Common Analgesic Use for Menstrual Pain and Ovarian Cancer Risk

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ABSTRACT

Menstrual pain has been associated with increased ovarian cancer risk, presumably through increased inflammation, which is known to play a critical role in ovarian carcinogenesis. Analgesic medications are frequently used to treat menstrual pain, some of which lower ovarian cancer risk. In this study, we examined the association between analgesic use for menstrual pain during the premenopausal period and ovarian cancer risk among women with history of menstrual pain. We used data from the New England Case-Control Study, including 1,187 epithelial ovarian cancer cases and 1,225 population-based controls enrolled between 1998 and 2008 with detailed information on analgesic use for their menstrual pain. We used unconditional logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between analgesic use (i.e., aspirin, ibuprofen, acetaminophen) for menstrual pain and ovarian cancer risk. We further conducted a stratified analysis by intensity of menstrual pain (mild/moderate, severe). Among women with menstrual pain during their 20s and 30s, ever use of analgesics for menstrual pain was not significantly associated with ovarian cancer risk. However, among women with severe menstrual pain, ever use of aspirin or acetaminophen for menstrual pain was inversely associated with risk (OR, 0.41; 95% CI, 0.18–0.94 and OR, 0.43; 95% CI, 0.21–0.88 compared with never users, respectively). No significant association was observed between analgesic use and ovarian cancer risk among women with mild/moderate menstrual pain ($P_{interaction} \leq 0.03$). Our results suggest that use of aspirin or acetaminophen for severe menstrual pain may be associated with lower risk of ovarian cancer.

Prevention Relevance: This study investigates whether analgesic use specifically for menstrual pain during the premenopausal period influences ovarian cancer risk. Our results suggest use of aspirin or acetaminophen for severe menstrual pain may be associated with lower risk of ovarian cancer among women with severe menstrual pain.

Introduction

We and others have previously reported that severe menstrual pain is associated with a small but significant increase in ovarian cancer risk (1–7), likely, at least in part, through increased inflammation (8, 9). A study using pooled data from international ovarian cancer consortia reported severe menstrual pain being associated with a 7% increase in ovarian cancer risk (7). Accumulating evidence supports the role of inflammation in ovarian carcinogenesis (10–12). Inflammatory factors, such as endometriosis, pelvic inflammatory disease, and higher number of ovulatory cycles over the reproductive span, are associated with increased ovarian cancer risk (13–16). On the other hand, anti-inflammatory factors such as low-dose aspirin use decrease risk (17, 18).

Aspirin and other analgesics [e.g., non-aspirin nonsteroidal anti-inflammatory drugs (NSAID), acetaminophen] are commonly used to treat severe menstrual pain. A U.S.-based cohort reported that among women ages 33–51, aspirin was used more than one day per week by 14.1% women, NSAIDs by 42.3% women, and acetaminophen by 25.8% women (19). While aspirin and NSAIDs primarily reduce inflammation through inhibition of COX enzymes in prostaglandin synthesis (20, 21), acetaminophen has also been reported to have a weak anti-inflammatory effect (22). Two studies using pooled data from international ovarian cancer consortia examined the associations between aspirin, NSAIDs, and acetaminophen and ovarian cancer risk and reported that frequent aspirin use was associated with a 10% to 20% reduction in ovarian cancer, although no clear associations were observed for the other analgesic types (17, 18).

While large studies with different study designs have examined associations between analgesic use and ovarian cancer risk (17, 18), no previous study has investigated whether

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analgesic use specifically for menstrual pain during the premenopausal period influences ovarian cancer risk. Combining indication and use of analgesics may further inform potential groups of women who may most benefit from such chemoprevention strategies for ovarian cancer. Thus, in this study, we examined the association between use of analgesics, including duration and timing of their use, and ovarian cancer risk among 1,187 cases and 1,225 controls from the New England Case Control Study who reported having menstrual pain.

