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Article

Analgesic use and ovarian cancer risk: an analysis in the Ovarian Cancer Cohort Consortium

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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 3,514 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/week) vs. infrequent/non-use experienced a 10% reduction in ovarian cancer risk [rate ratio (95% confidence interval): 0.90 (0.82 -1.00), p=0.05]. Frequent use (≥4 days/week) of aspirin [0.95 (0.88-1.03)], non-aspirin NSAIDs [1.00 (0.90-1.11)], or acetaminophen [1.05 (0.88-1.24)] was not associated with risk. Daily acetaminophen use [1.28 (1.00-1.65), p=0.05] was associated with elevated ovarian cancer risk. Risk estimates for frequent, long-term (10+ years) use of aspirin [1.15 (0.98-1.34)] or non-aspirin NSAIDs [1.19 (0.84-1.68)] were modestly elevated, although not statistically significant.

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/non-use)—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.

INTRODUCTION

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 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 anti-neoplastic 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 anti-gonadotropic effects (11). It also may inhibit ovarian carcinogenesis through the depletion of glutathione leading to necrosis (12). Aspirin, non-aspirin 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 (e.g., colorectal cancer) (13). However, the limited number of women in these trials are insufficient to evaluate ovarian cancer endpoints (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 non-aspirin 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 non-responders 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 non-aspirin 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, non-aspirin 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**; (16, 17, 19, 21-35)). Eligible

studies were a cohort study or clinical trial with prospective follow-up including women, determination of ovarian cancer endpoints 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, non-aspirin NSAID, or acetaminophen (paracetamol) use over at least a 6-month period (n=758,829). All studies obtained institutional approval at their respective institution(s); 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**; (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/week) when possible. Frequency was available in ten of 13 studies (16, 17, 21, 24, 25, 29-32); while three studies included frequency in their definition of regular medication use (19, 22, 26). Frequent use was defined as use at least 4-5 times per week for at least 6 months duration; less frequent use or non-regular 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: 6-7 days/week, 7 days/week, or ≥28 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; 4 studies (16, 19, 23, 31)).

Potential confounding variables were harmonized from the studies as part of a core dataset. *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=3,514). Second, we evaluated associations for invasive epithelial ovarian cancers (n=3,147) and third, evaluated associations for the four most common tumor histotypes: serous (n=1,475, including tumors coded as poorly differentiated), endometrioid (n=233), mucinous (n=125), and clear cell (n=111). The remaining 1,203 cases had another histology (e.g., 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 non-melanoma skin cancer) at baseline, bilateral oophorectomy prior to study entry, or

were missing age. We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) 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) to a model with a single estimate across histotypes (reduced model) (37).

Effect modification by factors that influence inflammation (e.g., smoking, BMI, history of chronic disease) and established ovarian cancer risk factors (e.g., age, parity, OC use, endometriosis) was evaluated using multiplicative interaction terms, with significance assess by a likelihood ratio test.

In sensitivity analyses, we considered a common reference group, coding “non-frequent users” as women who reported no or infrequent use of aspirin, non-aspirin 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 <5 years, 5-<10 years, and ≥10 years after baseline. Another sensitivity analysis considered death as 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<0.05 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 <50 years, while 52.2% were 60 years of age or older (**Table 1**). Compared to women who did not use aspirin or who used it infrequently, women who frequently used aspirin were more likely to be older, 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); individual cohort follow-up is reported in **Supplementary Table 1**.

Aspirin

Women who used aspirin at least 4-5 times per week (n=851 exposed cases [events]) developed ovarian cancer at about the same rate as women who did not use or used only infrequently [HR (95% CI): 0.95 (0.88-1.03)] (**Table 2**). However, compared to infrequent/non-users, women reporting daily or almost daily use (at least 6 days/week or more; n=449 cases) had a 10% reduction in ovarian cancer risk [0.90 (0.82-1.00),

p=0.05]. This association was statistically significant for women reporting daily or almost daily use for 0.5-<5 years in duration [0.79 (0.63-0.99), p=0.04; n=87 cases], and suggestively associated for daily users for 5-10 years duration [0.88 (0.65-1.18), n=50 cases]. Conversely, women who frequently used (vs. infrequent/non-use) aspirin for long durations (≥10 years at baseline) had a non-statistically significant elevated risk of ovarian cancer [1.15 (0.98-1.34), p=0.09; 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 to infrequent/non-use, daily aspirin use was associated with a 15% decrease for serous tumors [95% CI: 0.71-1.00; n=159 cases], whereas 10 or more years of frequent aspirin use was related to a suggestively elevated risk [1.27 (0.99-1.62); 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.

