Nonsteroidal Anti-Inflammatory Drugs and Risk for Ovarian and Endometrial Cancers in the Iowa Women's Health Study

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Abstract

Background: Several epidemiologic studies have shown inverse associations between use of nonsteroidal anti-inflammatory drugs (NSAID) and incident ovarian cancer, but the results are inconsistent. There have been only a few studies examining possible links between NSAIDs and endometrial cancer risk. We investigated associations between use of NSAIDs and incident ovarian and endometrial cancers in a prospective cohort of about 20,000 women with ages from 58 to 76 years in 1992. Participants were asked how often they used aspirin and nonaspirin NSAIDs. Over 15 years, 311 endometrial and 167 ovarian incident malignancies were identified. Multivariate-adjusted hazard ratios were estimated using Cox proportional regression.

Results: Compared with women who reported no use of aspirin, the relative risks for ovarian cancer for those who used aspirin <2, 2 to 5 times, and ≥6 times per week were 0.83, 0.77, and 0.61, respectively (P_trend = 0.04). We did not observe any association between nonaspirin NSAIDs use and ovarian cancer risk. Neither did we find associations between aspirin or nonaspirin NSAIDs use and risk for endometrial cancer.

Conclusions: Our results suggest a possible inverse association between frequency of aspirin use and risk for ovarian cancer.

Introduction

Chronic inflammation is implicated in cancer etiology and progression (1-3). Chronic inflammation is characterized by production of cyclooxygenase (COX) and prostaglandins, generation of reactive oxygen species, and secretion of inflammatory cytokines, which may induce rapid cell division, DNA damage and mutations, and tumor growth (4).

Evidence for an association between inflammation and carcinogenesis is strongest for colorectal cancer, but relationships with inflammation have been also shown for malignancies of the pancreas, kidney, bladder, stomach, and ovaries (1). The following evidence supports the hypothesis that inflammation increases ovarian cancer risk: exposure to talc and endometriosis are associated with inflammation and increased ovarian cancer risk (5, 6); increased C-reactive protein, a biological marker of chronic systemic inflammation, has been shown to be associated with increased ovarian cancer risk (7); and in vitro studies showed that nonsteroidal anti-inflammatory drugs (NSAID), both aspirin and nonaspirin types, may potentially inhibit the tumor growth and induce apoptosis of ovarian cancer cell lines (8-10). Several epidemiologic studies (at least 10 case-control and 3 cohort studies) examined associations between NSAIDs and ovarian cancer risk, but their results were not consistent (11-25). In a review of the risk factors for ovarian cancer, Hankinson et al. (5) concluded that there is a moderate inverse association between ovarian cancer and analgesic use, but data are limited and more large epidemiologic studies are needed.

There is also laboratory evidence that aspirin and nonaspirin NSAIDs suppress proliferation and induce apoptosis of endometrial cancer cell lines in a dose-dependent manner (26-28). However, none of the three published epidemiologic studies found associations between any NSAIDs and endometrial cancer overall (29-31). Yet, a significant risk reduction for NSAIDs was observed among nonusers of hormone replacement therapy in one of these studies (31) and among obese women in two of the studies (30, 31). It is important to better understand the potential chemopreventive effects of NSAIDs for the two most common gynecologic cancers, ovarian and endometrial cancers. Our goal was to evaluate the association between self-reported frequency of aspirin and nonaspirin NSAID use and incidence of these cancers among elderly women in the Iowa Women’s Health Study (IWHS), a large prospective cohort study.

Materials and Methods

Detailed descriptions of the IWHS cohort have been published previously (32-34). In brief, IWHS was initiated in 1986 when a baseline questionnaire was mailed to 98,030 women with ages from 55 to 69 y, randomly
selected from the Iowa driver's license list. The 41,836 women who completed the questionnaire (42.7%) constituted the cohort.

Five follow-up questionnaires were mailed to cohort subjects to update vital status, residence, and exposure information; the response rates were 91% in 1987, 90% in 1989, 83% in 1992, 79% in 1997, and 70% in 2004. Data from follow-up surveys indicated that the migration rate from Iowa among cohort members is <1% annually, allowing nearly complete follow-up for cancer incidence end points (35). The vital status of all nonresponders to follow-up questionnaires was identified by linkage with the National Death Index.