Materials and Methods

Study population

The New England Case Control Study (NEC) is a large, population-based case–control study including participants in Eastern Massachusetts and New Hampshire identified through statewide registries and tumor boards. The study consists of three phases: 1992–1997, 1998–2003, and 2003–2008. Details of the study, including enrollment criteria and participation rates have previously been described in detail (23). All participants completed in-person interviews and provided detailed information on lifestyle and reproductive factors, as well as personal medical history and family history of breast and ovarian cancer. Controls and cases were frequency-matched on age and state of residence. This analysis was based on participants enrolled between 1998–2003 and 2003–2008, as detailed information was collected on analgesic use to alleviate menstrual symptoms in these study phases. Among the 3,091 participants (1,513 cases and 1,578 controls) enrolled between 1998 and 2008, we excluded women missing information on menstrual pain ($n = 20$) and women who reported no menstrual pain ($n = 659$), resulting in the final study population of 1,187 cases and 1,225 controls. Cases included 978 invasive and 209 borderline tumors. Invasive tumors were further categorized as high-grade serous (grade 2,3, unknown; $n = 542$), low-grade serous (grade 1; $n = 27$), endometrioid ($n = 208$), mucinous ($n = 52$), clear cell ($n = 74$), and other/unknown ($n = 75$) subtypes. Borderline tumors included serous ($n = 130$), mucinous ($n = 63$), and other/unknown ($n = 16$). The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board at Brigham and Women's Hospital (Boston, MA) and Dartmouth College (Hanover, NH). All participants provided written informed consent.

Study variables

Participants were asked about menstrual pain experienced during their 20s and 30s when not pregnant, breastfeeding or using birth control pills. There were four potential response categories: no pain, mild cramps with medication seldom needed, moderate cramps with medication usually needed, and severe cramps with medications and bed-rest required. Participants that reported pain were further asked about using prescription or over-the-counter pain relievers for either menstrual pain or other menstrual symptoms. Participants enrolled between 1998 and 2003 were asked to report details on up to four medications; those enrolled between 2003 and 2008 reported details on up to seven medications. Details included medication name, age at first use, and duration of use. In a separate question, participants were asked about ever having used prescription or over the counter pain medications (up to five medications could be reported for at least six consecutive months) for other indications. Participants were asked to provide age at first use, duration, and frequency of use per menstrual cycle. If a participant reported using an analgesic, she was considered an ever user regardless of duration of use. Ever use of any analgesics was defined as having ever used aspirin, ibuprofen, or acetaminophen for menstrual pain. The following variables were also collected from the questionnaire: reference age (i.e., 1 year before diagnosis for cases and 1 year before the date of interview for controls), lifetime use of oral contraceptives (OC), parity, height, weight one year prior to diagnosis or interview, history of endometriosis, history of fibroids, history of tubal ligation, history of hysterectomy, and history of breast or ovarian cancer in first-degree relatives.

Statistical analysis

Because use of different analgesics might be correlated (for example, nonusers of aspirin are likely to be users of other analgesics), we created combined variables for each individual analgesic to separate the effect of individual medications using the following categories (example shown for aspirin): (i) never use of any of the three analgesic types (i.e., aspirin, ibuprofen, and acetaminophen) for any indications (reference group), (ii) use of aspirin for menstrual symptoms (with or without use for other indications), (iii) use of aspirin for non-menstrual indication only, and (iv) use of ibuprofen or acetaminophen only for menstrual pain or other indications. The model estimates for the final two categories are not shown; similar variables were created for ibuprofen and acetaminophen.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between analgesic use for menstrual pain and ovarian cancer risk were calculated using unconditional logistic regression adjusted for *a priori* chosen ovarian cancer risk factors: age (continuous), study center (Massachusetts, New Hampshire), parity (0, 1, 2, 3, ≥4 births), OC use (<3 months, 3-<12, 12-<60, ≥60 months), family history of breast or ovarian cancer (no, yes), and history of tubal ligation (no, yes). We also evaluated potential confounding by history of endometriosis (no, yes) and fibroids (no, yes). For the analysis of duration of analgesic use for menstrual pain in relation to ovarian cancer risk, duration was modeled as: never users of any type of analgesics, duration of use <5 years, 5-<10 years of use, 10-<20 years of use, and ≥20 years of use. For evaluation of age at first use of analgesics for menstrual pain, age was modeled as: never user of any analgesic, ≤18 years, >18–25 years, and >25 years of age at first use. Frequency of use per menstrual cycle was modeled as: ≤3 pills per cycle, 3–6 pills per cycle, and ≥6 pills per cycle. P_{trend} values for duration and age at first use were calculated by performing Wald test using

