Published in final edited form as:

Lancet Oncol. 2018 August ; 19(8): 1107–1116. doi:10.1016/S1470-2045(18)30373-5.

Pre- and post-diagnosis use of common analgesics and ovarian cancer prognosis (NHS/NHSII): a prospective cohort study

Melissa A. Merritt, PhD^{1,*}, Megan S. Rice, ScD^{2,3}, Mollie E. Barnard, ScD⁴, Susan E. Hankinson, ScD^{4,5} [Professor], Ursula A. Matulonis, MD⁶ [Professor], Elizabeth M. Poole, PhD^{#2}, and Shelley S. Tworoger, PhD^{#4,7} [Professor]

¹Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI

²Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

³Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA

⁴Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

⁵Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA

⁶Gynecologic Oncology Program, Dana-Farber Cancer Institute, Boston, MA

⁷Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL

These authors contributed equally to this work.

Abstract

Background—Ovarian cancer is the fifth most common cause of cancer death among US women. Our objective was to determine whether modifiable exposures to common analgesics outside of standard treatment influence prognosis in patients with ovarian cancer.

Methods—The Nurses' Health Study (NHS) and NHSII are prospective studies of 121,700 and 116,429 US nurses who have completed biennial questionnaires since 1976 and 1989, respectively. Eligible participants in the current study included women who were diagnosed with confirmed invasive, stage I-III epithelial ovarian cancer from medical records, death certificate or linkage to a state or SEER cancer registry and who had data available on analgesic use. Our main objective

*Correspondence to: Melissa A. Merritt, University of Hawaii Cancer Center, Epidemiology Program, 701 Ilalo Street, Honolulu, HI, 96813, USA, melissa.merritt@hawaii.edu.

Authors' contributions

Literature search: MAM, EMP and SST.

Study design: MAM, MSR, MEB, SEH, UAM, EMP and SST.

Data collection: SEH, EMP and SST.

Analysis and interpretation of data: MAM, MSR, MEB, SEH, UAM, EMP and SST.

Writing, review, and/or revision of the manuscript: MAM, MSR, MEB, SEH, UAM, EMP and SST.

Declaration of interests

The authors declared no conflicts of interest.

Ethics committee approval

Informed consent was provided by all participants and the study design, data collection and analyses were performed in accordance with the ethical standards of the institutional review board at the Brigham and Women's Hospital (Boston, MA).

was to determine whether self-reported regular pre- and post-diagnosis use (≥ 2 days/week) of aspirin, non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), or acetaminophen, taken on average over the past 2 years, was associated with risk of dying due to ovarian cancer. The endpoint was defined as death from ovarian cancer (ICD8 1830, 1831 and 1580). We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CI), adjusting for age and year of diagnosis, disease stage and histology.

Findings—Our analyses included 1031 cases of epithelial ovarian cancer (630 deaths) for pre-diagnosis exposure and 964 cases (512 deaths) for post-diagnosis exposure from then NHS/NHSII. Pre-diagnosis analgesic use of any type and post-diagnosis acetaminophen use were not associated with survival. Compared with never users, recent (current use in the past 2 years) post-diagnosis use of aspirin (HR, 0.68 [95% CI, 0.52 to 0.89]) and non-aspirin NSAIDs (HR, 0.67 [95% CI, 0.51 to 0.87]) was associated with improved ovarian cancer-specific survival. In analyses of change in analgesic use from pre-diagnosis to post-diagnosis, compared with women who remained never users, those who became recent users of aspirin (HR, 0.44 [95% CI, 0.26 to 0.74]) or became recent users of non-aspirin NSAIDs (HR, 0.46 [95% CI, 0.29 to 0.73]) post-diagnosis had the lowest risk of ovarian cancer-specific death.

Interpretation—Recent use of aspirin or non-aspirin NSAIDs after diagnosis appeared to improve ovarian cancer-specific survival. If these results are confirmed, it will be of interest to test for synergistic effects of anti-inflammatory medications used in combination with standard therapies in order to improve the outlook for ovarian cancer patients.

Funding—NIH NCI and The Marsha Rivkin Center for Ovarian Cancer Research.

Keywords

epithelial ovarian cancer; aspirin; nonsteroidal anti-inflammatory drugs; acetaminophen; survival; post-diagnosis

Introduction

Ovarian cancer is the eighth most common cause of cancer mortality among women worldwide and the fifth leading cause of cancer death in US women.¹ There is a lack of early detection strategies and 60% of women with ovarian cancer are diagnosed with distant disease with <30% five-year survival.² Although there have been advances in therapy, outcomes have not substantively improved.³ A National Academy of Medicine report recommended leveraging our growing understanding of unique immunologic and molecular characteristics of ovarian cancer to assess novel pharmacologic and non-pharmacologic therapies.⁴ Increasing evidence suggests that inflammatory factors are associated with worse outcomes in ovarian cancer patients.^{5–7} Aspirin and non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are known anti-inflammatory agents that can influence all stages of carcinogenesis.^{8,9} A recent pooled analysis of 12 population-based ovarian cancer case-control studies in the Ovarian Cancer Association Consortium (OCAC) with 7776 cases observed that aspirin use versus non-use was associated with a significant 9% lower risk of developing ovarian cancer.¹⁰ This study reported a similar, but non-significant, lower risk with non-aspirin NSAIDs use. In the same population, Dixon *et al.*¹¹ observed that pre-diagnosis analgesic use was not associated with survival.

Currently there are very limited data available to evaluate whether post-diagnosis use of common analgesic medications influence ovarian cancer survival.^{12,13} In a large Danish cohort study including 4117 women with ovarian cancer, post-diagnosis use of low-dose aspirin was not associated with mortality risk.¹² Further studies of post-diagnosis exposures, and changes in exposures from pre-diagnosis to post-diagnosis, are important as these modifiable factors could be used to improve the prognosis for women with ovarian cancer. Here, we evaluated whether use of aspirin, non-aspirin NSAIDs and acetaminophen was associated with improved ovarian cancer-specific survival among women with epithelial ovarian cancer in the observational, prospective Nurses' Health Study (NHS) and NHSII.

Material and methods

Study design and participants

The NHS was established in 1976 among 121,700 female registered nurses, ages 30-55 years, and NHSII began in 1989 among 116,429 female registered nurses, ages 25-42 years.^{14,15} In the NHS, the study population included nurses who were residing in the 11 states with the largest number of state registrants (New York, California, Pennsylvania, Ohio, Massachusetts, New Jersey, Michigan, Texas, Florida, Connecticut and Maryland). In the NHSII, the study population included nurses from 14 states with large populations (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina and Texas). Participants completed questionnaires on medication use, lifestyle factors and disease outcomes (including ovarian cancer) every two years subsequently. For all ovarian cancer cases reported by participants and ovarian cancer deaths identified by family members, the National Death Index, or the U.S. Postal Service, we obtained medical records or linked to a state or SEER cancer registry to confirm the diagnosis and cause of death (as appropriate). Follow-up for death is very high (98%).^{16,17} The cause of death determination is highly accurate; the underlying cause of death was determined by physicians using information from the death certificate, medical records, and occasionally information from next of kin. A gynecologic pathologist blinded to participants' exposure status abstracted disease stage, histologic subtype, grade and invasiveness. For the subset of cases for whom we obtained surgical records, we abstracted information on debulking status/residual disease. Ovarian, primary peritoneal and fallopian tube cancer cases were included in this analysis and are subsequently referred to as ovarian cancer cases.

