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

Akila N. Viswanathan, Diane Feskanich, Eva S. Schernhammer, and Susan E. Hankinson

1Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute and Harvard Medical School; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

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, ≥30 kg/m²) 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.

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aspirin nonuser</th>
<th>Past aspirin user</th>
<th>Current aspirin user</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y; SD)</td>
<td>55.4 (7.4)</td>
<td>55.1 (7.2)</td>
<td>55.9 (7.2)</td>
</tr>
<tr>
<td>Height (in inches; SD)</td>
<td>64.3 (3.5)</td>
<td>64.4 (3.4)</td>
<td>64.4 (3.6)</td>
</tr>
<tr>
<td>BMI (kg/m²; SD)</td>
<td>25.4 (5.0)</td>
<td>25.8 (5.0)</td>
<td>25.7 (4.9)</td>
</tr>
<tr>
<td>Age at menarche (y; SD)</td>
<td>12.6 (1.4)</td>
<td>12.5 (1.4)</td>
<td>12.6 (1.4)</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>5.4</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Age at birth of first child (y; SD)</td>
<td>25.1 (3.5)</td>
<td>24.9 (3.4)</td>
<td>24.9 (3.4)</td>
</tr>
<tr>
<td>Oral contraceptive use (% ever)</td>
<td>44</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>65</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Age at menopause (y; SD)</td>
<td>49.2 (3.9)</td>
<td>49.4 (3.7)</td>
<td>49.4 (3.8)</td>
</tr>
<tr>
<td>PMH use (% ever)</td>
<td>42</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>24</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Ever smoked (%)</td>
<td>57</td>
<td>58</td>
<td>56</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>20</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

NOTE: BMI, weight in kg/height in m². Directly standardized to the age distribution of the entire population in 1990.

*Mean values.
† Among postmenopausal women only.

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 m²) 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 taking PMH and the type by brand name; these were categorized into estrogen only, progestosterone only, or combination estrogen and progestosterone. 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.

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.
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-yr 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 at age 18 years (20). Members who 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>
<thead>
<tr>
<th>Aspirin use</th>
<th>No. of cases</th>
<th>Total person-years</th>
<th>Age-adjusted RR (95% CI)</th>
<th>MV RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status of aspirin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never†</td>
<td>123</td>
<td>321,114</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Past</td>
<td>235</td>
<td>326,209</td>
<td>1.22 (0.98–1.52)</td>
<td>1.12 (0.89–1.42)</td>
</tr>
<tr>
<td>Current†</td>
<td>389</td>
<td>717,821</td>
<td>1.07 (0.87–1.32)</td>
<td>1.03 (0.83–1.27)</td>
</tr>
<tr>
<td>Current, 1–2 tablets/wk</td>
<td>163</td>
<td>328,944</td>
<td>1.03 (0.81–1.31)</td>
<td>1.05 (0.82–1.34)</td>
</tr>
<tr>
<td>Current, 3–5 tablets/wk</td>
<td>74</td>
<td>145,544</td>
<td>1.01 (0.75–1.35)</td>
<td>1.00 (0.74–1.34)</td>
</tr>
<tr>
<td>Current, 6+ tablets/wk</td>
<td>136</td>
<td>204,947</td>
<td>1.23 (0.96–1.57)</td>
<td>1.07 (0.85–1.37)</td>
</tr>
<tr>
<td>Duration of aspirin use (current users only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never†</td>
<td>123</td>
<td>321,114</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;2 y</td>
<td>132</td>
<td>247,433</td>
<td>1.06 (0.82–1.36)</td>
<td>1.02 (0.79–1.32)</td>
</tr>
<tr>
<td>2–10 y</td>
<td>72</td>
<td>122,083</td>
<td>1.04 (0.77–1.40)</td>
<td>0.96 (0.71–1.30)</td>
</tr>
<tr>
<td>&gt;10 y</td>
<td>119</td>
<td>230,099</td>
<td>1.06 (0.82–1.37)</td>
<td>1.01 (0.78–1.30)</td>
</tr>
<tr>
<td>P_trend</td>
<td></td>
<td></td>
<td>0.92</td>
<td>0.97</td>
</tr>
<tr>
<td>Dosage of aspirin use (cumulative average no. of tablets/wk among current and past users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never†</td>
<td>123</td>
<td>321,114</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;0 to &lt;2 tablets/wk</td>
<td>283</td>
<td>488,589</td>
<td>1.11 (0.89–1.37)</td>
<td>1.10 (0.88–1.38)</td>
</tr>
<tr>
<td>2–7 tablets/wk</td>
<td>218</td>
<td>355,837</td>
<td>1.07 (0.85–1.34)</td>
<td>0.98 (0.77–1.29)</td>
</tr>
<tr>
<td>&gt;7 tablets/wk</td>
<td>104</td>
<td>157,764</td>
<td>1.30 (1.00–1.70)</td>
<td>1.10 (0.84–1.44)</td>
</tr>
<tr>
<td>P_trend</td>
<td></td>
<td></td>
<td>0.09</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*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/m²], 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 ($P_{\text{trend}} = 0.96$) or duration ($P_{\text{trend}} = 0.97$). The frequency of aspirin use (days per week) from 1984 forward was not significantly associated with risk (for increasing number of days per week, $P_{\text{interaction}} = 0.49$; 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; $P_{\text{interaction}} = 0.009$; 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; $P_{\text{interaction}} = 0.046$). 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 $P_{\text{trend}} > 0.07$). 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 $\sim35\%$ reduction in risk of endometrial cancer for current aspirin users with a BMI of $\geq30$ 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 (PGF2), 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

