

UC Irvine

UC Irvine Previously Published Works

Title

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.

Permalink

<https://escholarship.org/uc/item/77h0j6mz>

Journal

Journal of the National Cancer Institute, 106(2)

Authors

Trabert, Britton
Ness, Roberta
Lo-Ciganic, Wei-Hsuan
et al.

Publication Date

2014-02-01

DOI

10.1093/jnci/djt431

Peer reviewed

ARTICLE |

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

Britton Trabert, Roberta B. Ness, Wei-Hsuan Lo-Ciganic, Megan A. Murphy, Ellen L. Goode, Elizabeth M. Poole, Louise A. Brinton, Penelope M. Webb, Christina M. Nagle, Susan J. Jordan, Australian Ovarian Cancer Study Group, the Australian Cancer Study (Ovarian Cancer), Harvey A. Risch, Mary Anne Rossing, Jennifer A. Doherty, Marc T. Goodman, Galina Lurie, Susanne K. Kjær, Estrid Hogdall, Allan Jensen, Daniel W. Cramer, Kathryn L. Terry, Allison Vitonis, Elisa V. Bandera, Sara Olson, Melony G. King, Urmila Chandran, Hoda Anton-Culver, Argyrios Ziogas, Usha Menon, Simon A. Gayther, Susan J. Ramus, Aleksandra Gentry-Maharaj, Anna H. Wu, Celeste Leigh Pearce, Malcolm C. Pike, Andrew Berchuck, Joellen M. Schildkraut, Nicolas Wentzensen; on behalf of the Ovarian Cancer Association Consortium

Manuscript received April 10, 2013; revised November 10, 2013; accepted November 14, 2013.

Correspondence to: Britton Trabert, PhD, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, 6120 Executive Blvd, Ste 550, MSC-7234, Rockville, MD 20852 (e-mail: britton.trabert@nih.gov).

- Background** Regular aspirin use is associated with reduced risk of several malignancies. Epidemiologic studies analyzing aspirin, nonaspirin nonsteroidal anti-inflammatory drug (NSAID), and acetaminophen use and ovarian cancer risk have been inconclusive.
- Methods** We analyzed pooled data from 12 population-based case-control studies of ovarian cancer, including 7776 case patients and 11 843 control subjects accrued between 1992 and 2007. Odds ratios (ORs) for associations of medication use with invasive epithelial ovarian cancer were estimated in individual studies using logistic regression and combined using random effects meta-analysis. Associations between frequency, dose, and duration of analgesic use and risk of ovarian cancer were also assessed. All statistical tests were two-sided.
- Results** Aspirin use was associated with a reduced risk of ovarian cancer (OR = 0.91; 95% confidence interval [CI] = 0.84 to 0.99). Results were similar but not statistically significant for nonaspirin NSAIDs, and there was no association with acetaminophen. In seven studies with frequency data, the reduced risk was strongest among daily aspirin users (OR = 0.80; 95% CI = 0.67 to 0.96). In three studies with dose information, the reduced risk was strongest among users of low dose (<100 mg) aspirin (OR = 0.66; 95% CI = 0.53 to 0.83), whereas for nonaspirin NSAIDs, the reduced risk was strongest for high dose (≥ 500 mg) usage (OR = 0.76; 95% CI = 0.64 to 0.91).
- Conclusions** Aspirin use was associated with a reduced risk of ovarian cancer, especially among daily users of low-dose aspirin. These findings suggest that the same aspirin regimen proven to protect against cardiovascular events and several cancers could reduce the risk of ovarian cancer 20% to 34% depending on frequency and dose of use.

JNCI J Natl Cancer Inst (2014) 106(2): djt431 doi:10.1093/jnci/djt431

Ovarian cancer is the most fatal gynecologic malignancy, causing more than 140 000 deaths each year worldwide (1). Although early stage ovarian cancer can be successfully treated, the disease is commonly detected at advanced stages with extensive local and systemic spread and poor survival. Early detection strategies have not been shown to reduce mortality (2,3), and biomarker candidates have had insufficient performance to improve early detection efforts thus far (4,5). Primary prevention strategies have not been widely studied but may present alternatives to reduce ovarian cancer burden.

Multiple lines of evidence suggest that ovarian cancer may be related to chronic inflammation (6). In addition to inflammatory

factors associated with ovarian epithelial disruption through ovulation (7–9), inflammation-related exposures such as endometriosis (10–12) and exposure to talc or genital powder and asbestos (13) have been associated with increased ovarian cancer risk.

Recently, intervention trials have shown that regular aspirin use is associated with reduced risk of several malignancies (14). However, these trials were not powered for rare cancer endpoints, and none of the clinical trials to date have evaluated ovarian cancer separately. Recent meta-analyses of aspirin use have reached various conclusions that range from no effect (15) to a weak risk reduction among regular users of aspirin (16–18). For nonsteroidal

anti-inflammatory drug (NSAID) use, a recent summary suggested a greater risk reduction among cohort studies than among case-control studies (15), whereas, the results from individual epidemiologic studies have been largely inconclusive (13,19–33), possibly because of limited sample size and limited data on dose, duration, and frequency of use across the studies.

We conducted an analysis of pooled individual-level data of NSAID use and ovarian cancer risk in the Ovarian Cancer Association Consortium (OCAC), including more than 7500 ovarian cancer cases from 12 population-based case-control studies.

Methods

Study Population

We analyzed individual-level data from 12 population-based case-control studies participating in OCAC that had available data on aspirin, nonaspirin NSAID, or acetaminophen (paracetamol) use. All studies had approval from ethics committees, and written informed consent was obtained from study participants. Data acquisition and data pooling for each study were approved by the institutional review board or research ethics committees of the institutes sponsoring the study.

The 12 studies were as follows: the Australian Ovarian Cancer Study and Australian Cancer Study (26), the Connecticut Ovarian Cancer Study (34), the Diseases of the Ovary and their Evaluation Study (23,35), the Hawaii Ovarian Cancer Case-Control Study (36,37), the Hormones and Ovarian Cancer Prediction Study (38), the Malignant Ovarian Cancer Study (39), the North Carolina Ovarian Cancer Study (40,41), the New England Case-Control Study of Ovarian Cancer (42), the New Jersey Ovarian Cancer Study (43), the University of California, Irvine Ovarian Cancer Study (44), the United Kingdom Ovarian Cancer Population Study (45), and the University of Southern California Study of Lifestyle and Women's Health (13) (Table 1). In total, the study included data from nine case-control studies conducted in the United States (13,23,34,37,38,40,42–44), one study conducted in Denmark (39), one study conducted in the United Kingdom (45), and one study conducted in Australia (26).