Potentially eligible women included cases with confirmed invasive, International Federation of Gynecology and Obstetrics (FIGO) stage I-III epithelial ovarian cancer identified from medical records, death certificate or linkage to a state or SEER cancer registry and who had data available on analgesic use. The following factors were not considered in determining eligibility: grade, histology, performance status criteria, previous or concomitant treatments and co-morbidities. Specifically, we identified 1789 confirmed ovarian cancer cases (NHS = 1410; NHSII = 379) diagnosed between 1976-2012 (NHS) and 1989-2013 (NHSII). Of these we excluded non-epithelial cancer (NHS = 58; NHSII = 29) [there are few non-epithelial cancers as these are less common among older women and they have distinct survival trajectories from epithelial tumors], borderline cancer (NHS = 112; NHSII = 62), stage IV

cancer (NHS = 136; NHSII = 22) or missing stage (NHS = 110; NHSII = 21), cases deceased within one month of diagnosis (NHS = 15; NHSII = 2), and participants with missing data on non-aspirin NSAIDs, aspirin and acetaminophen use (NHS = 72; NHSII = 7). After exclusions, 1143 total ovarian cancer cases (NHS = 907; NHSII = 236) remained. Participants could be included in both pre-diagnosis and post-diagnosis medication use analyses as long as they had information on the relevant exposures. The institutional review board at the Brigham and Women's Hospital (Boston, MA) approved this study. Completion of the questionnaire was considered to imply informed consent.

Procedures

In NHS, aspirin use and quantity (number of tablets per week) were assessed in 1980 and every two years afterwards except for 1986 (data from 1984 were carried forward to 1986). Data on aspirin frequency (days per week) were collected using predetermined categories in 1984, 1988 and every two years thereafter. In 2000 and all subsequent questionnaires, data on the use, quantity and frequency of "Baby" or low dose aspirin (100 mg/tablet) and high dose aspirin (325 mg/tablet) were collected separately. Use of non-aspirin NSAIDs (e.g., ibuprofen and naproxen except for COX-2 inhibitors) and acetaminophen were queried in 1990 and every questionnaire thereafter similarly to aspirin. The frequency of non-aspirin NSAIDs and acetaminophen use was evaluated in 1990 and every two years afterwards (except 1994 and 1996), while quantity of use was first assessed in 1998 and each two years thereafter.

In the NHSII, use of aspirin, non-aspirin NSAIDs and acetaminophen were assessed in 1989, 1993 and every two years afterwards. Data from 1989 were carried forward for 1991. Biennial information on frequency was first collected in 1993 (aspirin) and 1995 (non-aspirin NSAIDs, acetaminophen), and quantity for all three medications was first assessed in 1999. Beginning in 2001 and in all questionnaires thereafter data on low and high dose aspirin use were collected separately. In general the time period of use reported in each questionnaire referred to average use over the past two years. Further detailed information on how analgesic use was assessed is provided in the online questionnaires that are posted at: <http://www.nurseshealthstudy.org/participants/questionnaires>

Regular use (2 days/week) of aspirin, non-aspirin NSAIDs and acetaminophen was classified as never, past and current. We also examined quantity (never; past; current use of 1-5, 6-14, >14 tablets per week) and frequency (never; past; current use for 1, 2-5, >5 days per week) of use. We evaluated the total duration of use in the pre-diagnosis time period as: never user; <5, 5+ years (combined categories for past/recent users).

Pre-diagnosis medication use was assessed at the questionnaire that preceded the ovarian cancer diagnosis (i.e., exposure on the 1988 questionnaire if ovarian cancer was reported on the 1990 questionnaire). Post-diagnosis medication use was obtained from the first questionnaire after diagnosis (e.g., the questionnaire return date occurred after the date of diagnosis).

Outcomes

The outcomes of interest were all-cause mortality based on death certificates obtained from the National Death Index, and ovarian cancer-specific death (ICD8 1830, 1831 and 1580).

Statistical analysis

There were no predefined rules to exclude participants (for example, if they were not assessable) and all women in the cohort were included in the analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models.¹⁸ Results were very similar for analyses of all-cause death (data not shown) and ovarian cancer-specific death, thus we show results for the latter. For pre-diagnosis exposures, the analytic time scale was measured in months from diagnosis until death or the end of follow-up (NHS = 2014; NHSII = 2015). For post-diagnosis exposures, we left-censored the cases until the date of first post-diagnosis questionnaire return. Multivariable models were adjusted for *a priori* covariates selected because of their influence on ovarian cancer prognosis, including age of diagnosis (continuous), stage (I [reference], II, III) and histology (serous [reference], endometrioid, other). To account for potential changes in ovarian cancer treatment over time, we adjusted for the calendar year of diagnosis (continuous). We further tested whether additional adjustment for possible confounders: parity (continuous); duration of oral contraceptive use (continuous); tubal ligation (yes, no); menopausal status (premenopausal, postmenopausal [reference], unknown); family history of ovarian cancer (yes, no); smoking (never smoker [reference], past, current); body mass index (BMI) (<21 kg/m², 21-<23 [reference], 23-<25, 25-<30, 30-<35, 35+); smoking and BMI in the same model; postmenopausal hormone therapy (continuous duration of use for estrogen only, estrogen plus progesterone, other types); or tumor grade (1, 2, 3 [reference], missing) altered the risk estimates by 10% or more and observed that the risk estimates were similar, therefore these factors were not included in the final models. Tests for linear trend were performed using the Wald test with an ordinal trend variable entered into the model as a single continuous variable. To test the proportional hazards assumption, we computed multiplicative interaction terms with time period of diagnosis and compared a reduced multivariate model (main exposures) with a model that contained the main exposures and interaction terms using the likelihood ratio test. To test for heterogeneity between the NHS and NHSII, we analyzed the data separately and pooled them using random-effects meta-analysis.¹⁹ We performed power calculations (2-sided tests, $\alpha=0.05$, 80% power) and estimated the maximum detectable risk estimate for recent use of aspirin or NSAIDs in relation to risk of ovarian cancer-specific mortality or all-cause mortality. For post-diagnosis use, the maximum detectable HRs were 0.83-0.87 for recent aspirin use and 0.81-0.85 for recent NSAIDs use; these estimates are closer to 1 than what we actually observed). For pre-diagnosis use, the maximum detectable HRs were 0.87-0.90 for recent aspirin use and 0.84-0.87 for recent NSAIDs use; as the observed HRs in our study were closer to 1 than these estimates, we cannot preclude that there was a modest effect.

We carried out stratified analyses by histology (serous/poorly differentiated versus non-serous; we did not exclude low-grade serous as only a very small proportion of the serous cases are low grade) and stage (I/II versus III).²⁰ Interaction terms were calculated by multiplying binary stratifying variables with categorical medication use. The multivariate

models including the interaction terms were compared with similar multivariate models that did not include interaction terms using the likelihood ratio test.

The following sensitivity analyses were carried out: excluding women who reported comorbidities prior to their diagnosis that may explain their analgesic use (diabetes, autoimmune disease or cardiovascular disease); exploring missing values for covariates (stage, histology) and the main exposures (use of aspirin and non-aspirin NSAIDs) by multiple imputation; for post-diagnosis exposure, excluding medication use that was reported during the first 12 months after diagnosis; testing whether the post-diagnosis results were sensitive to the timing of when women completed their first post-diagnosis questionnaire (i.e., restricting to questionnaires that were completed within four years after diagnosis). For pre-diagnosis exposure, we carried out secondary analyses of exposures that were reported at least four years prior to diagnosis to ensure that subclinical disease did not influence reporting in cases. Lastly, we carried out an analysis that adjusted for the amount of residual disease/debulking status (optimal [less than 1 cm] [reference], suboptimal [more than 1 cm]) by restricting to the 14-19% of cases with these data. For all analyses statistical significance was defined as having a P-value < 0.05. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). In addition, multinomial logistic regression imputation and Kaplan-Meier analyses were performed using the MICE and survminer packages, respectively, in R version 3.5.0 (<http://www.R-project.org/>). We have carried out and reported this cohort study following the guidelines in the STROBE statement.

