzing dose, the degree of attenuation by control for BMI was greatest for those consuming seven or more tablets per week, as this category had a higher median BMI than those consuming less than seven tablets per week. The dosage and duration of aspirin use was also

Table 2. RR of invasive endometrial cancer by status, dose, and duration of aspirin use with prospective follow-up from 1980 to 2004 in the NHS

Aspirin use	No. of cases	Total person-years	Age-adjusted RR (95% CI)	MV RR* (95% CI)
Status of aspirin use				
Never †	123	321,114	1.0	1.0
Past	235	326,209	1.22 (0.98–1.52)	1.12 (0.89–1.42)
Current ‡	389	717,821	1.07 (0.87–1.32)	1.03 (0.83–1.27)
Current, 1–2 tablets/wk	163	328,944	1.03 (0.81–1.31)	1.05 (0.82–1.34)
Current, 3–5 tablets/wk	74	145,544	1.01 (0.75–1.35)	1.00 (0.74–1.34)
Current, 6+ tablets/wk	136	204,947	1.23 (0.96–1.57)	1.07 (0.83–1.37)
Duration of aspirin use§ (current users only)				
Never †	123	321,114	1.0	1.0
<2 y	132	247,433	1.06 (0.82–1.36)	1.02 (0.79–1.32)
2–10 y	72	122,083	1.04 (0.77–1.40)	0.96 (0.71–1.30)
>10 y	119	230,099	1.06 (0.82–1.37)	1.01 (0.78–1.30)
P_{trend}			0.92	0.97
Dosage of aspirin use (cumulative average no. of tablets/wk among current and past users)				
Never †	123	321,114	1.0	1.0
>0 to <2 tablets/wk	283	488,589	1.11 (0.89–1.37)	1.10 (0.88–1.38)
2–7 tablets/wk	218	355,837	1.07 (0.85–1.34)	0.98 (0.77–1.24)
>7 tablets/wk	104	157,764	1.30 (1.00–1.70)	1.10 (0.84–1.44)
P_{trend}			0.09	0.96

*Multivariate risks from proportional hazards models are adjusted for BMI [<20 (ref), 20–<21, 21–<22, 22–<23, 23–<24, 24–<25, 25–<27, 27–<29, 29–<30, 30–<32, 32–<35, 35–<40, and ≥40 kg/m^2], duration of oral contraceptive use [never (ref), past use <3 y, past 3–5 y, and past >5 y], pack-years of smoking (never, >0–20 y, >20–40 y, and >40 y), use and duration of PMHs [never/premenopausal (ref), past use <5 y, past use >5 y, current use <5 y, and current use >5 y], age at menopause [premenopausal (ref), postmenopausal <45 y, 45–49 y, 50–52 y, and ≥53 y], parity [1–2 (ref), 3–4, and ≥5], age at menarche [<12 y, 12 y (ref), and >12 y], hypertension (present or absent), and diabetes (present or absent).

† No reported use during the follow-up period.

‡ Includes current users with unknown quantity.

§ Cumulative average no. of years among current users.

unassociated with disease risk, and no trend was observed with increasing cumulative average dose (P_{trend} = 0.96) or duration (P_{trend} = 0.97). The frequency of aspirin use (days per week) from 1984 forward was not significantly associated with risk (for increasing number of days per week, P_{trend} = 0.49; data not shown).

