Association of Analgesic Use With Risk of Ovarian Cancer in the Nurses' Health Studies

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IMPORTANCE Ovarian cancer is a highly fatal malignant neoplasm with few modifiable risk factors. Case-control studies have reported a modest reduced risk of ovarian cancer among women who frequently use aspirin or regularly use low-dose aspirin.

OBJECTIVE To evaluate whether regular aspirin or nonaspirin nonsteroidal anti-inflammatory drug (NSAID) use and patterns of use are associated with lower ovarian cancer risk.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed NSAID use and ovarian cancer diagnosis data from 2 prospective cohorts, 93,664 women in the Nurses' Health Study (NHS), who were followed up from 1980 to 2014, and 111,834 in the Nurses' Health Study II (NHSII), who were followed up from 1989 to 2015. Follow-up was completed on June 30, 2014, for the NHS and June 30, 2015, for NHSII. Data were analyzed from June 13, 2016, to September 18, 2017.

EXPOSURES For each analgesic type (aspirin, low-dose aspirin, nonaspirin NSAIDs, and acetaminophen), timing, duration, frequency, and number of tablets used were evaluated; exposure information was updated every 2 to 4 years.

MAIN OUTCOMES AND MEASURES Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for associations of aspirin, nonaspirin NSAIDs, and acetaminophen with risk of epithelial ovarian cancer. All statistical tests were 2-sided, with a significance level of .05.

RESULTS In the NHS, the mean (SD) age at baseline (1980) was 45.9 (7.2) years, and 93% of participants identified as non-Hispanic white. In the NHSII, the mean age at baseline (1989) was 34.2 (4.7) years, and 92% identified as non-Hispanic white. Among the 205,498 women in both cohorts, there were 10,54 cases of incident epithelial ovarian cancer. Significant associations between aspirin and ovarian cancer risk were not observed when current vs nonuse of any aspirin was evaluated regardless of dose (HR, 0.99; 95% CI, 0.83-1.19). However, when low-dose (<100-mg) and standard-dose (325-mg) aspirin were evaluated separately, an inverse association for low-dose aspirin (HR, 0.77; 95% CI, 0.61-0.96), but no association for standard-dose aspirin (HR, 1.17; 95% CI, 0.92-1.49) was observed. Current use of nonaspirin NSAIDs was positively associated with risk of ovarian cancer compared with nonuse (HR, 1.19; 95% CI, 1.00-1.41), and significant positive trends for duration of use (P = .02 for trend) and cumulative average tablets per week (P = .03 for trend) were observed. There were no clear associations for the use of acetaminophen.

CONCLUSIONS AND RELEVANCE These results appear to be consistent with case-control studies that show a reduced risk of ovarian cancer among regular users of low-dose aspirin. An increased risk of ovarian cancer with long-term high-quantity use of other analgesics, particularly nonaspirin NSAIDs, was observed, although this finding requires confirmation.

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Ovarian cancer is the fifth most common cause of cancer-related death among women in the United States. There is growing evidence to support a role for inflammation in the development of ovarian cancer. Localized inflammation, as occurs with ovulation, may contribute to ovarian tumorigenesis, and epidemiologic studies have consistently observed positive associations between a higher number of lifetime ovulatory cycles and risk of ovarian cancer. Systemic inflammation has also been associated with increased risk of ovarian cancer. For example, meta-analyses of studies of circulating C-reactive protein, a marker of systemic inflammation, reported a nearly 2-fold increased risk of ovarian cancer for those with high vs low C-reactive protein levels.

Anti-inflammatory agents, including aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), are common medications that may influence ovarian cancer development; however, results of previous studies have been mixed. Several large case-control studies reported significantly lower ovarian cancer risk among aspirin users, particularly low-dose aspirin users, and a suggestion of a lower risk among nonaspirin NSAID users. In contrast, past analyses in prospective cohort studies, including ours, did not observe clear associations with regular use of aspirin or nonaspirin NSAIDs. Possible explanations for these mixed results include evaluation of prospective vs retrospective data, differences in age distributions across study designs, and heterogeneity in the measurement and definition of medication use across studies.