Table 1. Demographic and reproductive characteristics by use of medication for menstrual pain among controls in the New England Case Control Study (NEC), 1998–2008.

	Aspirin		Ibuprofen		Acetaminophen	
	Nonusers (*N* = 1034)	Users (*N* = 191)	Nonusers (*N* = 943)	Users (*N* = 282)	Nonusers (*N* = 851)	Users (*N* = 374)
Pain severity, *n* (%)						
Mild	647 (63)	66 (35)	599 (64)	114 (40)	586 (69)	127 (34)
Moderate	295 (29)	87 (46)	252 (27)	130 (46)	197 (23)	185 (49)
Severe	92 (9)	38 (20)	92 (10)	38 (13)	68 (8)	62 (17)
Age, years, mean (SD)	51.9 (12.3)	58.8 (9.4)	55.6 (11.4)	44.3 (10.4)	53.3 (12.7)	52.2 (10.6)
Body mass index, kg/m^2, *n* (%)						
<25	506 (49)	83 (43)	440 (47)	149 (53)	421 (49)	168 (45)
25–30	322 (31)	68 (36)	314 (33)	76 (27)	264 (31)	126 (34)
>30	206 (20)	40 (21)	189 (20)	57 (20)	166 (20)	80 (21)
Oral contraceptive use, years, *n* (%)						
<3	316 (31)	68 (36)	329 (35)	55 (20)	282 (33)	102 (27)
3–12	80 (8)	19 (10)	79 (8)	20 (7)	60 (7)	39 (10)
12–60	286 (28)	59 (31)	256 (27)	89 (32)	228 (27)	117 (31)
>60	352 (34)	45 (24)	279 (30)	118 (42)	281 (33)	116 (31)
Parity, *n* (%)						
0	190 (18)	33 (17)	142 (15)	81 (29)	164 (19)	59 (16)
1	151 (15)	26 (14)	127 (13)	50 (18)	124 (15)	53 (14)
2	356 (34)	51 (27)	307 (33)	100 (35)	264 (31)	143 (38)
3	183 (18)	41 (21)	191 (20)	33 (12)	151 (18)	73 (20)
4+	154 (15)	40 (21)	176 (19)	18 (6)	148 (17)	46 (12)
History of endometriosis, *n* (%)	88 (9)	27 (14)	84 (9)	31 (11)	68 (8)	47 (13)
History of fibroids, *n* (%)	171 (17)	39 (20)	166 (18)	41 (15)	132 (16)	78 (21)
History of tubal ligation, *n* (%)	207 (20)	44 (23)	204 (22)	47 (17)	159 (19)	92 (25)
History of hysterectomy, *n* (%)	89 (9)	21 (11)	103 (11)	7 (2)	73 (9)	37 (10)
Family history of breast or ovarian cancer, *n* (%)	173 (17)	27 (14)	160 (17)	40 (14)	151 (18)	49 (13)

the continuous variable among ever users. To evaluate the association by histotypes, we evaluated medication use in relation to risk of high-grade serous and endometrioid/clear cell tumor types using polytomous logistic regression. Because of limited number of cases, analyses among other histotypes were not performed. We performed stratified analyses by menstrual pain intensity (mild/moderate, severe) for the overall association, by histotypes, duration of use, and age at first use. We also performed stratified analyses of the overall association by OC use (<3 months, ≥3 months) and endometriosis (yes, no). Statistical significance of the interaction was tested by creating a cross product between the stratifying variable and medication use and calculating the likelihood-ratio statistics comparing models with and without the interaction terms. All analyses were performed using SAS v9.4 (SAS Institute). All the *P* values were two-sided, and a significance level of 0.05 was used.

