Menstrual pain and risk of epithelial ovarian cancer: results from the Ovarian Cancer Association Consortium

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Running title: Menstrual pain and ovarian cancer risk

Novelty and impact: In this large international pooled analysis of case-control studies, we observed a small increase in risk of ovarian cancer for women reporting severe menstrual pain. Given the high prevalence of menstrual pain, this association should be further examined in prospective studies.

Keywords: Ovarian cancer, case-control studies, menstrual pain, inflammation

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Abstract

Menstrual pain, a common gynecological condition, has been associated with increased risk of ovarian cancer in some, but not all studies. Furthermore, potential variations in the association between menstrual pain and ovarian cancer by histologic subtype have not been adequately evaluated due to lack of power. We assessed menstrual pain using either direct questions about having experienced menstrual pain, or indirect questions about menstrual pain as indication for use of hormones or medications. We used multivariate logistic regression to calculate the odds ratio (OR) for the association between severe menstrual pain and ovarian cancer, adjusting for potential confounders, and multinomial logistic regression to calculate odds ratios for specific histologic subtypes. We observed no association between ovarian cancer and menstrual pain assessed by indirect questions. Among studies using direct question, severe pain was associated with a small but significant increase in overall risk of ovarian cancer (OR=1.07, 95% CI: 1.01-1.13), after adjusting for endometriosis and other potential confounders. The association appeared to be more relevant for clear cell (OR=1.48, 95% CI: 1.10-1.99) and serous borderline (OR=1.31, 95% CI: 1.05-1.63) subtypes. In this large international pooled analysis of case-control studies, we observed a small increase in risk of ovarian cancer for women reporting severe menstrual pain. While we observed an increased ovarian cancer risk with severe menstrual pain, the possibility of recall bias and undiagnosed endometriosis cannot be excluded. Future validation in prospective studies with detailed information on endometriosis is needed.

INTRODUCTION

With more than 14,000 estimated deaths in 2017, ovarian cancer is the fifth leading cause of female cancer deaths in the U.S., and the most lethal gynecologic malignancy (1). Less than 15% of ovarian cancers are diagnosed at an early stage before cancer has spread outside of the ovary. Overall prognosis is poor with a 5-year survival of 45% (1). Understanding novel ovarian cancer risk factors could help identify women at higher risk of disease who might benefit from screening.

Inflammation has been hypothesized to play an important role in ovarian carcinogenesis (2). Inflammatory conditions including endometriosis (3) and pelvic inflammatory disease (4) have been associated with an increased risk of ovarian cancer, while tubal ligation, which may reduce exposure to proinflammatory factors, (5) and regular use of non-steroidal anti-inflammatory drugs (NSAID) (6) have been associated with a reduction in risk.

Menstrual pain, also known as dysmenorrhea is a common gynecological condition associated with increased inflammation (7) and has previously been evaluated in relation to ovarian cancer risk (8-14). However, the majority of the studies were small and inadequately adjusted for potential confounders. Furthermore, due to relatively small numbers of participants, previous studies were not adequately powered to evaluate whether this association might differ by histological subtype, which is important for understanding the potential mechanism underlying any observed association.

We examined the association between severe menstrual pain and ovarian cancer risk among 10,592 cases and 13,320 controls participating in the Ovarian Cancer Association Consortium,

an international collaboration dedicated to studying factors affecting ovarian cancer risk and survival.

MATERIALS AND METHODS

Study population

The Ovarian Cancer Association Consortium (OCAC) was founded in 2005 to foster collaborations in discovering and validating genetic variants associated with ovarian cancer risk (3,15). The analyses presented here are restricted to nine studies with available information on menstrual pain: Australian Ovarian Cancer Study (AUS) (11), the Connecticut Ovarian Cancer Study (CON) (16), Diseases of the Ovary and their Evaluation (DOV) (17,18) , Hawaii Ovarian Cancer Study (HAW) (19,20), Hormones and Ovarian Cancer Prediction Study (HOP) (21), Malignant Ovarian Cancer Study (MAL) (22), New England Case Control Study (NEC) (23), North Carolina Ovarian Cancer Study (NCO) (24,25), and Los Angeles County Case-Control Studies of Ovarian Cancer (USC) (26). Characteristics of the studies are shown in Supplementary Table 1. In total, our analysis included data from seven case-control studies conducted in the United States (CON, DOV, HAW, HOP, NCO, NEC, USC), one study conducted in Australia (AUS), and one study conducted in Denmark (MAL).

We excluded women with non-epithelial tumors or tumors of unknown origin (n=78) and women with no available information on menstrual pain (n=605), resulting in a final analytic dataset of 10,592 cases and 13,320 controls. There were 8,275 invasive and 2,062 borderline cases, as well as 255 cases of unknown morphology (Table 1). Invasive epithelial tumors were further categorized by histologic subtype: high-grade serous (n=3,255), low-grade serous

(n=1,199), mucinous (n=521), endometrioid (n=1,251), clear cell (n=639), and other (n=953). Borderline tumors were characterized as serous (n=1,165), mucinous (n=801) or other (n=67). All studies included in this analysis had obtained written informed consents from all study participants, and had approval from the relevant ethics committees.