The current use of aspirin and nonaspirin NSAIDs in the cohort was ascertained on the 1992 questionnaire. Respondents were asked "How often do you take aspirin? Examples of aspirin included Bufferin, Anacin, entericoated aspirin, Ecotrin, and Excedrin: never, less than one per week, one per week, 2-5 per week, and 6+ per week." Use of nonaspirin NSAIDs was assessed by asking "How often do you take other nonsteroidal anti-inflammatory drugs or arthritis medicines? Examples included Ibuprofen, Advil, Nuprin, Motrin, Naprosyn, Feldene, and Clinoril: never, less than one per week, one per week, 2-5 per week, and 6+ per week." Respondents were instructed to exclude acetaminophen and Tylenol use in both questions. Data on dose and duration were not available.

The baseline questionnaire asked standard information about lifestyle behaviors and sociodemographic factors, medical histories, and anthropometric factors. The participants reported their current weight and height, and their hip and waist circumferences measured by a friend, using a paper tape measure provided with the questionnaire. Detailed information about their reproductive history was collected: age at menarche, age at menopause and the reason for it, details of each pregnancy (up to 10), and whether or not they had had their uterus and/or one or both ovaries surgically removed (updated in 1992). In addition, they were asked about their family history of cancer, the history of endometriosis, history of oral contraceptive use and duration, and history of hormone replacement therapy. Information about weight, alcohol intake, and smoking status was updated in 1992, and questions about heart disease, diabetes, hypertension, and hormone replacement therapy use were asked at each follow-up. The 1992 survey also queried whether participants had been diagnosed with migraines, rheumatoid arthritis, and osteoarthritis. Data about hysterectomy and oophorectomy status were collected at a third time in 2004.

Ovarian and endometrial cancer cases were ascertained through the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, through an annual computer match of name, maiden name, date of birth, address, and social security number. Primary site, morphology, extent of disease, and date of diagnosis were obtained for each incident cancer case from 1992 through 2006. Only cases diagnosed within the state of Iowa were captured.

We firstly excluded participants if they did not complete 1992 survey (n=8,819), then if they had cancer at baseline or were diagnosed with cancer other than skin cancer before 1992 (n=4,439), and if they did not complete both questions about NSAIDs (n=540). In addition, women with full oophorectomy and unknown oophorectomy status were excluded for ovarian cancer analysis (n=6,338), and women with hysterectomy and unknown hysterectomy status were excluded for endometrial cancer analysis (n=10,328). Among ovarian cancer cases, nonepithelial cancer cases were excluded (n=6), and among endometrial cancer cases, endometrial sarcomas and Muellerian mixed tumors (n=13) were excluded.

As a result, 21,694 women were available for the ovarian cancer analysis, with 157 epithelial ovarian cancers detected over 15 y of follow-up. For the endometrial cancer analysis, the cohort consisted of 17,697 women and 311 endometrial cancers.

Person-years of follow-up for endometrial and ovarian cancer cases were calculated as the time between 1992 to endometrial or ovarian cancer, respectively. All other participants were followed up to the date of death, the estimated date of emigration from Iowa (assigned as midpoint between the last completed questionnaire in Iowa and the next follow-up questionnaire completed elsewhere or non-Iowa death), or December 31, 2006, whichever occurred first.

We used SAS (SAS Institute, Inc.) for analysis. χ² Tests were done to determine whether or not characteristics differed according to frequency of aspirin and nonaspirin NSAIDs use. Age-adjusted and multivariate-adjusted hazard ratios of ovarian and endometrial cancers and their 95% confidence intervals (95% CI) were computed by proportional hazards regression (program PHREG) separately for aspirin and nonaspirin NSAIDs. For each exposure, women who reported using NSAIDs ≤1 time per week were combined into one group, resulting in categories of never (reference), <2 times per week, 2 to 5 times per week, and 6+ times per week.

Potential covariates in a multivariate-adjusted model were tested if they were associated with ovarian or endometrial cancer (depending on the analysis) or NSAIDs use in this analysis. The final model for ovarian cancer included age, body mass index (BMI; continuous), history of hormone replacement therapy use (yes/no), number of live births (0, 1-2, 3-4, >4), history of heart disease (yes/no), and partial oophorectomy (yes/no). Alcohol, physical activity, smoking status and pack-years of smoking, education, waist-to-hip ratio, age at menopause, age at menarche, endometriosis, hysterectomy status, and family history of breast and/or ovarian cancer were not associated with ovarian cancer in this analysis and were not included. In addition, we adjusted for personal history of migraines and history of either rheumatoid arthritis or osteoarthritis. Because they did not
markedly change the estimates, they were not included in the final model. To minimize potential confounding by indication, we also examined associations after excluding women who had reported heart disease, arthritis, and migraines.