Role of the funding source

The study sponsor had no role in the study design, in the collection, analysis or interpretation of the data or in the writing of the manuscript. MAM, EMP and SST had full access to all the data in the study and had the final responsibility for the decision to submit this paper for publication.

Results

The NHS and NHSII prospective cohorts were established in 1976 and 1989, respectively. From these studies we included 823 (NHS) and 208 (NHSII) women with ovarian cancer in analyses of pre-diagnosis medication use and 735 (NHS) and 229 (NHSII) in analyses of post-diagnosis use (Table 1). In the NHS and NHSII analytical populations, 735 (81%) of 907 and 229 (97%) of 236 of cases had a post-diagnosis questionnaire available, respectively. The distribution of survival time, stage, grade and histology varied by cohort. The median (interquartile range [IQR]) survival time for NHS and NHSII participants was 3.7 years (IQR=1.7-8.3) and 6.2 (IQR=3.6-10.6) for the pre-diagnosis medication use analysis and 5.1 years (IQR=2.6-12.2) and 6.5 (IQR=3.8-11.3) for the analysis of post-diagnosis medication use, respectively. For analysis of post-diagnosis exposures, the median (IQR) years between diagnosis and the aspirin questionnaire return date ranged from 1.1 years (IQR=0.6-1.7) for the NHS and 1.0 years (IQR= 0.6-1.6) for the NHSII. The corresponding median time between the post-diagnosis aspirin questionnaire date and the date of death or censoring was 3.8 years (IQR=1.5-10.3) in the NHS and 5.7 years

(IQR=2.8-9.9) in the NHSII. These timeframes were very similar for the assessment of NSAIDs (data not shown).

Women in NHS had higher age at diagnosis (pre-diagnosis, median=66 (IQR=58-72); post-diagnosis, median=65 (IQR=56-71)) versus NHSII cases (pre-diagnosis, median=51 (IQR=47-55); post-diagnosis, median=51 (IQR=46-55). NHS cases also had a higher rate of ovarian cancer-specific death (pre-diagnosis, 559 [68%] of 823 patients; post-diagnosis, 433 [59%] of 735 patients) versus NHSII (pre-diagnosis, 71 [34%] of 208 patients; post-diagnosis, 79 [35%] of 229 patients).

NHS participants were more likely to be stage III (pre-diagnosis, 597 [73%] of 823 patients; post-diagnosis, 486 [66%] of 735 patients) or grade 3 (G3) (pre-diagnosis, 407 [49%] of 823 patients; post-diagnosis, 344 [47%] of 735 patients) versus NHSII (stage III, pre-diagnosis, 97 [47%] of 208 patients; post-diagnosis, 110 [48%] of 229 patients; G3, pre-diagnosis, 84 [40%] of 208 patients; post-diagnosis, 92 [40%] of 229 patients). A higher proportion of NHS versus NHSII women had serous/poorly differentiated histology (pre-diagnosis NHS, 571 [69%] of 823 patients; post-diagnosis NHS, 491 [67%] of 735 patients; pre-diagnosis NHSII, 96 [46%] of 208 patients; post-diagnosis NHSII, 107 [47%] of 229 patients). Consistent with patterns in the full cohorts, we observed notable differences between NHS and NHSII ovarian cancer cases in use of pre-diagnosis aspirin and non-aspirin NSAIDs; namely, NHS participants had higher prevalence of recent aspirin use (i.e., current use in the past 2 years; pre-diagnosis dataset, 379 [47%] of 815 patients; post-diagnosis dataset, 303 [47%] of 645 patients) and lower recent pre-diagnosis NSAIDs use (NHS pre-diagnosis dataset, 189 [30%] of 625 patients; post-diagnosis dataset, 156 [31%] of 498 patients). In contrast, in NHSII there were fewer recent pre-diagnosis aspirin users (pre-diagnosis dataset, 51 [25%] of 207 patients; post-diagnosis dataset, 49 [24%] of 201 patients) and a higher proportion of recent pre-diagnosis non-aspirin NSAIDs users (NHSII pre-diagnosis dataset, 94 [47%] of 199 patients; post-diagnosis dataset, 89 [46%] of 192 patients).

When comparing cases who were included in the pre-diagnosis medication use analysis with those in the post-diagnosis analysis within the same cohort, there were similar patterns of pre-diagnosis aspirin and NSAIDs use as well as a similar distribution by tumor grade and histology. In NHS, there was a shift to more stage I disease in the post-diagnosis analysis (192 [26%] of 735 patients) versus the pre-diagnosis analysis (158 [19%] of 823 patients). However, this difference was not observed in NHSII.

We observed no association between pre-diagnosis aspirin use and ovarian cancer-specific survival (Table 2). In contrast, compared with never users, women who reported recent use of aspirin post-diagnosis had an improved ovarian cancer-specific survival (HR, 0.68 [95% CI, 0.52 to 0.89]) (Appendix p 8), with significant associations for recent post-diagnosis aspirin intake of 1-5 tablets/week (HR, 0.69 [95% CI, 0.51 to 0.94]) (P-trend, current users = 0.77) and 2-5 days/week (HR, 0.59 [95% CI, 0.39 to 0.89]) (P-trend, current users = 0.72). There was no evidence of heterogeneity in these analyses between the two cohorts (P-heterogeneity = 0.05). We further evaluated the association between aspirin use and ovarian cancer-specific survival when accounting for the aspirin dose (i.e., low dose versus high dose tablets) and observed that the associations were consistent with the overall findings for

recent post-diagnosis aspirin use but they were attenuated and non-significant (Appendix p 1).

There were no associations between pre-diagnosis non-aspirin NSAIDs use (Table 3) or for pre-or post-diagnosis acetaminophen use (Appendix p 2) with ovarian cancer-specific survival. For post-diagnosis use of non-aspirin NSAIDs, compared with never users, women who reported recent post-diagnosis use (HR, 0.67 [95% CI, 0.51 to 0.87]) (Table 3, Appendix p 9) had an improved ovarian cancer-specific survival. Results were significant for recent post-diagnosis NSAIDs use of 1-5 tablets/week (HR, 0.62 [95% CI, 0.42 to 0.92]) (P-trend, current users = 0.12) and 2-5 days/week (HR, 0.63 [95% CI, 0.43 to 0.93]) (P-trend = 0.92). We observed similar results in analyses of non-aspirin NSAIDs use between NHS and NHSII (P-heterogeneity = 0.07), with one exception. NHS women who reported recent post-diagnosis use of non-aspirin NSAIDs of >14 tablets/week versus never use had a higher risk of mortality (HR, 2.33 [95% CI, 1.18 to 4.61]). However, this finding was based on a small number (n = 20) of cases and this association was non-significant after excluding women with co-morbidities (data not shown).

We assessed whether changes in analgesic use from pre-diagnosis to post-diagnosis were related to ovarian cancer-specific survival. Compared with cases who remained never users, women who became recent users of aspirin post-diagnosis (i.e. changed from a never/past user pre-diagnosis to a current user post-diagnosis) had an improved ovarian cancer-specific survival (HR, 0.44 [95% CI, 0.26 to 0.74]) (Table 4). A similar pattern was observed for non-aspirin NSAIDs (compared to consistent never users, became recent users, HR, 0.46 [95% CI, 0.29 to 0.73]). Similar inverse but non-significant relationships were observed for women who remained recent users of aspirin or non-aspirin NSAIDs. The findings were similar across cohorts (P-heterogeneity = 0.24).