Previously, no prospective cohort studies had both adequate power and sufficiently detailed exposure data to evaluate whether timing and patterns of analgesic use are associated with ovarian cancer risk. We used prospectively collected data from the Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHSII) on type, timing, frequency, quantity, dose, and duration of analgesic use to conduct detailed analyses of aspirin, nonaspirin NSAID, and acetaminophen use and risk of ovarian cancer. We included acetaminophen because it is an analgesic with weaker anti-inflammatory properties than aspirin and nonaspirin NSAIDs and therefore an informative comparator.

Methods

Study Population
The NHS and NHSII are large prospective cohort studies. The NHS enrolled 121,700 female registered nurses aged 30 to 55 years in 1976. In 1989, the NHSII enrolled a similar cohort of 116,429 women aged 25 to 42 years. All women in the NHS/NHSII have been followed up biennially to collect data on lifestyle, health factors, and disease outcomes, including analgesic use and ovarian cancer diagnosis. Follow-up was completed on June 30, 2014, for the NHS and June 30, 2015, for NHSII. Data were analyzed from June 13, 2016, to September 18, 2017. Study protocols for NHS/NHSII were approved by the institutional review board at Brigham and Women’s Hospital. Participant return of a baseline questionnaire was considered to imply informed consent.

Identification of Ovarian Cancer Cases
We identified incident cases of epithelial ovarian cancer by self-report on biennial questionnaires or when a participant was reported deceased by a family member or the US Postal Service, with cause of death identified via linkage to the National Death Index. We requested permission to review medical records from all participants with a reported diagnosis of ovarian or primary peritoneal cancer. A gynecologic pathologist, who was blinded to exposure status, reviewed the reports to confirm the ovarian cancer diagnosis and classify the cancer by grade, morphologic features, and histotype. When pathology reports could not be obtained, information on the diagnosis was accessed via linkage to cancer registries.

Key Points

Question Are findings from case-control studies that report lower ovarian cancer risk among low-dose aspirin users reproducible in a large prospective study?

Findings This cohort study using data from the Nurses’ Health Study and Nurses’ Health Study II observed a 23% lower risk of ovarian cancer among current low-dose aspirin users compared with nonusers. However, current use of nonaspirin nonsteroidal anti-inflammatory drugs was associated with a 19% higher risk of ovarian cancer compared with nonuse, and positive trends were observed for duration and cumulative average tablets per week.

Meaning These results support a lower risk of ovarian cancer among low-dose aspirin users, although the association between other nonsteroidal anti-inflammatory drugs and ovarian cancer may be more complex.

Assessment of Analgesic Use
The NHS has collected biennial information on aspirin use since 1980, when women were asked if they used aspirin most weeks; those who responded affirmatively were asked to report the number of aspirin tablets used per week and duration of use. Data on current regular aspirin use were collected biennially thereafter (except 1986), and information on frequency of aspirin use was first collected in 1984 and updated biennially beginning in 1988. The number of aspirin tablets taken during a typical week was first queried in 1994 with instructions to count 4 baby aspirin as 1 regular 325-mg tablet; beginning in 2000, women reported the number of tablets separately for regular (325-mg) and low-dose (≤100-mg) aspirin. The NHSII first collected data on current aspirin use in 1989. Questions on current regular use and frequency of use were repeated biennially beginning in 1993, and questions on the number of tablets per week were added in 1999. Beginning in 2001, women reported the number of tablets separately for regular and low-dose aspirin.