The final model for endometrial cancer included age, BMI ($<25$, $25-29.9$, and $\geq 30$ kg/m$^2$), alcohol use (never/ever), age at menopause ($\leq 44$, $45-49$, $50-54$, $\geq 55$ y), age at menarche ($\leq 11$, $12$, $13$, $\geq 14$ y), history of oral contraceptive and hormone replacement therapy use (yes/no), and history of diabetes and hypertension (yes/no). Physical activity, education, smoking status and pack-years, number of live births, age at first live birth, and family history of uterine cancer were not associated with endometrial cancer and were not included. To compare our results with Moysich et al. (30), who reported associations between NSAIDs and endometrial cancer for obese women, and Viswanathan et al. (31), who observed an association for never users of hormone replacement therapy, the analysis was repeated after stratifying by BMI categories (normal, $<25$ kg/m$^2$; overweight, $25-29.9$ kg/m$^2$; and obese, $\geq 30$ kg/m$^2$) and hormone replacement therapy use (yes/no).

We also repeated analyses after excluding ovarian or endometrial cancer cases (depending on the analysis) diagnosed within 2 and 3 y after start of follow-up to exclude women who may have used NSAIDs more frequently to treat symptoms of preclinical cancer. In addition, we stratified the time of follow-up approximately at midpoint (1992-1999 and 2000-2006) and compared hazard risk for ovarian or endometrial cancer in relation to NSAIDs use in each period. Because we did not know the dates of oophorectomy and hysterectomy during the follow-up, we were not able to censor participants at the time of their surgery. So, we conducted a sensitivity analysis among respondents to 2004 surveys to allow us to exclude women who reported a bilateral oophorectomy or hysterectomy in 2004 in the analysis of ovarian or endometrial cancer, respectively. Although the power was decreased, all associations were similar before and after exclusions. In our primary analysis, all women at risk in 1992 were included.

The IWHS was approved by the University of Minnesota Institutional Review Board, and return of the questionnaire was considered informed consent.

**Results**

The mean age of women at risk for ovarian cancer and for endometrial cancer was 67.5 years (range, 58-76 y) in 1992. Among women at risk for ovarian cancer, 72.0% ever used aspirin, 38.5% ever used nonaspirin NSAIDs, 28.1% used both, and 17.7% did not use any NSAIDs. Among aspirin users and nonusers, 37.1% and 39.1% ever used nonaspirin NSAIDs, respectively. The percentages were very similar in the cohort at risk for endometrial cancer, but the fraction of nonaspirin NSAIDs use (37.1%) was slightly smaller. Because the patterns of distribution of characteristics across aspirin and nonaspirin NSAIDs were similar among participants at risk for ovarian and endometrial cancers, the prevalence of characteristics is presented for those at risk for ovarian cancer (Table 1).

Frequent users of aspirin and nonaspirin NSAIDs were more likely to report history of arthritis (rheumatoid arthritis and/or osteoarthritis), migraines, and cardiovascular disease. Women using nonaspirin NSAIDs more frequently were more likely to be obese, have history of oral contraceptive and hormone replacement therapy use, have had a hysterectomy, and were somewhat more likely to report endometriosis. These associations were less pronounced for aspirin users. Other risk factors for ovarian or endometrial cancer (such as number of live births; age at first live birth; age at menopause and menarche; nulliparity; family history of breast, ovarian, and uterine cancers; education; alcohol; and smoking) were not associated with frequency of aspirin or nonaspirin NSAIDs use.

In an age-adjusted model, there was an indication of an inverse association between frequency of aspirin use and incident ovarian cancer (Table 2). After further adjustment for covariates, the trend became slightly stronger and statistically significant. Compared with aspirin nonusers, the hazard ratio of ovarian cancer for women who reported using aspirin $<2$ times per week, 2 to 5 times per week, or 6+ times per week were 0.83 (95% CI, 0.56-1.22), 0.77 (95% CI, 0.48-1.24), and 0.61 (95% CI, 0.37-0.99), respectively ($P$ trend $= 0.04$). Adjustment for nonaspirin NSAIDs use did not noticeably change the relationship between aspirin use and ovarian cancer. After restricting analysis to the women without heart disease, the hazard ratio for ever users of aspirin versus no use was 0.69 (95% CI, 0.48-0.99), and a dose-dependent relationship persisted (not shown here). Inverse dose-dependent relationships (not shown here) held among those who did not have a history of any arthritis and among those without a history of migraines.