In general the results were similar in analyses that were only adjusted for age (Appendix p 4) and when we explored missing values by multiple imputation (Appendix p 10). In sensitivity analyses, findings for analyses of pre-diagnosis and post-diagnosis exposures were similar when excluding women with co-morbidities that may be related to analgesic use (data not shown). In a subset of women (14-19%) with data on debulking status, we assessed additional adjustment for debulking status and observed similar findings (Appendix p 5). In analyses of post-diagnosis exposures, results were similar when assessing analgesic use reported at least 12 months after diagnosis (data not shown). We carried out further analyses of post-diagnosis medication use to determine if results were sensitive to timing of when women entered the analysis (within four years post-diagnosis) and of pre-diagnosis medication use to analyze exposures that occurred at least four years prior to diagnosis (to ensure that subclinical disease did not influence the results). For both analyses the results did not change substantially (data not shown).

In stratified analyses by stage (I/II versus III) and histology (serous/poorly differentiated versus other) there was no evidence of heterogeneity (P-interaction = 0.12). However, we observed a suggestively stronger association for recent post-diagnosis aspirin use versus never use in subjects with stage I/II disease (HR, 0.45 [95% CI, 0.24 to 0.85]) compared to cases with stage III disease (HR, 0.77 [95% CI, 0.57 to 1.04]) (Appendix p 6). In analyses of

post-diagnosis use of NSAIDs, there were improvements in ovarian cancer-specific survival for cases with both stage I/II (HR, 0.59 [95% CI, 0.30 to 1.18]) and stage III (HR, 0.70 [95% CI, 0.52 to 0.93]) disease. For analyses that were stratified by histologic subtype, the risk associations were similar to the overall findings (Appendix p 7). For women with serous histology, compared with never users, there was an improved ovarian cancer-specific survival with recent post-diagnosis aspirin use (HR, 0.72 [95% CI, 0.53 to 0.97]) or with recent post-diagnosis NSAIDs use (HR, 0.63 [95% CI, 0.46 to 0.85]).

Discussion

To our knowledge this was the largest, prospective analysis to date of pre-diagnosis and post-diagnosis use of several types of common analgesic medications. We observed that women who reported recent use of aspirin and non-aspirin NSAIDs in the post-diagnosis period had an improved ovarian cancer-specific survival. If these results are confirmed, it will be of interest to assess post-diagnosis use of anti-inflammatory medications used in combination with standard therapies as an intervention aimed at women diagnosed with ovarian cancer in order to improve their prognosis. In contrast, post-diagnosis use of acetaminophen, and pre-diagnosis use of any type of analgesic, were not significantly associated with survival. The latter findings are consistent with the earlier OCAC study that showed pre-diagnosis analgesic use was not associated with survival.¹¹

Several mechanisms may link aspirin and non-aspirin NSAIDs use to an improved survival in ovarian cancer patients. Aspirin and non-aspirin NSAIDs have the ability to block the conversion of arachidonic acid into pro-inflammatory prostaglandins via the inhibition of the cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes.²¹ Prostaglandins are involved in processes that may promote the growth and spread of cancer including cellular proliferation, migration, and invasiveness.⁹ Another key mechanism is the antiplatelet effects of non-aspirin NSAIDs and aspirin. One third of women with ovarian cancer have thrombocytosis (a disorder in which the body produces too many platelets) and there is accumulating evidence to suggest that platelets play a role in ovarian cancer growth, angiogenesis and metastasis.^{22–24} Additionally, high platelet to lymphocyte ratio has been associated with worse survival among ovarian cancer patients.^{25–27} Further studies are needed to define the molecular mechanisms that explain the survival benefit of post-diagnosis aspirin and NSAID use for women with ovarian cancer and to determine whether certain molecular subtypes of ovarian cancer may be more sensitive to the effects of aspirin and NSAIDs. The importance of considering the impact of aspirin and NSAIDs use in the context of tumor markers is demonstrated by colorectal cancer studies in which aspirin use was associated with survival among patients with COX-2 positive tumors as well as tumors with PIK3CA mutations, a pathway downregulated by COX-2 activation.^{28,29}

Strengths of this study included the prospective design with a large number of cases, the high follow-up rate for ascertainment of deaths and highly accurate cause of death information, and the detailed and updated collection of data on medication use that allowed the evaluation of pre-diagnosis and post-diagnosis medication use. To our knowledge, this is the first report that has evaluated use of several types of common analgesic medications after diagnosis in relation to ovarian cancer survival. Our results for aspirin use are consistent

with an earlier study that reported an improved recurrence free and overall survival among 143 ovarian cancer patients who used post-diagnosis aspirin.¹³ In contrast, in a Danish cohort study there was no association between post-diagnosis use of low-dose aspirin and mortality.¹² However, there were differences in our study designs as the current study focused on reported actual aspirin use whereas the Danish study focused only on low-dose aspirin based on filled prescriptions thus it was possible that users of high-dose aspirin could have been included in the referent category which could attenuate their risk estimates. The current finding that post-diagnosis use of aspirin and non-aspirin NSAIDs may improve ovarian cancer survival is promising and, if these results are confirmed, this could provide a simple and cost-effective strategy to test in combination with standard therapies.

There are some limitations that should be considered: there was limited power to finely examine the full range of frequency and quantity of use and to carry out analyses stratified by stage. Furthermore, statistical tests for interaction have low power which may limit their usefulness.³⁰ We explored missing data using multiple imputation; however, these results should be interpreted with caution since there are time trends in the use of these medications which may limit the validity of imputation models that leverage data from later time periods. Information on medication use was self-reported however these data were collected in a prospective setting and completing biannual questionnaires likely improves data accuracy. A possible limitation of studying populations of registered nurses is that the results may not be generalizable to the general population and to non-Caucasian women. Confounding may influence the results as this was an observational study; however, we evaluated a large range of potential confounders and the findings did not change substantially. We did not have data available on BRCA mutation status therefore we were unable to assess whether the associations differed by this factor. Information on tumor grade was unavailable for 25-33% of the participants but when we adjusted for grade the results were similar. We were unable to adjust for treatment, but we had data on the amount of residual disease for a subset of participants and in this subset we observed similar results in our primary analyses after adjusting for debulking status. Cases with stage IV disease were excluded from this analysis because having metastatic disease could influence post-diagnosis questionnaire return rates. Furthermore, the mortality among Stage IV cases is very high therefore there may be limited opportunity to alter their survival. To account for possible changes in the treatment of ovarian cancer over time, all models were adjusted for year of diagnosis, but in general during the period under study chemotherapy was relatively standardized, and few of the women had evidence of neoadjuvant chemotherapy based on their pathology reports. We also did not identify evidence of differences in associations by year of diagnosis (data not shown). There are no indications for using aspirin/non-aspirin NSAIDs in ovarian cancer patients from an oncological perspective. We addressed the issue of confounding by indication by excluding participants who had co-morbidities that could be related to analgesic use and observed similar results. It is possible that reverse causality could influence the findings if patients who were unwell were less likely to take aspirin and/or non-aspirin NSAIDs. However, several observations suggest that reverse causality does not explain these findings. First, when excluding medication use that occurred within the first year post-diagnosis the results were similar. Second, we observed similar and often stronger associations with recent use of aspirin and non-aspirin NSAIDs when restricting analyses to

NHSII participants, or cases with stage I/II disease, both of whom had better survival and less aggressive disease. Selection bias could influence the results if women who died quickly were not included in the analysis of post-diagnosis medication use. It was therefore reassuring to note that cases who were included in the post-diagnosis analysis had similar pre-diagnosis distributions of analgesic use to cases who were in the pre-diagnosis analysis, and with the exception of stage in NHS, had similar tumor characteristics. Lastly, our analysis focused on ovarian cancer-specific deaths and we expect that the number of deaths that we missed would be very small as ovarian cancer is highly fatal and 80% of the deaths in our study were due to ovarian cancer.

