Use of common analgesic medications and ovarian cancer survival: results from a pooled analysis in the Ovarian Cancer Association Consortium

Suzanne C Dixon*,1,2, Christina M Nagle1,2, Nicolas Wentzensen3, Britton Trabert3, Alicia Beeghly-Fadiel4, Joellen M Schildkraut5,6, Kirsten B Moysich7, Anna deFazio8,9, Australian Ovarian Cancer Study Group1,10, Harvey A Risch11, Mary Anne Rossing12,13, Jennifer A Doherty14, Kristine G Wicklund12, Marc T Goodman15,16, Francesmary Modugno17,18,19, Roberta B Ness20, Robert P Edwards17,18, Allan Jensen21, Susanne K Kjær21,22, Estrid Høgdal21,23, Andrew Berchuck24, Daniel W Cramer25, Kathryn L Terry25,26, Elizabeth M Poole27, Elisa V Bandera28,29, Lisa E Paddock29,30, Hoda Anton-Culver31,32, Argyrios Ziegas31, Usha Menon33, Simon A Gayther34, Susan J Ramus35,36, Aleksandra Gentry-Maharaj33, Celeste Leigh Pearce34,37, Anna H Wu34, Malcolm C Pike38 and Penelope M Webb1,2 on behalf of the Ovarian Cancer Association Consortium

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with improved survival in some cancers, but evidence for ovarian cancer is limited.

Methods: Pooling individual-level data from 12 Ovarian Cancer Association Consortium studies, we evaluated the association between self-reported, pre-diagnosis use of common analgesics and overall/progression-free/disease-specific survival among 7694 women with invasive epithelial ovarian cancer (4273 deaths).

Results: Regular analgesic use (at least once per week) was not associated with overall survival (pooled hazard ratios, pHRs (95% confidence intervals): aspirin 0.96 (0.88–1.04); non-aspirin NSAIDs 0.97 (0.89–1.05); acetaminophen 1.01 (0.93–1.10)), nor with progression-free/disease-specific survival. There was however a survival advantage for users of any NSAIDs in studies clearly defining non-use as less than once per week (pHR = 0.89 (0.82–0.98)).

Conclusions: Although this study did not show a clear association between analgesic use and ovarian cancer survival, further investigation with clearer definitions of use and information about post-diagnosis use is warranted.

Over 238,000 women are diagnosed with ovarian cancer annually (International Agency for Research on Cancer, 2014) and 5-year survival is poor at ~45% (Howlader et al, 2015). Identifying modifiable factors that could improve survival is therefore important. One possible factor is the use of analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs). Nonsteroidal anti-inflammatory drugs, including aspirin and non-aspirin NSAIDs (NA-NSAIDs), inhibit the pro-inflammatory enzyme cyclooxygenase (COX). COX-2 is over-expressed in many cancers including ovarian (Maccio and Madeddu, 2012), and COX-inhibition can reduce angiogenesis and trigger apoptosis (Xin et al, 2007). While improved survival among NSAID users has been reported for breast (Huang et al, 2015), prostate (Liu et al, 2014), and colorectal (Ye et al, 2014) cancers, two previous
observational studies of ovarian cancer found no evidence that pre-diagnosis aspirin, NA-NSAID, or acetaminophen use was associated with survival (Minilkeeva et al, 2015; Nagle et al, 2015). However, both studies were underpowered to detect the likely modest effects. One trial reported no short-term (median follow-up up to 34 months) survival advantage among women with advanced ovarian cancer when a NA-NSAID was added to standard chemotherapy, but did not examine long-term outcomes (Reyners et al, 2012). Interestingly, a preliminary report (published as a conference abstract) has suggested that NSAID use post-diagnosis may be associated with improved survival (Poole et al, 2016). We used data from a large international consortium to examine the association between pre-diagnosis use of common analgesics and survival after a diagnosis of ovarian cancer. We hypothesised that NSAID users would experience a survival benefit compared to non-users.

**Study population.** We pooled data from 12 case-control studies, which included 7694 women with invasive epithelial ovarian tumours, aged <85 years at diagnosis (Supplementary Table 1). Cancers of unknown behaviour (n = 93 high grade; n = 25 low grade) were assumed to be invasive (Trabert et al, 2014). Most women (59%) had serous cancers; 5%, 15%, and 8% had mucinous, endometrioid, and clear cell cancers, respectively. Most cancers (63%) had distant spread.