Study variables

Questions relating to severe menstrual pain differed between sites included in this analysis (summarized in Table 2). In AUS, CON, NCO and NEC the questionnaire asked whether the participant experienced severe or significant menstrual pain. These questions will be referred to here as direct. Five studies (DOV, HAW, HOP, MAL and USC) asked about menstrual pain as an indication for using various over the counter or prescription medications, including NSAIDs, oral contraceptives, hormones or intrauterine devices (IUD). These questions will be referred to here as indirect. Menstrual pain requiring use of any of those medications was considered severe. In NCO, participants were asked if they experienced severe cramping during periods in the two years prior to diagnosis (cases), or in the last two years (controls). Since these questions only pertained to women who were menstruating within the last two years, the analysis of NCO was restricted to premenopausal women.

Participants of AUS and NCO who reported severe pain were further asked to provide additional details about menstrual pain, such as frequency of pain (AUS, NCO), age at onset of pain (AUS, NCO), total number of years with pain (AUS, NCO), whether they had seen a doctor about the pain (AUS, NCO), or taken a medication for the pain (NCO). For AUS and NCO, we created a variable combining information about menstrual pain severity and frequency, with

the following values: no pain or pain not severe, severe pain occurring sometimes or rarely, severe pain occurring often.

The following variables were obtained as part of the core dataset and were harmonized by OCAC study sites: age (continuous), race (white, other), duration of use of oral contraceptives (OC; continuous), parity (0, 1, 2, 3, 4 or more pregnancies), family history of breast or ovarian cancer in a first-degree relative (yes, no), tubal ligation (yes, no), self-reported endometriosis (yes, no), body mass index (BMI, continuous) 1 year before diagnosis (cases) or interview (controls), BMI (continuous) at the age 18, age at menarche (continuous), genital powder use (nonuser, genital use, non-genital use, unknown), regular (at least once per week) use of aspirin, regular (at least once per week) use of other NSAIDs, menopausal status (peri/premenopausal, postmenopausal, unknown), and smoking status (never, former, current, unknown).

Information on the following variables was obtained from individual studies, and harmonized for this analysis: history of pelvic inflammatory disease, polycystic ovary syndrome, fibroids, ovarian cysts and irregular periods (all coded as yes, no, unknown).

Statistical analysis

Study-specific odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between severe menstrual pain and risk of ovarian cancer were estimated using unconditional logistic regression. In the minimally adjusted model, we adjusted for race and age. In the fully adjusted model we additionally adjusted for a priori selected ovarian cancer risk factors including parity, OC use, family history of breast or ovarian cancer, tubal ligation, and

endometriosis (3,5,27-29), even though none of the factors changed the observed association by more than 10%. We also considered potential confounding by BMI, age at menarche, genital powder use, history of pelvic inflammatory disease, ovarian cysts, polycystic ovary disease, irregular periods, fibroids, menopausal status and smoking; however, none of those factors altered the effect estimates by more than 10% and they were therefore not included in the final models. To evaluate heterogeneity between studies we pooled the study-specific estimates using random-effects meta-analysis. Heterogeneity between studies was evaluated using I^2. Multinomial logistic regression was used to estimate the association between menstrual pain and risk of ovarian cancer by behavior (borderline vs. invasive) and histologic subtype. Likelihood ratio tests were performed to test the association differs significantly by behavior and histologic subtype.

We performed stratified analyses to evaluate effect modification by age (< 50 or ≥ 50 years, study population median), menopausal status (premenopausal, postmenopausal), BMI 1 year before diagnosis or interview (<25 kg/m^2, ≥25 kg/m^2), median BMI at age 18 (<20.8 kg/m^2, ≥20.8 kg/m^2), endometriosis (yes, no, unknown), regular aspirin use (yes, no), regular NSAID use (yes, no), parity (nulliparous, parous), and OC use (<1 year, ≥ 1 year). The stratified analyses were performed using a pooled dataset of all studies, adjusting for study site in addition to other variables described above. To test for significance of any effect modification, we created a cross product between menstrual pain and each stratifying variable and performed likelihood ratio tests to compare models with or without interaction terms. We performed a sensitivity analysis to evaluate the influence of exposure misclassification using a method previously described (30). Briefly, we evaluated how different degrees of misclassification of menstrual

pain might influence the associations. Specifically, we were interested in what degree of misclassification would lead to the observed effect estimate if the true effect estimate was 1.00. Furthermore, we also performed a sensitivity analysis excluding NCO participants since the question about menstrual pain in this study was referring to a recent period (Table 2) and therefore more prone to reverse causation.

All analyses were performed using SAS v9.3 (SAS Institute, Cary, NC), except for meta-analysis and multinomial logistic regression, which were performed using Stata IC/12 (StataCorp, College Station, TX). All p values were two-sided, and a significance level of 0.05 was used.

RESULTS

Characteristics of ovarian cancer cases and controls are shown in Table 1. Compared to controls, cases were more likely to be nulliparous, less likely to have had a history of tubal ligation, and had a shorter duration of OC use. In addition, ovarian cysts, fibroids, family history of breast or ovarian cancer, use of genital powder, and severe menstrual pain were more frequent in cases than in controls.

The prevalence of severe menstrual pain in controls varied widely across the different sites included in this analysis (2.7% to 55.6%; Table 2), as expected given the heterogeneity of the questions pertaining to menstrual pain. Overall, severe menstrual pain was less common among sites that asked an indirect question (2.7% to 10.0%, average prevalence = 5.3%) compared to those that asked direct questions (9.5% to 55.6%, average prevalence = 30.3%).