Results

The distribution of demographic and reproductive characteristics by use of analgesics (i.e., aspirin, ibuprofen, acetaminophen) for menstrual pain were similar between ovarian cancer cases and controls (**Table 1**; Supplementary Table S1). Overall, 17% reported ever use of aspirin, 23% ever use of ibuprofen, and 33% ever use of acetaminophen for menstrual pain. Women who reported ever use of ibuprofen for menstrual pain were more likely to be younger and nulliparous (**Table 1**).

Among women with menstrual pain, ever use of analgesics was not significantly associated with ovarian cancer risk (**Table 2**). In analyses stratified by pain intensity, ever use of any analgesics for menstrual pain (i.e., aspirin or ibuprofen or acetaminophen) was inversely associated with ovarian cancer risk among women with severe menstrual pain (OR, 0.45; 95% CI, 0.23–0.88) but no associations among women with mild or moderate pain ($P_{\text{interaction}} = 0.04$). Specifically, ever use of aspirin or acetaminophen was inversely associated with ovarian cancer risk among women with severe menstrual pain (OR, 0.41; 95% CI, 0.18–0.94 and OR, 0.43; 95% CI, 0.21–0.88, respectively), but no associations among women with mild or moderate pain ($P_{\text{interaction}} \leq 0.03$). Although the data suggested an inverse association between ever use of ibuprofen among women with severe menstrual pain, the findings were not statistically significant (OR, 0.54; 95% CI, 0.23–1.28, $P_{\text{interaction}} = 0.48$).

Duration of aspirin or ibuprofen use for menstrual pain among those who reported having menstrual pain was not associated with ovarian cancer risk, although longer duration of acetaminophen use (>20 years) was associated with increased ovarian cancer risk (OR, 1.68; 95% CI, 1.20–2.36; Supplementary Table S2). When stratified by pain intensity, longer duration of acetaminophen use (>20 years) was associated with increased ovarian cancer risk only among women with mild or moderate pain (OR, 1.91; 95% CI, 1.33–2.76). In terms

Table 2. Association between analgesic use for menstrual pain[a] and ovarian cancer risk among women who reported menstrual pain in the New England Case Control Study (NEC), 1998–2008.

	Any pain		Mild/moderate pain		Severe pain		
	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	$P_{interaction}$
Any analgesic use[c]							
Never use of any analgesic for any indication	430/431	Ref	386/413	Ref	44/18	Ref	
Ever use for menstrual pain[a]	654/630	1.00 (0.83–1.20)	528/527	1.03 (0.85–1.26)	126/103	0.45 (0.23–0.88)	0.04
Aspirin[d]							
Never use of any analgesic for any indication	430/431	Ref	386/413	Ref	44/18	Ref	
Ever use for menstrual pain[a]	222/191	1.13 (0.88–1.46)	182/153	1.21 (0.92–1.60)	40/38	0.41 (0.18–0.94)	0.01
Ibuprofen[e]							
Never use of any analgesic for any indication	430/431	Ref	386/413	Ref	44/18	Ref	
Ever use for menstrual pain[a]	261/282	0.86 (0.67–1.10)	202/244	0.83 (0.64–1.08)	59/38	0.54 (0.23–1.28)	0.48
Acetaminophen[f]							
Never use of any analgesic for any indication	430/431	Ref	386/413	Ref	44/18	Ref	
Ever use for menstrual pain[a]	411/374	1.11 (0.90–1.36)	334/312	1.17 (0.94–1.46)	77/62	0.43 (0.21–0.88)	0.03