Nonaspirin NSAIDs and acetaminophen (current use and frequency) were queried biennially in the NHS starting in 1990. Information on tablets per week was collected biennially beginning in 1998. The NHSII queried current use of nonaspirin NSAIDs and acetaminophen starting in 1989. Current use and frequency were queried biennially beginning in 1995 for both drugs, and questions on tablets per week were added in 1999.
Assessment of Covariates
We regularly collected data on ovarian cancer risk factors, including age, menopausal status, parity, oral contraceptive use, hormone therapy use, tubal ligation, hysterectomy, family history of breast or ovarian cancer, and body mass index. Most factors were queried every 2 to 4 years. We also asked about markers of health care use (eg, physical examinations, mammography screening), health-related behaviors (eg, physical activity, smoking), medication use (eg, antihypertensive drugs) and comorbidities (eg, cardiovascular disease, hypertension, diabetes, gout, rheumatoid arthritis, osteoarthritis, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis).

Statistical Analysis
Follow-up for this analysis began in 1980 (NHS) and 1989 (NHSII). We excluded participants at baseline if they reported a previous diagnosis of cancer (other than nonmelanoma skin cancer), bilateral oophorectomy, or menopause due to pelvic irradiation. After exclusions, 93 664 NHS participants and 111 834 NHSII participants were eligible for the analysis and were followed up until the first of the following events: diagnosis of ovarian cancer, diagnosis of other cancer (except nonmelanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, loss to follow-up, or end of study (June 30, 2014, for NHS; June 30, 2015, for NHSII).

We used Cox proportional hazards models with time-updated exposures and covariates to estimate hazard ratios (HRs) and 95% CIs for the associations between analgesic use and ovarian cancer. Participants contributed person-time when they had responded to questions on analgesic use within the past 4 years. Because pain and abdominal discomfort are commonly reported in the year leading up to ovarian cancer diagnosis,24 we incorporated a latency period of 2 to 4 years to limit the potential for reverse causation. For example, aspirin use in 1980 was used when evaluating ovarian cancer incidence from 1982 to 1984, aspirin use in 1982 was used when evaluating incidence from 1984 to 1986, and so on.

Our analyses separately evaluated regular use (≥2 times per week) of aspirin, nonaspirin NSAIDs, and acetaminophen during the study. We evaluated total aspirin use in the main analysis (1980-2015) and assessed low-dose and standard-dose aspirin use separately in additional analyses (2000-2015). Nonaspirin NSAIDs and acetaminophen were considered from 1989 to 2015. For each drug type, we evaluated regular use and duration of use during study follow-up. Frequency was evaluated using time-updated frequency data (ie, simple update) and mean frequency data calculated across all previous questionnaires (ie, cumulative average) to better capture long-term patterns of use. Tablets per week were similarly evaluated. In a post hoc analysis, we combined duration of use and tablets per week to create a composite variable, cumulative tablet-days, that captured more extreme patterns of analgesic use. Tests for trend were conducted by linearly modeling category medians.

Models allowed for variation in baseline hazards by cohort, age in months (continuous), and calendar years (continuous), and multivariable analyses further adjusted for menopausal status (premenopausal vs postmenopausal), parity (ever vs never and number of children), duration of oral contraceptive use (never, <1, 1-5, or >5 years), duration of estrogen, estrogen-plus-progestin, or other postmenopausal hormone therapy by type (years), history of tubal ligation (yes/no), history of hysterectomy (yes/no), family history of breast cancer or ovarian cancer (yes/no), and body mass index (calculated as weight in kilograms divided by height in meters squared) (<20, 20 to <25, 25 to <30, or ≥30). We evaluated the influence of mutually adjusting for other analgesics and considered the potential for confounding by other medication use, comorbidities, and inflammatory factors. To test the proportional hazards assumption, we compared models with and without interactions between calendar time and exposure and between age and exposure.