The inverse relationships remained after exclusion of cases diagnosed during the first 2 and 3 years of follow-up. In addition, results stratified by follow-up period, that is, 1992 to 1999 and 1999 to 2006, were similar to each other and to the overall period of study (data not shown).

Contrary to use of aspirin, use of nonaspirin NSAIDs (Table 2) was not associated with ovarian cancer incidence. The multivariate-adjusted hazard ratios were 0.65, 1.08, and 1.12 for women who used nonaspirin NSAIDs $<2$, 2 to 5 times, and 6+ times per week compared with nonusers of nonaspirin NSAIDs ($P = 0.27$). These results were not substantively changed when adjusted for aspirin use.

Compared with never use of either aspirin or nonaspirin NSAIDs, use of both medications was inversely associated with ovarian cancer incidence (multivariate hazard ratio, 0.65; 95% CI, 0.40-1.07). There was no evidence for an interaction between use of aspirin and...
nonaspirin NSAIDs ($P = 0.39$), but power for this analysis was small.

Table 3 shows the relationship between incident endometrial cancer and frequency of aspirin and nonaspirin NSAIDs use. Compared with nonusers of aspirin, the multivariate-adjusted hazard ratios for women who reported use of aspirin <2 times, 2 to 5 times, and 6+ weekly were 0.78 (95% CI, 0.58-1.04), 0.89 (95% CI, 0.63-1.25), and 0.85 (95% CI, 0.61-1.18), respectively ($P_{\text{trend}} = 0.50$). After stratification by BMI categories or history of hormone replacement therapy use, there were still no patterns of relationships between aspirin use and endometrial cancer risk in any of the categories (data not shown).

When use of nonaspirin NSAIDs and incident endometrial cancer were examined, the multivariate hazard ratios (use versus no use) were 0.86 (95% CI, 0.63-1.18), 1.16 (95% CI, 0.78-1.72), and 0.85 (95% CI, 0.58-1.22) for those who reported use of NSAIDs <2, 2 to 5, and 6+ times weekly, respectively ($P_{\text{trend}} = 0.73$; Table 3).

**Discussion**

In this prospective cohort of elderly women, there was an inverse association between frequency of aspirin use and ovarian cancer risk. Adjustment for the use of nonaspirin NSAIDs did not substantively change these results. The findings were similar when we excluded women diagnosed with ovarian cancer during the first 2 and 3 years of follow-up.

There was no association between frequency of nonaspirin NSAIDs use and ovarian cancer risk. For endometrial cancer, we observed no associations between frequency of any NSAIDs and endometrial cancer risk,