[a]This includes ever use with or without use for other indications.
[b]Adjusted for age, center, family history of breast or ovarian cancer, oral contraceptive use, parity, tubal ligation.
[c]Estimates not shown for participants using analgesics only for indication other than menstrual pain (103 cases, 164 controls).
[d]Estimates not shown for participants using aspirin only for indication other than menstrual pain (74 cases, 86 controls), and participants using non-aspirin medication for menstrual pain or other indications (461 cases, 517 controls).
[e]Estimates not shown for participants using ibuprofen only for indication other than menstrual pain (90 cases, 111 controls), and participants using non-ibuprofen medication for menstrual pain or other indications (406 cases, 401 controls).
[f]Estimates not shown for participants using acetaminophen only for indication other than menstrual pain (62 cases, 77 controls) and participants using non-acetaminophen medication for menstrual pain or other indications (284 cases, 343 controls).

of frequency, women who reported taking 6 or more pills per cycle of ibuprofen or acetaminophen for menstrual pain was associated with increased ovarian cancer risk overall (OR, 1.41; 95% CI, 1.00–2.00 and OR, 1.57; 95% CI, 1.14–2.16, respectively; Supplementary Table S3). When stratified by pain intensity, similar associations were observed among women with mild or moderate pain. Interestingly, among women with severe menstrual pain, analgesic use was inversely associated with risk regardless of frequency, although the association attenuated in women taking 6 or more pills per menstrual cycle. Age at first use of analgesics for menstrual pain was not associated with ovarian cancer risk among those experiencing any menstrual pain (Supplementary Table S4). Associations between analgesic use for menstrual pain and ovarian cancer risk were similar by strata of OC use and history of endometriosis with no significant interactions (Supplementary Table S5). While we did not observe any significant interactions, the direction of association between aspirin use for menstrual pain and ovarian cancer risk was suggestively inverse for women with a history of endometriosis (OR, 0.53; 95% CI, 0.23–1.24).

When we examined the associations by histotype, ever use of aspirin, ibuprofen, and acetaminophen for menstrual pain among all women reporting menstrual pain were not associated with risk of high-grade serous tumors (**Table 3**). Ever use of aspirin or acetaminophen were suggestively associated with increased risk of endometrioid and clear cell tumors (OR, 1.53; 95% CI, 0.99–2.35 and OR, 1.42; 95% CI, 1.01–2.00, respectively), although there was no significant heterogeneity across histotypes ($P_{heterogeneity} = 0.08$ for aspirin, 0.19 for ibuprofen, and 0.11 for acetaminophen). When we stratified by pain intensity, ever use of aspirin or acetaminophen was inversely associated with risk of high-grade serous tumors among women with severe menstrual pain (OR, 0.33; 95% CI, 0.12–0.93 and OR, 0.38; 95% CI, 0.16–0.89, respectively) but not among women with mild or moderate pain ($P_{interaction} \leq 0.02$). For endometrioid and clear cell tumors, although there were no significant interactions, we observed similar positive associations among women with mild or moderate pain (OR, 1.66; 95% CI, 1.03–2.66 and OR, 1.43; 95% CI, 0.98–2.09, respectively) but not among women with severe pain.

Discussion

In this population-based case–control study of analgesic use among women with history of menstrual pain, we examined the association between analgesic use for menstrual pain and ovarian cancer risk, combining both indication and use of analgesics. Aspirin or acetaminophen use was associated with lower risk of ovarian cancer specifically among women with severe menstrual pain. While ever use of ibuprofen was not associated with reduced risk among women with severe menstrual pain, the point estimate suggested an inverse association. Few associations were observed when

Table 3. Association between analgesic use for menstrual pain[a] and ovarian cancer risk among women who reported menstrual pain by histologic subtypes in the New England Case Control Study (NEC), 1998–2008.