The highest prevalence was reported for AUS (55.6%), where participants were asked about ever having experienced very painful period pain, followed by NCO (43.2%) where participants were asked about severe menstrual cramping for duration of least 1 year in the 2 years preceding diagnosis, and CON (34.9%) that asked about typically experiencing significant pain. Report of severe menstrual pain was lowest in the USC study (2.7%) which asked whether painful periods were an indication for taking birth control pills or hormones.

Figure 1A shows the association between several menstrual pain and ovarian cancer risk for the four studies that asked direct questions about menstrual pain. Severe pain was associated with a small but statistically significant increase in risk for women who reported severe menstrual pain, compared to women without severe menstrual pain (OR = 1.07, 95% CI: 1.01-1.13). For studies that used indirect questions, there was no association between severe menstrual pain and ovarian cancer risk (OR = 0.98, 95% CI: 0.89-1.07) (Figure 1B). There was no heterogeneity between study sites with either direct (*P*-heterogeneity=0.74) or indirect questions about menstrual pain (*P*-heterogeneity=0.27).

Since indirect questions likely failed to identify women with severe pain (as only those who reported pain as a reason for medication use would have been identified by these questions), we restricted the following analyses to the four studies that asked direct questions (AUS, CON, NCO, NEC). In the pooled analysis, we evaluated the association between ovarian cancer risk and the combined variable for severe menstrual pain presence and frequency (AUS, NCO). Compared to women with no severe pain, those with rare severe pain were not at a significantly higher risk (OR: 0.99, 95% CI: 0.83-1.17), while those with frequent severe pain

were at a 17% increased risk of ovarian cancer (OR: 1.17, 95% CI: 1.00-1.38) (Table 3). Compared to women with no severe pain, those with duration of severe pain of less than 12 years (median duration of pain among women with severe pain) were not at increased risk of ovarian cancer (OR=0.95, 95% CI: 0.80-1.12), while those with duration longer than 12 years had a 18% increase in risk of ovarian cancer (OR=1.18, 95% CI: 0.99-1.40) (Table 3). Age at menstrual pain onset (AUS, NCO) was not associated with risk of ovarian cancer (Table 3).

In stratified pooled analyses (Supplementary Table 2), we observed no statistically significant effect modification by age, menopausal status, regular aspirin use, regular NSAID use, parity, OC use, endometriosis, and tubal ligation (*P*-interaction ≥ 0.15). Although not significant, differences in the association by BMI 1 year before diagnosis or interview were suggestive (*P*-interaction = 0.06). The association was not significant among women with BMI < 25 kg/m^2 (OR=1.01, 95% CI: 0.87-1.23), while there was a 21% increase in risk among women with BMI > 25 kg/m^2 (OR: 1.21, 95% CI: 1.04-1.41).

Severe menstrual pain was more frequent among women with endometriosis (51%), compared to those without endometriosis (30%). There was no difference in the association between menstrual pain and ovarian cancer risk with (OR=1.07, 95% CI: 1.01-1.13) or without (OR=1.08, 95% CI: 1.02-1.14) adjusting for endometriosis.

Since severe pain might lead to OC use, and OC use could therefore lie on a causal pathway between severe pain and ovarian cancer, adjusting for OC use could bias the association toward null. We therefore evaluated the association between menstrual pain and overall risk of ovarian

cancer in a multivariate model with no adjustment for OC use, and observed no change in association (OR=1.06, 95% CI: 1.01-1.12).

In analyses by histological subtypes (Figure 2 A-E), we observed a statistically significant association between severe menstrual pain and clear cell ovarian cancer (OR=1.48, 95% CI: 1.10-1.99), and a suggestion of association for endometrioid (OR=1.24, 95% CI: 0.99-1.54) and high-grade serous cancers (OR=1.13, 95% CI: 0.97-1.31). We observed no association for low-grade serous (OR=1.12, 95% CI: 0.90-1.39), or mucinous subtypes (OR=1.18, 95% CI: 0.63-2.19) although these analyses were limited by small numbers. However, the overall likelihood test has shown no significant difference in association by histological subtype (P-heterogeneity=0.53). Severe menstrual pain was associated with increased risk of the serous borderline (OR=1.31, 95% CI: 1.05-1.83), but not mucinous borderline subtype (OR=1.00, 95% CI: 0.77-1.29; Figure 3 A-B), although there was no overall significant difference in association among those two subtypes (*P*-heterogeneity=0.61). There was no significant heterogeneity for associations by histological subtypes across study sites, except for the mucinous invasive subtype (n=169) (*P*-heterogeneity=0.05). Since the association between menstrual pain and clear cell tumors was previously reported for NEC study, we performed a sensitivity analysis excluding NEC participants, and observed a suggestive association between menstrual pain and clear cell ovarian cancer (OR=1.40, 95% CI: 0.96-2.40). We performed a sensitivity analysis of sites with direct questions after excluding NCO, since this site asked about menstrual pain in a period shortly before diagnosis, and therefore had a higher potential for recall bias or reverse causation. Excluding NCO did not significantly change the association between severe menstrual pain and overall ovarian cancer (OR: 1.13, 95% CI: 1.01-1.27).