Results seemed to vary by BMI and PMH use. The association of current aspirin use with endometrial cancer was significantly reduced among obese women (BMI $\geq$ 30 kg/m^2; MV RR, 0.66; 95% CI, 0.46–0.95) versus nonobese women (BMI < 30 kg/m^2; MV RR 1.41; 95% CI, 1.05–1.89; $P_{interaction}$ = 0.009; Table 3). Similarly, postmenopausal women who had never used PMHs had a significant reduction in risk with current aspirin use (MV RR, 0.64; 95% CI, 0.45–0.91) compared with those who had ever used PMHs (MV RR, 1.34; 95% CI, 0.94–1.89; $P_{interaction}$ = 0.046). The strongest inverse association was seen for obese women (BMI $\geq$ 30 kg/m^2) who never used PMHs; current aspirin users had a MV RR of 0.46 (95% CI, 0.26–0.81), compared with those with a BMI <30 kg/m^2 (MV RR, 1.19; 95% CI, 0.67–2.14). Similarly, among obese women who never used PMH, current users of 3 or more tablets per week had a MV RR of 0.37 (95% CI, 0.20–0.66; data not shown). However, there was no dose- or duration-related linear trend of increasing risk with increasing frequency or duration of aspirin use in lean women or PMH users or decreasing risk in heavy women and non-PMH users (all P_{trend} > 0.07). Results did not vary when stratified according to menopausal status, parity, oral contraceptive use, or smoking history. The use of analgesics at the time of diagnosis was also evaluated to assess whether use varied by stage at diagnosis, including preinvasive disease (MV RR, 0.76; 95% CI, 0.56–1.03) or metastatic disease (MV RR, 1.21; 95% CI, 0.65–2.24). No significant differences were noted. Analyses of women with long duration (>10 years of consumption) and with the highest category of use did not show a significant effect but was limited by small numbers in this subgroup.

In analyses from 1990 to 2004, nonaspirin NSAID use was not associated with endometrial cancer risk (Table 4). Similarly, no association was observed for use of either acetaminophen or aspirin use specifically from 1990 to 2004. Mutual adjustment for other NSAIDs and acetaminophen with aspirin use in the same model did not significantly alter the results. These associations did not vary substantially by level of other endometrial cancer risk factors, although the analysis was limited by small numbers in each subgroup.

Discussion

To our knowledge, this study represents the first prospective evaluation of analgesic use and risk of endometrial cancer. Overall, neither regular use nor the duration of aspirin use was associated with risk of disease. Similarly, use of other NSAIDs or acetaminophen was unrelated to risk. However, when the results were stratified by BMI or PMH use, we observed an ~35% reduction in risk of endometrial cancer for current aspirin users with a BMI of $\geq$30 kg/m^2 or who never used PMHs.

Anti-inflammatory medications reduce systemic inflammation by inhibiting the biosynthesis of prostaglandins. Prostaglandins are generated by the enzyme prostaglandin G/H-synthetase, which has two isoforms, the cyclooxygenases COX-1 and COX-2. Progesterone withdrawal regulates COX-2 expression in the uterus (11). Malignant endometrial cells have enhanced levels of COX-2 (12–15). High COX-2 expression is also associated with increasing grade and depth of myometrial invasion of endometrial carcinoma (16). Up-regulation of COX-2 increases the production of prostaglandin E2 (PgE2), which in turn up-regulates the aromatase enzyme, as shown in studies of breast cancer (17, 18). Aspirin inhibits COX-2, reducing aromatase expression (13, 15, 19). In several *in vitro* studies, aspirin and other NSAIDs inhibited the proliferation of endometrial cancer cells through several other

Table 3. Multivariable RR of invasive endometrial cancer by aspirin use stratified by BMI and by PMH use among women in the NHS, 1980 to 2004

Aspirin use	BMI < 30 (kg/m$_2$)	BMI $\geq$ 30 (kg/m$_2$)	Never used PMH*	Ever used PMH*
Never [†]	71/279,620 1.0	48/41,739 1.0	56/83,094 1.0	40/57,019 1.0
Past				
No. of users/no. of person-years	141/260,400	95/65,151	66/99,315	125/132,215
MV RR (95% CI) [‡]	1.50 (1.08–2.09)	0.88 (0.60–1.28)	0.66 (0.45–0.98)	1.36 (0.93–1.97)
Current				
No. of users/no. of person-years	261/596,521	125/119,642	110/207,649	208/209,357
MV RR (95% CI) [‡]	1.41 (1.05–1.89)	0.66 (0.46–0.95)	0.64 (0.45–0.91)	1.34 (0.94–1.89)
$P_{interaction}$ [§]	0.009		0.046	

*Among postmenopausal women.

[†] No use reported during the follow-up period.

