Title

Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium

Journal

Journal of the National Cancer Institute, 111(2)

ISSN

0027-8874

Authors

Trabert, Britton
Poole, Elizabeth M
White, Emily
et al.

Publication Date

2019-02-01

DOI

10.1093/jnci/djy100

Peer reviewed

JNCI J Natl Cancer Inst (2019) 111(2): djy100

doi: 10.1093/jnci/djy100
First published online May 31, 2018
Article

ARTICLE

Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium

Britton Trabert, Elizabeth M. Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L. Anderson, Theodore M. Brasky, Louise A. Brinton, Renee T. Fortner, Mia Gaudet, Patricia Hartge, Judith Hoffman-Bolton, Michael Jones, James V. Lacey Jr., Susanna C. Larsson, Gerardo G. Mackenzie, Leo J. Schouten, Dale P. Sandler, Katie O'Brien, Alpa V. Patel, Ulrike Peters, Anna Prizment, Kim Robien, V. Wendy Setiawan, Anthony Swerdlow, Piet A. van den Brandt, Elisabete Weiderpass, Lynne R. Wilkens, Alicja Wolk, Nicolas Wentzensen, Shelley S. Tworoger; on behalf of the Ovarian Cancer Cohort Consortium (OC3)

See the Notes section for the full list of authors' affiliations.
Correspondence to: Britton Trabert, PhD, 9609 Medical Center Drive, Bethesda, MD 20892 (e-mail: britton.trabert@nih.gov).

Abstract

Background: Aspirin use is associated with reduced risk of several cancers. A pooled analysis of 12 case–control studies showed a 10% decrease in ovarian cancer risk with regular aspirin use, which was stronger for daily and low-dose users. To prospectively investigate associations of analgesic use with ovarian cancer, we analyzed data from 13 studies in the Ovarian Cancer Cohort Consortium (OC3).
Methods: The current study included 758 829 women who at study enrollment self-reported analgesic use, among whom 3514 developed ovarian cancer. Using Cox regression, we assessed associations between frequent medication use and risk of ovarian cancer. Dose and duration were also evaluated. All statistical tests were two-sided.
Results: Women who used aspirin almost daily (≥6 days/wk) vs infrequent/nonuse experienced a 10% reduction in ovarian cancer risk (rate ratio [RR] = 0.90, 95% confidence interval [CI] = 0.82 to 1.00, $P = .05$). Frequent use (≥4 days/wk) of aspirin (RR = 0.95, 95% CI = 0.88 to 1.03), nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs; RR = 1.00, 95% CI = 0.90 to 1.11), or acetaminophen (RR = 1.05, 95% CI = 0.88 to 1.24) was not associated with risk. Daily acetaminophen use (RR = 1.28, 95% CI = 1.00 to 1.65, $P = .05$) was associated with elevated ovarian cancer risk. Risk estimates for frequent, long-term (10+ years) use of aspirin (RR = 1.15, 95% CI = 0.98 to 1.34) or nonaspirin NSAIDs (RR = 1.19, 95% CI = 0.84 to 1.68) were modestly elevated, although not statistically significantly so.
Conclusions: This large, prospective analysis suggests that women who use aspirin daily have a slightly lower risk of developing ovarian cancer (~10% lower than infrequent/nonuse)—similar to the risk reduction observed in case–control analyses. The observed potential elevated risks for 10+ years of frequent aspirin and NSAID use require further study but could be due to confounding by medical indications for use or variation in drug dosing.

Ovarian cancer is the most fatal gynecologic cancer, largely due to delayed symptom presentation and lack of early detection strategies. Chemoprevention has not been widely studied but may present approaches to reduce ovarian cancer burden. Chronic inflammation likely plays a key role in ovarian carcinogenesis (1). Factors associated with epithelial disruption

Received: January 15, 2018; **Revised:** March 14, 2018; **Accepted:** April 30, 2018

through ovulation (2,3), inflammation-related exposures such as endometriosis and pelvic inflammatory disease (4,5), and circulating biomarkers of inflammation (6,7) have been associated with ovarian cancer risk.

Inhibition of cyclooxygenase (COX) enzymes in prostaglandin synthesis is a primary mechanism responsible for the anti-inflammatory and antineoplastic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) (8,9), and may play a role in ovarian carcinogenesis. Additionally, NSAIDs may suppress ovulation and affect cell proliferation, angiogenesis, and apoptosis of the epithelium (10). Acetaminophen, another common analgesic and antipyretic, has weak anti-inflammatory activity and antigonadotropic effects (11). It also may inhibit ovarian carcinogenesis through the depletion of glutathione leading to necrosis (12). Aspirin, nonaspirin NSAIDs, and acetaminophen are widely used, so any increased or decreased cancer risk may have important public health implications.

Cardiovascular disease prevention trials have shown that daily aspirin use is associated with reduced risk and mortality of several malignancies (eg, colorectal cancer) (13). However, the limited number of women in these trials is insufficient to evaluate ovarian cancer end points (14).

A recent pooled analysis of 12 case–control studies in the Ovarian Cancer Association Consortium (OCAC) reported a reduced risk of ovarian cancer with aspirin use, particularly for daily aspirin users (15). High-dose nonaspirin NSAID use, but not acetaminophen, was also associated with lower risk (15). The few prospective observational studies between aspirin or other NSAID use and ovarian cancer risk have had inconsistent results (16–20). Prospective studies avoid potential biases that may occur in case–control studies, including differences between nonresponders and responders among cases or controls or differences in recollection or reporting of medication use after being diagnosed with ovarian cancer. However, the decreased risk observed for aspirin or nonaspirin NSAIDs and the lack of association with acetaminophen in case–control studies argues against substantial differential recall (15). Further, the exposure window being evaluated in case–control studies is often shortly before cancer diagnosis, during which use may be influenced by preclinical disease. Prospective assessment of analgesic use many years before ovarian cancer diagnosis is necessary to confirm the association with an eye toward improving prevention recommendations. Thus, we evaluated the association between frequent aspirin, nonaspirin NSAID, and acetaminophen use with ovarian cancer risk using prospective individual-level data from the Ovarian Cancer Cohort Consortium (OC3).

Methods

Study Population

The study population included women participating in 16 prospective cohort studies from North America and Europe (Supplementary Table 1, available online) (16,17,19,21–35). Eligible studies were a cohort study or clinical trial with prospective follow-up including women, determination of ovarian cancer end points through questionnaire/medical record follow-up or confirmation by cancer registries, and follow-up for death. This analysis was limited to 13 studies that collected information on frequent aspirin, nonaspirin NSAID, or acetaminophen (paracetamol) use over at least a six-month period (n = 758 829). All studies obtained institutional approval at their respective institutions; participants provided either written informed consent or implicit consent through return of the study questionnaire. The OC3 Data Coordinating Center and analytic approaches were approved by the institutional review board of the Brigham and Women's Hospital.