<table>
<thead>
<tr>
<th>Aspirin use</th>
<th>BMI &lt; 30 (kg/m$^2$)</th>
<th>BMI $\geq$ 30 (kg/m$^2$)</th>
<th>Never used PMH*</th>
<th>Ever used PMH*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never $^\dagger$</td>
<td>71/279,620</td>
<td>48/41,739</td>
<td>56/83,094</td>
<td>40/57,019</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Past</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of users/no. of person-years</td>
<td>141/260,400</td>
<td>95/65,151</td>
<td>66/99,315</td>
<td>125/132,215</td>
</tr>
<tr>
<td>MV RR (95% CI) $^\dagger$</td>
<td>1.50 (1.08–2.09)</td>
<td>0.88 (0.60–1.28)</td>
<td>0.66 (0.45–0.98)</td>
<td>1.36 (0.93–1.97)</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of users/no. of person-years</td>
<td>261/596,521</td>
<td>125/119,642</td>
<td>110/207,649</td>
<td>208/209,357</td>
</tr>
<tr>
<td>MV RR (95% CI) $^\dagger$</td>
<td>1.41 (1.05–1.89)</td>
<td>0.66 (0.46–0.95)</td>
<td>0.64 (0.45–0.91)</td>
<td>1.34 (0.94–1.89)</td>
</tr>
<tr>
<td>$P_{\text{interaction}}$ $^\dagger$</td>
<td>0.009</td>
<td>0.046</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^\dagger$ Among postmenopausal women.

$^\dagger$ No use reported during the follow-up period.

Multivariate risks from proportional hazards models are adjusted for BMI $<$20 (ref), 20–22, 22–24, 24–25, 25–27, 27–29, and 29–$<$30 kg/m$^2$; or BMI $\geq$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).

$^\dagger$ $P$ for interaction between BMI and PMH categories.
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/m² who use aspirin may have lower aromatization of androgens in the peripheral adipose tissues 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 (never used PMH, past use, current use estrogen only, and current use estrogen and progesterone), age at menopause (premenopausal, postmenopausal <45 y, 45–49 y, 50–52 y, and ≥53 y), parity (1–2, 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.

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

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

*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/m²], 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.
contrary to aspirin and other NSAIDs, acetaminophen does not affect systemic PG2 concentrations (49). However, acetamino-
phen 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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Aspirin, NSAID, and Acetaminophen Use and the Risk of Endometrial Cancer

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