We hypothesized a priori that premenopausal aspirin and nonaspirin NSAID use may be more strongly associated with risk of ovarian cancer; therefore, we separately evaluated analgesic use during the premenopausal and postmenopausal time periods using the same approach described above. We evaluated the association of premenopausal analgesic exposure with risk of premenopausal and postmenopausal ovarian cancer and the association of postmenopausal analgesic exposure with risk of postmenopausal ovarian cancer. Finally, we used competing risks regression25,26 to evaluate whether analgesic use was differentially associated with risk of serous vs nonserous ovarian cancer or risk of rapidly fatal (fatal within 3 years) vs non-rapidly fatal ovarian cancer. For example, to evaluate risk of serous vs nonserous ovarian cancer, we used a likelihood ratio test to compare a model that constrained the association to be the same across histotypes with one that allowed different associations.

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc). All statistical tests were 2-sided, and P values less than .05 were considered statistically significant.

Results
In the NHS, the mean (SD) age at baseline (1980) was 45.9 (7.2) years, and 93% of participants identified as non-Hispanic white. In the NHSII, the mean age at baseline (1989) was 34.2 (4.7) years, and 92% identified as non-Hispanic white. Across 1779 572 person-years in the NHS and 1 884 999 person-years in the NHSII, we observed 1054 incident cases of epithelial ovarian cancer. In both studies, current aspirin users were more likely to use other medications, including oral contraceptives and hormone therapy (eTable 1 in the Supplement). Current aspirin users were also more likely to report cardiovascular events, hypertension, and chronic inflammatory diseases. In the NHS, current aspirin users were less likely to report a history of gastric or duodenal ulcer.

We did not observe an association for total (low- and standard-dose) current aspirin use (HR, 0.99; 95% CI, 0.83-1.19), years of aspirin use (≥15 years vs <1 year) (HR, 1.13; 95% CI, 0.91-1.39; P = .22 for trend), or cumulative average tablets per week (≥10 vs <1) (HR, 1.02; 95% CI, 0.78-1.33; P = .65 for trend) with ovarian cancer risk.
There was a nonsignificantly lower risk of ovarian cancer among women with high cumulative average frequency (≥5 days per week) of aspirin use compared with nonusers (HR, 0.86; 95% CI, 0.66-1.12; \( P = .52 \) for trend). A post hoc analysis of cumulative tablet-days showed no evidence of an association for moderate aspirin intake (data not shown); however, we observed a positive association for 2500 or more tablet-days of standard-dose aspirin (≥5 years vs <1 year) (HR, 1.19; 95% CI, 1.00-1.41; \( P = .02 \) for trend). The associations between aspirin use and risk of ovarian cancer did not differ for premenopausal vs postmenopausal use (ever vs never and number of children), duration of oral contraceptive use (never, <1, 1 to 5, or >5) in years, duration in years of postmenopausal hormone use by type, history of tubal ligation (yes vs no), history of hysterectomy (yes vs no), family history of breast cancer or ovarian cancer (yes vs no), and BMI (<20, 20 to <25, 25 to <30, or ≥30). Results for cumulative average frequency and tablets were nonsignificant for low-dose and standard-dose aspirin. We observed a nonsignificant inverse association for 2500 or more tablet-days of low-dose aspirin compared with no regular use (HR, 0.77; 95% CI, 0.50-1.19; \( P = .05 \) for trend; Table 3) and a positive association for 2500 or more tablet-days of standard-dose aspirin compared with no regular use (HR, 1.58; 95% CI, 1.00-2.48; \( P = .02 \) for trend; Table 3).

Current nonaspirin NSAID use was positively associated with risk of ovarian cancer compared with no use (HR, 1.19; 95% CI, 1.00-1.41; Table 1). Furthermore, we observed significant positive associations for 10 or more years’ duration of NSAID use compared with no regular use (HR, 1.34; 95% CI, 1.06-1.70; \( P = .02 \) for trend; Table 1), greater cumulative average tablets per week (≥10 vs <1) (HR, 1.35; 95% CI, 1.02-1.79; \( P = .03 \) for trend; Table 1), and 2500 or more tablet-days (HR, 1.65; 95% CI, 1.19-2.28, \( P = .006 \) for trend; Table 2).
Table 2. Aspirin Use and Risk of Epithelial Ovarian Cancer in the NHS and NHSII by Aspirin Dose During Follow-up From 2000 to 2015