Exposure Definitions

Medication use was self-reported at enrollment (Supplementary Table 1, available online) (16,17,19,21,22,24–27,29–34). Given the rationale for assessment of frequent use based on biologic mechanisms and published research (13–15), we focused on frequent medication use (at least 4–5 days/wk) when possible. Frequency was available in 10 of 13 studies (16,17,21,24,25,29–32), whereas three studies included frequency in their definition of regular medication use (19,22,26). Frequent use was defined as use at least four to five times per week for at least six months' duration; less frequent use or nonregular use/no use were combined to form the reference group. We also evaluated very frequent (daily/almost daily) use for at least 6 months' duration as one of the following: six to seven days per week, seven days per week, or 28 or more days per month (11 studies) (16,17,21,22,24,25,29–32). Frequency variables were further divided by duration of use (all medications: ≥0.5–5, >5–10, >10 years, 9 studies) (16,19,24–26,30–32) and aspirin dose (<100 [or "baby aspirin"] and ≥100 mg, four studies) (16,19,23,31).

Potential confounding variables were harmonized from the studies as part of a core data set. A priori adjustment factors included baseline age (continuous), body mass index (<20, 20–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2), number of births (0, 1, 2, 3, ≥4 full-term births), duration of oral contraceptive (OC) use (never, ≤1, >1–5, >5–10, >10 years), and menopause/duration of menopausal hormone therapy (premenopausal, postmenopausal: never, ≤5, >5–10, >10 years).

Outcome Definitions

We included epithelial ovarian or peritoneal tumors identified either through cancer registries or medical record review (ICD9 codes 183 and 158; ICD10 codes C56). We first evaluated associations of medications with all tumors combined (ovarian and peritoneal, n = 3514). Second, we evaluated associations for invasive epithelial ovarian cancers (n = 3147), and, third, we evaluated associations for the four most common tumor histotypes: serous (n = 1475, including tumors coded as poorly differentiated), endometrioid (n = 233), mucinous (n = 125), and clear cell (n = 111). The remaining 1203 cases had another histology (eg, mixed) or were missing histology information (n = 817) and were censored at diagnosis date in histology-specific analyses.

Statistical Methods

Women were excluded from primary analyses if they had a history of cancer (other than nonmelanoma skin cancer) at baseline, bilateral oophorectomy before study entry, or were missing age. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression to evaluate the association between the analgesic medications and risk of ovarian cancer. Women entered the analysis at age at study entry and contributed person-time until the age at first diagnosis of ovarian cancer (event), death (censored), or end of

follow-up (censored), whichever came first. In primary analyses, we pooled data from all cohorts, stratifying on cohort to account for potential differences in baseline hazards. Secondarily, we used meta-analysis of cohort-specific estimates to assess between-study heterogeneity. Associations between analgesic medication use and ovarian cancer histotype were calculated using competing-risks Cox regression (36). Statistical heterogeneity of associations across histotypes was assessed via likelihood ratio test comparing a model that assumed different associations for the exposure of interest by histotype (full model) with a model with a single estimate across histotypes (reduced model) (37).

Effect modification by factors that influence inflammation (eg, smoking, body mass index [BMI], history of chronic disease) and established ovarian cancer risk factors (eg, age, parity, OC use, endometriosis) was evaluated using multiplicative interaction terms, with statistical significance assessed by a likelihood ratio test.

In sensitivity analyses, we considered a common reference group, coding "nonfrequent users" as women who reported no or infrequent use of aspirin, nonaspirin NSAIDs, and acetaminophen to account for analgesic usage patterns. We also excluded women who reported a history of chronic disease at baseline to assess potential indication for medication use and explored the potential for reverse causation by evaluating associations of frequent analgesic use with ovarian cancer cases that occurred less than five years, five to less than 10 years, and 10 or more years after baseline. Another sensitivity analysis considered death a competing risk (rather than censoring). Exposure curves from survivor function plots were parallel, suggesting no deviation from proportional hazards. All statistical tests were two-sided, and *P* values of less than .05 were considered statistically significant; analyses were performed using SAS 9.1.

Results

Study Characteristics

The proportion of women reporting frequent analgesic use increased with age; for example, among women reporting frequent aspirin use, 17.7% were younger than age 50 years, whereas 52.2% were 60 years of age or older (Table 1). Compared with women who did not use aspirin or who used it infrequently, women who frequently used aspirin were more likely to be older, be postmenopausal, have a history of a chronic disease, have higher BMI, and were less likely to have previously used OCs. Average follow-up after exposure assessment was 10.8 years (maximum = 18.9 years); individual cohort follow-up is reported in Supplementary Table 1 (available online).

Aspirin

Women who used aspirin at least four to five times per week (n = 851 exposed cases [events]) developed ovarian cancer at about the same rate as women who did not use aspirin or used it only infrequently (HR = 0.95, 95% CI = 0.88 to 1.03) (Table 2). However, compared with infrequent/nonusers, women reporting daily or almost daily use (at least 6 days/wk or more, n = 449 cases) had a 10% reduction in ovarian cancer risk (HR = 0.90, 95% CI = 0.82 to 1.00, *P* = .05). This association was statistically significant for women reporting daily or almost daily use for 0.5 to less than five years' duration (HR = 0.79, 95% CI = 0.63 to 0.99, *P* = .04, n = 87 cases) and was suggestively associated for daily users of five to 10 years' duration (HR = 0.88, 95% CI = 0.65 to 1.18, n = 50 cases). Conversely, women who frequently used (vs infrequent/nonuse) aspirin for long durations (≥10 years at baseline) had a non–statistically significantly elevated risk of ovarian cancer (HR = 1.15, 95% CI = 0.98 to 1.34, *P* =.09, n = 212 cases). No associations were observed when analyzing aspirin dose or other patterns of duration. In analyses by histotype (Table 3), results for serous ovarian cancers were similar to those seen for all ovarian cancer: compared with infrequent/nonuse, daily aspirin use was associated with a 15% decrease for serous tumors (95% CI = 0.71 to 1.00, n = 159 cases), whereas 10 or more years of frequent aspirin use was related to a suggestively elevated risk (HR = 1.27, 95% CI = 0.99 to 1.62, n = 74 cases). A similar pattern was observed for clear cell tumors; however, risk estimates were imprecise due to limited numbers. No associations were observed for endometrioid or mucinous tumors.