In summary, this is the first report to investigate the use of several types of common medications (aspirin, non-aspirin NSAIDs and acetaminophen) prior to and after a diagnosis of ovarian cancer in relation to survival. Compared with never users, cases who were recent users of non-aspirin NSAIDs or aspirin post-diagnosis had improved survival. It is of great interest to confirm these findings in other observational studies, and to carry out larger studies to identify specific doses that are most protective, as these results would support the assessment of whether post-diagnosis aspirin and non-aspirin NSAIDs use may improve ovarian cancer survival in a randomized controlled trial setting. Ultimately if these findings are confirmed, this could open up new treatment options that when used in combination with standard therapies could improve survival for ovarian cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the participants and staff of the Nurses' Health Study (NHS) and NHSII for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The multiple imputation work has been supported in part by the Biostatistics Core at the H. Lee Moffitt Cancer Center & Research Institute, a comprehensive cancer center designated by the National Cancer Institute.

Funding

This work was supported in part by the National Institutes of Health Award Numbers UM1 CA186107, UM1 CA176726, P01 CA87969 and R01 CA50385 and The Marsha Rivkin Center for Ovarian Cancer Research, Skacel Family Scholar Award. M. Barnard was supported by the National Cancer Institute of the National Institutes of Health under Award Number T32 CA09001 and Award Number F99 CA212222. The authors take full responsibility for the analysis and interpretation of data.

References

1. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2014; 385(9972):977–1010. [PubMed: 25467588]
2. Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Ovarian Cancer. Accessed: 9/1/2017. Available from: <https://seer.cancer.gov/statfacts/html/ovary.html>.
3. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. *Lancet* 2014; 384(9951): 1376–88. [PubMed: 24767708]

4. Institute of Medicine. Ovarian cancers: Evolving paradigms in research and care. Accessed: 10/05/2017 Available from: <http://nationalacademies.org/HMD/reports/2016/state-of-ovarian-cancer>.
5. Maccio A, Madeddu C. Inflammation and ovarian cancer. *Cytokine* 2012; 58(2):133–47. [PubMed: 22349527]
6. Kolomeyevskaya N, Eng KH, Khan AN, et al. Cytokine profiling of ascites at primary surgery identifies an interaction of tumor necrosis factor-alpha and interleukin-6 in predicting reduced progression-free survival in epithelial ovarian cancer. *Gynecol Oncol* 2015; 138(2):352–7. [PubMed: 26001328]
7. Dijkgraaf EM, Welters MJ, Nortier JW, van der Burg SH, Kroep JR. Interleukin-6/interleukin-6 receptor pathway as a new therapy target in epithelial ovarian cancer. *Current pharmaceutical design* 2012; 18(25):3816–27. [PubMed: 22591418]
8. Pereg D, Lishner M. Non-steroidal anti-inflammatory drugs for the prevention and treatment of cancer. *J Intern Med* 2005; 258(2):115–23. [PubMed: 16018788]
9. Ulrich CM, Bigler J, Potter JD. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. *Nat Rev Cancer* 2006; 6(2):130–40. [PubMed: 16491072]
10. Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst* 2014; 106(2):djt431. [PubMed: 24503200]
11. Dixon SC, Nagle CM, Wentzensen N, et al. Use of common analgesic medications and ovarian cancer survival: results from a pooled analysis in the Ovarian Cancer Association Consortium. *Br J Cancer* 2017; 116(9):1223–8. [PubMed: 28350790]
12. Verdoodt F, Kjaer SK, Dehlendorff C, Friis S. Aspirin use and ovarian cancer mortality in a Danish nationwide cohort study. *Br J Cancer* 2018; 118(4):611–5. [PubMed: 29315293]
13. Bar D, Lavie O, Stein N, Feferkorn I, Shai A. The effect of metabolic comorbidities and commonly used drugs on the prognosis of patients with ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* 2016; 207:227–31. [PubMed: 27890326]
14. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer* 2005; 5(5):388–96. [PubMed: 15864280]
15. Rockhill B, Willett WC, Hunter DJ, et al. Physical activity and breast cancer risk in a cohort of young women. *J Natl Cancer Inst* 1998; 90(15):1155–60. [PubMed: 9701365]
16. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol* 1994; 140(11):1016–9. [PubMed: 7985649]
17. Bao Y, Bertoia ML, Lenart EB, et al. Origin, Methods, and Evolution of the Three Nurses' Health Studies. *Am J Public Health* 2016; 106(9):1573–81. [PubMed: 27459450]
18. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. *J Clin Epidemiol* 1995; 48(12):1495–501. [PubMed: 8543963]
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7(3):177–88. [PubMed: 3802833]
20. Prat J Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 2014; 124(1):1–5. [PubMed: 24219974]
21. Liggett JL, Zhang X, Eling TE, Baek SJ. Anti-tumor activity of non-steroidal anti-inflammatory drugs: cyclooxygenase-independent targets. *Cancer Lett* 2014; 346(2):217–24. [PubMed: 24486220]
22. Stone RL, Nick AM, McNeish IA, et al. Paraneoplastic thrombocytosis in ovarian cancer. *N Engl J Med* 2012; 366(7):610–8. [PubMed: 22335738]
23. Davis AN, Afshar-Kharghan V, Sood AK. Platelet effects on ovarian cancer. *Semin Oncol* 2014; 41(3):378–84. [PubMed: 25023353]
24. Allensworth SK, Langstraat CL, Martin JR, et al. Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer. *Gynecol Oncol* 2013; 130(3):499–504. [PubMed: 23747328]

25. Hu D, Lin Y, Liu F, et al. Elevated Preoperative Platelet to Lymphocyte Ratio Indicates Poor Survival in Patients with Resected High-grade Serous Ovarian Carcinoma. *Clinical laboratory* 2016; 62(8):1443–9. [PubMed: 28164624]
26. Miao Y, Yan Q, Li S, Li B, Feng Y. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are predictive of chemotherapeutic response and prognosis in epithelial ovarian cancer patients treated with platinum-based chemotherapy. *Cancer Biomark* 2016; 17(1):33–40. [PubMed: 27314290]
27. Cozzi GD, Samuel JM, Fromal JT, et al. Thresholds and timing of pre-operative thrombocytosis and ovarian cancer survival: analysis of laboratory measures from electronic medical records. *BMC Cancer* 2016; 16:612. [PubMed: 27502272]
28. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *Jama* 2009; 302(6):649–58. [PubMed: 19671906]
29. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med* 2012; 367(17):1596–606. [PubMed: 23094721]
30. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *Bmj* 2003; 326(7382):219. [PubMed: 12543843]

Research in context

Evidence before this study

To identify previous studies of analgesic medication use and ovarian cancer survival, we searched PubMed and Google Scholar for reports published in English between Jan 1, 1973, and Mar 1, 2018. We used the terms “ovarian cancer”, “survival”, “prognosis”, “aspirin”, “nonsteroidal anti-inflammatory drugs”, “NSAIDs” and “acetaminophen”. We manually searched the references in reviews. To our knowledge only two previous studies have examined post-diagnosis aspirin use in relation to ovarian cancer survival, and no published reports have examined the use of several types of analgesic medications (aspirin, non-aspirin NSAIDs and acetaminophen) in pre-diagnosis and post-diagnosis time periods, as well as changes in use from pre-diagnosis to post-diagnosis, in relation to ovarian cancer survival. Studies were needed to examine whether use of these common medications, in particular after diagnosis, may improve survival in ovarian cancer patients.