Non-aspirin NSAID

Women who frequently used non-aspirin NSAIDs had a similar rate of ovarian cancer as infrequent/non-users [1.00 (0.90-1.11); n=426 cases] (**Table 2**). Longer duration or daily frequency of non-aspirin NSAID was not related to ovarian cancer risk, although the risk estimate for ovarian cancer for frequent, long duration (≥10 years) use of non-aspirin NSAID was suggestively elevated [1.19 (0.84-1.68), n=36 cases)]. In analyses by histotype, women who frequently used (vs. infrequent/non-use) non-aspirin NSAIDs for

long durations had an increased risk of serous tumors than women who used it infrequently or not at all [2.06 (1.14-3.74); n=10 cases] (**Table 3**).

Acetaminophen

Frequent use compared to infrequent/non-use of acetaminophen was not associated with ovarian cancer risk [1.05 (0.88-1.24); n=152 exposed cases] (**Table 2**). However, there was a suggestive elevated risk with daily acetaminophen use [1.28 (1.00-1.65), p=0.05; n=71 cases] that was stronger for serous tumors [1.70 (1.14-2.55); 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**). Compared to infrequent/non-users, daily aspirin use was related to reduced ovarian cancer risk among women <50 [0.89 (0.43-1.84)], 50-59 [0.92 (0.73-1.17)], and 60-69 [0.88 (0.75-1.04)] years old at baseline, but was null for women ≥70 years old [1.05 (0.82-1.36), p-interaction=0.73]. Daily acetaminophen use was only associated with increased ovarian cancer risk among women ≥70 years old [1.78 (1.17-2.72), p-interaction<0.001]. 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 longer duration use of aspirin or non-aspirin NSAIDs were

attenuated [aspirin: 1.11 (0.93-1.33); non-aspirin NSAIDs: 1.04 (0.68-1.60)], 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 5 years of baseline compared to ≥5 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+ years was associated with a null or slightly elevated risk. Non-aspirin 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 non-aspirin NSAID use was associated, at least suggestively, with elevated risk of ovarian cancer. The modest 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 versus 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 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 as well as risk related adverse events (e.g. 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 versus 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 over a decade long) that could attenuate results. Conversely, we observed a consistently elevated ovarian cancer risk with frequent, long duration use of aspirin and non-aspirin NSAIDs,

suggesting potential confounding by medical indications for long-term use. We could not directly address this since indication for use was not collected in most studies. To address in sensitivity analyses, we excluded women who 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. non-regular use: 0.95 (0.74-1.23)). Acetaminophen and non-aspirin NSAIDs are commonly used interchangeably; however acetaminophen has only 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 non-aspirin 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, pre-diagnostic 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) meant 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 United States Preventive Services Taskforce (USPSTF) recommendations regarding aspirin use for cardiovascular-prevention (45), as

decreased ovarian cancer risk estimates associated with daily aspirin use were only observed among women <70 years old. The USPSTF does not recommend frequent aspirin use in women ≥70 years because of increased risks for adverse events. While the potential increased risk associated with daily acetaminophen as well as frequent aspirin and non-aspirin NSAID use for more than 10 years duration requires further study, daily aspirin use may provide a very modest reduced risk with respect to incident ovarian cancer.