Nonaspirin NSAIDs

Women who frequently used nonaspirin NSAIDs had a similar rate of ovarian cancer as infrequent/nonusers (HR = 1.00, 95% CI = 0.90 to 1.11, n = 426 cases) (Table 2). Longer duration or daily frequency of nonaspirin NSAIDs was not related to ovarian cancer risk, although the risk estimate for ovarian cancer for frequent, frequent, long-duration (>10 years) of use of nonaspirin NSAIDs was suggestively elevated (HR = 1.19, 95% CI = 0.84 to 1.68, n = 36 cases). In analyses by histotype, women who frequently used (vs infrequent/nonuse) nonaspirin NSAIDs for long durations had an increased risk of serous tumors than women who used them infrequently or not at all (HR = 2.06, 95% CI = 1.14 to 3.74, n = 10 cases) (Table 3).

Acetaminophen

Frequent use compared with infrequent/nonuse of acetaminophen was not associated with ovarian cancer risk (HR = 1.05, 95% CI = 0.88 to 1.24, n = 152 exposed cases) (Table 2). However, there was a suggestive elevated risk with daily acetaminophen use (HR = 1.28, 95% CI = 1.00 to 1.65, *P* = .05, n = 71 cases) that was stronger for serous tumors (HR = 1.70, 95% CI = 1.14 to 2.55, n = 26 cases) (Table 3).

Additional Analyses

There was little heterogeneity across studies (data not shown). Risk estimates were generally similar across age strata (Supplementary Table 2, available online). Compared with infrequent/nonusers, daily aspirin use was related to reduced ovarian cancer risk among women younger than age 50 years (HR = 0.89, 95% CI = 0.43 to 1.84), age 50 to 59 years (HR = 0.92, 95% CI = 0.73 to 1.17), and age 60 to 69 years (HR = 0.88, 95% CI = 0.75 to 1.04) at baseline but was null for women age 70 years or older (HR = 1.05, 95% CI = 0.82 to 1.36, $P_{interaction}$ = .73). Daily acetaminophen use was only associated with increased ovarian cancer risk among women age 70 years or older (HR = 1.78, 95% CI = 1.17 to 2.72, $P_{interaction}$ < .001). Results were similar across strata of other ovarian cancer risk factors (data not shown).

Results were similar in analyses restricted to invasive ovarian cancers, utilizing a common reference group, and accounting for death as a competing risk (data not shown). In analyses excluding women with a history of chronic disease, elevated risk estimates with frequent long-duration use of aspirin or

Table 1. Distribution of frequent analgesic use by baseline demographic and health characteristics in the Ovarian Cancer Cohort Consortium (n = 758 829)

Characteristics	Aspirin		Nonaspirin NSAID		Acetaminophen	
	Infrequent/nonuse No. (%)	Frequent use* No. (%)	Infrequent/nonuse No. (%)	Frequent use* No. (%)	Infrequent/nonuse No. (%)	Frequent use* No. (%)
Age, mean (SD), y	54.7 (11.4)	59.4 (10.1)	59.1 (9.5)	59.6 (8.5)	57.7 (10.6)	60.9 (10.0)
Age, y						
<50	171 049 (31.0)	28 462 (17.7)	68 208 (15.8)	10 496 (12.9)	69 762 (22.9)	3973 (14.4)
50–59	182 326 (33.0)	48 432 (30.1)	144 873 (33.6)	29 425 (36.1)	101 553 (33.4)	8351 (30.3)
60+	198 689 (36.0)	84 044 (52.2)	218 295 (50.6)	41 609 (51.0)	132 697 (43.6)	15 244 (55.3)
BMI, kg/m^2						
<20	38 712 (7.0)	9460 (5.9)	28 981 (6.7)	3239 (4.0)	20 937 (6.9)	1513 (5.5)
20–24.9	246 476 (44.6)	63 791 (39.6)	183 064 (42.4)	25 614 (31.4)	127 806 (42)	9216 (33.4)
25–29.9	157 968 (28.6)	49 716 (30.9)	130 232 (30.2)	25 969 (31.9)	89 960 (29.6)	8560 (31.1)
30–34.9	61 441 (11.1)	21 816 (13.6)	51 919 (12.0)	14 072 (17.3)	36 797 (12.1)	4342 (15.8)
35+	33 201 (6.0)	12 620 (7.8)	26 604 (6.2)	10 813 (13.3)	21 015 (6.9)	3068 (11.1)
Missing	14 266 (2.6)	3535 (2.2)	10 576 (2.5)	1823 (2.2)	7497 (2.5)	869 (3.2)
Age at menarche, y						
≤11	129 521 (23.5)	39 029 (24.3)	104 278 (24.2)	22 428 (27.5)	58 358 (19.2)	5549 (20.1)
12	132 550 (24.0)	43 314 (26.9)	107 177 (24.8)	22 151 (27.2)	82 000 (27.0)	8085 (29.3)
13	155 896 (28.2)	42 510 (26.4)	122 489 (28.4)	19 967 (24.5)	87 684 (28.8)	6628 (24.0)
14	71 928 (13.0)	21 378 (13.3)	55 615 (12.9)	10 314 (12.7)	44 990 (14.8)	4640 (16.8)
≥15	48 479 (8.8)	13 304 (8.3)	38 367 (8.9)	6361 (7.8)	27 904 (9.2)	2428 (8.8)
Missing	13 690 (2.5)	1403 (0.9)	3450 (0.8)	309 (0.4)	3076 (1.0)	238 (0.9)
Duration, oral contraceptive use, y						
Never	210 399 (38.1)	79 036 (49.1)	193 635 (44.9)	32 992 (40.5)	112 760 (37.1)	11 756 (42.6)
>0–1	43 208 (7.8)	14 589 (9.1)	32 672 (7.6)	7606 (9.3)	27 743 (9.1)	2557 (9.3)
>1–5	97 165 (17.6)	24 065 (15.0)	67 121 (15.6)	13 458 (16.5)	47 757 (15.7)	3612 (13.1)
>5–10	78 116 (14.1)	16 254 (10.1)	48 201 (11.2)	9520 (11.7)	36 471 (12.0)	2323 (8.4)
>10	104 143 (18.9)	24 316 (15.1)	76 349 (17.7)	16 530 (20.3)	65 839 (21.7)	6257 (22.7)
Missing	19 033 (3.4)	2678 (1.7)	13 398 (3.1)	1424 (1.7)	13 442 (4.4)	1063 (3.9)
No. of pregnancies						
0	85 920 (15.6)	16 579 (10.3)	56 916 (13.2)	9977 (12.2)	42 630 (14.0)	2899 (10.5)
1	60 572 (11.0)	14 426 (9.0)	45 993 (10.7)	8030 (9.8)	35 178 (11.6)	2988 (10.8)
2	177 064 (32.1)	44 857 (27.9)	128 389 (29.8)	23 169 (28.4)	97 780 (32.2)	7997 (29.0)
3	131 053 (23.7)	42 162 (26.2)	110 188 (25.5)	21 291 (26.1)	67 767 (22.3)	6372 (23.1)
4+	93 130 (16.9)	41 287 (25.7)	85 208 (19.8)	17 992 (22.1)	55 969 (18.4)	6706 (24.3)
Missing	4325 (0.8)	1627 (1.0)	4682 (1.1)	1071 (1.3)	4688 (1.5)	606 (2.2)
Menopausal status						
Premenopausal	188 738 (34.2)	31 168 (19.4)	83 184 (19.3)	12 792 (15.7)	82 248 (27.1)	3986 (14.5)
Postmenopausal	348 494 (63.1)	125 619 (78.1)	342 938 (79.5)	67 335 (82.6)	216 731 (71.3)	22 957 (83.3)
Missing	14 832 (2.7)	4151 (2.6)	5254 (1.2)	5254 (1.7)	5033 (1.7)	625 (2.3)
Age at menopause among postmenopausal women, y						
≤45	45 905 (12.6)	15 523 (12.0)	45 476 (13.1)	8341 (12.1)	33 314 (15.0)	3162 (13.4)
46–50	89 057 (24.5)	32 661 (25.2)	86 398 (24.8)	15 875 (23.1)	60 363 (27.2)	6024 (25.5)
51–55	123 290 (33.9)	43 577 (33.6)	125 242 (36.0)	22 357 (32.5)	77 772 (35.1)	7313 (31.0)
>55	24 452 (6.7)	9294 9294 (7.2)	25 889 (7.4)	5503 (8.0)	14 587 (6.6)	1600 (6.8)
Missing	80 622 (22.2)	28 715 (22.1)	65 187 (18.7)	16 662 (24.2)	35 728 (16.1)	5483 (23.3)
Duration, menopausal hormone use, y						
Never	273 (49.6)	73 279 (45.5)	165 228 (38.3)	26 744 (32.8)	112 911 (37.1)	9282 (33.7)
>0–5	78 (14.3)	29 980 (18.6)	73 431 (17.0)	16 284 (20.0)	54 914 (18.1)	6446 (23.4)
>5–10	43 (7.9)	16 040 (10.0)	41 755 (9.7)	9652 (11.8)	30 399 (10.0)	3512 (12.7)
>10	42 (7.7)	20 700 (12.9)	44 658 (10.4)	13 673 (16.8)	28 174 (9.3)	4487 (16.3)
Missing	113 (20.5)	20 939 (13.0)	106 304 (24.6)	15 177 (18.6)	77 614 (25.5)	3841 (13.9)
History of chronic diseases at baseline included:						
Any cardiovascular disease						
No	19 146 (3.5)	11 630 (7.2)	22 121 (5.1)	8655 (10.6)	26 078 (8.6)	4698 (17.0)
Yes	1763 (0.3)	1545 (1.0)	2500 (0.6)	808 (1.0)	2859 (0.9)	449 (1.6)
Missing	531 155 (96.2)	147 763 (91.8)	406 755 (94.3)	72 067 (88.4)	275 075 (90.5)	22 421 (81.3)
Diabetes						
No	440 316 (85.2)	113 913 (82.0)	308 678 (79.5)	55 152 (81.8)	200 184 (72.8)	14 468 (64.5)
Yes	15 142 (2.9)	9472 (6.8)	16 115 (4.2)	4131 (6.1)	9268 (3.4)	1500 (6.7)
Missing	61 381 (11.9)	15 541 (11.2)	63 500 (16.4)	8161 (12.1)	65 623 (23.9)	6453 (28.8)