From these 12 studies, 10 161 ovarian cancer case patients and 12 382 control subjects were available for the analysis. For the primary analysis, we excluded case patients whose cancers were non-epithelial ($n = 43$), of low malignant potential ($n = 2059$), or missing data on both the malignant potential of the tumor and tumor grade ($n = 68$). We further excluded study participants with missing data for all three exposure variables ($n = 215$ case patients and $n = 539$ control subjects), leaving 7776 invasive ovarian cancer case patients and 11 843 control subjects for our analysis. The case patients were divided into four categories by the four main histologic subtypes of the cancer: serous ($n = 4510$), endometrioid ($n = 1163$), clear cell ($n = 677$), and mucinous ($n = 423$). The remaining 1003 case patients with cancers of other histologic type were not included in subtype analyses. We also evaluated associations for high-grade serous ovarian tumors (grade II–IV; $n = 3786$) based on the prevailing view that high-grade serous tumors are distinct from low-grade (grade I; $n = 330$) serous tumors (46). We evaluated 2059 case patients with cancers of low malignant potential in a separate analysis.

Study Variables

Data for medication use was self-reported in all studies (Table 1). Ten of the 12 studies asked about “regular use” of medications over a specified time period with a minimum frequency of use (13,23,34,38–40,42–45). The duration of regular use varied in the 10 studies, from 1 month to 1 year of use. The majority of the studies, six of 10, specified 6 months or more as the minimum duration (23,38,42–45). The definition for frequency of regular use also varied by study, ranging from once per week to daily; the majority of the studies ($n = 8$ of 10) specified once or twice per week as the minimum frequency of regular use (13,23,34,38,39,42,44,45). The two remaining studies did not specify regular use, so we reclassified study participants as regular users if their reported frequency of use was at least once per week (26) or if their frequency of use was at least five pills per month and their duration of use was at least 6 months (37).

The exposures used in this analysis were regular (at least once per week) use of aspirin, nonaspirin NSAIDs, and acetaminophen and nonregular use (reference group; less than once a week use for each category). Data for nonaspirin NSAID use were provided in all studies except for two studies that combined aspirin use with other NSAIDs (44,45). Medication use was further classified by frequency [<30 days per month and daily; $n = 7$ studies (13,23,26,37–40)], dose [<100 and ≥ 100 mg for aspirin to differentiate between use of low- and regular/high-dose formulations; <500 mg and ≥ 500 mg for non-aspirin NSAID and acetaminophen to differentiate between standard and high-dose formulations; $n = 8$ studies (37,38,40)], and duration [<60 months and ≥ 60 months; $n = 8$ studies (13,23,34,37–39,42,43)] of use based on available data from the individual studies. We created a frequency-dose combination exposure variable based on cross-tabulations of the original categorical variables [$(n = 3$ studies) (37,38,40)].

Potential confounding variables were available from all studies as part of a core dataset and were harmonized by the coordinating center. Continuous variables were categorized in all analyses for ease of interpretation and to reduce the effect of any outliers. Variables that were selected a priori as adjustment factors included age (5-year categories), race (white, black, other), body mass index (<25 , 25 – 29 , ≥ 30 kg/m²), use of oral contraceptives (ever, never), parity (nulliparous, 1 full-term birth, >1 full-term birth), menopausal status (pre- or postmenopausal based on study-specific algorithm), and family history of breast or ovarian cancer in a first-degree relative (defined as any breast or ovarian cancer reported in mother, sister, or daughter or breast cancer reported in father). Potential confounding was also evaluated, but not found, for the following variables: Hispanic ethnicity, history of breast feeding, use of estrogen menopausal hormone therapy, use of estrogen plus progestin menopausal hormone therapy, tubal ligation, hysterectomy, and history of endometriosis.

Statistical Analyses

We used multivariable logistic regression models to estimate study-specific odds ratios (ORs) and 95% confidence intervals (CIs) for the association between NSAID exposure and ovarian cancer risk. Study-specific odds ratios were pooled using random-effects meta-analysis to generate a summary odds ratio. For the analyses of the primary exposures (regular use, dose, duration, and frequency), two

Table 1. Characteristics of population-based case-control studies from the Ovarian Cancer Association Consortium included in the pooled analysis*

Study	OCAC acronym	Location	Ascertainment period	Study subjects		Question pertaining to drug use	Prevalence of exposure in control subjects		
				Case patients (n = 7776)	Control subjects (n = 11 843)		Aspirin %	Nonaspirin NSAID [†] %	Acetaminophen %
Australian Ovarian Cancer Study & Australian Cancer Study [†] (26)	AUS	Australia	2002–2005	1311	1505	How often have you taken the following over-the-counter (aspirin, paracetamol, anti-inflammatory drugs) medications during PAST 5 years?	10	16	25
Connecticut Ovarian Cancer Study (34)	CON	USA	1999–2003	388	551	Have you ever taken any of the medications shown on this card regularly (at least once per week on average over a duration of 3 months or more)?	26	28	16
Diseases of the Ovary and their Evaluation Study (23,35)	DOV	USA	2002–2009	1159	1849	Before reference date have you taken any of these medications (show card) 5 or more days per month for at least 6 months?	22	27	16
Hawaii Ovarian Cancer Case-Control Study (36,37)	HAW	USA	2001–2008	256	485	Did you ever take an aspirin product (show card) at least 12 times a year? Identical questions ascertained use of acetaminophen (aspirin-free) and NSAIDs.	26	25	22
Hormones and Ovarian Cancer Prediction Study (38)	HOP	USA	2003–2008	683	1513	Prior to reference date have you ever used aspirin (show card) for at least two tablets per week continuously for a period of 6 months or longer? Identical questions ascertained use of over-the-counter pain or inflammation reliever other than aspirin.	34	33	19
Malignant Ovarian Cancer Study (39)	MAL	Denmark	1994–1999	554	1564	Did you ever take medicine on a regular basis, i.e. two times or more per week for more than one month for any of the following conditions?	8	9	5
North Carolina Ovarian Cancer Study (40,41)	NCO	USA	1999–2008	939	1085	For the 5 years prior to diagnosis, did you take any of these over-the-counter medications (show card) on a regular basis for at least 3 months?	11	38	20
New England Case-Control Study of Ovarian Cancer (42)	NEC	USA	1992–2003	870	1243	Prior to reference date have you ever used any over-the-counter pain reliever (show card) continuously at least once a week for a period of 6 months or longer?	18	25	22

(Table continues)

Table 1 (Continued).