To evaluate the impact of potential over-reporting of menstrual pain on the overall effect estimate, we performed an analysis where specificity of menstrual pain reporting in cases varied but in controls was set to 0.99. We observed that a specificity of 0.94 among cases would be required to inflate the effect estimate to the observed OR = 1.07. We also examined whether the prevalence of pain severe enough to seek medical treatment differed between cases and controls who reported severe menstrual pain. This more objective measure of menstrual pain was assessed in the AUS and NCO studies. Among women who reported experiencing severe pain, 43% of cases (n=1,011) and 42% of controls (n=954) had consulted a physician suggesting that cases were not simply over-reporting less severe pain compared to controls.

DISCUSSION

In this large pooled analysis of case control studies, we observed a suggestive increase in ovarian cancer risk for women who reported severe menstrual pain, compared to those without such pain. Furthermore, we observed that the association was restricted to women who experienced menstrual pain more frequently or for a longer duration (>12 years). The risk associated with severe menstrual pain appeared to be most relevant for clear cell and borderline serous subtypes.

The association between menstrual pain and risk of ovarian cancer was evaluated using two distinct types of question. While certain sites asked whether the participant experienced severe or significant menstrual pain (direct question), the others asked about menstrual pain as an indication for using various medications (indirect question). While there is likely a comparable

specificity between two question types, the indirect question is likely to be less sensitive to detect women with severe menstrual pain since it would fail to identify women with severe pain that did not use any of the listed medications. The type of question used to assess severe menstrual pain varied widely between studies. As expected, the prevalence of severe menstrual pain varied between the study sites, which was likely related to the difference in the questions asked, but could also be due to difference in perception of pain across cultures. While we initially considered sites with both direct and indirect questions, the added potential for misclassification given the indirect nature of the question, which required a woman to indicate pain as a reason for taking analgesics or hormones, led us to restrict our remaining analyses to the studies that asked directly about severe menstrual pain. We cannot rule the possibility that women with most severe pain would have been identified using indirect question and that stronger association would be expected among these women. However, since the prevalence of severe menstrual pain in studies with indirect question was low (2.7% to 10%) we would likely not have power to detect a significant association. Furthermore, since this question is less sensitive, and would fail to identify all the women with severe menstrual pain, this would lead to exposure misclassification and bias the association toward the null.

Two studies included in this analysis had previously evaluated the association between menstrual pain and ovarian cancer using direct question (8,11) and had shown differing results. One reported a significant increase in ovarian cancer risk (8), while the other reported no significant association (11). Four additional studies reported no significant association; however, it is not clear what type of question was used to assess history of menstrual pain in those studies. Therefore, we are not able to directly compare our results (9,10,13,14).

The large number of cases in the analysis allowed us to evaluate the association between menstrual pain and individual histologic subtypes. We observed an increased risk for clear cell and serous borderline tumors, however there was no statistically significant difference in the association neither among invasive, nor among borderline subtypes. Increased risk of clear cell subtype had been previously reported by NEC study, which is included in this analysis, and results remained borderline significant after excluding NEC participants. However, one cannot exclude the possibility that observed significant association is due to chance or multiple comparisons.

Menstrual pain (dysmenorrhea) can be either primary or secondary. While secondary dysmenorrhea is caused by endometriosis, fibroids, adenomyosis, or pelvic inflammatory disease (31), primary dysmenorrhea is thought to be caused by inflammatory processes. We observed no significant change in effect estimate after adjusting for endometriosis, fibroids, and pelvic inflammatory disease, suggesting that the observed association is not due to secondary dysmenorrhea as a result of these conditions. Primary dysmenorrhea is thought to be a consequence of increased prostaglandin synthesis shortly before menstruation onset, which increases uterine contractility (7,32). Women with severe menstrual pain have higher levels of prostaglandins (33-35) as well as other inflammatory molecules such as leukotrienes (36,37) and platelet activating factors (36) in menstrual blood. Through the process of retrograde menstruation, which occurs in up to 90% of women with intact fallopian tubes (38-40), those inflammatory factors could reach the tubal epithelium as well as ovarian tissue, and promote carcinogenesis at those sites. Our results support such a hypothesis, since severe

menstrual pain was not associated with ovarian cancer in women with a history of tubal ligation.

The association between menstrual pain and ovarian cancer was similar among aspirin or NSAID users, and non-users. If the mechanism underlying the association between menstrual pain and ovarian cancer is inflammation, one would expect the association to be attenuated among aspirin or NSAID users. However, our question on regular medication use did not assess dose of intake but only distinguished between non-weekly versus one or more times of use per week. Furthermore, it is unknown whether the use of aspirin and NSAIDs coincided with occurrence of menstrual pain.

Endometriosis is a common gynecological condition associated with significant menstrual pain (41), and an established ovarian cancer risk factor (3). In our study adjusting for endometriosis did not alter the association between severe menstrual pain and ovarian cancer risk. Since endometriosis in our study was self-reported, and final diagnosis of endometriosis requires laparoscopy, it is possible that there might be residual confounding by undiagnosed endometriosis among our participants. However, if menstrual pain was merely a symptom of undiagnosed endometriosis, one would expect a stronger association among women with diagnosed endometriosis, which is not the case in this analysis (Supplementary Table 2). Further studies where the presence of endometriosis is clinically evaluated are needed to disentangle menstrual pain from endometriosis.