A. High-grade serous

	Overall		Mild/moderate pain		Severe pain		
	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	$P_{interaction}$
Any analgesic use[c]							
Never use of any analgesic for any indication	214/431	Ref	194/413	Ref	20/18	Ref	
Ever use for menstrual pain[a]	279/630	1.02 (0.81–1.29)	236/527	1.11 (0.87–1.42)	43/103	0.36 (0.16–0.80)	0.02
Aspirin[d]							
Never use of any analgesic, for any indication	214/431	Ref	194/413	Ref	20/18	Ref	
Ever use for menstrual pain[a]	119/191	1.17 (0.87–1.57)	100/153	1.27 (0.92–1.75)	19/38	0.33 (0.12–0.93)	0.02
Ibuprofen[e]							
Never use of any analgesic, for any indication	214/431	Ref	194/413	Ref	20/18	Ref	
Ever use for menstrual pain[a]	84/282	0.89 (0.64–1.24)	71/244	0.91 (0.63–1.31)	13/38	0.43 (0.14–1.28)	0.18
Acetaminophen[f]							
Never use of any analgesic, for any indication	214/431	Ref	194/413	Ref	20/18	Ref	
Ever use for menstrual pain[a]	181/374	1.11 (0.86–1.43)	154/312	1.24 (0.94–1.64)	27/62	0.38 (0.16–0.89)	0.01

B. Endometrioid and clear cell

	Overall		Mild/moderate pain		Severe pain		
	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	Cases/controls	OR (95% CI)[b]	$P_{interaction}$
Any analgesic use[g]							
Never use of any analgesic for any indication	82/431	Ref	72/413	Ref	10/18	Ref	
Ever use for menstrual pain[a]	184/630	1.22 (0.89–1.66)	140/527	1.19 (0.85–1.67)	44/103	0.59 (0.21–1.67)	0.30
Aspirin[h]							
Never use of any analgesic, for any indication	82/431	Ref	72/413	Ref	10/18	Ref	
Ever use for menstrual pain[a]	58/191	1.53 (0.99–2.35)	47/153	1.66 (1.03–2.66)	11/38	0.50 (0.14–1.82)	0.07
Ibuprofen[i]							
Never use of any analgesic, for any indication	82/431	Ref	72/413	Ref	10/18	Ref	
Ever use for menstrual pain[a]	90/282	1.14 (0.78–1.67)	64/244	1.03 (0.68–1.58)	26/28	0.76 (0.22–2.58)	0.80
Acetaminophen[j]							
Never use of any analgesic, for any indication	82/431	Ref	72/413	Ref	10/18	Ref	
Ever use for menstrual pain[a]	115/374	1.42 (1.01–2.00)	89/312	1.43 (0.98–2.09)	26/62	0.50 (0.16–1.63)	0.24

[a]This includes ever use with or without use for other indications.
[b]Adjusted for age, center, family history of breast or ovarian cancer, oral contraceptive use, parity, tubal ligation.
[c]Estimates not shown for participants using analgesics only for indication other than menstrual pain (49 cases, 164 controls).
[d]Estimates not shown for participants using aspirin only for indication other than menstrual pain (32 cases, 86 controls) and participants using non-aspirin medication for menstrual pain or other indications (177 cases, 517 controls).
[e]Estimates not shown for participants using ibuprofen only for indication other than menstrual pain (42 cases, 111 controls) and participants using non-ibuprofen medication for menstrual pain or other indications (202 cases, 401 controls).
[f]Estimates not shown for participants using acetaminophen only for indication other than menstrual pain (29 cases, 77 controls) and participants using non-acetaminophen medication for menstrual pain or other indications (118 cases, 343 controls).
[g]Estimates not shown for participants using analgesics only for indication other than menstrual pain (21 cases, 164 controls).
[h]Estimates not shown for participants using aspirin only for indication other than menstrual pain (20 cases, 86 controls) and participants using non-aspirin medication for menstrual pain or other indications (127 cases, 517 controls).
[i]Estimates not shown for participants using ibuprofen only for indication other than menstrual pain (18 cases, 111 controls) and participants using non-ibuprofen medication for menstrual pain or other indications (97 cases, 401 controls).
[j]Estimates not shown for participants using acetaminophen only for indication other than menstrual pain (15 cases, 77 controls) and participants using non-acetaminophen medication for menstrual pain or other indications (75 cases, 343 controls).