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**Table 1.** Mean age (year) and prevalence of participant characteristics (percentage) by frequency of aspirin or nonaspirin NSAIDs use, IWHS 1992 to 2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin use, times per week</th>
<th>Nonaspirin NSAIDs use, times per week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 ≤1 2-5 6+</td>
<td>0 ≤1 2-5 6+</td>
</tr>
<tr>
<td>Prevalence of use, n (%)</td>
<td>6,084 7,353 3,838 4,419</td>
<td>13,342 4,027 1,689 2,636</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>(28.0) 33.9 (17.7) (20.4)</td>
<td>(61.5) (18.6) (7.8) (12.2)</td>
</tr>
<tr>
<td>Age (≥65 y)*</td>
<td>71.7 67.2 67.8 73.1</td>
<td>71.6 65.6 67.4 71.1</td>
</tr>
<tr>
<td>BMI (≥30 kg/m²)*</td>
<td>24.8 21.2 21.8 26.5</td>
<td>20.3 23.7 27.0 36.1</td>
</tr>
<tr>
<td>WHR highest tertile (≥0.87)†</td>
<td>34.8 29.9 32.2 37.5</td>
<td>32.2 32.2 33.7 39.5</td>
</tr>
<tr>
<td>Education (up to high school)†</td>
<td>60.6 56.1 58.4 59.8</td>
<td>58.7 56.6 62.8 58.0</td>
</tr>
<tr>
<td>Current smoking*</td>
<td>9.3 8.0 9.1 9.7</td>
<td>9.3 8.2 9.2 8.0</td>
</tr>
<tr>
<td>Alcohol (ever)†</td>
<td>40.6 47.1 48.8 44.6</td>
<td>43.4 49.8 49.1 43.6</td>
</tr>
<tr>
<td>Oral contraceptive use (ever)†</td>
<td>19.1 20.7 20.8 18.8</td>
<td>17.9 22.6 22.6 24.1</td>
</tr>
<tr>
<td>HRT use (ever) *</td>
<td>35.0 33.4 38.1 41.1</td>
<td>32.9 38.0 43.5 46.0</td>
</tr>
<tr>
<td>Age at menarche (≤11 y)†</td>
<td>15.3 14.4 15.4 16.1</td>
<td>14.4 15.8 14.9 18.5</td>
</tr>
<tr>
<td>Age at menopause (≥55 y)‡</td>
<td>14.7 14.4 15.1 13.8</td>
<td>14.5 14.0 15.4 14.6</td>
</tr>
<tr>
<td>Age at first live birth (≥30 y)†</td>
<td>4.7 5.4 4.0 8.3</td>
<td>5.0 4.7 4.0 5.1</td>
</tr>
<tr>
<td>Nulliparity†</td>
<td>9.5 8.6 7.4 8.2</td>
<td>9.4 7.2 5.7 8.3</td>
</tr>
<tr>
<td>Hysterectomy*</td>
<td>20.1 17.3 20.3 21.6</td>
<td>17.5 20.3 23.5 26.0</td>
</tr>
<tr>
<td>Partial oophorectomy†</td>
<td>10.0 9.7 10.7 10.8</td>
<td>9.6 9.7 12.0 12.8</td>
</tr>
<tr>
<td>History of endometriosis</td>
<td>2.3 2.2 1.9 2.6</td>
<td>2.0 2.5 2.5 3.3</td>
</tr>
<tr>
<td>History of heart disease*</td>
<td>13.1 8.2 11.5 28.0</td>
<td>14.2 12.1 14.3 17.5</td>
</tr>
<tr>
<td>History of migraines*</td>
<td>8.8 6.9 10.5 12.4</td>
<td>7.6 9.8 12.3 13.5</td>
</tr>
<tr>
<td>History of arthritis*</td>
<td>27.1 18.0 22.0 34.4</td>
<td>16.7 21.2 36.2 64.0</td>
</tr>
<tr>
<td>History of diabetes*</td>
<td>9.1 6.2 6.2 11.1</td>
<td>7.9 7.1 8.2 10.1</td>
</tr>
<tr>
<td>History of hypertension*</td>
<td>41.6 35.5 41.8 51.4</td>
<td>40.5 39.5 42.9 49.4</td>
</tr>
<tr>
<td>Family history of ovarian and/or breast cancer†</td>
<td>13.5 12.9 13.1 13.3</td>
<td>13.2 12.8 13.5 12.8</td>
</tr>
<tr>
<td>Family history of uterine cancer†</td>
<td>4.9 4.4 4.0 4.8</td>
<td>4.3 4.6 4.8 5.6</td>
</tr>
</tbody>
</table>

Abbreviations: HRT, hormone replacement therapy; WHR, waist-to-hip ratio.
*Reported up to 1992.
†Reported at baseline, 1986.
‡For this analysis, women with hysterectomy and partial oophorectomy were excluded (n = 3,474) because their age at menopause was unknown.
even after stratification by BMI categories and use of hormone replacement therapy.

Our null findings for NSAIDs use and endometrial cancer, overall, are in agreement with previous findings from one case-control (30) and two cohort studies (29, 31). However, Moysich et al. (30) and Viswanathan et al. (31) reported inverse associations among obese women, and Viswanathan et al. also observed an inverse association among never users of hormone replacement therapy. These two studies suggested that, in obese

### Table 3. Age- and multivariate-adjusted hazard ratios for endometrial cancer in relation to the use of aspirin and nonaspirin NSAIDs, IWHS 1992 to 2006