**Exposure, outcome, and covariates.** Studies provided data on self-reported pre-diagnosis analgesic use (Supplementary Table 2; harmonisation described previously (Trabert et al, 2014)). Two studies (UCI/UKO) did not report NA-NSAIDs data, so were only included in ‘aspirin’ and ‘any NSAIDs’ (aspirin plus non-aspirin) analyses. Regular use was defined as at least once per week vs less often. Frequency, dose, and duration information was available for seven, three, and nine studies, respectively (Table 1). Studies provided data on vital status and time from diagnosis to death or end of follow-up. Disease recurrence/progression (from 3 studies) and cause of death (two studies) was known for 28% and 12% of women, respectively. Ethnicity, smoking status, education, body mass index (BMI), tumour stage, and residual disease was known for 99.8%, 89%, 87%, 92%, 99%, and 24% of women, respectively.

**Statistical analysis.** Using Cox proportional hazards regression, we obtained hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between analgesic use and overall survival (OS) in each study. Potential confounders were selected a priori. We did not adjust for treatment type because treatment cannot influence pre-diagnosis analgesic use (as treatment occurs later) and these data were only available for 25% of the cohort. Main models were adjusted for age, education, and ethnicity. Survival time was left-truncated at recruitment to minimise potential bias from eligible women dying before they could be enrolled. Following proportional hazards assumption checking (inspecting covariate associations with survival over time), we re-ran models including covariate*time interactions where these interactions were statistically significant (two studies). As the resulting estimates were virtually unchanged, final models did not include these interactions. Site-specific HRs for OS were combined using random-effects meta-analysis. F and P-values for heterogeneity (from chi-square tests) were inspected to assess inter-study heterogeneity. Associations between analgesic use and progression-free (PFS) and disease-specific survival (DSS) were estimated from single models, stratified by study, to maximise power. In the same manner we

| Table 1. The association between regular pre-diagnosis use of common analgesic medications and overall survival following a diagnosis of invasive ovarian cancer |
|---|---|---|---|---|---|---|---|
| Exposure categorisation | Aspirin | Non-aspirin NSAIDs | Any NSAIDs | Acetaminophen |
| | n | pHR* | 95% CI | p | n | pHR* | 95% CI | p | n | pHR* | 95% CI | p |
| Regular use<sup>b</sup> | | | | | | | | | | | | |
| No | 6190 | 0.96 | 0.88–1.04 | 0.0 | 3091 | 0.95 | 0.87–1.04 | 0.0 | 364 | 0.90 | 0.73–1.10 | 0.0 |
| Yes | 1286 | 0.94 | 0.87–1.02 | 0.3 | 753 | 0.94 | 0.87–1.02 | 0.3 | 68 | 0.88 | 0.72–1.10 | 0.0 |
| Frequency (7 studies)<sup>c</sup> | | | | | | | | | | | | |
| No regular use | 4268 | 0.96 | 0.88–1.05 | 0.0 | 3379 | 0.94 | 0.87–1.02 | 0.3 | 232 | 0.94 | 0.86–1.02 | 0.0 |
| <30 days per month | 234 | 0.90 | 0.69–1.17 | 0.3 | 307 | 0.93 | 0.78–1.13 | 0.0 | 26 | 0.94 | 0.69–1.27 | 0.0 |
| Daily | 593 | 1.01 | 0.91–1.13 | 0.0 | 498 | 0.99 | 0.90–1.09 | 0.0 | 30 | 0.90 | 0.65–1.24 | 0.0 |
| Regular use<sup>b</sup> | | | | | | | | | | | | |
| No | 1330 | 0.90 | 0.86–1.04 | 0.0 | 1104 | 0.90 | 0.86–1.04 | 0.0 | 98 | 0.96 | 0.77–1.20 | 0.0 |
| Low | 125 | 0.90 | 0.69–1.21 | 0.0 | 102 | 0.95 | 0.76–1.20 | 0.0 | 12 | 0.96 | 0.66–1.43 | 0.0 |
| High | 205 | 0.92 | 0.69–1.23 | 0.0 | 176 | 0.99 | 0.82–1.21 | 0.0 | 19 | 0.96 | 0.66–1.43 | 0.0 |
| Duration (9 studies)<sup>d</sup> | | | | | | | | | | | | |
| No regular use | 3919 | 0.96 | 0.86–1.07 | 0.0 | 3433 | 0.94 | 0.86–1.04 | 0.0 | 152 | 0.94 | 0.79–1.11 | 0.0 |
| <60 months | 426 | 0.96 | 0.82–1.13 | 0.0 | 367 | 0.94 | 0.82–1.11 | 0.0 | 24 | 0.96 | 0.73–1.30 | 0.0 |
| >60 months | 559 | 1.01 | 0.89–1.14 | 0.0 | 457 | 0.99 | 0.87–1.13 | 0.0 | 52 | 0.94 | 0.74–1.21 | 0.0 |

Abbreviations: CI = confidence interval, NSAID = non-steroidal anti-inflammatory drug, pHR = pooled hazard ratio.

<sup>a</sup> Adjusted for age (in years), ethnicity (if <95% of participants were of the same ethnicity) (Whites/Hispanic/Black/Asian/Other), and education (Less than high-school/Completed high-school including some college/College graduate/Education status unknown).