considering all women with menstrual pain regardless of severity, although there was some suggestion of a higher risk with use of acetaminophen for long durations and for endometrioid and clear cell disease.

Several previous studies suggest an increased risk of ovarian cancer in women with menstrual pain (1–7), with a large pooled analyses reporting 7% increase in risk (7). One hypothesis explaining this association is increased

inflammation (8, 9). Inflammation plays a key role in ovarian carcinogenesis (10–12), with epidemiologic studies reporting inflammatory factors, such as endometriosis, pelvic inflammatory disease, and higher number of ovulatory cycles over the reproductive span, being associated with increased ovarian cancer risk (13–16). On the other hand, anti-inflammatory factors such as frequent aspirin use have been associated with a 10% to 20% decrease in ovarian cancer risk (17, 18). Because inflammation can be reduced by analgesic medications (although to a varying degree), it is biologically plausible that anti-inflammatory medications reduce the pro-inflammatory milieu in the local pelvic environment, reducing risk in women experiencing menstrual pain. Furthermore, ovulation itself is an inflammatory event via release of proinflammatory factors in follicular fluid and initiation of wound healing (24–28). Overall, none of the medications we examined were related to lower risk when examining all women experiencing menstrual pain, regardless of severity, suggesting that these medications may not be targeting the inflammatory pathways primarily related to the event of ovulation. However, both aspirin and acetaminophen use, with suggestive results for ibuprofen, were related to lower ovarian cancer risk among those with severe menstrual pain. Interestingly, a small Indonesian study showed that women who had severe menstrual pain had higher prostaglandin levels than those with mild or moderate pain (29). Aspirin inhibits cyclooxygenases, which are responsible for the production of prostaglandins (21), supporting our findings. Higher expression of COX enzyme isoforms, COX1 and COX2, as well as increased prostaglandin E2 (PGE2) have been observed in ovarian tumors (30–32). COX2 expression has also been associated with worse ovarian cancer survival (33–35) and is thought to play a role in ovarian cancer progression through promoting ovarian cancer cell invasion (36). Therefore, it is plausible that one of the pathways through which aspirin may be reducing ovarian cancer risk among women with severe menstrual pain is through modulation of the prostaglandin pathway. Potential mechanisms for acetaminophen are less clear, given that it only weakly reduces function of COXs (24). Ibuprofen, which also has COX inhibition properties, was not significantly associated with risk among women with severe menstrual pain, although the strength of the OR was similar to aspirin; power may have limited the ability to detect an association with this medication.

Blood biomarker studies also support the epidemiologic findings of severe menstrual pain being associated with increased ovarian cancer risk through increased inflammation. Higher circulating levels of inflammatory markers have been associated with increased ovarian cancer risk (37–39). In addition, women with dysmenorrhea have been reported to have increased circulating inflammatory markers (8, 9), although the long-term impact of severe menstrual pain during the premenopausal period on systemic inflammation during the peri- and postmenopausal period is not clear. Additional research into the specific inflammatory pathways underlying severe menstrual pain may provide insight into our observed associations. Furthermore, investigation incorporating biomarker data will help identify specific biologic pathways altered by exposure to these analgesic medications and also associated with ovarian cancer risk, elucidating how these analgesics impact the risk of ovarian cancer among women with severe menstrual pain.