Study	Study subjects					Question pertaining to drug use	Prevalence of exposure in control subjects			
	OCAC acronym	Location	Ascertainment period	Case patients (n = 7776)	Control subjects (n = 11 843)		Aspirin		Nonaspirin NSAID†	
							%	%	%	%
New Jersey Ovarian Cancer Study (43)	NJO	USA	2002–2008	238	458	Prior to reference date did you ever take any over-the-counter medications continuously for 6 months or longer (this includes prescriptions, over-the-counter medications, and any natural or alternative treatments you may have taken).	16	9	3	
University of California, Irvine Ovarian Cancer Study (44)	UCI	USA	1995–2005	393	313	Have you taken medication listed (aspirin, ibuprofen, acetaminophen, naproxen) regularly? By regular, we are referring to use of the drug or medication at least once a week for a year, or more than 50 pills during a one year-period.	26	41‡	17	
United Kingdom Ovarian Cancer Population Study (45)	UKO	UK	2006–2007	516	598	Have you ever used any medication containing the drugs (aspirin, ibuprofen) on a regular basis (by regular we mean every day or almost every day for 6 months or longer)?	15	16‡	—	
University of Southern California Study of Lifestyle and Women's Health (13)	USC	USA	2000–2005	469	679	Before reference date, as an adult, did you ever take any prescription or non-prescription medicine at least 2 or more times per week for one month or longer?	15	16	13	
					Overall		18	24	16	

* NSAID = nonsteroidal antiinflammatory drug; OCAC = Ovarian Cancer Association Consortium.

† Combined for the purpose of this analysis.

‡ UCI and UKO reported data on NSAIDs, including aspirin; the remaining studies provided data on nonaspirin NSAIDs.

multivariable logistic regression models were used: 1) a minimally adjusted model that included covariables for age and race and 2) a fully adjusted model that included age, race, body mass index, oral contraceptive use, parity, menopausal status, and family history of breast or ovarian cancer in a first-degree relative. The summary odds ratios from the fully adjusted model were attenuated slightly compared with the minimally adjusted model. We present the results from the fully adjusted model. We further evaluated models stratified by age (<55 and ≥55 years old), body mass index (<25 and ≥25 kg/m²), oral contraceptive use (ever/never), and history of endometriosis (yes/no). We assessed asymmetry in study estimates using a funnel plot, and when data were sufficient (n > 5 studies), we formally assessed asymmetry using the adjusted rank correlation (47) and regression asymmetry tests (48). Interstudy heterogeneity was evaluated using *I*².

The following sensitivity analyses were performed: 1) exclusion of tubal or primary peritoneal cases (n = 461); 2) restriction to white non-Hispanic participants because 85% of the participants were of white race and non-Hispanic ethnicity; 3) use of a common reference group analysis, coding “nonregular users” as women who reported no regular use of aspirin or nonaspirin NSAIDs or acetaminophen; 4) restriction of pooled analysis to the six studies that specified 6 months or more as the minimum duration; 5) restriction of pooled analysis to the nine US studies; and 6) exclusion from the pooled analysis the two studies (23,45) with the most restrictive definition of medication use given concerns for misclassification of regular users as unexposed. All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant. All analyses were performed using STATA software version 11.2 (StataCorp LP, College Station, TX).

Results

Study site, number of case patients and control subjects, and exposure prevalence for each of the 12 OCAC studies are described in Table 1. Overall, 18% of the study population reported regular use (at least once per week) of aspirin, 24% reported regular use of nonaspirin NSAIDs, and 16% reported regular use of acetaminophen.

Aspirin

Figure 1A shows the association between aspirin use (regular vs nonregular use) and ovarian cancer risk. Regular aspirin use was associated with a reduced risk of ovarian cancer (OR = 0.91; 95% CI = 0.84 to 0.99; *P* = 5.2%). Among seven studies that reported information on frequency of use, daily use was associated with a 20% reduction in ovarian cancer risk (OR = 0.80; 95% CI = 0.67 to 0.96) (Table 2). Among three studies that reported information on dose, low-dose aspirin use (<100 mg/day) was associated with a 34% reduction in ovarian cancer risk (OR = 0.66; 95% CI = 0.53 to 0.83) (Table 2). In analyses of combined categories of frequency and dose of aspirin use, the reduced risk was apparent for daily users of aspirin regardless of dose (low dose: OR = 0.64, 95% CI = 0.50 to 0.81; high dose: OR = 0.78, 95% CI = 0.62 to 0.97) (Table 3).

In subtype analyses, regular aspirin use was associated with reduced risks of serous, endometrioid, and mucinous ovarian cancer, but only the results for serous cancer reached statistical significance (OR = 0.89; 95% CI = 0.80 to 0.99) (Table 4). Pairwise

comparisons showed no significant differences in risk between the subtypes (*P* > .05).

Nonaspirin NSAIDs

Regular nonaspirin NSAID use was associated with a reduced, albeit not statistically significant, risk of ovarian cancer (OR = 0.90; 95% CI = 0.77 to 1.05; *P* = 73.2%) (Figure 1B). Among the three studies that reported information on dose, high-dose nonaspirin NSAID use (≥500 mg/day) was associated with a 24% reduction in ovarian cancer risk (OR = 0.76; 95% CI = 0.64 to 0.91) (Table 2). In analyses of combined categories of frequency and dose, the reduced risk of ovarian cancer was apparent among both categories of high-dose nonaspirin NSAID use (<30 days per month: OR = 0.77, 95% CI = 0.57 to 1.04; daily: OR = 0.75; 95% CI = 0.60 to 0.94), with a weaker association with daily users of low-dose nonaspirin NSAIDs (OR = 0.88; 95% CI = 0.70 to 1.11) (Table 3). The association between nonaspirin NSAIDs and risk was strongest for serous cancers but did not differ across histologic subtypes of ovarian cancer (Table 4).

Acetaminophen

Acetaminophen use was not associated with ovarian cancer risk (OR = 0.99; 95% CI = 0.88 to 1.12; *P*: 40.0%) (Figure 1C). No associations were observed when analyzing dose, duration, or frequency of acetaminophen use and ovarian cancer risk (Table 2). Further we observed no association between acetaminophen use and histologic subtypes of ovarian cancer (Table 4).

Additional Analyses

The association between NSAID use and high-grade serous tumors was not substantially different than the results reported for all serous tumors combined (results not shown). Tumors of low malignant potential (n = 2059) were not associated with analgesic use (data not shown). In analyses stratified by age, body mass index, oral contraception use, and history of endometriosis, similar NSAID use and ovarian cancer associations were observed as in the overall population (results not shown). Based on the adjusted rank correlation and regression asymmetry tests, there was no indication of small study effects (all *P* > .05) in the summary estimates for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer. Although there was heterogeneity in the definition of nonaspirin NSAID use, individual exclusion of each study did not substantially change the summary odds ratio (results not shown); however, the exclusion of two studies (13,44) resulted in a decrease in *I*² from 73.2% to 27.8% but no substantial change in the summary odds ratio (results not shown).