<sup>b</sup> Regular use defined as at least once per week (depending on the question used by each study to collect information on medication use); includes all 12 studies for aspirin, 10 studies for non-aspirin NSAIDs (excluding UCI/UKO, which did not report these data), 10 studies for any NSAIDs (aspirin or non-aspirin), and 9 studies (excluding UKO) for acetaminophen.

<sup>c</sup> Frequency analyses were conducted in 7 studies with available data (AUS, DOV, HAW, HOP, MAL, NCO, and USC). Frequency of daily use of any NSAID may be slightly underestimated (while less than daily use may be overestimated), because if aspirin and non-aspirin NSAIDs were each taken >7 days per week, this is categorised as less than daily use of any NSAID although it is possible that at least one type of NSAID was taken 7 days per week (this cannot be determined from the data available).

<sup>d</sup> Statistically significant heterogeneity in the pHR across studies.
conducted analyses stratified by characteristics likely to modify the association (age, BMI, and disease stage).

This analysis and each contributing study received approval from the appropriate institutional review board/ethics committee. All participants provided written informed consent.

RESULTS

Population characteristics. Mean age at diagnosis was 58 years, 88% of women were non-Hispanic white, and 27% were tertiary-educated. Of the 7694 women, 17%, 23%, and 18% had regularly used aspirin, NA-NSAIDs, and acetaminophen, respectively (Supplementary Table 1). Median follow-up (using reverse Kaplan-Meier (Schemper and Smith, 1996)) was 8.0 years. Over half the women (n = 4273, 56%) died and 5-year survival was 55% (Supplementary Table 1), yielding 90% power to detect a half the women (\( n = 2346 \), 56%) died and 5-year survival was 55% (Supplementary Table 1), yielding 90% power to detect a HR of .90 for NSAID users. Among studies with progression/cause-of-death information, 73% of women experienced progression and 95% of deaths were from ovarian cancer.

Primary results. Regular use of analgesics was not associated with OS (pHRs (95% CI); aspirin 0.96 (0.88–1.04); NA-NSAIDs 0.97 (0.89–1.05); any NSAIDs 0.94 (0.86–1.03); acetaminophen 1.01 (0.93–1.10)), nor were frequency, dose, or duration of use (Table 1; Figure 1). There was no significant inter-study heterogeneity (Figure 1). Additional adjustment for tumour stage and grade, residual disease, BMI and smoking status did not appreciably alter effect estimates. Cross-classifying frequency by dosage (among five studies with data) did not demonstrate consistent associations, and long-term (≥ 5 years) daily use was not associated with survival.

Truncating follow-up at five years (when most deaths would be cancer-related) did not affect results. No significant associations were observed with PFS (any NSAIDs, HR = 0.96; 95% CI 0.80–1.14) or DSS (HR = 0.98; 95% CI 0.82–1.17). There was no significant variation by tumour histology (Table 2; P-interaction = 0.3–0.7). Excluding the two studies which had previously examined this association (Minlikeeva et al, 2015; Nagle et al, 2015) (whose participants comprised 25% of this analysis), two studies with high survival rates (these studies recruited a number of prevalent cases), or two studies who asked only about recent use (past 5 years), did not substantially alter effect estimates.

To minimise exposure misclassification due to heterogeneous questions between studies, we repeated analyses restricted to six studies clearly defining non-use as less than once per week (Supplementary Table 3). This showed a significant survival advantage among regular users of any NSAIDs (pHR = 0.89; 95% CI 0.82–0.97).

![Figure 1](https://www.bjcancer.com/doi:10.1038/bjc.2017.68)

Figure 1. The association between regular pre-diagnosis use of common analgesic medications and overall survival following a diagnosis of invasive ovarian cancer, adjusted for age, ethnicity (if <95% of participants are of the same ethnicity), and education. (A) Aspirin, (B) non-aspirin NSAIDs, (C) any NSAIDs, (D) acetaminophen.
CI 0.82–0.98). When we excluded studies with low exposure prevalence (<10%), a similar association was seen among the eight remaining studies (including the six above; any NSAIDs HR = 0.92; 95% CI 0.85–0.99).

In stratified analyses, an inverse association between any NSAID use and survival was seen among women aged ≥60 at diagnosis (pHR = 0.90; 95% CI 0.82–0.99) or with BMI <25 kg m⁻² (0.86; 0.77–0.95). A non-significant inverse association was seen among women with early-stage (localised/regional) tumours (pHR = 0.87; 95% CI 0.74–1.04; Supplementary Table 4).