Interestingly, our results show a suggestive inverse association between ever use of aspirin for menstrual pain and ovarian cancer risk among women with history of endometriosis, a condition associated with increased inflammation that mostly occurs in the premenopausal period. This also supports our hypothesis that women with a proinflammatory condition in the premenopausal period may benefit from analgesic use which leads to reduced ovarian cancer risk. However, while this result implies that aspirin may be particularly beneficial among women with pelvic inflammation (10), given the limited sample size of women with history of endometriosis who reported ever use of aspirin for menstrual pain, the result should be interpreted with caution.

We also observed that very long duration of acetaminophen use for menstrual pain was associated with increased ovarian cancer risk overall and among women with mild or moderate pain. Frequent, longer duration use of acetaminophen has also been observed to be associated with increased risk in the prior pooled cohort study (18). This may be in part due to underlying chronic pelvic pain conditions leading to long term use of analgesics, such as undiagnosed endometriosis, which is known to increase ovarian cancer risk (13), although this association may be due to residual confounding or chance since we do not observe a consistent increased trend in all the categories.

Ever use of aspirin and acetaminophen for menstrual pain of any severity was suggestively associated with increased risk of endometrioid and clear cell tumors, but not for high-grade serous carcinoma, consistent with studies of other risk factors (40). Interestingly, a pooled analysis of prospective cohort studies reported that longer duration of aspirin and frequent use of acetaminophen were suggestively associated with higher risk of endometrioid and clear cell tumors (17). It is possible that women who reported ever use of aspirin or acetaminophen for menstrual pain in our study may have continued to use these medications for other indications, possibly explaining our observations. Interestingly, when we stratified by pain intensity, among women with severe pain, analgesic use was suggestively inversely associated with risk with similar magnitude of association in both histotypes. However, our small sample size within the severe pain strata has limited our ability to detect significant associations and therefore the findings by histotype should be interpreted with caution.

This study has several strengths. First, this large study provided sufficient power to examine the association of analgesic use among women who experienced menstrual pain. Second, we had unique data on the indication for analgesic

use (by type of medication) for menstrual pain, and notably we observed stronger associations for this indication compared to other non-menstrual reasons among those with severe versus mild/moderate menstrual pain. Third, we had detailed information on potential confounders (e.g., history of endometriosis). Our study also has several limitations. First, while we were able to distinguish analgesics indicated for treating menstrual pain or for other reasons, we were not able to further examine other specific indications of analgesic use, such as for cardiovascular disease prevention. We also did not have detailed information on dose and formulations of use for analgesics used for menstrual pain. Due to the case-control study design, there is potential for differential reporting in analgesic use by cases and controls. We acknowledge that there may be undiagnosed endometriosis cases among women who self-reported they experienced severe menstrual pain and although the results did not change after adjusting for endometriosis, this could bias our results. Because of the relatively small sample size of women with severe menstrual pain, we had limited power to detect statistically significant associations or interactions for some exposure categories. We also acknowledge that there may be unmeasured factor associated with severe pain unrelated to analgesic use which may in part account for the observed associations.

In summary, our results suggest use of aspirin or acetaminophen for severe menstrual pain in the premenopausal period may be associated with lower risk of ovarian cancer among women with severe menstrual pain. Further studies are needed to validate our findings and understand the biological role in which analgesics may modify the association between severe menstrual pain and ovarian cancer risk.

Authors' Disclosures

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Disclaimer

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Authors' Contributions

N. Sasamoto: Conceptualization, methodology, writing–original draft, writing–review and editing. **A. Babic:** Formal analysis, methodology, writing–review and editing. **A.F. Vitonis:** Methodology, writing–review and editing. **L. Titus:** Writing–review and editing. **D.W. Cramer:** Writing–review and editing. **B. Trabert:** Writing–review and editing. **S.S. Tworoger:** Funding acquisition, writing–review and editing. **K.L. Terry:** Conceptualization, supervision, funding acquisition, writing–review and editing.

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