Retrospective studies are susceptible to potential recall bias, where exposure recall may differ between cases and controls. For example, cases might be prone to over-report severe

menstrual pain, which would lead to an overestimation of the association between pain and ovarian cancer risk. We found that a decrease in specificity of accurately reporting severe menstrual pain of 6% among cases would nullify the observed effect estimate. To further address this potential over-reporting of menstrual pain by cases, we examined a more objective indicator, namely menstrual pain that was severe enough to result in consultation with a physician. If cases were indeed over reporting pain, one would expect a smaller proportion of cases who reported severe menstrual pain to have consulted a physician, compared to controls. However, we observed a comparable percentage of cases with severe pain (43%) and control subjects (42%) who consulted a physician, suggesting recall bias was not a likely problem in our study population. Furthermore, recall bias would be unlikely to lead to differences in the association by histologic subtype as there is no reason to suspect that women with endometrioid or clear cell tumors would be more likely to over report menstrual pain compared to women with high grade serous tumors.

To our knowledge, this is the largest study and only international collaborative study that has evaluated menstrual pain in relation to ovarian cancer. Furthermore, we were able to evaluate features of menstrual pain such as age at onset as well as duration and frequency of menstrual pain. Due to a large sample size, we were able to examine the association even for the rare subtypes of ovarian cancer and identify previously unknown differential associations, in particular for borderline cases. We were also able to consider and control for several factors associated with underlying causes of menstrual pain.

A limitation of this study was the heterogeneity of questions pertaining to severe menstrual pain, even among study sites with a direct question. For instance, NCO asked participants about severe menstrual pain in the past two years, whereas most studies asked about any history of menstrual pain. However, our results remained unchanged after excluding NCO in a sensitivity analysis. Since the questions were asked specifically about severe or significant pain, we were not able to evaluate the increase in risk for women with milder pain. Our study population was predominantly white (87%), and therefore our results might not be generalizable to other racial/ethnic groups.

In summary, our results suggest that severe menstrual pain is associated with a modest, but statistically significant, increase in ovarian cancer risk. Furthermore, among women with severe menstrual pain ovarian cancer risk increased with higher frequency and longer duration of menstrual pain. Since severe menstrual pain is a common condition, even a small increase in risk would translate into a substantial impact on a population level. Future studies should disentangle the impact of menstrual pain from the one of endometriosis in more detail.

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Figure Titles and Legends:

Figure 1.

Title:

A. Association between risk of overall ovarian cancer and severe menstrual pain ascertained by direct question

B. Association between risk of overall ovarian cancer and severe menstrual pain ascertained by indirect question

Legend:

A. Adjusted for age (continuous, in years), parity (0, 1, 2, 3, 4 or more children), oral contraceptive use (<3months, 3 months - < 1 year, 1 - < 5 years, ≥ 5 years), family history of ovarian or breast cancer, tubal ligation, race (white, non-white), endometriosis (yes, no, unknown).

Abbreviations: AUS, Australian Ovarian Cancer Study; CON, Connecticut Ovary Study; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case Control Study

B. Adjusted for age (continuous, in years), parity (0, 1, 2, 3, 4 or more children), oral contraceptive use (<3months, 3 months - < 1 year, 1 - < 5 years, ≥ 5 years), family history of ovarian or breast cancer, tubal ligation, race (white, non-white), endometriosis (yes, no, unknown).

Abbreviations: 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; USC, Los Angeles Count Case-Control Studies of Ovarian Cancer.

Figure 2.

Title: Association between severe menstrual pain evaluated using direct question and histological subtypes of invasive ovarian cancer

Legend:

(A) High-grade serous, (B) Low-grade serous, (C) Mucinous, (D) Clear cell, (E) Endometrioid.

Abbreviations: AUS, Australian Ovarian Cancer Study; CON, Connecticut Ovary Study; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case Control Study

Figure 3.

Title: Association between severe menstrual pain evaluated using direct question and histological subtypes of borderline ovarian cancer

Legend:

(A) Serous, (B) Mucinous. Adjusted for age (continuous, in years), parity (0, 1, 2, 3, 4 or more children), oral contraceptive use (<3months, 3 months - < 1 year, 1 - < 5 years, ≥ 5 years), family history of ovarian or breast cancer, tubal ligation, race (white, non-white), endometriosis (yes, no, unknown).

Abbreviations: AUS, Australian Ovarian Cancer Study; CON, Connecticut Ovary Study; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case Control Study

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Table 1. Characteristics of ovarian cancer cases and controls

Characteristics	**Cases (n=10,592)**	**Controls (n=13,320)**
	Mean (SD)	
Age (years)	55.4 (12.1)	55.3 (12.2)
Age at menarche (years)	12.8 (7.6)	12.8 (1.6)
BMI at 1 year before diagnosis or interview (kg/m^2)	26.9 (6.5)	26.6 (6.2)
BMI at 18 years (kg/m^2)	21.5 (3.7)	21.2 (3.4)
	N (%)	
History of tubal ligation)	1,724 (16)	3,026 (23)
Parity		
0	2,761 (26)	2,068 (16)
1	1,577 (15)	1,814 (14)
2	2,981 (28)	4,442 (33)
3	1,866 (18)	2,865 (22)
4+	1,407 (13)	2,131 (16)
Oral contraceptives use		
<3 months	4,587 (43)	4,478 (34)
3months-1 year	1,452 (14)	1,548 (12)
1-5 years	2,220 (21)	3,021 (23)
>5 years	2,333 (22)	4,273 (32)
Menopause[a]		
Pre/perimenopausal	3,731 (36)	4,920 (37)
Postmenopausal	6,742 (64)	8,196 (62)
Severe menstrual pain	1,782 (17)	1,815 (14)
History of endometriosis[a]	978 (9)	870 (7)
Polycystic ovary syndrome[a]	110 (1)	124 (1)
History of pelvic inflammatory disease[a]	248 (3)	257 (3)
History of irregular periods[a]	1,363 (14)	1,791 (15)
History of ovarian cysts[a]	1,807 (17)	1,842 (14)
Fibroids[a]	2,130 (21)	2,352 (18)
Family history of breast or ovarian cancer	1,944 (18)	1,985 (15)
Race		