Added value of this study

To our knowledge, this study provides the first comprehensive assessment of use of aspirin, non-aspirin NSAIDs and acetaminophen in pre-diagnosis and post-diagnosis time periods in relation to ovarian cancer-specific survival. The US Nurses' Health Study (NHS) and NHSII cohorts were ideal populations to carry out this study as repeated data on medication use were collected every two years. We showed that ovarian cancer cases who reported using aspirin and non-aspirin NSAIDs after their diagnosis had an improved ovarian cancer-specific survival. If these findings are confirmed, clinical trials will be needed to test whether the use of post-diagnosis aspirin and non-aspirin NSAIDs may improve the prognosis for women with ovarian cancer and to determine the specific doses that are most protective. Our results suggest that the use of post-diagnosis aspirin and non-aspirin NSAIDs may open up new treatment options that when used in combination with standard therapies may improve survival for ovarian cancer patients.

Implications of all the available evidence

If confirmed in other studies, these findings support the assessment of aspirin and non-aspirin NSAIDs use as an intervention aimed at women diagnosed with ovarian cancer in order to improve their prognosis.

Table 1.

Crude characteristics of women with ovarian cancer who were included in the analysis of pre-diagnosis and post-diagnosis analgesic use

	Pre-diagnosis		Post-diagnosis	
	NHS	NHSII	NHS	NHSII
Total number cases	823	208	735	229
Deaths from ovarian cancer, n (%)	559 (68)	71 (34)	433 (59)	79 (35)
Deaths from all causes, n (%)	661 (80)	75 (36)	555 (76)	85 (37)
Age at diagnosis, median (IQR)	66 (58-72)	51 (47-55)	65 (56-71)	51 (46-55)
Survival time (years), median (IQR) ^a	3.7 (1.7-8.3)	6.2 (3.6-10.6)	5.1 (2.6-12.2)	6.5 (3.8-11.3)
Stage, n (%)				
I	158 (19)	84 (40)	192 (26)	89 (39)
II	68 (8)	27 (13)	57 (8)	30 (13)
III	597 (73)	97 (47)	486 (66)	110 (48)
Grade, n (%)				
G1/well differentiated	48 (6)	28 (13)	55 (7)	33 (14)
G2/moderately differentiated	104 (13)	43 (21)	94 (13)	46 (20)
G3/poorly differentiated	407 (49)	84 (40)	344 (47)	92 (40)
Unknown	264 (32)	53 (25)	242 (33)	58 (25)
Histology, n (%)				
Serous/poorly differentiated	571 (69)	96 (46)	491 (67)	107 (47)
Mucinous	33 (4)	10 (5)	32 (4)	12 (5)
Endometrioid	111 (13)	40 (19)	116 (16)	46 (20)
Clear cell	31 (4)	27 (13)	32 (4)	29 (13)
Other/Unknown	77 (9)	35 (17)	64 (9)	35 (15)
Year of diagnosis, n (%)				
<1997	360 (44)	19 (9)	348 (47)	36 (16)
1997-<2000	102 (12)	23 (11)	83 (11)	21 (9)
2000-<2004	131 (16)	41 (20)	106 (14)	42 (18)
2004+	230 (28)	125 (60)	198 (27)	130 (57)
Pre-diagnosis aspirin use, n (%) ^b				
Never	135 (17)	115 (56)	100 (16)	111 (55)
Past	301 (37)	41 (20)	242 (38)	41 (20)
Recent	379 (47)	51 (25)	303 (47)	49 (24)
Pre-diagnosis NSAIDs use, n (%) ^c				
Never	241 (39)	37 (19)	185 (37)	36 (19)
Past	195 (31)	68 (34)	157 (32)	67 (35)
Recent	189 (30)	94 (47)	156 (31)	89 (46)

^aYears between the date of diagnosis and the date of death or last follow-up.

^bData on pre-diagnosis aspirin use were unknown mostly due to non-completion of questionnaires for N=8 NHS and N=1 NHSII participants (pre-diagnosis dataset) and for N=90 NHS and N=28 NHSII participants (post-diagnosis dataset).

^cData on pre-diagnosis NSAIDs use were unknown for N=198 of NHS and N=9 of NHSII participants (pre-diagnosis dataset) and for N=237 of NHS and N=37 of NHSII participants (post-diagnosis dataset). Much of the unknown data on NSAIDs use occurs because this information was not collected until 1990.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Hazard ratio^a of ovarian cancer-specific mortality according to pre-diagnosis and post-diagnosis aspirin intake

	Combined ^b			NHS			NHSII		
	Deaths	Cases	HR	Deaths	Cases	HR	Deaths	Cases	HR
Pre-diagnosis aspirin use^c	n=623	n=1022		n=553	n=815		n=70	n=207	
Never	143 (23)	250 (24)	1.00	95 (17)	135 (17)	1.00	48 (69)	115 (56)	1.00
Past	202 (32)	342 (33)	0.95	193 (35)	301 (37)	1.02	9 (13)	41 (20)	0.81
Recent	278 (45)	430 (42)	0.99	265 (48)	379 (47)	1.06	13 (19)	51 (25)	0.94
Pre-diagnosis aspirin quantity^d	n=581	n=941		n=528	n=776		n=53	n=165	
Never	129 (22)	218 (23)	1.00	95 (18)	135 (17)	1.00	34 (64)	83 (50)	1.00
Past	201 (35)	340 (36)	0.94	(37) 193	301 (39)	1.02	8 (15)	39 (24)	0.66
Recent: 1-5 tablets/week	160 (28)	252 (27)	0.96	149 (28)	219 (28)	1.01	11 (21)	33 (20)	1.11
Recent: 6-14 tablets/week	72 (12)	102 (11)	1.10	72 (14)	92 (12)	1.23	0	10 (6)	NA
Recent: >14 tablets/week	19 (3)	29 (3)	0.89	19 (4)	29 (4)	0.95	0	0	NA
P-trend ^e			0.92			0.65			NA
Pre-diagnosis aspirin frequency^f	n=564	n=926		n=494	n=720		n=70	n=206	
Never	120 (21)	210 (23)	1.00	72 (15)	95 (13)	1.00	48 (69)	115 (56)	1.00
Past	196 (35)	335 (36)	0.93	187 (38)	294 (41)	1.00	9 (13)	41 (20)	0.81
Recent: 1 day/week	10 (2)	17 (2)	0.82	10 (2)	16 (2)	0.88	0	1 (0.005)	NA
Recent: 2-5 days/week	84 (15)	128 (14)	1.02	80 (16)	108 (15)	1.11	4 (6)	20 (10)	0.78
Recent: >5 days/week	154 (27)	236 (25)	0.97	145 (29)	207 (29)	1.02	9 (13)	29 (14)	1.07
P-trend ^e			0.88			0.82			0.97
Pre-diagnosis aspirin duration^g	n=536	n=903		n=456	n=678		n=80	n=225	
Never	138 (26)	245 (27)	1.00	80 (18)	115 (17)	1.00	58 (73)	130 (58)	1.00
<5 years	74 (14)	140 (16)	0.80	62 (14)	96 (14)	0.84	12 (15)	44 (20)	0.89
5+ years	324 (60)	518 (57)	0.94	314 (69)	467 (69)	1.05	10 (13)	51 (23)	0.55
Post-diagnosis aspirin use^c	n=491	n=940		n=413	n=712		n=78	n=228	
Never (pre- and post-diagnosis)	119 (24)	231 (25)	1.00	64 (15)	114 (16)	1.00	55 (71)	117 (51)	1.00