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Table 1. Distribution of frequent analgesic use by baseline demographic and health characteristics in the Ovarian Cancer Cohort Consortium (OC3), n=758,829

Characteristics	Aspirin				non-aspirin NSAID				Acetaminophen			
	Infrequent/ non-use		Frequent* use		Infrequent/ non-use		Frequent* use		Infrequent/ non-use		Frequent* use	
	n	%	n	%	n	%	n	%	n	%	n	%
Age mean (SD)	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 (years)												
<50	171,049	31.0	28,462	17.7	68,208	15.8	10,496	12.9	69,762	22.9	3,973	14.4
50-59	182,326	33.0	48,432	30.1	144,873	33.6	29,425	36.1	101,553	33.4	8,351	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	9,460	5.9	28,981	6.7	3,239	4.0	20,937	6.9	1,513	5.5
20-24.9	246,476	44.6	63,791	39.6	183,064	42.4	25,614	31.4	127,806	42.0	9,216	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	8,560	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	4,342	15.8
35+	33,201	6.0	12,620	7.8	26,604	6.2	10,813	13.3	21,015	6.9	3,068	11.1
Missing	14,266	2.6	3,535	2.2	10,576	2.5	1,823	2.2	7,497	2.5	869	3.2
Age at menarche (years)												
≤11	129,521	23.5	39,029	24.3	104,278	24.2	22,428	27.5	58,358	19.2	5,549	20.1
12	132,550	24.0	43,314	26.9	107,177	24.8	22,151	27.2	82,000	27.0	8,085	29.3
13	155,896	28.2	42,510	26.4	122,489	28.4	19,967	24.5	87,684	28.8	6,628	24.0
14	71,928	13.0	21,378	13.3	55,615	12.9	10,314	12.7	44,990	14.8	4,640	16.8
≥15	48,479	8.8	13,304	8.3	38,367	8.9	6,361	7.8	27,904	9.2	2,428	8.8
Missing	13,690	2.5	1,403	0.9	3,450	0.8	309	0.4	3,076	1.0	238	0.9
Duration, oral contraceptive use (years)												
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	7,606	9.3	27,743	9.1	2,557	9.3
>1-5	97,165	17.6	24,065	15.0	67,121	15.6	13,458	16.5	47,757	15.7	3,612	13.1
>5-10	78,116	14.1	16,254	10.1	48,201	11.2	9,520	11.7	36,471	12.0	2,323	8.4
>10	104,143	18.9	24,316	15.1	76,349	17.7	16,530	20.3	65,839	21.7	6,257	22.7
Missing	19,033	3.4	2,678	1.7	13,398	3.1	1,424	1.7	13,442	4.4	1,063	3.9
Number pregnancies												
0	85,920	15.6	16,579	10.3	56,916	13.2	9,977	12.2	42,630	14.0	2,899	10.5
1	60,572	11.0	14,426	9.0	45,993	10.7	8,030	9.8	35,178	11.6	2,988	10.8
2	177,064	32.1	44,857	27.9	128,389	29.8	23,169	28.4	97,780	32.2	7,997	29.0
3	131,053	23.7	42,162	26.2	110,188	25.5	21,291	26.1	67,767	22.3	6,372	23.1
4+	93,130	16.9	41,287	25.7	85,208	19.8	17,992	22.1	55,969	18.4	6,706	24.3
Missing	4,325	0.8	1,627	1.0	4,682	1.1	1,071	1.3	4,688	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	3,986	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	4,151	2.6	5,254	1.2	1,403	1.7	5,033	1.7	625	2.3
Age at menopause (years) among postmenopausal women												
39-45	45,905	12.6	15,523	12.0	45,476	13.1	8,341	12.1	33,314	15.0	3,162	13.4
46-50	89,057	24.5	32,661	25.2	86,398	24.8	15,875	23.1	60,363	27.2	6,024	25.5
51-55	123,290	33.9	43,577	33.6	125,242	36.0	22,357	32.5	77,772	35.1	7,313	31.0
>55	24,452	6.7	9,294	7.2	25,889	7.4	5,503	8.0	14,587	6.6	1,600	6.8
Missing	80,622	22.2	28,715	22.1	65,187	18.7	16,662	24.2	35,728	16.1	5,483	23.3