(continued)

Table 1. (continued)

Characteristics	Aspirin		Nonaspirin NSAID		Acetaminophen	
	Infrequent/nonuse No. (%)	Frequent use* No. (%)	Infrequent/nonuse No. (%)	Frequent use* No. (%)	Infrequent/nonuse No. (%)	Frequent use* No. (%)
Autoimmune disease						
No	86 690 (18.2)	35 539 (25.5)	104 565 (28.7)	20 401 (31.8)	115 614 (49.5)	9414 (49.4)
Yes	6192 (1.3)	4179 (3.0)	7292 (2.0)	3159 (4.9)	9630 (4.1)	1855 (9.7)
Missing	383 645 (80.5)	99 626 (71.5)	252 748 (69.3)	40 667 (63.3)	108 156 (46.3)	7787 (40.9)

*Frequent: use at least ~4–5 days/wk for 6 months or longer. BMI = body mass index; NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Associations between analgesic use and ovarian cancer risk in the Ovarian Cancer Cohort Consortium (n = 758 829)

Analgesic use	No. of events (cases)	Person-years	HR* (95% CI)	P†
Aspirin				
Infrequent/nonuse	2404	4 946 886	1.00 (ref)	
Frequent use‡	851	1 408 656	0.95 (0.88 to 1.03)	.23
Frequent use by duration vs infrequent/nonuse				
Infrequent/nonuse	1402	3 150 285	1.00 (ref)	
Frequent/0.5–<5 y	239	504 116	0.92 (0.80 to 1.06)	.24
Frequent/5–<10 y	93	171 582	0.90 (0.72 to 1.12)	.33
Frequent/10+ y	212	305 987	1.15 (0.98 to 1.34)	.09
Categories of frequent use vs infrequent/nonuse				
Infrequent/nonuse	1936	3 245 903	1.00 (ref)	
<Daily use	156	161 238	1.06 (0.90 to 1.26)	.49
Daily use§	449	545 499	0.90 (0.82 to 1.00)	.05
Categories of frequent use by duration vs infrequent/nonuse				
Infrequent/nonuse	1402	3 150 285	1.00 (ref)	
<Daily/0.5–<5 y	152	379 640	1.02 (0.85 to 1.21)	.87
<Daily/5–<10 y	43	108 355	0.92 (0.67 to 1.26)	.60
<Daily/10+ y	113	260 503	1.12 (0.92 to 1.37)	.26
Daily/0.5–<5 y	87	124 476	0.79 (0.63 to 0.99)	.04
Daily/5–10 y	50	63 227	0.88 (0.65 to 1.18)	.39
Daily/10+ y	99	45 484	1.18 (0.93 to 1.50)	.18
Frequent use by dose vs infrequent/nonuse				
Infrequent/nonuse	392	436 742	1.00 (ref)	
Frequent low dose	115	72 719	0.99 (0.79 to 1.23)	.91
Frequent normal dose	144	130 684	0.94 (0.77 to 1.15)	.55
Nonaspirin NSAID				
Infrequent/nonuse	2305	3 798 980	1.00 (ref)	
Frequent use‡	426	614 745	1.00 (0.90 to 1.11)	.96
Frequent use by duration vs infrequent/nonuse				
Infrequent/nonuse	1168	2 051 666	1.00 (ref)	
Frequent/0.5–<5 y	122	237 614	0.94 (0.78 to 1.14)	.54
Frequent/5–<10 y	64	75 230	1.10 (0.85 to 1.42)	.49
Frequent/10+ y	36	29 429	1.19 (0.84 to 1.68)	.33
Categories of frequent use vs infrequent/nonuse				
Infrequent/nonuse	1982	3 049 045	1.00 (ref)	
<Daily use	104	124 937	1.07 (0.88 to 1.31)	.50
Daily use§	237	319 625	0.97 (0.84 to 1.11)	.65
Categories of frequent use vs infrequent/nonuse				
Infrequent/nonuse	1168	2 051 666	1.00 (ref)	
<Daily/0.5–<5 y	83	159 749	1.02 (0.81 to 1.28)	.88
<Daily/5–<10 y	39	43 940	1.31 (0.95 to 1.81)	.10
<Daily/10+ y	15	18 356	1.10 (0.66 to 1.84)	.72
Daily/0.5–<5 y	39	77 865	0.81 (0.58 to 1.14)	.23
Daily/5–<10 y	25	31 290	0.86 (0.57 to 1.30)	.48
Daily/10+ y	21	11 074	1.27 (0.80 to 2.01)	.32