[‡] Multivariate risks from proportional hazards models are adjusted for BMI [<20 (ref), 20–<21, 21–<22, 22–<23, 23–<24, 24–<25, 25–<27, 27–<29, and 29–<30 kg/m^2], or BMI [30 (ref), >30–<32, 32–<35, 35–< 40, and 40+ kg/m^2] or all BMI categories together for PMH analyses, duration of oral contraceptive use [never (ref), past use <3 y, past 3–5 y, and past >5 y], pack-years of smoking (never, >0–20 y, >20–40 y, and >40 y), use and duration of PMHs [never/premenopausal (ref), past use <5 y, past use >5 y, current use <5 y, and current use >5 y BMI analyses only], age at menopause [premenopausal (ref), postmenopausal <45 y, 45–49 y, 50–52 y, and $\geq$53 y; BMI analyses only], parity [1–2 (ref), 3–4, and $\geq$5], age at menarche [<12 y, 12 y (ref), and >12 y), hypertension (present or absent), and diabetes (present or absent).

[§] P for interaction between BMI and PMH categories.

Table 4. RR of invasive endometrial cancer by frequency of NSAID, acetaminophen, or aspirin use (1990–2004)

	No. of cases	Total person-years	Age-adjusted RR (95% CI)	MV RR* (95% CI)
Nonaspirin NSAID use				
Nonuser †	372	473,427	1.0	1.0
1 d/wk	41	70,508	0.91 (0.65–1.27)	0.91 (0.65–1.27)
2–3 d/wk	32	48,439	0.95 (0.66–1.36)	0.89 (0.61–1.28)
4–5 d/wk	12	20,395	0.78 (0.44–1.39)	0.71 (0.40–1.27)
6–7 d/wk	40	50,729	1.02 (0.73–1.41)	0.78 (0.56–1.08)
P_{trend}			0.80	0.31
Acetaminophen use				
Nonuser †	370	485,037	1.0	1.0
1 d/wk	68	90,751	1.17 (0.90–1.53)	1.21 (0.92–1.60)
2–3 d/wk	32	47,911	0.92 (0.64–1.32)	0.86 (0.60–1.25)
4–5 d/wk	16	19,153	1.08 (0.71–1.56)	0.98 (0.59–1.62)
6–7 d/wk	26	30,806	1.05 (0.71–1.56)	0.86 (0.57–1.30)
P_{trend}			0.87	0.20
Aspirin use				
Nonuser †	275	367,693	1.0	1.0
1 d/wk	58	91,703	0.93 (0.70–1.23)	0.96 (0.72–1.29)
2–3 d/wk	33	55,373	0.80 (0.56–1.14)	0.84 (0.58–1.20)
4–5 d/wk	34	38,507	1.10 (0.77–1.57)	1.08 (0.75–1.55)
6–7 d/wk	126	145,634	0.98 (0.79–1.22)	0.89 (0.72–1.11)
P_{trend}			0.99	0.37

*Multivariate risks from proportional hazards models are adjusted for BMI [<20 (ref), 20–<21, 21–<22, 22–<23, 23–<24, 24–<25, 25–<27, 27–<29, 29–<30, 30–<32, 32–<35, 35–<40, and ≥40 kg/m^2], duration of oral contraceptive use [never (ref), past use <3 y, past 3–5 y, past >5 y], pack-years of smoking (never, >0–20 y, >20–40 y, and >40 y), type of PMH use (never used PMH, past use, current use estrogen only, and current use estrogen and progesterone), age at menopause [premenopausal (ref), postmenopausal <45 y, 45–49 y, 50–52 y, and ≥53 y], parity [1–2 (ref), 3–4, and ≥5), age at menarche [<12 y, 12 y (ref), and >12 y), hypertension (present or absent), and diabetes (present or absent).

† Nonusers are women who did not report use on at least 1 d/wk, and includes both current and past use.

mechanisms involving mismatch repair gene expression, the cell cycle, and apoptosis (20–22).