Duration, menopausal hormone use (years)												
Never	273,921	49.6	73,279	45.5	165,228	38.3	26,744	32.8	112,911	37.1	9,282	33.7
>0-5	78,836	14.3	29,980	18.6	73,431	17.0	16,284	20.0	54,914	18.1	6,446	23.4
>5-10	43,492	7.9	16,040	10.0	41,755	9.7	9,652	11.8	30,399	10.0	3,512	12.7
>10	42,380	7.7	20,700	12.9	44,658	10.4	13,673	16.8	28,174	9.3	4,487	16.3
Missing	113,435	20.5	20,939	13.0	106,304	24.6	15,177	18.6	77,614	25.5	3,841	13.9
History of chronic diseases a baseline included:												
Any cardiovascular disease												
No	19,146	3.5	11,630	7.2	22,121	5.1	8,655	10.6	26,078	8.6	4,698	17.0
Yes	1,763	0.3	1,545	1.0	2,500	0.6	808	1.0	2,859	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	9,472	6.8	16,115	4.2	4,131	6.1	9,268	3.4	1,500	6.7
Missing	61,381	11.9	15,541	11.2	63,500	16.4	8,161	12.1	65,623	23.9	6,453	28.8
Autoimmune disease												
No	86,690	18.2	35,539	25.5	104,565	28.7	20,401	31.8	115,614	49.5	9,414	49.4
Yes	6,192	1.3	4,179	3.0	7,292	2.0	3,159	4.9	9,630	4.1	1,855	9.7
Missing	383,645	80.5	99,626	71.5	252,748	69.3	40,667	63.3	108,156	46.3	7,787	40.9

*Frequent: use at least ~4-5 days/week for 6 months or longer. BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

Table 2. Associations between analgesic use and ovarian cancer risk in the Ovarian Cancer Cohort Consortium (OC3), n=758,829

Analgesic use	N events (cases)	Person-years	HR* (95% CI)	P†
Aspirin				
Infrequent/non-use	2404	4,946,886	1.00 ref	
Frequent use‡	851	1,408,656	0.95 (0.88-1.03)	0.23
Frequent use by duration vs. infrequent/non-use				
infrequent/non-use	1402	3,150,285	1.00 ref	
frequent/0.5-<5 years	239	504,116	0.92 (0.80-1.06)	0.24
frequent/5-<10 years	93	171,582	0.90 (0.72-1.12)	0.33
frequent/10+ years	212	305,987	1.15 (0.98-1.34)	0.09
Categories of frequent use vs. infrequent/non-use				
infrequent/non-use	1936	3,245,903	1.00 ref	
<daily use	156	161,238	1.06 (0.90-1.26)	0.49
daily use§	449	545,499	0.90 (0.82-1.00)	0.05
Categories of frequent use by duration vs. infrequent/non-use				
infrequent/non-use	1402	3,150,285	1.00 ref	
<daily/0.5-<5 years	152	379,640	1.02 (0.85-1.21)	0.87
<daily/5-<10 years	43	108,355	0.92 (0.67-1.26)	0.60
<daily/10+ years	113	260,503	1.12 (0.92-1.37)	0.26
daily/0.5-<5 years	87	124,476	0.79 (0.63-0.99)	0.04
daily/5-10 years	50	63,227	0.88 (0.65-1.18)	0.39
daily/10+ years	99	45,484	1.18 (0.93-1.50)	0.18
Frequent use by dose vs. infrequent/non-use				
infrequent/non-use	392	436,742	1.00 ref	
frequent low dose	115	72,719	0.99 (0.79-1.23)	0.91
frequent normal dose	144	130,684	0.94 (0.77-1.15)	0.55
Non-aspirin NSAID				
Infrequent/non-use	2305	3,798,980	1.00 ref	
Frequent use‡	426	614,745	1.00 (0.90-1.11)	0.96
Frequent use by duration vs. infrequent/non-use				
infrequent/non-use	1168	2,051,666	1.00 ref	
frequent/0.5-<5 years	122	237,614	0.94 (0.78-1.14)	0.54
frequent/5-<10 years	64	75,230	1.10 (0.85-1.42)	0.49
frequent/10+ years	36	29,429	1.19 (0.84-1.68)	0.33
Categories of frequent use vs. infrequent/non-use				
infrequent/non-use	1982	3,049,045	1.00 ref	
<daily use	104	124,937	1.07 (0.88-1.31)	0.50
daily use§	237	319,625	0.97 (0.84-1.11)	0.65
Categories of frequent use vs. infrequent/non-use				