(continued)

Table 2. (continued)

Analgesic use	No. of events (cases)	Person-years	HR* (95% CI)	P†
Acetaminophen				
Infrequent/nonuse	1421	2 583 452	1.00 (ref)	
Frequent use‡	152	213 668	1.05 (0.88 to 1.24)	.61
Frequent use by duration vs infrequent/nonuse				
Infrequent/nonuse	1386	2 425 711	1.00 (ref)	
Frequent/0.5–<5 y	61	95 060	0.99 (0.76 to 1.29)	.93
Frequent/5–<10 y	50	50 683	1.16 (0.87 to 1.54)	.32
Frequent/10+ y	37	51 266	1.01 (0.73 to 1.41)	.96
Categories of frequent use vs infrequent/nonuse				
Infrequent/nonuse	1179	2 120 248	1.00 (ref)	
<Daily use	35	43 645	0.99 (0.70 to 1.39)	.94
Daily use§	71	62 759	1.28 (1.00 to 1.65)	.05
Categories of frequent use by duration vs infrequent/nonuse				
Infrequent/nonuse	1386	2 425 711	1.00 (ref)	
<Daily/0.5–<5 y	33	69 923	0.87 (0.62 to 1.22)	.42
<Daily/5–<10 y	25	35 311	0.98 (0.66 to 1.46)	.93
<Daily/10+ y	22	39 950	0.89 (0.58 to 1.36)	.58
Daily/0.5–<5 y	28	25 137	1.21 (0.81 to 1.81)	.35
Daily/5–<10 y	25	15 372	1.42 (0.94 to 2.13)	.09
Daily/10+ y	15	11 315	1.24 (0.75 to 2.08)	.40

*Hazard ratios and 95% confidence intervals were estimated from Cox proportional hazards models stratified by study cohort and adjusted for baseline age (continuous), body mass index (<20, 20–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2), number of births (none, one, two, three, four or more full–term births), duration of oral contraceptive (OC) use (never, ≤1, >1–5, >5–10, >10 years), and duration of menopausal hormone therapy use (premenopausal, never, ≤5, >5–10, >10 years). CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.

†P value was calculated using a two-sided Wald test.

‡Frequent: use at least ~4–5 days/wk for 6 months or longer.

§Daily: use at least ~6–7 days/wk or ≥28 days per month for 6 months or longer.

nonaspirin NSAIDs were attenuated (aspirin: HR = 1.11, 95% CI = 0.93 to 1.33; nonaspirin NSAIDs: HR = 1.04, 95% CI = 0.68 to 1.60); other associations, including for acetaminophen, remained unchanged. Associations were slightly stronger for frequent long-duration use of aspirin or daily acetaminophen use for cases diagnosed within five years of baseline compared with five or more years after baseline (data not shown).

Discussion

We observed a 10% reduced ovarian cancer risk for daily aspirin use, although only for women who had used aspirin for less than 10 years; use for 10 or more years was associated with a null or slightly elevated risk. Nonaspirin NSAID and acetaminophen use was not clearly related to ovarian cancer risk overall; however, we observed an increased risk for very frequent (daily/almost daily for at least six months) acetaminophen use. Further, like aspirin, long-duration, frequent nonaspirin NSAID use was associated, at least suggestively, with elevated risk of ovarian cancer. The modestly reduced risk for daily aspirin use is consistent with previous observations from case–control studies (15), although the suggestively elevated risk with long duration of frequent analgesic use requires further evaluation.

Importantly, in this analysis, we were able to evaluate patterns of duration to characterize a dose–response association; however, unlike colorectal cancer, in which longer duration of use is associated with further risk reductions (38), the reduced risk of ovarian cancer with frequent aspirin use was only apparent with short to moderate duration (the largest exposure stratum) and appeared null or slightly elevated with longer-duration use (≥10 years). This may be because those who frequently used aspirin for many years may be more likely to use standard vs low-dose aspirin. That said, availability of data on very long durations of use was limited, as evidenced by the less precise estimates in this group. A better understanding of the relationship between frequency and duration of use leveraging updated exposure data is needed to assess the potential causality of the daily aspirin–ovarian cancer relationship, including ascertainment of use during potentially critical time periods given that the increased risk for long-duration use was strongest for cases diagnosed early in follow-up. Further, consideration of associations for daily aspirin use and its timing/duration with ovarian cancer is needed to fully assess potential for primary prevention, particularly given the relatively low prevalence of ovarian cancer and risk-related adverse events (eg, upper gastrointestinal bleeding). Consistent with our results, pooled analyses of clinical trial data demonstrate that daily aspirin use is most relevant for risk reduction of colorectal cancer and cancer risk overall (39), as alternate dosing trials (higher dose or every other day use) did not show clear benefits (40).