In a sensitivity analysis excluding peritoneal and fallopian tube cancers, the pooled summary odds ratios for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer were not substantially different from the odds ratios observed for the overall case group (data not shown). The associations between regular use of NSAIDs and ovarian cancer did not substantially change when the analyses were restricted to non-Hispanic white case patients and control subjects (data not shown). In analyses using women who reported nonregular use of all three NSAIDs as the reference group, a stronger reduced risk was observed for regular use of aspirin (OR = 0.81;

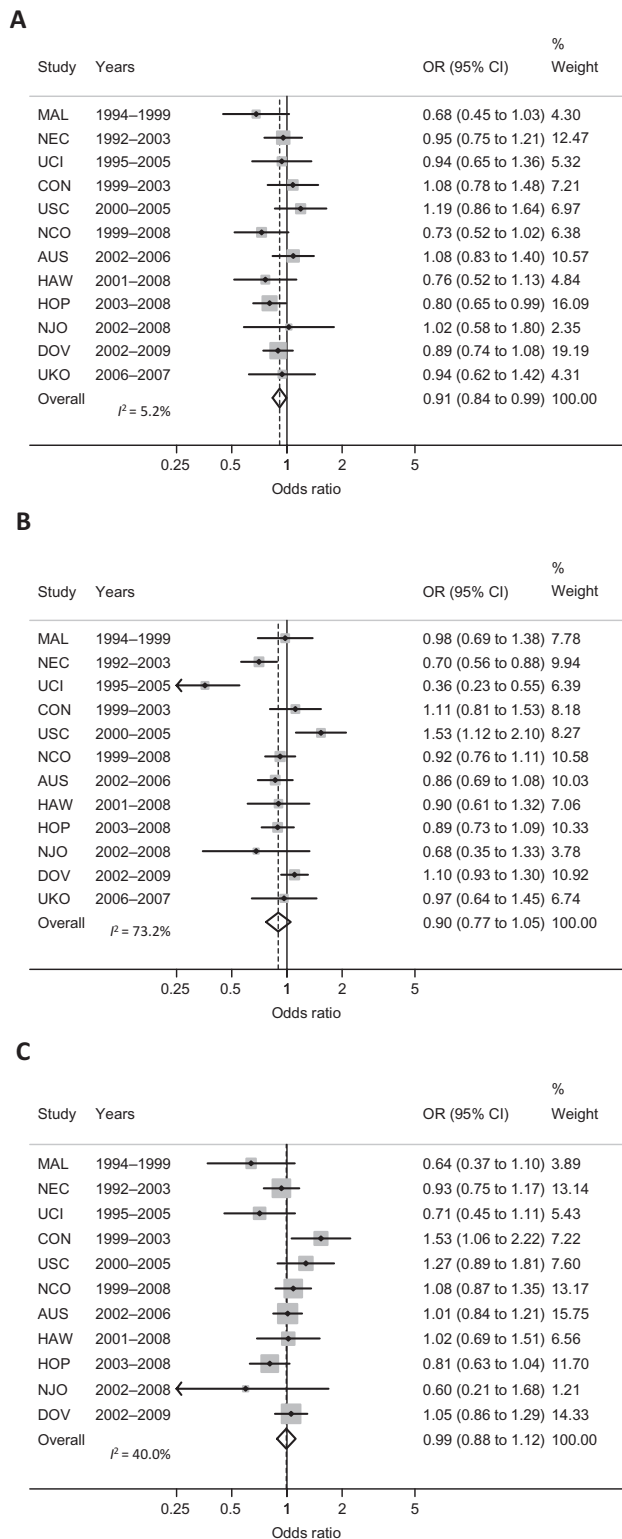


Figure 1. The summary odds ratios (ORs) and 95% confidence intervals (CIs) for the association between regular (at least once per week) use of aspirin (A), nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) (B), and acetaminophen (C) and ovarian cancer risk. Summary odds ratios and 95% confidence intervals were estimated using a random-effect meta-analytic model. All statistical tests were two-sided. I^2 is the percentage of variation across studies due to heterogeneity rather than chance. % Weight describes the weight (inverse variance) each study contributed to the summary odds ratio, and the size of the surrounding

95% CI = 0.68–0.99) and nonaspirin NSAID (OR = 0.86; 95% CI = 0.71–1.05), possibly reflecting reduced “contamination” of the referent group with users of NSAID types other than the medication under examination in each specific analysis (data not shown). In sensitivity analyses restricted to the six studies that specified 6 months or more as the minimum duration or the nine US studies, the pooled summary odds ratios for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer were not substantially different from the odds ratios observed for the overall pooled analysis (data not shown). Finally, in the sensitivity analysis excluding case patients with the most restrictive definition of medication use, the pooled summary odds ratios for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer were not substantially different from the pooled odds ratios observed for all 12 studies (data not shown).

Discussion

To our knowledge, this is the largest evaluation of aspirin, nonaspirin NSAID, and acetaminophen use and ovarian cancer risk to date. We observed a 20% risk reduction for daily users of aspirin and 34% risk reduction for regular users of low-dose aspirin. Regular (at least once per week) use of high doses of nonaspirin NSAIDs was associated with a 24% reduction in ovarian cancer risk. In contrast, acetaminophen use was not associated with ovarian cancer risk. We did not observe any substantial differences in risk by histologic subtypes of ovarian cancer.

Several established risk factors for ovarian cancer are related to inflammatory processes. During ovulation, follicles rupture and inflammatory mediators are released locally that may initiate cell transformation or that may promote growth of transformed cells (49). Proinflammatory agents are also released in inflammatory processes related to endometriosis (10). Aspirin and nonaspirin NSAIDs may reduce exposure to these inflammatory processes; thus, the reduced risk of ovarian cancer with frequent aspirin and nonaspirin NSAID use is consistent with the hypothesized inflammatory etiology of ovarian cancer (50). Several observational studies have evaluated NSAID use and the risk of ovarian cancer. (13,15,19–33,51) A recent meta-analysis reported comparable summary odds ratios for any use of aspirin (OR = 0.91; 95% CI = 0.82 to 1.01) and nonaspirin NSAIDs (OR = 0.89; 95% CI = 0.74 to 1.08), but the estimates did not reach statistical significance (51).

square is an illustrative representation of study weighting. The **horizontal lines** represent study-specific confidence intervals; if ending in an **arrow**, this indicates that the interval transcends the region plotted. The **diamond** represents the summary odds ratio and 95% confidence interval. Studies are presented in order of median year of case accrual from earliest to most recent. AUS = Australian Ovarian Cancer Study, Australian Cancer Study; CON = Connecticut Ovary Study; DOV = Diseases of the Ovary and their Evaluation Study; HAW = Hawaii Ovarian Cancer Study; HOP = Hormones and Ovarian Cancer Prediction Study; MAL = Malignant Ovarian Cancer Study; NCO = North Carolina Ovarian Cancer Study; NEC = New England Case–Control Study of Ovarian Cancer; NJO = New Jersey Ovarian Cancer Study; UCI = University of California, Irvine Ovarian Cancer Study; UKO = United Kingdom Ovarian Cancer Population Study; USC = University of Southern California Study of Lifestyle and Women’s Health.