White	9,224 (87)	11,877 (89)
Black	301 (3)	317 (2)
Asian	601 (6)	594 (4)
Other/unknown	466 (4)	532 (4)
Smoking status		
Never	4,605 (43)	6,208 (47)
Current	1,482 (14)	2,067 (16)
Former	2,801 (26)	3,733 (28)
Regular aspirin use	1,056 (19)	1,785 (19)
Regular NSAID use	1,307 (23)	2,208 (23)
Use of genital powder[a]		
Non-user	3,297 (50)	4,571 (34)
Genital use	2,030 (31)	2,070 (16)
Non-genital use	1,176 (18)	1,439 (11)
Histological subtype[a]		
Borderline (n=2,062)		
Serous	1165 (56)	-
Mucinous	801 (39)	-
Other	67 (5)	-
Invasive (n=8,275)		
Serous	4,911 (59)	-
Mucinous	521 (6)	-
Endometrioid	1,251 (15)	-
Clear cell	639 (8)	-
Other	953 (12)	-

[a]Data were missing on menopausal status for 119 cases and 204 controls, endometriosis for 39 cases and 43 controls, on polycystic syndrome for 1,144 cases and 2,120 controls, on pelvic inflammatory disease for 3,479 cases and 5,459 controls, on history of irregular periods for 1,168 cases and 1,397 controls, on history of ovarian cysts for 40 cases and 54 controls, on fibroids for 540 cases and 615 controls, on use of powder for 4,089 cases and 5,240 controls, on smoking status for 1,704 cases and 1,312 controls, on regular aspirin use for 4,910 cases and 3,665 controls, on regular NSAID use on 4,862 cases and 3,665 controls, on cancer invasiveness for 255 cases.

Table 2. Questions relating to menstrual pain by study

Study acronym	Question relating to severe menstrual pain	Type of question	Prevalence of severe pain in controls
AUS	Ever suffered from very painful periods	Direct	55.6 %
CON	Typically had significant pain or discomfort during menstruation in your 20's, 30's or 40's	Direct	34.9 %
NEC	Severe cramps in 20s and 30s when not pregnant, breastfeeding or using birth control pills	Direct	9.5 %
NCO	Severe menstrual cramping during the periods for at least 1 year, in 2 years prior to diagnosis (cases) or in the past two years (for controls) Painful periods as reason for using birth control, IUD, over the counter or prescription medications	Direct	43.2 %
DOVE	Cramps or painful ovulation as the main reason you used pill/shot/implant other than for birth control Severe menstrual cramps as a reason for hormone pill use Menstrual pain as indication for taking medication for 5 or more days per month for at least 6 months	Indirect	5.5 %
HAW	Painful periods as a reason for birth control pill use Painful periods as a reason for use of hormones, aspirin products, aspirin-free products, over the counter NSAID, prescription NSAID, prescription pain relievers	Indirect	10.0 %
HOP	Menstrual pain as indication for hormone shot/implant, patch, ring, other hormone medication, over the counter aspirin, over the counter inflammation reliever other than aspirin, prescription medicine for pain or inflammation	Indirect	7.4 %
MAL	Pain during the period as a reason for taking birth control pills or hormone therapy	Indirect	3.6 %
USC	Painful periods as indication for taking birth control or hormones	Indirect	2.7 %

Table 3. Association between menstrual pain characteristics and risk of ovarian cancer[a] in the pooled dataset

	Cases/controls	OR[b] (95% CI)
Menstrual pain frequency		
No pain/pain not severe	803/842	1.00 (ref)
Severe pain, sometimes/rarely	417/436	0.99 (0.83-1.17)
Severe pain, often	573/502	1.17 (1.00-1.38)
Duration of menstrual pain		
No severe menstrual pain	803/842	1.00 (ref)
Severe pain <12 years	412/485	0.95 (0.80-1.12)
Severe pain ≥ 12 years	500/406	1.18 (0.99-1.40)
P-trend[c]		0.03
Age at menstrual pain onset		
No severe menstrual pain	803/842	1.00 (ref)
Pain onset at <15 years of age[d]	399/372	1.10 (0.92-1.31)
Pain onset at ≥15 years of age[d]	612/582	1.08 (0.93-1.26)
P-trend		0.52

[a]Restricted to sites with available information on menstrual pain frequency, duration, and age at onset (AUS and NCO)
[b]Adjusted for age (years, continuous), site, parity (0, 1, 2, 3, 4 or more children), oral contraceptive use (<3months, 3 months - < 1 year, 1 - < 5 years, ≥ 5 years), family history of ovarian or breast cancer, tubal ligation, race (white, non-white), and endometriosis (yes, no, unknown).
[c]Years of menstrual pain
[d]Median age at menstrual pain onset