The previous pooled case–control study and our current study support that daily aspirin use is associated with lower ovarian cancer risk. The weaker association in the prospective studies vs case–control studies is similar to results for breast cancer risk (14). Although recall bias may lead to a stronger association in case–control studies, we would expect this to attenuate any true reductions in risk with daily aspirin use. Alternately, considering analgesic use collected at study entry may lead to misclassification of exposure status over follow-up (which averaged more than a decade long) that could attenuate results. Conversely, we observed a consistently elevated ovarian cancer risk with frequent, long-duration use of aspirin and nonaspirin NSAIDs, suggesting potential confounding by medical indications for long-term use. We could not directly address this as indication for use was not collected in most studies. To address this in sensitivity analyses, we excluded women who

Table 3. Associations between analgesic use and ovarian carcinoma histologic subtypes, Ovarian Cancer Cohort Consortium

Analgesic use	P_{het}*	Serous (n = 1470) No. of events	Serous (n = 1470) HR† (95% CI)	Endometrioid (n = 233) No. of events	Endometrioid (n = 233) HR† (95% CI)	Mucinous (n = 125) No. of events	Mucinous (n = 125) HR† (95% CI)	Clear cell (n = 111) No. of events	Clear cell (n = 111) HR† (95% CI)
Aspirin									
Infrequent/nonuse	.26	1141	1.00 (ref)	181	1.00 (ref)	93	1.00 (ref)	85	1.00 (ref)
Frequent use‡		307	0.93 (0.81 to 1.05)	45	0.90 (0.64 to 1.27)	29	1.13 (0.73 to 1.75)	25	1.11 (0.71 to 1.74)
Frequent use by duration vs infrequent/nonuse									
Infrequent/nonuse	.03	680	1.00 (ref)	132	1.00 (ref)	52	1.00 (ref)	59	1.00 (ref)
Frequent/0.5–<5 y		69	0.85 (0.73 to 0.99)	18	0.93 (0.62 to 1.40)	10	1.03 (0.60 to 1.74)	5	0.75 (0.40 to 1.42)
Frequent/5–<10 y		37	0.89 (0.64 to 1.24)	8	1.28 (0.62 to 2.66)	2	0.67 (0.16 to 2.87)	4	1.46 (0.52 to 4.12)
Frequent/10+ y		74	1.27 (0.99 to 1.62)	8	0.64 (0.31 to 1.31)	10	1.69 (0.83 to 3.42)	10	1.97 (0.98 to 3.97)
Categories of frequent use vs infrequent/nonuse									
Infrequent/nonuse	.13	938	1.00 (ref)	139	1.00 (ref)	62	1.00 (ref)	67	1.00 (ref)
<Daily use		57	1.04 (0.86 to 1.25)	3	0.86 (0.55 to 1.34)	1	0.93 (0.53 to 1.63)	4	1.35 (0.75 to 2.41)
Daily use§		159	0.85 (0.71 to 1.00)	20	0.95 (0.59 to 1.54)	14	1.40 (0.77 to 2.56)	9	0.87 (0.44 to 1.73)
Nonaspirin NSAID									
Infrequent/nonuse	.06	984	1.00 (ref)	139	1.00 (ref)	67	1.00 (ref)	75	1.00 (ref)
Frequent use‡		157	1.09 (0.92 to 1.30)	18	1.03 (0.61 to 1.73)	8	0.86 (0.41 to 1.77)	6	0.53 (0.23 to 1.22)
Frequent use by duration vs infrequent/nonuse									
Infrequent/nonuse	.03	456	1.00 (ref)	71	1.00 (ref)	31	1.00 (ref)	47	1.00 (ref)
Frequent/0.5–<5 y		38	1.01 (0.83 to 1.23)	7	1.09 (0.63 to 1.89)	2	0.84 (0.38 to 1.86)	2	0.54 (0.22 to 1.34)
Frequent/5–<10 y		20	1.39 (0.87 to 2.22)	2	1.04 (0.25 to 4.31)	1	1.51 (0.20 to 11.63)	1	0.71 (0.10 to 4.95)
Frequent/10+ y		10	2.06 (1.14 to 3.74)	0	–	0	–	0	–
Categories of frequent use vs infrequent/nonuse									
Infrequent/nonuse	.04	883	1.00 (ref)	115	1.00 (ref)	61	1.00 (ref)	69	1.00 (ref)
<Daily use		38	1.15 (0.87 to 1.53)	7	1.36 (0.61 to 3.00)	3	1.65 (0.65 to 4.20)	1	0.45 (0.11 to 1.83)
Daily use§		102	1.06 (0.86 to 1.31)	9	0.87 (0.45 to 1.67)	3	0.49 (0.15 to 1.58)	4	0.58 (0.21 to 1.59)
Acetaminophen									
Infrequent/nonuse	.21	577	1.00 (ref)	103	1.00 (ref)	38	1.00 (ref)	50	1.00 (ref)
Frequent use‡		47	1.29 (0.94 to 1.77)	11	1.77 (0.96 to 3.29)	2	0.70 (0.16 to 2.99)	4	1.49 (0.43 to 5.17)
Frequent use by duration vs infrequent/nonuse									
Infrequent/nonuse	.01	557	1.00 (ref)	100	1.00 (ref)	38	1.00 (ref)	46	1.00 (ref)
Frequent/0.5–<5 y		22	1.36 (0.87 to 2.12)	3	0.72 (0.20 to 2.64)	0	–	3	2.42 (0.57 to 10.35)
Frequent/5–<10 y		15	1.44 (0.85 to 2.43)	5	3.66 (1.54 to 8.69)	1	1.68 (0.23 to 12.17)	1	1.48 (0.18 to 11.91)
Frequent/10+ y		8	0.97 (0.48 to 1.96)	3	1.92 (0.58 to 6.32)	1	1.30 (0.16 to 10.48)	0	–
Categories of frequent use vs infrequent/nonuse									
Infrequent/nonuse	.09	554	1.00 (ref)	102	1.00 (ref)	35	1.00 (ref)	46	1.00 (ref)
<Daily use		9	0.95 (0.60 to 1.51)	1	1.70 (0.78 to 3.69)	1	1.15 (0.22 to 6.03)	3	1.69 (0.33 to 8.59)
Daily use§		26	1.70 (1.14 to 2.55)	6	1.85 (0.75 to 4.57)	0	–	1	1.15 (0.17 to 8.01)

*The $P_{heterogeneity}$ value was calculated using a two-sided likelihood ratio test (37). CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.

†Hazard ratios and 95% confidence intervals were estimated from competing risk (37). Cox proportional hazards models were stratified on study cohort and adjusted for baseline age (continuous), body mass index (<20, 20–24.9, 25–29.9, 30–34.9, ≥35 kg/m²), number of births (none, one, two, three, four, or more full-term births), duration of oral contraceptive (OC) use (never, ≤1, >1–5, >5–10, >10 years), and duration of menopausal hormone therapy use (premenopausal, never, ≤5, >5–10, >10 years). Competing risk models were based on fixed covariate effects; variable covariate effect results were practically identical (data not shown).

‡Frequent: use at least ~4–5 days/wk for 6 months or longer.

§Daily: use at least ~6–7 days/wk or ≥28 days per month for 6 months or longer.

ARTICLE

reported a history of chronic disease at baseline and observed some attenuation in risk estimates. That said, further assessment of confounding by medical indications for long-term use, such as joint pain, osteoarthritis, cardiovascular disease, or other factors, is needed, as well as consideration of potential biologic mechanisms by which long-term use may increase risk.