Table 2. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of aspirin, nonaspirin NSAID, and acetaminophen/paracetamol use with risk of ovarian cancer in the Ovarian Cancer Association Consortium (1992–2009)*

Exposure categorization	Aspirin			Nonaspirin NSAID			Acetaminophen				
	Control	Case	ORT (95% CI) I ²	Control	Case	ORT (95% CI) I ²	Control	Case	ORT (95% CI) I ²		
Frequency†											
No regular use	6366	3826	1.00 (referent)	6007	3565	1.00 (referent)	6189	3497	1.00 (referent)		
<30 days per month	917	739	1.04 (0.92 to 1.18)	1357	994	1.04 (0.88 to 1.22)	1805	1439	1.10 (0.96 to 1.26)	0.0	
Daily	1179	607	0.80 (0.67 to 0.96)	1285	776	0.97 (0.83 to 1.12)	665	427	0.95 (0.74 to 1.23)	63.4	
Dose‡§											
No regular use	2138	1359	1.00 (referent)	2053	1274	1.00 (referent)	2465	1516	1.00 (referent)		
Low	320	129	0.66 (0.53 to 0.83)	439	259	0.96 (0.79 to 1.16)	113	68	1.15 (0.84 to 1.59)	0.0	
High	415	211	0.89 (0.73 to 1.08)	490	233	0.76 (0.64 to 0.91)	500	293	0.90 (0.68 to 1.19)	60.4	
Duration†											
No regular use	6625	3667	1.00 (referent)	6451	3568	1.00 (referent)	7106	3918	1.00 (referent)		
<60 months	819	401	0.83 (0.68 to 1.01)	1002	490	0.86 (0.71 to 1.04)	477	243	0.88 (0.72 to 1.08)	26.5	
≥60 months	833	527	0.98 (0.86 to 1.11)	824	525	1.08 (0.86 to 1.34)	712	438	1.13 (0.92 to 1.39)	44.4	

* NSAID = nonsteroidal anti-inflammatory drug.

† Summary odds ratios were estimated using random-effects meta-analytic model. Results were adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), race (white, black, other), oral contraceptive use (ever/never), parity (0, 1, ≥2), menopausal status (premenopausal/postmenopausal), body mass index category (<25, 25–29.9, ≥30kg/m²) if available, and first-degree family history of breast cancer, male breast cancer, or ovarian cancer. All statistical tests were two-sided.

‡ Analyses included seven studies for frequency (13,23,26,37–40), three studies for dose (37,38,40), and eight studies for duration.(13,23,34,37–39,42,43).

§ Dose categories for aspirin: low: <100 mg, high: ≥100 mg; for nonaspirin NSAIDs and acetaminophen: low: <500 mg, high: ≥500 mg.

|| I² is the percentage of variation across studies due to heterogeneity rather than chance.

Table 3. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of aspirin and NSAID use with risk of ovarian cancer in the Ovarian Cancer Association Consortium (1992–2009)*

Exposure categorization	Aspirin					Nonaspirin NSAID				
	Control	Case	OR†	(95% CI)	I ² §	Control	Case	OR†	(95% CI)	I ² §
Frequency and dose‡										
No regular use	2138	1359	1.00	(referent)		2053	1274	1.00	(referent)	
<30 days per month, low dose	19	11	1.12	(0.52 to 2.43)	0.0	175	115	1.08	(0.74 to 1.59)	52.1
Daily, low Dose	298	118	0.64	(0.50 to 0.81)	0.0	263	143	0.88	(0.70 to 1.11)	0.0
<30 days per month, high dose	93	66	1.25	(0.88 to 1.76)	0.0	136	82	0.77	(0.57 to 1.04)	0.0
Daily, high Dose	322	144	0.78	(0.62 to 0.97)	0.0	353	148	0.75	(0.60 to 0.94)	3.8

* NSAID = nonsteroidal anti-inflammatory drug.

† Summary odds ratios were estimated using random-effects meta-analytic model. Results were adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), race (white, black, other), oral contraceptive use (ever/never), parity (0, 1, ≥2), menopausal status (premenopausal/postmenopausal), body mass index category (<25, 25–29.9, ≥30 kg/m²) if available, and first-degree family history of breast cancer, male breast cancer, or ovarian cancer. All statistical tests were two-sided.

‡ Analyses included three studies for frequency and dose analyses (37,38,40). Dose categories for aspirin: low: <100 mg, high: ≥100 mg; for nonaspirin NSAIDs and acetaminophen: low: <500 mg, high: ≥500 mg.

§ I² is the percentage of variation across studies due to heterogeneity rather than chance.

However, daily and/or low-dose aspirin use was not specifically evaluated in the meta-analysis. In contrast, the use of individual-level data in this study facilitated the evaluation of usage patterns beyond what was available in the meta-analysis of published studies.

The pharmacological effects of NSAIDs that lead to reduced risks of cancer or improved cancer prognosis are not well understood and may differ by cancer site. Aspirin is a strong, irreversible inhibitor of COX-1. Nonaspirin NSAIDs are nonselective and reversible inhibitors of both COX-1 and COX-2, whereas acetaminophen is a more effective inhibitor of COX-2 (52,53). The different effects observed in our study for aspirin/nonaspirin NSAIDs and acetaminophen may suggest that COX-1 inhibition is important for ovarian cancer risk reduction, a notion that is further supported by frequent overexpression of COX-1 in ovarian cancer tissue, but more biological and pharmacological research is needed to understand the underlying mechanisms (54).

Both epidemiologic studies and randomized trials have reported inverse associations between aspirin use and colorectal cancer, with a relative risk of approximately 0.5 for regular users (55). There is some evidence that regular and prolonged aspirin use is also associated with reduced risk of cancers of the esophagus (16), bladder (56), liver (57), lung (16), endometrium (58), and female breast (16). A recent pooled analysis of individual patient data from 51 randomized trials of aspirin use for cardiovascular disease prevention reported a 12% reduction in cancer incidence with 3 or more years of daily aspirin use (14). In women, the reduction in incidence was greatest for cancers of the female reproductive organs; however, ovarian cancer incidence was very low (14).