infrequent/non-use	1168	2,051,666	1.00 ref	
<daily/0.5-<5 years	83	159,749	1.02 (0.81-1.28)	0.88
<daily/5-<10 years	39	43,940	1.31 (0.95-1.81)	0.10
<daily/10+ years	15	18,356	1.10 (0.66-1.84)	0.72
daily/0.5-<5 years	39	77,865	0.81 (0.58-1.14)	0.23
daily/5-<10 years	25	31,290	0.86 (0.57-1.30)	0.48
daily/10+ years	21	11,074	1.27 (0.80-2.01)	0.32
Acetaminophen				
Infrequent/non-use	1421	2,583,452	1.00 ref	
Frequent use‡	152	213,668	1.05 (0.88-1.24)	0.61
Frequent use by duration vs. infrequent/non-use				
infrequent/non-use	1386	2,425,711	1.00 ref	
frequent/0.5-<5 years	61	95,060	0.99 (0.76-1.29)	0.93
frequent/5-<10 years	50	50,683	1.16 (0.87-1.54)	0.32
frequent/10+ years	37	51,266	1.01 (0.73-1.41)	0.96
Categories of frequent use vs. infrequent/non-use				
infrequent/non-use	1179	2,120,248	1.00 ref	
<daily use	35	43,645	0.99 (0.70-1.39)	0.94
daily use§	71	62,759	1.28 (1.00-1.65)	0.05
Categories of frequent use by duration vs. infrequent/non-use				
infrequent/non-use	1386	2,425,711	1.00 ref	
<daily/0.5-<5 years	33	69,923	0.87 (0.62-1.22)	0.42
<daily/5-<10 years	25	35,311	0.98 (0.66-1.46)	0.93
<daily/10+ years	22	39,950	0.89 (0.58-1.36)	0.58
daily/0.5-<5 years	28	25,137	1.21 (0.81-1.81)	0.35
daily/5-<10 years	25	15,372	1.42 (0.94-2.13)	0.09
daily/10+ years	15	11,315	1.24 (0.75-2.08)	0.40

* Hazard ratios (HR) and 95% confidence intervals (CI) are estimated from Cox proportional hazards models 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/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 (MHT) use (premenopausal, never, ≤5, >5-10, >10 years).
† P value calculated using a two-sided Wald test
‡Frequent: use at least ~4-5 days/week for 6 months or longer
§Daily: use at least ~6-7 days/week or ≥28 days per month for 6 months or longer

Table 3. Associations between analgesic use and ovarian carcinoma histologic subtypes, Ovarian Cancer Cohort Consortium (OC3).