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Multivariate-adjusted* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>95</td>
<td>54,322</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>216</td>
<td>145,900</td>
<td>0.85 (0.67-1.08)</td>
<td>0.83 (0.64-1.06)</td>
</tr>
<tr>
<td>≤1 time/wk</td>
<td>94</td>
<td>71,840</td>
<td>0.75 (0.57-1.00)</td>
<td>0.78 (0.58-1.04)</td>
</tr>
<tr>
<td>≥6 times/wk</td>
<td>65</td>
<td>38,775</td>
<td>0.96 (0.70-1.31)</td>
<td>0.85 (0.61-1.18)</td>
</tr>
<tr>
<td><em>P</em></td>
<td></td>
<td></td>
<td>0.88</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Nonaspirin NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>190</td>
<td>125,993</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>121</td>
<td>74,229</td>
<td>1.09 (0.86-1.36)</td>
<td>0.91 (0.72-1.16)</td>
</tr>
<tr>
<td>≤1 time/wk</td>
<td>55</td>
<td>37,429</td>
<td>0.98 (0.73-1.33)</td>
<td>0.86 (0.63-1.18)</td>
</tr>
<tr>
<td>≥6 times/wk</td>
<td>37</td>
<td>21,852</td>
<td>1.12 (0.79-1.60)</td>
<td>0.85 (0.58-1.22)</td>
</tr>
<tr>
<td><em>P</em></td>
<td></td>
<td></td>
<td>0.29</td>
<td>0.73</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, age at menopause, age at menarche, history of oral contraceptive use, HRT use, alcohol, and history of diabetes and hypertension.
women, NSAIDs decrease production of COX-2 and inflammatory cytokines and reduce estrogen exposure in endometrial tissue through decreased aromatase expression (30, 31). We did not observe associations among never users of hormone replacement therapy or obese women; the latter being consistent with null findings among obese women in the NIH-AARP Diet and Health Study (29). Of note, findings from epidemiologic studies on NSAIDs use and endometrial cancer are not consistent with in vitro studies. Laboratory experiments have found that aspirin and nonaspirin NSAIDs inhibit human endometrial cancer cells in a time- and dose-dependent manner through COX-2–dependent and COX-2–independent mechanisms (26–28). There could be several explanations for the discrepancy between epidemiologic and in vitro studies: (a) NSAIDs may inhibit progression rather than induction of endometrial cancer, and (b) use of NSAIDs is irregular in epidemiologic studies and their dosage is much smaller than in in vitro studies (19), or measurement error in epidemiologic studies could mask a small effect.

More than 10 epidemiologic studies and three meta-analyses investigated associations between NSAIDs use and incident ovarian cancer (11-25, 36-39). Findings from all the meta-analyses for incident ovarian cancer in relation to aspirin use were similar (36-38). For example, the meta-analysis by Bosetti et al. (37) presented pooled results from six case-control and two cohort studies. In the analysis of case-control studies, the pooled relative risk was 0.82 (95% CI, 0.69-0.99) for aspirin users versus nonusers. No association of aspirin with ovarian cancer was reported in the pooled analysis of the two cohort studies; overall, the pooled relative risk for aspirin users was 0.89 (95% CI, 0.78-1.02) compared with nonusers of aspirin.

A randomized controlled trial, the Women’s Health Study, designed to study cardiovascular disease endpoints, reported that the relative risk of ovarian cancer was 0.95 (95% CI, 0.68-1.35) in relation to aspirin use (39). However, the dosage of aspirin assigned to the treatment group was small, 100 mg every other day for 10 years, and could be insufficient for prevention of cancer. It is noteworthy that the same trial reported no protective effect of low-dose aspirin on colorectal cancer incidence, whereas most observational studies, which assessed higher aspirin dosage (including IWHS cohort study), found inverse associations (37, 40).

Recently, five more studies have been published on associations between NSAIDs use and ovarian cancer risk, and the results are inconsistent. Two case-control studies observed inverse associations of ovarian cancer risk with NSAIDs use overall and with aspirin (all relative risks were about 0.7; refs. 21, 25), whereas two other case-control studies reported no inverse relationships (14, 17). An updated analysis in a large cohort study, Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHS-II; ref. 19), used a longer follow-up and a larger number of cases than their study in 2002 (13) that was included in the meta-analyses cited above (37). Their data again showed no overall association between aspirin and ovarian cancer risk (19). However, there was an indication of an inverse association between nonaspirin NSAIDs use and ovarian cancer risk and between any NSAIDs use and risk for borderline ovarian tumors.