	Combined ^b				NHS				NHSII			
	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)
<i>h</i> Past ^h	227 (46)	395 (42)	0.94	(0.73-1.21)	218 (53)	347 (49)	1.14	(0.84-1.55)	9 (12)	48 (21)	0.58	(0.28-1.20)
Recent	145 (30)	314 (33)	0.68	(0.52-0.89)	131 (32)	251 (35)	0.83	(0.60-1.15)	14 (18)	63 (28)	0.42	(0.22-0.77)
Post-diagnosis aspirin quantity^d	n=459	n=882			n=391	n=670			n=68	n=212		
Never (pre- and post-diagnosis)	109 (24)	218 (25)	1.00	(ref.)	64 (16)	114 (17)	1.00	(ref.)	45 (66)	104 (49)	1.00	(ref.)
<i>h</i> Past ^h	228 (50)	396 (45)	0.98	(0.76-1.28)	218 (56)	347 (52)	1.13	(0.83-1.54)	10 (15)	49 (23)	0.79	(0.38-1.63)
Recent: 1-5 tablets/week	88 (19)	185 (21)	0.69	(0.51-0.94)	77 (20)	140 (21)	0.80	(0.56-1.15)	11 (16)	45 (21)	0.48	(0.24-0.96)
Recent: 6-14 tablets/week	28 (6)	64 (7)	0.67	(0.44-1.03)	26 (7)	52 (8)	0.81	(0.51-1.29)	2 (3)	12 (6)	0.33	(0.08-1.38)
Recent: >14 tablets/week	6 (1)	19 (2)	0.59	(0.26-1.35)	6 (2)	17 (3)	0.75	(0.32-1.75)	0	2 (1)	NA	NA
P-trend ^e				0.77				0.80				0.66
Post-diagnosis aspirin frequency^f	n=458	n=906			n=380	n=678			n=78	n=228		
Never (pre- and post-diagnosis)	104 (23)	212 (23)	1.00	(ref.)	49 (13)	95 (14)	1.00	(ref.)	55 (71)	117 (51)	1.00	(ref.)
<i>h</i> Past ^h	227 (50)	405 (45)	0.93	(0.71-1.21)	218 (57)	357 (53)	1.16	(0.84-1.60)	9 (12)	48 (21)	0.58	(0.28-1.20)
Recent: 1 day/week	14 (3)	33 (4)	0.71	(0.41-1.26)	12 (3)	23 (3)	0.91	(0.48-1.73)	2 (3)	10 (4)	0.38	(0.09-1.63)
Recent: 2-5 days/week	31 (7)	82 (9)	0.59	(0.39-0.89)	27 (7)	63 (9)	0.73	(0.45-1.18)	4 (5)	19 (8)	0.43	(0.15-1.20)
Recent: >5 days/week	82 (18)	174 (19)	0.73	(0.53-1.00)	74 (19)	140 (21)	0.94	(0.64-1.39)	8 (10)	34 (15)	0.42	(0.18-0.96)
P-trend ^e				0.72				0.57				0.11

^a Adjusted for age at diagnosis, year of diagnosis, disease stage, histology and cohort (combined estimates).

^b P-heterogeneity comparing the NHS and the NHSII were 0.05.

^c Aspirin use (categorized as never, past and current use) was analyzed from 1980-2012 in the NHS and from 1993-2013 in the NHSII.

^d Aspirin quantity was analyzed from 1980-2012 in the NHS and from 1999-2013 in the NHSII.

^e Significance tests for trend were calculated among recent users only using ordinal variables (0-2) entered into the model as a single continuous variable.

^f Aspirin frequency was analyzed from 1984-2012 in the NHS and from 1993-2013 in the NHSII.

^g Aspirin duration was analyzed from 1980-2012 in the NHS and from 1989-2013 in the NHSII.

^h Most past use occurred prior to diagnosis.

Hazard ratio^a of ovarian cancer-specific mortality according to pre-diagnosis and post-diagnosis NSAIDs use

Combined ^b												NHS			NHSII		
	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)					
Pre-diagnosis NSAIDs use ^c	n=491	n=824			n=424	n=625			n=67	n=199							
	Never	278 (34)	1.00	(ref.)	175 (41)	241 (39)	1.00	(ref.)	16 (24)	37	1.00	(ref.)					
	Past	144 (29)	263 (32)	0.83 (0.66-1.05)	121 (29)	195 (31)	0.82 (0.64-1.06)	23 (34)	68	1.04 (0.53-2.02)							
	Recent	156 (32)	283 (34)	0.94 (0.75-1.18)	128 (30)	189 (30)	0.95 (0.75-1.21)	28 (42)	94	1.05 (0.54-2.01)							
Pre-diagnosis NSAIDs quantity ^d	n=287	n=507			n=242	n=354			n=45	n=153							
	Never	97 (34)	137 (27)	1.00 (ref.)	84 (35)	110 (31)	1.00 (ref.)	13 (29)	27 (18)	1.00 (ref.)							
	Past	109 (38)	210 (41)	0.72 (0.54-0.95)	94 (39)	153 (43)	0.74 (0.55-1.01)	15 (33)	57 (37)	0.57 (0.26-1.27)							
	Recent use: 1-5 tablets/week	46 (16)	87 (17)	0.85 (0.59-1.23)	35 (14)	49 (14)	0.91 (0.60-1.36)	11 (24)	38 (25)	0.64 (0.27-1.54)							
	Recent use: 6-14 tablets/week	24 (8)	48 (9)	1.07 (0.67-1.69)	19 (8)	26 (7)	1.12 (0.67-1.88)	5 (11)	22 (14)	0.86 (0.28-2.67)							
	Recent use: >14 tablets/week	11 (4)	25 (5)	0.75 (0.40-1.41)	10 (4)	16 (5)	0.84 (0.43-1.62)	1 (2)	9 (6)	0.38 (0.05-3.06)							
P-trend ^e				0.86				0.63				0.73					
Pre-diagnosis NSAIDs frequency ^f	n=454	n=763			n=392	n=575			n=62	n=188							
	Never	191 (42)	278 (36)	1.00 (ref.)	175 (45)	241 (42)	1.00 (ref.)	16 (26)	37 (20)	1.00 (ref.)							
	Past	144 (32)	263 (34)	0.83 (0.66-1.05)	121 (31)	195 (34)	0.82 (0.64-1.06)	23 (37)	68 (36)	0.98 (0.50-1.91)							
	Recent use 1 day/week	29 (6)	60 (8)	0.90 (0.60-1.35)	22 (6)	36 (6)	0.85 (0.54-1.35)	7 (11)	24 (13)	1.11 (0.43-2.85)							
	Recent use 2-5 days/week	55 (12)	104 (14)	0.97 (0.71-1.33)	39 (10)	56 (10)	0.96 (0.67-1.37)	16 (26)	48 (26)	1.15 (0.55-2.38)							
	Recent use >5 days/week	35 (8)	58 (8)	0.96 (0.67-1.39)	35 (9)	47 (8)	1.10 (0.76-1.59)	0	11 (6)	NA							
P-trend ^e				0.90				0.26				0.11					
Pre-diagnosis NSAIDs duration ^g	n=479	n=810			n=399	n=585			n=80	n=225							
	Never	191 (40)	286 (35)	1.00 (ref.)	166 (42)	230 (39)	1.00 (ref.)	25 (31)	56 (25)	1.00 (ref.)							
	<5 years	91 (19)	172 (21)	0.89 (0.68-1.15)	68 (17)	106 (18)	0.83 (0.62-1.12)	23 (29)	66 (29)	1.08 (0.59-1.97)							
	5+ years	197 (41)	352 (43)	0.91 (0.74-1.12)	165 (41)	249 (43)	0.92 (0.73-1.15)	32 (40)	103 (46)	0.93 (0.50-1.73)							
Post-diagnosis NSAIDs use ^c	n=433	n=881			n=358	n=656			n=75	n=225							
	Never (pre- and post-diagnosis)	174 (40)	335 (38)	1.00 (ref.)	154 (43)	291 (44)	1.00 (ref.)	20 (27)	44 (20)	1.00 (ref.)							