In the Women's Health Study, use of low-dose aspirin every other day was not associated with reduced incidence of colorectal cancer or cancer overall, suggesting that a daily use regimen is important for cancer protection (59). This notion is supported by our findings: the reduction of ovarian cancer risk was much stronger when daily use was considered, and the strongest reduction was observed among daily users of low-dose aspirin. This finding is likely explained by the regular use pattern of low-dose aspirin because low-dose aspirin regimens for cardiovascular protection are characterized by daily use over a long period of time.

Quantifying desired and adverse effects of aspirin will be important when evaluating future public health decisions about aspirin use for prevention of cardiovascular disease and cancer. Complications associated with aspirin use, including peptic ulcer, upper gastrointestinal bleeding, and hemorrhagic stroke, pose serious threats; current risk–benefit analyses favor aspirin use among high-risk groups but not for large-scale, population-based chemoprevention. Our study provides estimates on the effect of aspirin on ovarian cancer risk that should be considered in risk–benefit analyses for preventive aspirin use. However, detailed questions about frequency, dose, and duration will need to be evaluated in future studies including pooled data from cohort studies.

This pooled analysis of data from 12 studies offered several notable strengths. With more than 7500 case patients, we had greater power to detect associations than in any previous single study. Further, we were able to consistently adjust for potential confounders across studies and to evaluate NSAID exposure compared with a common reference group, reducing exposure misclassification (23). Observing consistent associations across studies and countries provided additional robustness to our findings, specifically for aspirin use, where the interstudy heterogeneity was the smallest. The use of individual-level data and the ability to consider and control for a wide range of potential confounders were additional strengths of this pooled analysis.

Potential limitations include possible differential recall of medication use between case patients and control subjects. However, the decreased risk observed for aspirin or nonaspirin NSAIDs and the lack of association with acetaminophen argues against substantial differential recall. Further, the study-specific prevalence of regular aspirin use in the US studies (11%–16%) included in the current analysis is consistent with estimates reported in US cohorts (60–62); differential recall (ie, greater reporting of medication use among case patients) would have biased our results toward the null. There was evidence of heterogeneity between study-specific estimates, but this was mostly restricted to analyses pertaining to nonaspirin NSAIDs and acetaminophen use. Nonaspirin NSAIDs include a variety of drugs and formulations with regional differences that may have contributed to heterogeneity. Another limitation of this pooled analysis was the variability in the definition of regular use across study

Table 4. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of aspirin, nonaspirin NSAID, and acetaminophen/paracetamol use with risk of ovarian cancer subtype in the Ovarian Cancer Association Consortium (1992–2009)*

Subtype	Aspirin			Nonaspirin NSAID			Acetaminophen			
	Controls	Cases	OR† (95% CI)	Controls	Cases	OR† (95% CI)	Controls	Cases	OR† (95% CI)	I ² ‡
Serous	9501	3622	1.00 (referent)	8940	3467	1.00 (referent)	9326	3478	1.00 (referent)	
	2123	769	0.89 (0.80 to 0.99)	2754	1002	0.83 (0.68 to 1.02)	1878	777	1.03 (0.91 to 1.18)	33.3
Endometrioid	9460	951	1.00 (referent)	8903	858	1.00 (referent)	9264	920	1.00 (referent)	
	2115	183	0.90 (0.74 to 1.09)	2742	290	0.93 (0.75 to 1.15)	2277	192	0.83 (0.66 to 1.05)	29.1
Clear cell	8800	507	1.00 (referent)	8215	456	1.00 (referent)	9070	510	1.00 (referent)	
	1906	110	1.09 (0.84 to 1.41)	2561	169	0.97 (0.73 to 1.27)	3222	166	1.22 (0.91 to 1.64)	32.7
Mucinous	8897	308	1.00 (referent)	8340	270	1.00 (referent)	8927	314	1.00 (referent)	
	2312	62	0.89 (0.58 to 1.38)	2625	96	0.99 (0.73 to 1.35)	1987	66	0.90 (0.66 to 1.23)	0.0

* NSAID = nonsteroidal anti-inflammatory drug.

† Summary odds ratios were estimated using random-effects meta-analytic model. Results were adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), race (white, black, other), oral contraceptive use (ever/never), parity (0, 1, ≥2), menopausal status (premenopausal/postmenopausal), body mass index category (<25, 25–29.9, ≥30 kg/m²) if available, and first-degree family history of breast cancer, male breast cancer, or ovarian cancer. All statistical tests were two-sided.

‡ I² is the percentage of variation across studies due to heterogeneity rather than chance.

populations. We addressed the misclassification of exposure definitions across the studies by using a standard definition for regular use as described in the Methods; in the two studies with the least restrictive definition of regular use (26,37), participants were reclassified accordingly. We conducted a sensitivity analysis restricting the pooled analysis to those studies with regular use for at least 6 or more months in duration and found similar results. We were not able to reclassify participants from two studies with the most restrictive definition of regular use (23,45). In a sensitivity analysis excluding these two studies from the pooled analysis, the results were essentially unchanged. The details of NSAID use patterns ascertained in each study population differed, and data on frequency, dose, and duration of use were not provided in all studies; thus some subgroup analyses are based on small numbers. Although the point estimates for duration of use suggest a counterintuitive trend of shorter duration of use associated with lower risk of ovarian cancer, the differences were not statistically significant. It will be important to follow up the findings in large pooled prospective studies to better understand the effects of duration and timing of aspirin use and ovarian cancer risk. Further, we were not able to evaluate indication of use.

In summary, this pooled analysis supports the hypothesis that regular aspirin use reduces ovarian cancer risk. Specifically, we report a statistically significant decreased risk of ovarian cancer with daily use of aspirin. Further biological and pharmacological research is necessary to understand the mechanisms of ovarian cancer risk reduction by aspirin use.

References

- Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61(2):69–90.
- Buyss SS, Partridge E, Greene MH, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. *Am J Obstet Gynecol.* 2005;193(5):1630–1639.
- Buyss SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA.* 2011;305(22):2295–2303.
- Zhu CS, Pinsky PF, Cramer DW, et al. A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer. *Cancer Prev Res (Phila).* 2011;4(3):375–383.
- Cramer DW, Bast RC, Jr., Berg CD, et al. Ovarian cancer biomarker performance in prostate, lung, colorectal, and ovarian cancer screening trial specimens. *Cancer Prev Res (Phila).* 2011;4(3):365–374.
- Ness RB, Grisso JA, Cotreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology.* 2000;11(2):111–117.
- Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet.* 1971;2(7716):163.
- 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.
- Fleming JS, Beaugie CR, Haviv I, Chenevix-Trench G, Tan OL. Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: revisiting old hypotheses. *Mol Cell Endocrinol.* 2006;247(1–2):4–21.
- Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *Am J Obstet Gynecol.* 2003;189(1):280–294.
- Brinton LA, Sakoda LC, Sherman ME, et al. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. *Cancer Epidemiol Biomarkers Prev.* 2005;14(12):2929–2935.
- Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol.* 2012;13(4):385–394.

13. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer*. 2009;124(6):1409–1415.
14. 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.
15. 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.
16. Bosetti C, Rosato V, Gallus S, Cuzick J, La VC. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol*. 2012;23(6):1403–1415.
17. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol*. 2005;60(2):194–203.
18. Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand*. 2013;92(3):245–255.
19. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, et al. Aspirin and epithelial ovarian cancer. *Prev Med*. 2001;33(6):682–687.
20. Ammundsen HB, Faber MT, Jensen A, et al. Use of analgesic drugs and risk of ovarian cancer: results from a Danish case-control study. *Acta Obstet Gynecol Scand*. 2012;91(9):1094–1102.
21. Cramer DW, Harlow BL, Titus-Ernstoff L, et al. Over-the-counter analgesics and risk of ovarian cancer. *Lancet*. 1998;351(9096):104–107.
22. Fairfield KM, Hunter DJ, Fuchs CS, Colditz GA, Hankinson SE. Aspirin, other NSAIDs, and ovarian cancer risk (United States). *Cancer Causes Control*. 2002;13(6):535–542.
23. Hannibal CG, Rossing MA, Wicklund KG, Cushing-Haugen KL. Analgesic drug use and risk of epithelial ovarian cancer. *Am J Epidemiol*. 2008;167(12):1430–1437.
24. Lacey JV, Jr., Sherman ME, Hartge P, Schatzkin A, Schairer C. Medication use and risk of ovarian carcinoma: a prospective study. *Int J Cancer*. 2004;108(2):281–286.
25. Lo-Cigamic WH, Zgibor JC, Bunker CH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory agents and risk of ovarian cancer. *Epidemiology*. 2012;23(2):311–319.
26. Merritt MA, Green AC, Nagle CM, Webb PM. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer*. 2008;122(1):170–176.
27. Pinheiro SP, Tworoger SS, Cramer DW, Rosner BA, Hankinson SE. Use of nonsteroidal anti-inflammatory agents and incidence of ovarian cancer in 2 large prospective cohorts. *Am J Epidemiol*. 2009;169(11):1378–1387.
28. 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.
29. Schildkraut JM, Moorman PG, Halabi S, et al. Analgesic drug use and risk of ovarian cancer. *Epidemiology*. 2006;17(1):104–107.
30. 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.
31. Rosenberg L, Palmer JR, Rao RS, et al. A case-control study of analgesic use and ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2000;9(9):933–937.
32. Moysich KB, Mettlin C, Piver MS, et al. Regular use of analgesic drugs and ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2001;10(8):903–906.
33. Tavani A, Gallus S, La VC, et al. Aspirin and ovarian cancer: an Italian case-control study. *Ann Oncol*. 2000;11(9):1171–1173.
34. Risch HA, Bale AE, Beck PA, Zheng W. PGR +331 A/G and increased risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15(9):1738–1741.
35. Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Menopausal hormone therapy and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2007;16(12):2548–2556.
36. Goodman MT, Lurie G, Thompson PJ, McDuffie KE, Carney ME. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocr Relat Cancer*. 2008;15(4):1055–1060.
37. Lurie G, Wilkens LR, Thompson PJ, et al. Combined oral contraceptive use and epithelial ovarian cancer risk: time-related effects. *Epidemiology*. 2008;19(2):237–243.
38. Ness RB, Dodge RC, Edwards RP, Baker JA, Moysich KB. Contraception methods, beyond oral contraceptives and tubal ligation, and risk of ovarian cancer. *Ann Epidemiol*. 2011;21(3):188–196.
39. Glud E, Kjaer SK, Thomsen BL, et al. Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. *Arch Intern Med*. 2004;164(20):2253–2259.
40. Moorman PG, Calingaert B, Palmieri RT, et al. Hormonal risk factors for ovarian cancer in premenopausal and postmenopausal women. *Am J Epidemiol*. 2008;167(9):1059–1069.
41. Schildkraut JM, Iversen ES, Wilson MA, et al. Association between DNA damage response and repair genes and risk of invasive serous ovarian cancer. *PLoS One*. 2010;5(4):e10061.
42. Terry KL, DeVivo I, Titus-Ernstoff L, Shih MC, Cramer DW. Androgen receptor cytosine, adenine, guanine repeats, and haplotypes in relation to ovarian cancer risk. *Cancer Res*. 2005;65(13):5974–5981.
43. Bandera EV, King M, Chandran U, et al. Phytoestrogen consumption from foods and supplements and epithelial ovarian cancer risk: a population-based case-control study. *BMC Womens Health*. 2011;11:40. doi:10.1186/1472-6874-11-40.
44. Ziogas A, Gildea M, Cohen P, et al. Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2000;9(1):103–111.
45. Balogun N, Gentry-Maharaj A, Wozniak EL, et al. Recruitment of newly diagnosed ovarian cancer patients proved challenging in a multicentre biobanking study. *J Clin Epidemiol*. 2011;64(5):525–530.
46. Gilks CB. Molecular abnormalities in ovarian cancer subtypes other than high-grade serous carcinoma. *J Oncol*. 2010;2010:7. doi:10.1186/1472-6874-11-40.
47. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101.
48. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
49. Richards JS, Russell DL, Ochsner S, Espey LL. Ovulation: new dimensions and new regulators of the inflammatory-like response. *Annu Rev Physiol*. 2002;64:69–92.
50. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999;91(17):1459–1467.
51. Ni X, Ma J, Zhao Y, Wang Y, Wang S. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. *Br J Clin Pharmacol*. 2013;75(1):26–35.
52. Sciulli MG, Seta F, Tacconelli S, et al. Effects of acetaminophen on constitutive and inducible prostanoic acid biosynthesis in human blood cells. *Br J Pharmacol*. 2003;138(4):634–641.
53. Altinoz MA, Korkmaz R. NF-kappaB, 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.
54. Khunrarong J, Tangitgamol S, Manusirivithaya S, Suekwattana P, Leelahakorn S. Expression of cyclooxygenase-1 in epithelial ovarian cancer: a clinicopathological study. *Asian Pac J Cancer Prev*. 2008;9(4):757–762.
55. Chan AT, Arber N, Burn J, et al. Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer Prev Res (Phila)*. 2012;5(2):164–178.
56. Daugherty SE, Pfeiffer RM, Sigurdson AJ, et al. Nonsteroidal anti-inflammatory drugs and bladder cancer: a pooled analysis. *Am J Epidemiol*. 2011;173(7):721–730.
57. Sahasrabudhe VV, Gunja MZ, Graubard BI, et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. *J Natl Cancer Inst*. 2012;104(23):1808–1814.
58. Neill AS, Nagle CM, Protani MM, et al. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control study, systematic review and meta-analysis. *Int J Cancer*. 2013;132(5):1146–1155.
59. 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.