Analgesic use	P het*	Serous (n=1,470)		Endometrioid (n=233)		Mucinous (n=125)		Clear Cell (n=111)	
		N events	HR† (95% CI)	N events	HR† (95% CI)	N events	HR† (95% CI)	N events	HR† (95% CI)
Aspirin									
Infrequent/non-use	0.26	1141	1.00 ref	181	1.00 ref	93	1.00 ref	85	1.00 ref
Frequent use‡		307	0.93 (0.81-1.05)	45	0.90 (0.64-1.27)	29	1.13 (0.73-1.75)	25	1.11 (0.71-1.74)
Frequent use by duration vs. infrequent/non-use									
infrequent/non-use	0.03	680	1.00 ref	132	1.00 ref	52	1.00 ref	59	1.00 ref
frequent/0.5-<5 years		69	0.85 (0.73-0.99)	18	0.93 (0.62-1.40)	10	1.03 (0.60-1.74)	5	0.75 (0.40-1.42)
frequent/5-<10 years		37	0.89 (0.64-1.24)	8	1.28 (0.62-2.66)	2	0.67 (0.16-2.87)	4	1.46 (0.52-4.12)
frequent/10+ years		74	1.27 (0.99-1.62)	8	0.64 (0.31-1.31)	10	1.69 (0.83-3.42)	10	1.97 (0.98-3.97)
Categories of frequent use vs. infrequent/non-use									
infrequent/non-use	0.13	938	1.00 ref	139	1.00 ref	62	1.00 ref	67	1.00 ref
<daily use		57	1.04 (0.86-1.25)	3	0.86 (0.55-1.34)	1	0.93 (0.53-1.63)	4	1.35 (0.75-2.41)
daily use§		159	0.85 (0.71-1.00)	20	0.95 (0.59-1.54)	14	1.40 (0.77-2.56)	9	0.87 (0.44-1.73)
Non-aspirin NSAID									
Infrequent/non-use	0.06	984	1.00 ref	139	1.00 ref	67	1.00 ref	75	1.00 ref
Frequent use‡		157	1.09 (0.92-1.30)	18	1.03 (0.61-1.73)	8	0.86 (0.41-1.77)	6	0.53 (0.23-1.22)
Frequent use by duration vs. infrequent/non-use									
infrequent/non-use	0.03	456	1.00 ref	71	1.00 ref	31	1.00 ref	47	1.00 ref
frequent/0.5-<5 years		38	1.01 (0.83-1.23)	7	1.09 (0.63-1.89)	2	0.84 (0.38-1.86)	2	0.54 (0.22-1.34)
frequent/5-<10 years		20	1.39 (0.87-2.22)	2	1.04 (0.25-4.31)	1	1.51 (0.20-11.63)	1	0.71 (0.10-4.95)
frequent/10+ years		10	2.06 (1.14-3.74)	0	--	0	--	0	--
Categories of frequent use vs. infrequent/non-use									
infrequent/non-use	0.04	883	1.00 ref	115	1.00 ref	61	1.00 ref	69	1.00 ref
<daily use		38	1.15 (0.87-1.53)	7	1.36 (0.61-3.00)	3	1.65 (0.65-4.20)	1	0.45 (0.11-1.83)
daily use§		102	1.06 (0.86-1.31)	9	0.87 (0.45-1.67)	3	0.49 (0.15-1.58)	4	0.58 (0.21-1.59)
Acetaminophen									
Infrequent/non-use	0.21	577	1.00 ref	103	1.00 ref	38	1.00 ref	50	1.00 ref
Frequent use‡		47	1.29 (0.94-1.77)	11	1.77 (0.96-3.29)	2	0.70 (0.16-2.99)	4	1.49 (0.43-5.17)
Frequent use by duration vs. infrequent/non-use									
infrequent/non-use	0.01	557	1.00 ref	100	1.00 ref	38	1.00 ref	46	1.00 ref
frequent/0.5-<5 years		22	1.36 (0.87-2.12)	3	0.72 (0.20-2.64)	0	--	3	2.42 (0.57-10.35)
frequent/5-<10 years		15	1.44 (0.85-2.43)	5	3.66 (1.54-8.69)	1	1.68 (0.23-12.17)	1	1.48 (0.18-11.91)

frequent/10+ years		8	0.97 (0.48-1.96)	3	1.92 (0.58-6.32)	1	1.30 (0.16-10.48)	0	--
Categories of frequent use vs. infrequent/non-use									
infrequent/non-use	0.09	554	1.00 ref	102	1.00 ref	35	1.00 ref	46	1.00 ref
<daily use		9	0.95 (0.60-1.51)	1	1.70 (0.78-3.69)	1	1.15 (0.22-6.03)	3	1.69 (0.33-8.59)
daily use§		26	1.70 (1.14-2.55)	6	1.85 (0.75-4.57)	0	--	1	1.15 (0.17-8.01)

*The P value for heterogeneity (P het) was calculated using a two-sided likelihood ratio test. [37, Gates et al. 2010]

†Hazard ratios (HR) and 95% confidence intervals (CI) are estimated from competing risk [Gates et al. citation] Cox proportional hazards models 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/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 (MHT) 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/week for 6 months or longer

§Daily: use at least ~6-7 days/week or ≥28 days per month for 6 months or longer