<table>
<thead>
<tr>
<th>Exposure Metric</th>
<th>Standard-Dose Aspirin</th>
<th>Low-Dose Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Multivariable-Adjusted HR (95% CI)*</td>
</tr>
<tr>
<td>Current regular use</td>
<td>None</td>
<td>276</td>
</tr>
<tr>
<td>Past</td>
<td>57</td>
<td>1.26 (0.93-1.70)</td>
</tr>
<tr>
<td>Current</td>
<td>91</td>
<td>1.17 (0.92-1.49)</td>
</tr>
<tr>
<td>Duration, y</td>
<td>&lt;1</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>24</td>
</tr>
<tr>
<td>P value for trend</td>
<td>.004</td>
<td>.41</td>
</tr>
<tr>
<td>Days per week (cumulative average)</td>
<td>&lt;2</td>
<td>355</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>36</td>
</tr>
<tr>
<td>P value for trend</td>
<td>.29</td>
<td>.08</td>
</tr>
<tr>
<td>Tablets per week (cumulative average)</td>
<td>&lt;1</td>
<td>316</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>6-9</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>≥10</td>
<td>27</td>
</tr>
<tr>
<td>P value for trend</td>
<td>.17</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; NHS, Nurses’ Health Study; NHSII, Nurses’ Health Study II.

* Hazard ratios and 95% CIs for each combination of drug type (ie, low-dose aspirin, standard-dose aspirin) and exposure metric (ie, current regular use, duration, days per week, and tablets per week) were estimated using separate Cox proportional hazards regression models. Models allowed for variation in baseline hazards by cohort, age in months (continuous), and calendar years (continuous) and were adjusted for menopausal status, parity (ever vs never and number of children), duration of oral contraceptive use (never, <1, 1 to 5, or >5) in years, duration of postmenopausal hormone use by type, history of tubal ligation (yes vs no), history of hysterectomy (yes vs no), family history of breast cancer or ovarian cancer (yes vs no), and BMI (<20, 20 to <25, 25 to <30, or ≥30).

Table 3. Cumulative Tablet-Days of Analgesic Use and Risk of Epithelial Ovarian Cancer in the NHS and NHSII During Follow-up From 2000 to 2015

<table>
<thead>
<tr>
<th>Tablet-Days</th>
<th>Low-Dose Aspirin</th>
<th>Standard-Dose Aspirin</th>
<th>NSAIDs</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Multivariable-Adjusted HR (95% CI)*</td>
<td>No. of Cases</td>
<td>Multivariable-Adjusted HR (95% CI)*</td>
</tr>
<tr>
<td>1-999</td>
<td>21</td>
<td>1.03 (0.66-1.61)</td>
<td>33</td>
<td>1.11 (0.77-1.60)</td>
</tr>
<tr>
<td>500-999</td>
<td>6</td>
<td>1.16 (0.51-2.63)</td>
<td>6</td>
<td>0.97 (0.43-2.19)</td>
</tr>
<tr>
<td>1000-2499</td>
<td>61</td>
<td>0.75 (0.57-1.00)</td>
<td>53</td>
<td>1.26 (0.93-1.70)</td>
</tr>
<tr>
<td>≥2500</td>
<td>27</td>
<td>0.77 (0.50-1.19)</td>
<td>21</td>
<td>1.58 (1.00-2.48)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>.05</td>
<td>.02</td>
<td>.006</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; NHS, Nurses’ Health Study; NHSII, Nurses’ Health Study II; NSAIDs, nonsteroidal anti-inflammatory drugs.