	Combined ^b					NHS					NHSII				
	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)			
Past ^h	160 (37)	292 (33)	0.93	(0.74-1.19)	134 (37)	213 (32)	0.94	(0.73-1.22)	26 (35)	79 (35)	0.80	(0.43-1.47)			
Recent	99 (23)	254 (29)	0.67	(0.51-0.87)	70 (20)	152 (23)	0.68	(0.50-0.91)	29 (39)	102 (45)	0.61	(0.33-1.13)			
Post-diagnosis NSAIDs quantity ^d	n=316	n=706			n=254	n=510			n=62	n=196					
Never (pre- and post-diagnosis)	101 (32)	209 (30)	1.00	(ref.)	84 (33)	173 (34)	1.00	(ref.)	17 (27)	36 (18)	1.00	(ref.)			
Past ^h	147 (47)	306 (43)	0.91	(0.70-1.19)	122 (48)	228 (45)	0.94	(0.70-1.25)	25 (40)	78 (40)	0.63	(0.33-1.20)			
Recent use: 1-5 tablets/week	38 (12)	101 (14)	0.62	(0.42-0.92)	24 (9)	59 (12)	0.57	(0.36-0.91)	14 (23)	42 (21)	0.55	(0.26-1.14)			
Recent use: 6-14 tablets/week	17 (5)	50 (7)	0.80	(0.48-1.36)	14 (6)	30 (6)	1.05	(0.59-1.86)	3 (5)	20 (10)	0.29	(0.08-1.02)			
Recent use: >14 tablets/week	13 (4)	40 (6)	1.07	(0.58-1.95)	10 (4)	20 (4)	2.33	(1.18-4.61)	3 (5)	20 (10)	0.35	(0.10-1.25)			
P-trend ^e				0.12				0.003				0.12			
Post-diagnosis NSAIDs frequency ^f	n=413	n=829			n=343	n=620			n=70	n=209					
Never (pre- and post-diagnosis)	174 (42)	335 (40)	1.00	(ref.)	154 (45)	291 (47)	1.00	(ref.)	20 (29)	44 (21)	1.00	(ref.)			
Past ^h	160 (39)	292 (35)	0.93	(0.74-1.19)	134 (39)	213 (34)	0.94	(0.72-1.22)	26 (37)	79 (38)	0.81	(0.44-1.49)			
Recent use 1 day/week	23 (6)	52 (6)	0.75	(0.47-1.17)	18 (5)	28 (5)	0.89	(0.53-1.47)	5 (7)	24 (11)	0.41	(0.15-1.14)			
Recent use 2-5 days/week	33 (8)	92 (11)	0.63	(0.43-0.93)	19 (6)	47 (8)	0.60	(0.37-0.98)	14 (20)	45 (22)	0.66	(0.32-1.34)			
Recent use >5 days/week	23 (6)	58 (7)	0.76	(0.49-1.18)	18 (5)	41 (7)	0.71	(0.44-1.17)	5 (7)	17 (8)	0.98	(0.36-2.71)			
P-trend ^e				0.92				0.44				0.36			

^a Adjusted for age at diagnosis, year of diagnosis, disease stage, histology and cohort (combined estimates).

^b P-heterogeneity comparing the NHS and the NHSII were 0.07 with the following exception: post-diagnosis NSAIDs quantity, recent use: >14 tablets/week (P-heterogeneity=0.01).

^c NSAIDs use (categorized as never, past and current use) was analyzed from 1990-2012 in the NHS and 1995-2013 in the NHSII.

^d NSAIDs quantity was analyzed from 1998-2012 in the NHS and 1999-2013 in the NHSII.

^e Significance tests for trend were calculated among recent users only using ordinal variables (0-2) entered into the model as a single continuous variable.

^f NSAIDs frequency was analyzed from 1990-2012 in the NHS and 1995-2013 in the NHSII.

^g NSAIDs duration was analyzed from 1990-2012 in the NHS and 1989-2013 in the NHSII.

^h Most past use occurred prior to diagnosis.

Table 4.

Hazard ratio^a of ovarian cancer-specific mortality according to changes in analgesic use from pre-diagnosis to post-diagnosis

	Combined ^b				NHS				NHSII			
	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)	Deaths	Cases	HR	(95% CI)
Aspirin use	n=433	n=814			n=368	n=615			n=65	n=199		
Never user	92 (21)	175 (21)	1.00	(ref.)	48 (13)	76 (12)	1.00	(ref.)	44 (68)	99 (50)	1.00	(ref.)
Past user ^c	212 (49)	367 (45)	0.95	(0.72-1.25)	203 (55)	322 (52)	1.12	(0.80-1.58)	9 (14)	45 (23)	0.74	(0.34-1.6)
Remained recent user ^d	111 (26)	213 (26)	0.80	(0.58-1.09)	102 (28)	175 (28)	0.95	(0.65-1.38)	9 (14)	38 (19)	0.65	(0.30-1.39)
Became recent user ^e	18 (4)	59 (7)	0.44	(0.26-0.74)	15 (4)	42 (7)	0.54	(0.29-1.00)	3 (5)	17 (9)	0.25	(0.07-0.93)
Non-aspirin NSAID use	n=356	n=676			n=295	n=487			n=61	n=189		
Never user	120 (34)	187 (28)	1.00	(ref.)	107 (36)	160 (33)	1.00	(ref.)	13 (21)	27 (14)	1.00	(ref.)
Past user ^c	150 (42)	273 (40)	0.95	(0.73-1.22)	126 (43)	202 (41)	0.95	(0.72-1.25)	24 (39)	71 (38)	0.82	(0.40-1.66)
Remained recent user ^d	64 (18)	150 (22)	0.79	(0.57-1.09)	47 (16)	83 (17)	0.83	(0.58-1.18)	17 (28)	67 (35)	0.67	(0.31-1.45)
Became recent user ^e	22 (6)	66 (10)	0.46	(0.29-0.73)	15 (5)	42 (9)	0.45	(0.26-0.78)	7 (11)	24 (13)	0.41	(0.16-1.07)

^a Adjusted for age at diagnosis, year of diagnosis, disease stage, histology and cohort (combined estimates).

^b P-heterogeneity comparing the NHS and the NHSII were 0.24.

^c Most past use occurred prior to diagnosis.

^d Participants who reported current use pre-diagnosis and current use post-diagnosis.

^e Participants who reported never or past use pre-diagnosis and current use post-diagnosis.