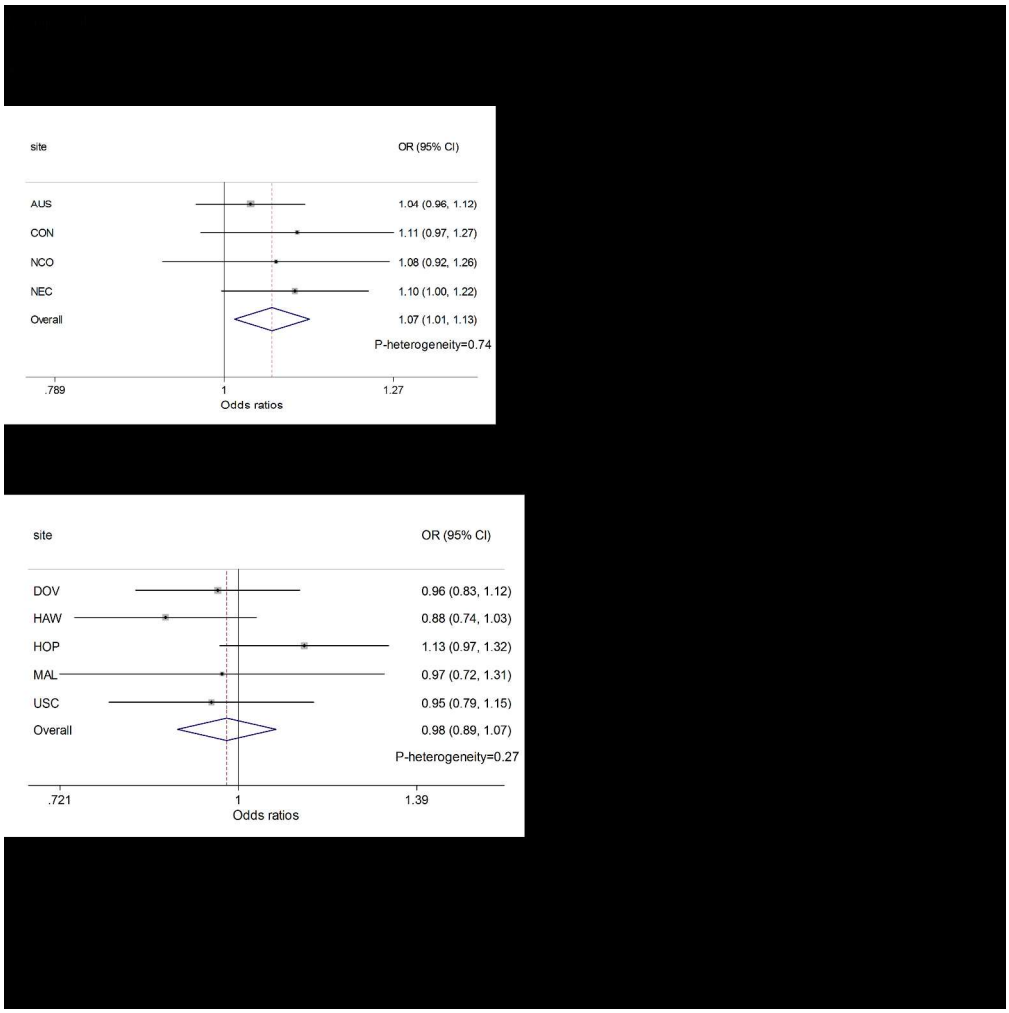

Figure 1

1030x1032mm (96 x 96 DPI)