60. Ajani UA, Ford ES, Greenland KJ, Giles WH, Mokdad AH. Aspirin use among U.S. adults: Behavioral Risk Factor Surveillance System. *Am J Prev Med.* 2006;30(1):74–77.
61. Sanchez DR, Diez Roux AV, Michos ED, et al. Comparison of the racial/ethnic prevalence of regular aspirin use for the primary prevention of coronary heart disease from the multi-ethnic study of atherosclerosis. *Am J Cardiol.* 2011;107(1):41–46.
62. Soni A. *Aspirin Use Among the Adult U.S. Noninstitutionalized Population, With and Without Indicators of Heart Disease.* Statistical Brief #179. Rockville, MD: Agency for Healthcare Research and Quality; 2005.

Funding

The Ovarian Cancer Association Consortium was supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith. This work was supported in part by the Intramural Research Program of the National Institutes of Health (NIH). Elizabeth Poole and Megan Murphy are both supported in part by training grant T32 CA 09001. Ellen Goode is supported by R01 CA122443 and P50-CA136393. The Australian Ovarian Cancer Study and Australian Cancer Study were funded by the US Army Medical Research and Materiel Command (DAMD17-01-1-0729), National Health and Medical Research Council of Australia (199600, 400413), Cancer Councils of New South Wales, Victoria, Queensland, South Australia and Tasmania, Cancer Foundation of Western Australia. The Connecticut Ovarian Cancer Study was funded by R01 CA074850 and R01 CA080742. The Diseases of the Ovary and their Evaluation Study was funded by R01 CA112523 and R01 CA87538. The Hawaii Ovarian Cancer Case–Control Study was funded by R01 CA58598, N01 CN55424 and N01 PC67001. The Hormones and Ovarian Cancer Prediction Study was funded by R01 CA95023 and Department of Defense (DOD) grant DAMD17-02-1-0669. The Malignant Ovarian Cancer Study was funded by R01 CA61107, research grant 94 222 52 from the Danish Cancer Society, Copenhagen, Denmark, and the Mermaid I project. The North Carolina Ovarian Cancer Study was funded by R01 CA76016 and DOD grant DAMD17-02-1-0666. The New England Case–Control Study of Ovarian Cancer was funded by R01 CA54419, P50 CA105009, and DOD grant W81XWH-10-1-02802. The New Jersey Ovarian Cancer Study was funded by the National Cancer Institute (K07 CA095666, R01 CA83918, and K22CA138563) and the Cancer Institute of New Jersey. The University of California, Irvine Ovarian Cancer Study was funded by R01 CA58860, R01 CA92044, PSA 042205, and the Lon V Smith Foundation grant LVS-39420. The United Kingdom Ovarian Cancer Population Study was funded by Cancer Research UK, the Eve Appeal and the OAK Foundation. The University of Southern California, Study of Lifestyle and Women's Health was funded by R01 CA17054, R01 CA14089, R01 CA61132, N01-PC-67010, P01 CA17054, California Cancer Research Program (00-01389V-20170, R03 CA113148, R03 CA115195, N01 CN25403), and California Cancer Research Program (2II0200) (USC). The funding agencies did not have any role in conducting the study or preparing the manuscript for publication.

Notes

The Australian Ovarian Cancer Study Management Group (D. Bowtell, G. Chenevix-Trench, A. deFazio, D. Gertig, A. Green, P. Webb) and Australian Cancer Study investigators (A. Green, P. Parsons, N. Hayward, P. Webb, D. Whiteman) thank all the clinical and scientific collaborators (see <http://www.aocstudy.org/>)

and the women for their contribution. The cooperation of the 32 Connecticut hospitals, including Stamford Hospital, in allowing patient access, is gratefully acknowledged. This study was approved by the State of Connecticut Department of Public Health Human Investigation Committee. Certain data used in this study were obtained from the Connecticut Tumor Registry in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data. The MALOVA group is grateful to Nick Martinussen for data management assistance. The NJO group thanks Drs Lorna Rodriguez and Lisa Paddock, the staff of the New Jersey State Cancer Registry, and Thanusha Puvanarayagam for their contribution to the study. Some of this work was undertaken at University College London Hospital/University College London, which received a proportion of funding from the Department of Health's National Institutes for Health Research Biomedical Research Centre funding scheme. We particularly thank I. Jacobs, M. Widschwendter, E. Wozniak, A. Ryan, J. Ford and N. Balogun for their contribution to the study.

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD (BT, LAB, NW); University of Texas School of Public Health, Houston, TX (RBN); Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA (WVL); Channing Division of Network Medicine (MAM, EMP) and Obstetrics and Gynecology Epidemiology Center (DWC, KLT), Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Department of Epidemiology, Harvard School of Public Health, Boston, MA (MAM, EMP, DWC, KLT); Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN (ELG); Queensland Institute of Medical Research, Brisbane, Australia (PMW, CMN, SJJ), Australian Ovarian Cancer Study Group, the Australian Cancer Study (Ovarian Cancer); Peter MacCallum Cancer Centre, East Melbourne, Australia (Australian Ovarian Cancer Study Group); Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT (HAR); Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA (MAR, JAD); Department of Community and Family Medicine, Section of Biostatistics & Epidemiology, Dartmouth Medical School, Lebanon, NH (JAD); Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA (MTG); Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI (GL); Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark (SKK, EH, AJ); Gynaecologic Clinic, Copenhagen University Hospital, Copenhagen, Denmark (SKK); The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ (EVB, MGK, UC); Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY (SO); Department of Epidemiology, School of Medicine, University of California Irvine, Irvine, CA (HA, AZ); Department of Women's Cancer, University College London, EGA Institute for Women's Health, London, UK (UM, AG); Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA (SAG, SJR, MCP); Department of Obstetrics and Gynecology (AB) and Department of Community and Family Medicine (JMS), Duke University Medical Center, Durham, NC; Cancer Prevention, Detection and Control Research Program, Duke Cancer Institute, Durham, NC (JMS).