### DISCUSSION

Overall, we did not find convincing evidence to support an association between use of aspirin, NA-NSAIDs, or acetaminophen prior to diagnosis and ovarian cancer survival. Although most HRs for aspirin and NA-NSAIDs were <1.0, none was statistically significant. Our results are consistent with the two previous observational studies (Minlikeeva et al, 2015; Nagle et al, 2015) examining pre-diagnosis use of NSAIDs. The relationship did not vary by histologic subtype.

Questions used to define regular use differed between studies. When we restricted analyses to a subset of studies clearly defining non-use as less than once per week (depending on the question used by each study to collect information on medication use).

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Common analgesics and ovarian cancer survival

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1Gynaecological Cancers Group, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, Queensland 4006, Australia; 2The University of Queensland, School of Public Health, Level 2 Public Health Building (887), Corner of Herston Road & Wyndham Street, Brisbane, Queensland 4006, Australia; 3Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892-9774, USA; 4Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, 2525 West End Avenue, Nashville, TN 37203, USA; 5Department of Community and Family Medicine, Duke University Medical Center, 2424 Erwin Road, Suite 602, Durham, NC 27710, USA; 6Cancer Control and Population Sciences, Duke Cancer Institute, DUMC Box 3917, 10 Bryan Searle Drive, Seeley Mudd Building, 2nd floor, Durham, NC 27710, USA; 7Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA; 8Centre for Cancer Research, the Westmead Institute for Medical Research, The University of Sydney, 176 Hawkesbury Road, Sydney, NSW 2145, Australia; 9Department of Gynaecological Oncology, Westmead Hospital, Cnr Hawkesbury Road and Darcy Road, Sydney, New South Wales 2145, Australia; 10Cancer Genetics and Genomics Laboratory, Peter MacCallum Cancer Centre, St Andrews Place, Melbourne, Victoria 3002, Australia; 11Department of Chronic Disease Epidemiology, Yale School of Public Health, LEPH 413, 60 College Street, New Haven, CT 06510, USA; 12Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA 98109-1024, USA; 13Department of Epidemiology, University of Washington, 1959 NE Pacific Street, Health Sciences Bldg, F-262, Seattle, WA 98195, USA; 14Department of Epidemiology, The Geisel School of Medicine at Dartmouth, 1 Medical Center Drive, 7927 Rubin Building, Lebanon, NH 03756, USA; 15Cancer Prevention and Control, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA; 16Community and Population Health Research Institute, Department of Biomedical Sciences, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA; 17Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, 300 Halket Street, Pittsburgh, PA 15213, USA; 18Ovarian Cancer Center of Excellence, Women’s Cancer Research Program, Magee-Women’s Research Institute and University of Pittsburgh Cancer Institute, 204 Craft Avenue, Pittsburgh, PA 15213, USA; 19Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, 130 De Soto Street, Pittsburgh, PA 15261, USA; 20The University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 21Department of Virus, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 22Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 23Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 24Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 25Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 26Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 27Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 28Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 29Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 30Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 31Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA; 32Department of Epidemiology, University of Texas School of Public Health, 1200 Herman Pressler, Suite W130, Houston, TX 77030, USA.
Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, Copenhagen Ø DK-2100, Denmark; 22Department of Gynaecology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, Copenhagen Ø DK-2100, Denmark; 23Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, Herlev DK-2370, Denmark; 24Department of Obstetrics and Gynecology, Duke University Medical Center, 25171 Morris Bldg, Durham, NC 27710, USA; 25Obstetrics and Gynecology Epidemiology Center, Brigham and Women’s Hospital, 221 Longwood Avenue, Richardson Fuller Building, Boston, MA 02115, USA; 26Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; 27Channing Division of Network Medicine, Brigham and Women’s Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA; 28Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, 195 Little Albany Street, New Brunswick, NJ 08903, USA; 29Rutgers School of Public Health, 683 Hoes Lane West, Piscataway, NJ 08854, USA; 30Cancer Surveillance Research Program, Rutgers Cancer Institute of New Jersey, 195 Little Albany Street, New Brunswick, NJ 08903, USA; 31Department of Epidemiology, University of California Irvine, 224 Irvine Hall, Irvine, CA 92697-7550, USA; 32Genetic Epidemiology Research Institute, UCI Center for Cancer Genetics Research & Prevention, School of Medicine, University of California Irvine, 224 Irvine Hall, Irvine, CA 92697-7550, USA; 33Women’s Cancer, Institute for Women’s Health, University College London, Maple House 1st Floor, 149 Tottenham Court Road, London W1T 7DN, UK; 34Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90033, USA; 35School of Women’s and Children’s Health, University of New South Wales, Level 1, Women’s Health Institute, Royal Hospital for Women, Barker Street, Randwick, New South Wales 2031, Australia; 36The Kinghorn Cancer Centre, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, New South Wales 2010, Australia; 37Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, SPH Tower, Ann Arbor, MI 48109-2029, USA and 38Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 307 East 63rd Street, New York, NY 10065, USA

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