* Hazard ratios and 95% CIs for each drug type (ie, low-dose aspirin, standard-dose aspirin, nonaspirin NSAIDs, and acetaminophen) were estimated using separate Cox proportional hazards regression models. Models allowed for variation in baseline hazards by cohort, age in months (continuous), and calendar years (continuous) and were adjusted for menopausal status, parity (ever vs never and number of children), duration of oral contraceptive use (never, <1, 1 to 5, or >5) in years, duration of postmenopausal hormone use by type, history of tubal ligation (yes vs no), history of hysterectomy (yes vs no), family history of breast cancer or ovarian cancer (yes vs no), and BMI (<20, 20 to <25, 25 to <30, or ≥30).

There was no evidence of an association for regular acetaminophen use (≥5 vs <2 days per week) was not associated with ovarian cancer risk (HR, 1.18; 95% CI, 0.90-1.54; P = .29 for trend). We did not observe consistent differences for premenopausal vs postmenopausal use of nonaspirin NSAIDs (eTable 2 in the Supplement).

There was no evidence of an association for regular acetaminophen use (Table 1). For example, the association between current acetaminophen use and ovarian cancer risk was 1.02 (95% CI, 0.86-1.21). We observed a positive but nonsignificant association for heavy acetaminophen use (≥2500 tablet-days) compared with no regular use (HR, 1.41; 95% CI, 0.99-2.00, P = .10 for trend; Table 3), and we did not observe any consistent differences for premenopausal vs postmenopausal use of acetaminophen (eTable 2 in the Supplement).

Results for all 3 analgesic types were robust to mutual adjustment for use of the other 2 analgesic types (data not shown) and to further adjustment for comorbidities and inflammatory factors (eTable 3 in the Supplement). We did...
not observe substantial changes in associations when we restricted our analyses to individuals without myocardial infarction, angina, stroke, arthritis, non–gastrointestinal tract autoimmune disease, or history of gastrointestinal tract ulcer (data not shown) or stratified by family history of breast or ovarian cancer (data not shown). Results remained similar when the latency period was reduced to 0 to 2 years or lengthened to 4 to 6 years. When we lengthened the latency period to 8 to 10 years, the results for nonaspirin NSAIDs remained similar, whereas associations for aspirin and acetaminophen use were weaker (data not shown). Results for simple updated frequency and tablets were similar to the results for cumulative averages (data not shown).

We evaluated associations by tumor type and observed similar associations for rapidly fatal and non–rapidly fatal ovarian cancer (data not shown). We also considered heterogeneity by tumor histotype and observed that results were somewhat stronger for type II carcinomas, although only 1 test for heterogeneity was significant (eTable 4 and eTable 5 in the Supplement). For example, participants with cumulative average aspirin use frequency of 5 or more vs less than 2 days per week had an HR of 0.84 (95% CI, 0.61-1.14) for risk of type II ovarian cancer and an HR of 0.95 (95% CI, 0.53-1.70) for risk of type I ovarian cancer (P = .65 for heterogeneity). The positive association for 10 or more years vs less than 1 year of nonaspirin NSAID use was significantly positive for type II tumors (HR, 1.61; 95% CI, 1.21-2.14, P = .001 for trend) but not type I tumors (HR, 1.00; 95% CI, 0.59-1.70, P = .51 for trend; P = .02 for heterogeneity).

Discussion

To our knowledge, this prospective cohort study is among the first to evaluate in detail the associations between type, timing, frequency, quantity, and duration of analgesic use with risk of ovarian cancer by using regularly updated exposure information. We did not observe associations between total aspirin use and ovarian cancer risk. However, when we evaluated low-dose and standard-dose aspirin separately, the results suggested an inverse association for low-dose aspirin, but no inverse association for standard-dose aspirin. Use of nonaspirin NSAIDs and use of acetaminophen were not inversely associated with ovarian cancer risk, and our results suggest that heavy use of these medications may be associated with an increased risk.