Consistent with our results, acetaminophen use was not associated with ovarian cancer risk in the pooled case–control study data (15), based on more than 400 exposed cases (odds ratio for daily vs nonregular use = 0.95, 95% CI = 0.74 to 1.23). Acetaminophen and nonaspirin NSAIDs are commonly used interchangeably; however, acetaminophen has weak anti-inflammatory properties and may have gonadotrophic effects (11), supporting the different associations we observed between NSAIDs and acetaminophen in our study and suggesting different anti-inflammatory effects or other mechanisms of action (8,9,11). Importantly, the increased risk with daily acetaminophen use observed in this study was based on a limited number of exposed cases and should be interpreted with caution.

The consistent positive relationship for frequent long-duration use of aspirin or nonaspirin NSAIDs with serous disease may suggest that long-term users likely have other factors that increase inflammation and thus risk of this histotype. Some data suggest that serous tumors may be more strongly related to inflammatory factors. For example, aggressive high-grade serous tumors have been more commonly associated with inducible nitric oxide synthase and other inflammatory markers than low-grade tumors (41). Further, prediagnostic circulating inflammatory marker, C-reactive protein, has been associated with the serous histotype (6,42). Lifetime ovulations also were more strongly associated with tumors expressing p53 (43), a hallmark of serous disease (44).

The prospective design of the pooled studies precludes recall bias. Additional strengths of the study include the large sample size, the ability to identify deaths as well as capture loss to follow-up, and the ability to account for many known and suspected risk factors for ovarian cancer. Limitations included the use of self-reported exposure data, limited information on low-dose aspirin use, and limited data on health conditions or medical indications underlying long-term analgesic use. The combination of long-term follow-up and ascertainment of exposure at baseline (in most studies) mean that individuals could have started or stopped use during follow-up, which would contribute to measurement error. Further, information on duration of use at baseline may not adequately represent exposure duration, as such confounding by indication may not fully explain the elevated risks. Residual confounding by age-related factors may also be present; however, we did not observe substantial differences in associations across age strata.

The incidence of ovarian cancer is low; thus, our modest findings are unlikely to alter the balance of more common and clinically significant risks and benefits associated with daily aspirin use. However, the associations stratified by age at baseline provide information relevant to current US Preventive Services Task Force recommendations regarding aspirin use for cardiovascular prevention (45), as decreased ovarian cancer risk estimates associated with daily aspirin use were only observed among women younger than age 70 years. The USPSTF does not recommend frequent aspirin use in women age 70 years or older because of increased risk for adverse events. Although the potential increased risk associated with daily acetaminophen and frequent aspirin and nonaspirin NSAID use for more than 10 years' duration requires further study, daily aspirin use may provide a very modestly reduced risk with respect to incident ovarian cancer.

Funding

This work was supported by Department of Defense Ovarian Cancer Research Program grant W81XWH-12-1-0561. The UKBGS thanks Breast Cancer Now and the Institute of Cancer Research (ICR) for support and funding. The ICR acknowledges National Health Service funding to the National Institute for Health Research Biomedical Research Centre. K05CA154337 from the National Cancer Institute (NCI) and Office of Dietary Supplements (VITAL); R01 CA39742 (Iowa Women's Health Study); research grants from the Swedish Research Council and Swedish Cancer Foundation (SMC, WLHS); UM1 CA164973 (Multiethnic Cohort Study [MEC]); NIH/NCI UM1 CA182876 (SCHS); UM1 CA186107, P01 CA87969, UM1 CA176726, R01 CA67262 (Nurses' Health Study, Nurses' Health Study II); and NIEHS Intramural Research Program (Project Z01-ES044005 to DPS). The Womens Health Initiative (WHI) program is funded by the National Heart, Lung, and Blood Institute, NIH/DHHS, through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. NCI Intramural Research Program.

Notes

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (BT, LAB, PH, NW); Brigham and Women's Hospital and Harvard Medical School, Boston, MA (EMP); Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, WA (EW, GLA, UP); Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (KV, JHB); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (HOA, EW); Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Oslo, Norway (HOA); Division of Cancer Prevention and Control, College of Medicine, The Ohio State University, Columbus, OH (TMB); Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany (RTF); Epidemiology Research Program, American Cancer Society, Atlanta, GA (MG, AVP); Division of Genetics and Epidemiology and Division of Breast Cancer Research, The Institute of Cancer Research, London, UK (MJ, AS); City of Hope, Duarte, CA (JVLJr); Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (SCL, AW); Department of Nutrition, University of California Davis, Davis, CA (GGM); Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, Maastricht, Netherlands (LJS, PAvdB); National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC (DPS, KO); Division of Epidemiology and Community Health, School of Public Health, and Masonic Cancer Center, University of Minnesota, Minneapolis, MN (AP); Department of Exercise and Nutrition Sciences, Milken Institute School of Public Health, George Washington University, Washington, DC (KR); University of Southern California, Los Angeles, CA (VWS); Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway (EWeiderpass); Department of Research, Cancer Registry of Norway, Institute of Population Based Cancer Research, Oslo, Norway (EWeiderpass); Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland (EW); University of Hawaii Cancer Center, Honolulu, HI (LRW); Department of Epidemiology, Harvard T. H. Chan School of Public Health,

ARTICLE

Boston, MA (SST); Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL (SST).

The funding agency did not have any role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Preliminary results from this study were presented at the AACR Rivkin Ovarian Cancer Meeting (September 2016) and at the NCI Cohort Consortium Annual Meeting (November 2016, same abstract).

The authors thank Ruifeng Li for assistance with computer programming and harmonization of covariate data. The UKBGS thanks the study participants, study staff, and the doctors, nurses, and other health care staff and data providers who contributed to the study. We would like to thank the participants and staff of the NHS/NHSII for their valuable contributions and 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, WY. The authors assume full responsibility for analyses and interpretation of these data. The NLCS thanks participants and staff who have contributed to the study. The authors thank the WHI investigators for their dedication and the WHI study participants for making the program possible.