Confirmed endometrial cancer risk factors include obesity (23) and PMH use (24, 25). The increased risk in obesity is attributed primarily to the excessive production of unopposed estrogens by aromatization of androgens in the peripheral adipose tissues (23). Women with a BMI of >30 kg/m^2 who use aspirin may have lower COX-2–induced aromatase levels than those who do not take aspirin. On the other hand, postmenopausal exogenous estrogen use induces endometrial cell proliferation and carcinogenesis independent of aromatase.

Other exposures that modulate hormonal status also affect endometrial cancer risk, including parity, age at birth of first child, oral contraceptive use, smoking, and ages at menarche and menopause (26–30). Current smokers have a nonsignificantly greater risk reduction than past smokers (31), current BMI increases risk greater than past BMI (32), and recent PMH use is correlated with risk greater than past use (25, 33), indicating that although there is evidence for long-term modulation, there may be a greater inherent sensitivity of the endometrium to the immediate environmental milieu. The process of endometrial carcinogenesis is likely due to a balance of several mediators in the past, such as previous inflammation, which may result in the retention of precancer clones from incomplete shedding of the endometrium, and also from current mediators that may directly act as carcinogenic promoters. Prostaglandins and matrix metalloproteinases break down the basement membrane of the endometrium (34). Premenopausal women using aspirin do not seem to have any change in menstrual regularity (35), although the immediate effect on the endometrium is unknown. Although speculative, incomplete sloughing of precancer clones present in the endometrium might account for the modestly increased risk of endometrial cancer seen in nonobese women taking aspirin. This effect may be superseded by the effect of COX-2–mediated reduced aromatase expression in obese women.

The epidemiologic evidence indicates that aspirin and NSAIDs significantly decrease the risk of colon adenocarcinoma (8, 36–41) and possibly hormone receptor–positive breast cancer (29, 42–44) but increase or have no effect on the risk of pancreatic carcinoma (45–47). Studies suggest that the maximal effectiveness of aspirin use in terms of decreasing colon cancer is achieved at higher doses of short duration, and that dose and duration are important factors not assessed by all studies. One case control study of 427 women with endometrial cancer showed no association overall but a significantly decreased risk [odds ratio (OR), 0.50; 95% CI, 0.27–0.92] among obese women in contrast to overweight (OR, 1.21; 95% CI, 0.65–2.23) women, similar to our findings (6). However, that study was not able to assess current versus past aspirin use and was hampered by its retrospective exposure assessment at a single time point. Furthermore, PMH use information was not available.

Acetaminophen, an analgesic that does not inhibit prostaglandin synthesis, lacks a systemic antiinflammatory effect (48). In

contrast to aspirin and other NSAIDs, acetaminophen does not affect systemic PgE2 concentrations (49). However, acetaminophen has some structural similarity to steroids and may have an antiestrogenic effect, lowering follicular levels of luteinizing hormone, follicle-stimulating hormone, and estradiol (50). Our study found no association of acetaminophen or nonaspirin NSAIDs with cancer risk either overall or within subgroups defined by BMI or PMH, although these analyses included relatively few cases, which constrained our ability to interpret these findings.

Strengths of this study include the repeated exposure assessment, detailed data on other endometrial cancer risk factors, updated exposure and covariate information, and high follow-up rates. Limitations of this study include possible residual confounding by other unidentified risk factors. Also, although the positive association persisted with careful control for BMI and PMH use, we cannot rule out residual confounding, particularly as the associations of BMI and PMH with endometrial cancer risk are strong, and the associations with aspirin use was modest. Because acetaminophen and NSAID analyses could be performed only from 1990 forward, we had limited ability to evaluate these exposures by duration of use or on stratification; further follow-up will be needed. Finally, our population is predominantly Caucasian; assessment in other populations is necessary.

In summary, this is the first prospective cohort study of endometrial cancer and aspirin. Although in this study no overall association was observed, aspirin use significantly decreased the risk of endometrial cancer among obese women and among women who have never used PMHs. Further studies are needed to confirm these findings. If confirmed, future public health strategies should consider the risks and benefits of aspirin use for obese women who have the highest risk of endometrial cancer, particularly as obesity rates increase worldwide.

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