Aspirin is thought to lower cancer risk by reducing inflammation.4 The mechanism underlying the dose-response relationship between aspirin and colon cancer is thought to be suppression of prostaglandin synthesis via inhibition of the cyclooxygenase 1 (COX-1) and COX-2 enzymes.29-30 We did not observe a dose-response relationship for ovarian cancer, suggesting that other mechanisms may be driving the association. For example, mechanisms unique to low-dose aspirin (eg, irreversible inhibition of platelet COX-1)29 may influence carcinogenesis by reducing platelet activation and recruitment.32 Nonaspirin NSAIDs and acetaminophen share some, but not all, mechanisms of action with aspirin.23,27-30 For example, although aspirin, nonaspirin NSAIDs, and acetaminophen can block the COX enzymes, the extent to which they each block COX-1 and COX-2 differs.23-27 In the present analysis, we observed a significant, positive association between high-quantity or long-term use of nonaspirin NSAIDs and risk of ovarian cancer and a suggestion of a positive association for acetaminophen use. Although our results differed from previous studies that observed no association for regular nonaspirin NSAID or acetaminophen use, the 2 population-based studies that previously evaluated long-term nonaspirin NSAID use for 10 or more years also observed positive associations with ovarian cancer risk.33,34 For acetaminophen, of the 2 earlier population-based studies that evaluated use for 10 or more years, one reported a positive association33 and the other reported an inverse association.35 To our knowledge, the present study is the first prospective, population-based study to assess acetaminophen use for 10 or more years.

Important strengths of this large prospective study include adequate power and sufficiently detailed exposure data to evaluate how timing and patterns of analgesic use are associated with ovarian cancer risk. Participants provided biennially updated exposure information that captured current type, frequency, quantity, dose (aspirin only), and duration of analgesic use. This level of detail allowed us to consider the patterns of aspirin use that may be most relevant to ovarian cancer risk and prevention.36 Furthermore, the frequently updated exposure data in conjunction with the prospective study design limited the potential for exposure misclassification and recall bias and allowed us to incorporate a 2- to 4-year latency period between exposure measurement and evaluation for ovarian cancer onset, thereby lowering the possibility of reverse causation.

Limitations

Our study had several limitations. Follow-up began when women were aged 25 to 59 years; therefore, we likely underestimated premenopausal use and overall duration of use. We also had limited power to consider medication quantity and dose. We did not query indication for analgesic use; however, when we conducted sensitivity analyses among women without common indications for use (eg, cardiovascular disease and arthritis), results were similar to our primary analysis. Furthermore, we were able to consider the distribution of indications reported among approximately 8000 NHS/NHSII participants in a substudy37; despite differences in the distribution of indications (data not shown), we observed a similar increased ovarian cancer risk among heavy users of all analgesic types. We lacked individual-level data on nonaspirin NSAID type, although previous work in the aforementioned NHS/NHSII substudy suggested that nonaspirin NSAIDs used were predominantly ibuprofen and naproxen sodium.37 We were limited in our ability to assess interactions with factors related to higher ovarian cancer risk (eg, germline mutations, endometriosis); we suggest that future research evaluate populations who might particularly benefit from low-dose aspirin. Finally, our study was conducted primarily among white women; therefore, we may not have captured all women in whom low-dose aspirin might be particularly advantageous.
Conclusions

Our results cannot rule out a reduced risk of ovarian cancer among frequent (≥5 days per week) aspirin users, and we observed a significantly lower risk for current (2-4 years before diagnosis) low-dose aspirin use. Our results also suggest an increased risk of ovarian cancer among long-term, high-frequency users of nonaspirin analgesics, although this finding may reflect unmeasured confounding. Further exploration is warranted to evaluate the mechanisms by which heavy use of aspirin, nonaspirin NSAIDs, and acetaminophen may contribute to the development of ovarian cancer and to replicate our findings. Meanwhile, our results suggest that the 2016 US Preventive Services Task Force recommendation advising adults aged 50 to 59 years with a 10-year risk of cardiovascular disease greater than 10% to initiate low-dose aspirin therapy is unlikely to increase the risk of ovarian cancer.

REFERENCES