Thus, our finding of an inverse association between aspirin and ovarian cancer risk are in agreement with findings from most case-control studies but not consistent with findings from the NHS–NHS-2 cohorts (19). A potential explanation is that our study population is different from those in these cohorts: 70% of IWHS women reported taking aspirin compared with 46% in the NHS cohort (13); and the percentage of those who regularly used aspirin (>2 times per week) was 38% in IWHS (1992), 21% in NHS (1990), and 11% in NHS-2 (1989; ref. 19). IWHS women were older (age range at the start of follow-up was 58-76 years in IWHS versus 30-55 years in NHS and 25-42 years in NHS-II). Thus, the IWHS cohort, compared with NHS-NHS-II cohort, is comprised of older women at risk for ovarian cancer who reported higher use of aspirin.

Our finding of an inverse association between aspirin use and incident ovarian cancer are consistent with positive associations between risk for ovarian cancer and increased CRP, a nonspecific marker of inflammation (7), and an inverse association between aspirin treatment and human ovarian cancer cell growth in in vitro studies. The mechanism of an association between aspirin and ovarian cancer may be an anti-inflammatory effect of aspirin through inhibition of COX-1 and COX-2 (9). Laboratory studies showed that COX-2 is expressed in human ovarian carcinoma cell lines and high expression of COX-2 leads to an increased production of prostaglandin E2, resulting in poor patient prognosis (8). Aspirin was reported to inhibit the growth of human ovarian tumor cells in a dose-dependent fashion (9). It is possible that aspirin also exerts its inhibitory effect through COX-independent mechanism, such as modulation of estrogen synthesis, the role of aspirin as an antioxidant, or some other mechanisms (8, 10, 39, 41), all of which may result in inhibition of angiogenesis, induction of apoptosis, and inhibition of oxidative DNA damage (42, 43).

We did not observe any dose-dependent relationship between frequency of nonaspirin NSAIDs use and ovarian cancer risk. This is compatible with the results of a meta-analysis by Bonovas et al. (36). The reason for different results between aspirin and nonaspirin NSAIDs in our cohort may be that the protective effect on ovarian cancer may be limited to aspirin and reflects differences in mechanisms between aspirin and nonaspirin NSAIDs. For example, nonaspirin NSAIDs reversibly inactivate COX, whereas aspirin inactivates COX irreversibly. Moreover, nonaspirin NSAIDs are a heterogeneous group of medications, each with slightly different properties, various half-lives, and effects on COX inhibition, and may have different effect on cancer risk (36). In addition, use of nonaspirin NSAID use in our cohort was assessed
in 1992, when most nonaspirin NSAIDs medications were not available over the counter and women may not have been very familiar with them and either recalled them poorly or took them only for a short time.

Our study has the following limitations: information about duration, dosage, and reason for NSAIDs use was not collected. We also had a concern about confounding by indication. For instance, women with heart disease could have taken aspirin because they had low-grade inflammation, which could be associated with ovarian cancer. To minimize potential confounding by indication, we examined women without heart disease and found an inverse statistically significant association similar to that in the main analysis. The inverse relationships also held among those without history of migraines or arthritis. Another limitation is that exposure was assessed by self-report; therefore, some misclassification undoubtedly occurred. In cohort studies, misclassification of exposure is usually not associated with the outcome, is nondifferential, and most likely biases toward the null. However, because of potential residual confounding by indication, differential misclassification may be present; for example, women with heart disease or arthritis might recall their exposure history better than women without. Moreover, in rare cases, nondifferential misclassification of a multilevel exposure may result in bias away from null (44, 45).

Furthermore, the questions about NSAIDs were asked only once at the start of follow-up, and the exposure could have changed over time. However, after stratification by the time of follow-up at the midpoint, the inverse relationships between aspirin use and ovarian cancer risk were similar in both subgroups. Finally, we did not have power to examine ovarian cancer by histologic subtype. The strengths of our study are that the IWHS is a large population-based prospective cohort with practically complete follow-up, reliable ascertainment of cancer cases, and detailed information about cancer risk factors. Moreover, we were able to separately examine frequency of aspirin and nonaspirin NSAIDs use.

Our findings support the hypothesis that aspirin use is inversely associated with ovarian cancer risk, but it has no effect on endometrial cancer risk. Large cohort studies or clinical trials with accurate assessment of dosage and duration of NSAIDs and information about age at the initiation of treatment are needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank the IWHS staff for consultation and assistance in data preparation.

Grant Support

National Cancer Institute grant R01 CA97472.

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Received 9/18/09; revised 12/1/09; accepted 12/3/09; published online 2/8/10.

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Nonsteroidal Anti-Inflammatory Drugs and Risk for Ovarian and Endometrial Cancers in the Iowa Women’s Health Study

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