References

1. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999;91(17):1459–1467.
2. Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet*. 1971; 2(7716):163.
3. Moorman PG, Schildkraut JM, Calingaert B, et al. Ovulation and ovarian cancer: A comparison of two methods for calculating lifetime ovulatory cycles (United States). *Cancer Causes Control*. 2002;13(9):807–811.
4. Wentzensen N, Poole EM, Trabert B, et al. Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium. *J Clin Oncol*. 2016;34(24):2888–2898.
5. Zhou Z, Zeng F, Yuan J, et al. Pelvic inflammatory disease and the risk of ovarian cancer: A meta-analysis. *Cancer Causes Control*. 2017;28(5):415–428.
6. Trabert B, Pinto L, Hartge P, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. *Gynecol Oncol*. 2014;135(2):297–304.
7. Poole EM, Lee IM, Ridker PM, et al. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor alpha receptor 2 levels and risk of ovarian cancer. *Am J Epidemiol*. 2013;178(8):1256–1264.
8. Sciulli MG, Seta F, Tacconelli S, et al. Effects of acetaminophen on constitutive and inducible prostanoid biosynthesis in human blood cells. *Br J Pharmacol*. 2003;138(4):634–641.
9. Altinoz MA, Korkmaz R. NF-kappa B, macrophage migration inhibitory factor and cyclooxygenase-inhibitions as likely mechanisms behind the acetaminophen- and NSAID-prevention of the ovarian cancer. *Neoplasma*. 2004;51(4): 239–247.
10. Khunnarong J, Tangjitgamol S, Manusirivithaya S, et al. Expression of cyclooxygenase-1 in epithelial ovarian cancer: A clinicopathological study. *Asian Pac J Cancer Prev*. 2008;9(4):757–762.
11. Cramer DW, Liberman RF, Hornstein MD, et al. Basal hormone levels in women who use acetaminophen for menstrual pain. *Fertil Steril*. 1998;70(2):371–373.
12. Rodriguez-Burford C, Barnes MN, Oelschlager DK, et al. Effects of nonsteroidal anti-inflammatory agents (NSAIDs) on ovarian carcinoma cell lines: Preclinical evaluation of NSAIDs as chemopreventive agents. *Clin Cancer Res*. 2002;8(1):202–209.
13. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet*. 2012; 379(9826):1602–1612.
14. Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: A quantitative review to 2011. *Ann Oncol*. 2012;23(6):1403–1415.
15. 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.
16. Pinheiro SP, Tworoger SS, Cramer DW, et al. Use of nonsteroidal antiinflammatory agents and incidence of ovarian cancer in 2 large prospective cohorts. *Am J Epidemiol*. 2009;169(11):1378–1387.
17. Prizment AE, Folsom AR, Anderson KE. Nonsteroidal anti-inflammatory drugs and risk for ovarian and endometrial cancers in the Iowa Women's Health Study. Cancer *Epidemiol Biomarkers Prev*. 2010;19(2):435–442.
18. Murphy MA, Trabert B, Yang HP, et al. Non-steroidal anti-inflammatory drug use and ovarian cancer risk: Findings from the NIH-AARP Diet and Health Study and systematic review. *Cancer Causes Control*. 2012;23(11):1839–1852.
19. Brasky TM, Liu J, White E, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: Results from the Women's Health Initiative. *Int J Cancer*. 2014;135(8):1869–1883.
20. Baandrup L, Kjaer SK, Olsen JH, et al. Low-dose aspirin use and the risk of ovarian cancer in Denmark. *Ann Oncol*. 2015;26(4):787–792.
21. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: The National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001;154(12):1119–1125.
22. Swerdlow AJ, Jones ME, Schoemaker MJ, et al. The Breakthrough Generations Study: Design of a long-term UK cohort study to investigate breast cancer aetiology. *Br J Cancer*. 2011;105(7):911–917.
23. Gallicchio L, Visvanathan K, Burke A, et al. Nonsteroidal anti-inflammatory drugs and the risk of developing breast cancer in a population-based prospective cohort study in Washington County, MD. *Int J Cancer*. 2007;121(1):211–215.
24. Jacobs EJ, Thun MJ, Connell CJ, et al. Aspirin and other nonsteroidal anti-inflammatory drugs and breast cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):261–264.
25. Clarke CA, Canchola AJ, Moy LM, et al. Regular and low-dose aspirin, other non-steroidal anti-inflammatory medications and prospective risk of HER2-defined breast cancer: The California Teachers Study. *Breast Cancer Res*. 2017;19(1):52.
26. Setiawan VW, Matsuno RK, Lurie G, et al. Use of nonsteroidal anti-inflammatory drugs and risk of ovarian and endometrial cancer: The Multiethnic Cohort. Cancer *Epidemiol Biomarkers Prev*. 2012;21(9):1441–1449.
27. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: Baseline characteristics. *Am J Epidemiol*. 2000;151(4):346–357.
28. Braem MG, Onland-Moret NC, van den Brandt PA, et al. Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. *Am J Epidemiol*. 2010;172(10):1181–1189.
29. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000; 21(6 Suppl):273S–309S.
30. Larsson SC, Giovannucci E, Wolk A. Dietary folate intake and incidence of ovarian cancer: The Swedish Mammography Cohort. *J Natl Cancer Inst*. 2004;96(5):396–402.
31. Kim S, Shore DL, Wilson LE, et al. Lifetime use of nonsteroidal anti-inflammatory drugs and breast cancer risk: Results from a prospective study of women with a sister with breast cancer. *BMC Cancer*. 2015;15:960.
32. Ready A, Velicer CM, McTiernan A, et al. NSAID use and breast cancer risk in the VITAL cohort. *Breast Cancer Res Treat*. 2008;109(3):533–543.
33. Langer RD, White E, Lewis CE, et al. The Women's Health Initiative Observational Study: Baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9 Suppl):S107–S121.
34. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin.Trials*. 1998;19(1):61–109.
35. Roswall N, Sandin S, Adami HO, et al. Cohort profile: The Swedish Women's Lifestyle and Health cohort. *Int J Epidemiol*. 2017;46(2):e8.
36. Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. 1995;51(2):524–532.
37. Gates MA, Rosner BA, Hecht JL, et al. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol*. 2010;171(1):45–53.
38. Chubak J, Kamineni A, Buist DSM, et al. Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force. US Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
39. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Ann Oncol*. 2015;26(1):47–57.
40. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: The Women's Health Study: A randomized controlled trial. *JAMA*. 2005;294(1):47–55.
41. Ali-Fehmi R, Semaan A, Sethi S, et al. Molecular typing of epithelial ovarian carcinomas using inflammatory markers. *Cancer*. 2011;117(2):301–309.
42. Ose J, Schock H, Tjonneland A, et al. Inflammatory markers and risk of epithelial ovarian cancer by tumor subtypes: The EPIC cohort. Cancer *Epidemiol Biomarkers Prev*. 2015;24(6):951–961.
43. Schildkraut JM, Bastos E, Berchuck A. Relationship between lifetime ovulatory cycles and overexpression of mutant p53 in epithelial ovarian cancer. *J Natl Cancer Inst*. 1997;89(13):932–938.
44. Kobel M, Kalloger SE, Lee S, et al. Biomarker-based ovarian carcinoma typing: A histologic investigation in the ovarian tumor tissue analysis consortium. *Cancer Epidemiol Biomarkers Prev*. 2013;22(10):1677–1686.
45. Bibbins-Domingo K; US Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: Recommendations from the U.S. *Preventive Services Task Force*. *Ann Intern Med*. 2016;164(12):836–845.