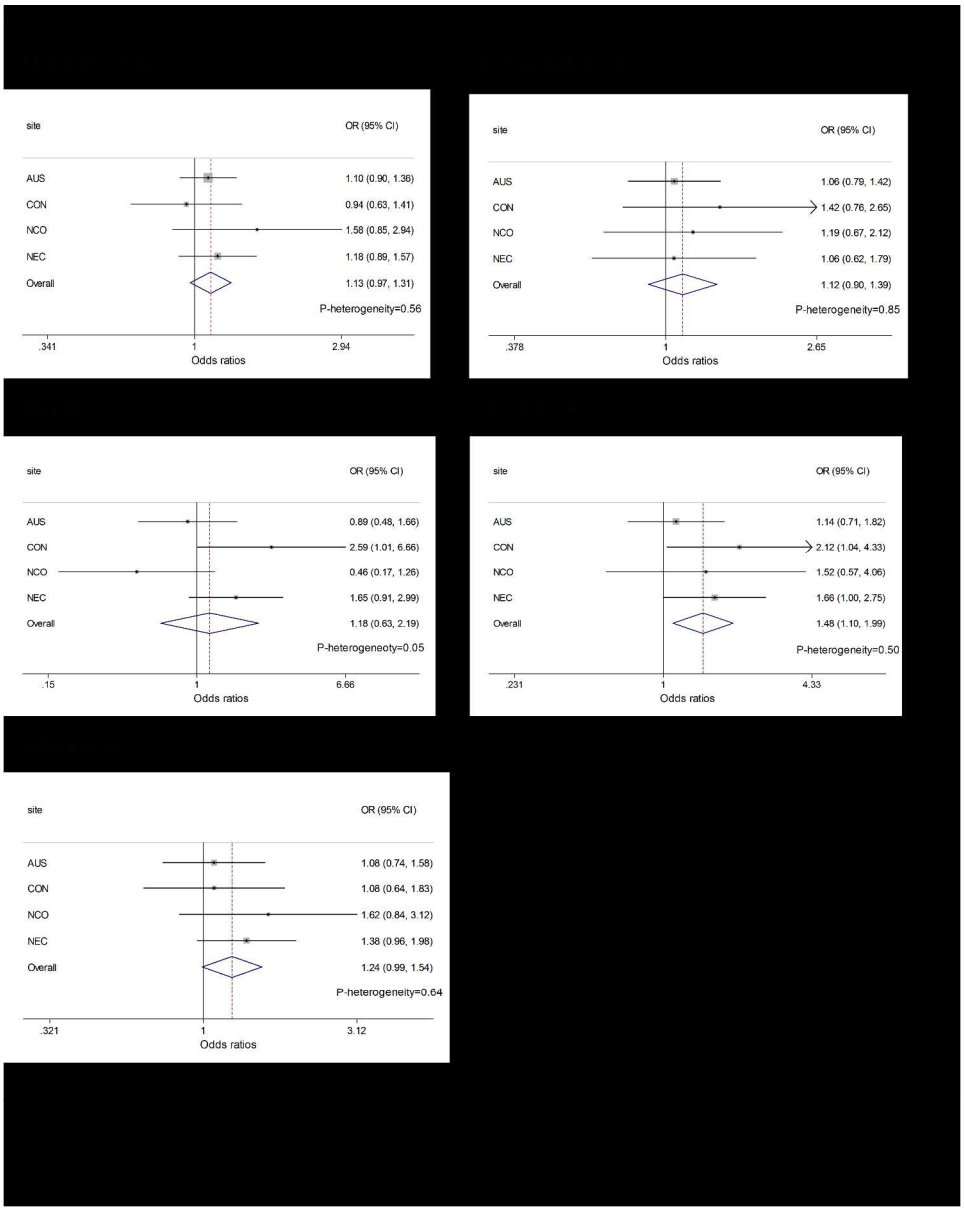

Figure 2

1189x1492mm (96 x 96 DPI)

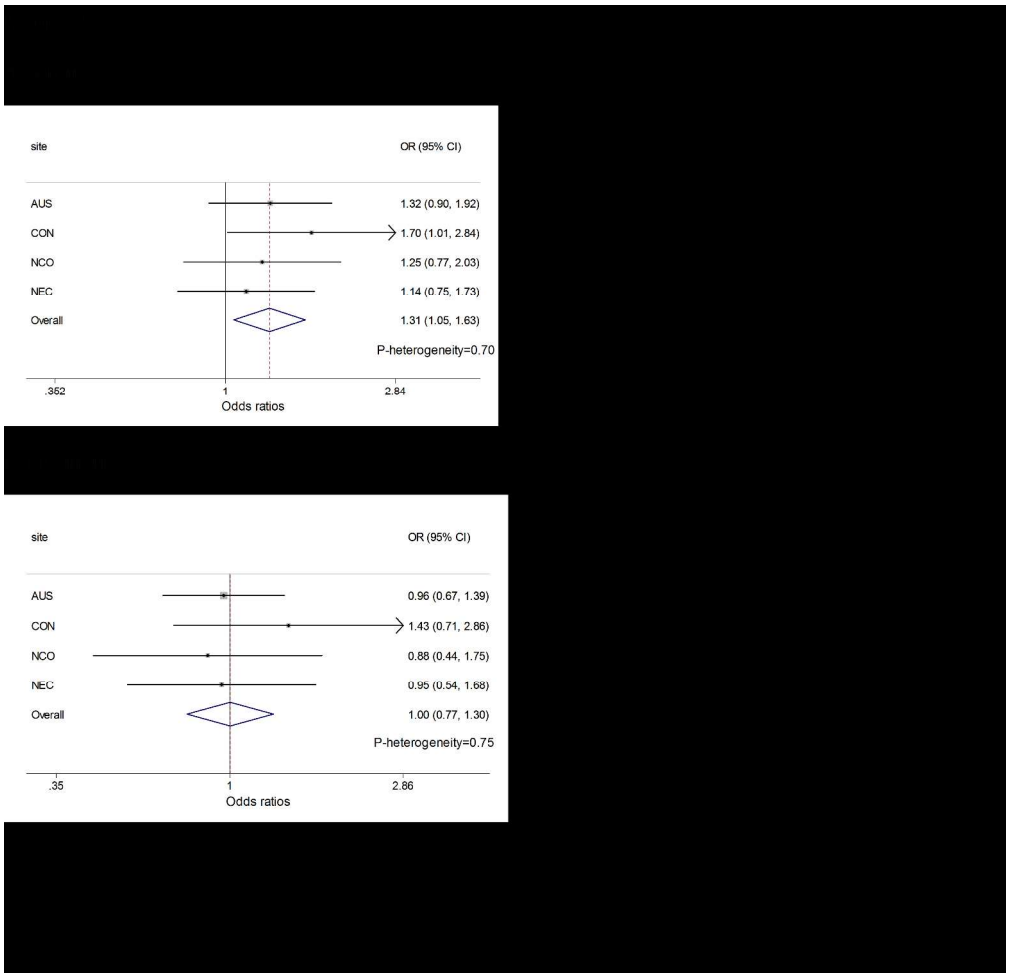

Figure 3

1030x996mm (96 x 96 DPI)