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Long and irregular menstrual cycles, polycystic ovary syndrome, and ovarian cancer risk in a population-based case-control study

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Abstract

Long and irregular menstrual cycles, a hallmark of polycystic ovary syndrome (PCOS), have been associated with higher androgen and lower sex hormone binding globulin levels and this altered hormonal environment may increase the risk of specific histologic subtypes of ovarian cancer. We investigated whether menstrual cycle characteristics and self-reported PCOS were associated with ovarian cancer risk among 2041 women with epithelial ovarian cancer and 2100 controls in the New England Case-Control Study (1992-2008). Menstrual cycle irregularity, menstrual cycle length, and PCOS were collected through in-person interview. Unconditional logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (95% CIs) for ovarian cancer risk overall, and polytomous logistic regression to evaluate whether risk differed between histologic subtypes. Overall, we observed no elevation in ovarian cancer risk for women who reported periods that were never regular or for those reporting a menstrual cycle length of >35 days with ORs of 0.87 (95% CI=0.69-1.10) and 0.83 (95% CI=0.44-1.54), respectively. We observed no overall association between self-reported PCOS and ovarian cancer (OR=0.97; 95% CI=0.61-1.56). However, we observed significant differences in the association with menstrual cycle irregularity and risk of ovarian cancer subtypes ($p_{heterogeneity}$=0.03) as well as by BMI and OC use ($p_{interaction}$<0.01). Most notable, menstrual cycle irregularity was associated with a decreased risk of high grade serous tumors but an increased risk of serous borderline tumors among women who had never used OCs and those who were overweight. Future research in a large collaborative consortium may help clarify these associations.

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Keywords

menstrual cycle characteristics; PCOS; ovarian cancer

Introduction

A wide range of factors influence menstrual cycle characteristics, including body size, smoking, alcohol intake, and physical activity, as well as pathologic conditions including polycystic ovary syndrome (PCOS)[1-5]. Approximately 85-90% of women with oligomenorrhea have PCOS, usually defined as cycle length greater than 35 days[6]. However, the diagnostic criteria for PCOS has evolved over time. Currently, there are three overlapping, but not entirely consistent, clinical definitions of PCOS[7-9]. Menstrual cycle irregularity and length are features included in all three PCOS definitions.

Longer menstrual cycle length and irregular cycles have been associated with higher androgen and lower sex hormone binding globulin levels (SHBG)[10-12], and this altered hormonal environment may increase the risk of specific histologic subtypes of ovarian cancer. Cirillo, et al. recently reported that among parous women, those with irregular menstrual cycles had over a two-fold increase in ovarian cancer risk[13]. However, other studies examining the association between menstrual cycle characteristics[14-21] or PCOS[15, 18, 22-27] and ovarian cancer risk have produced inconsistent results, and few have examined the associations by histologic subtype[21, 24].

Thus, we sought to investigate whether menstrual cycle characteristics and self-reported PCOS, were associated with ovarian cancer risk, overall and by histologic subtype, in the New England Case-Control Study. We also examined whether the associations varied by oral contraceptive use or body mass index (BMI).

Methods

Study population

The New England Case-Control (NECC) study of ovarian cancer was conducted in three enrollment phases (phase 1 1992-1997, phase 2 1998-2002, and phase 3 2003-2008). Briefly, 3957 women residing in eastern Massachusetts or New Hampshire with a diagnosis of incident ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Of these 3083 were eligible and 2203 (71%) agreed to participate. Controls were identified through a combination of random digit dialing, drivers' license lists, and town resident lists. In the first phase, 420 (72%) of the eligible women identified through random digit dialing agreed to participate and 102 (51%) of the eligible women identified through townbooks agreed to participate. In the second and third phases, 4366 potential controls were identified, 2940 were eligible, 1362 declined to participate by phone or by mail via an “opt-out” postcard, and 1578 (54%) were enrolled. Controls were frequency matched to cases on age and state of residence. Further details regarding case and control enrollment are described elsewhere[28].

All study participants were interviewed at the time of enrollment. We collected information about known and suspected ovarian cancer risk factors, including reproductive history, gynecologic conditions and procedures, height and weight, genital talc use, smoking, medication use, and family cancer history. To reduce the possible impact of pre-clinical disease on exposure status, cases were asked about exposures that occurred at least one-year before diagnosis, and controls were asked about exposures that occurred more than one year before the interview date. This study was approved by the Institutional Review Boards of Brigham and Women's Hospital and Dartmouth Medical School; each participant provided a signed informed consent.

Assessment of menstrual cycle characteristics and PCOS

Participants were asked about regularity of their menstrual cycle: 'How many months after start of your first period did you periods become regular?' with a responses ranging from 'number of months' to 'never became regular'. Cycle length was assessed with the following question: 'What was the average number of days from the start of one period to the start of another (when you were not pregnant, breastfeeding, or using birth control pills)?'. Participants in phases 2 and 3 were specifically asked if they had ever been diagnosed with polycystic ovaries. Patients could also report being diagnosed with PCOS in the fertility section of the questionnaire.

One of the defining characteristics of PCOS is anovulation or oligoovulation (infrequent or irregular ovulation). Therefore, our menstrual cycle characteristic exposures were defined as: menstrual cycle irregularity (ever reporting regular menstrual cycles, never reporting regular menstrual cycles) and menstrual cycle length (≤35 days, >35 days). Numbers were too small to examine longer menstrual cycle length categories.

Statistical Analysis

For analyses including all cases we calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression. We adjusted our multivariable models for age (continuous), center (Massachusetts or New Hampshire), study phase (1992-1997, 1998-2002, and 2003-2008), parity (nulliparous, 1, 2, 3, 4+ births), duration of oral contraceptive use (never, <5 years, ≥5 years), tubal ligation (yes/no), and family history of ovarian cancer (yes/no). We conducted additional analyses adjusting for BMI but as effect estimates were not materially different following adjustment it was not included as a covariate in the final model.

Polytomous logistic regression was used to simultaneously estimate separate ORs and 95% CIs for each histologic subtype (serous borderline, high grade serous, low grade serous, mucinous borderline, mucinous invasive, clear cell, and endometrioid)[29]. Likelihood ratio tests were used to calculate p-values for heterogeneity comparing models assuming different associations for each histologic subtype to models assuming the same association for all subtypes[30] adjusting for the potential confounders listed above. Based on previous analyses, center, study phase, oral contraceptive use, and family history of ovarian cancer were constrained to a single estimate across subtypes while age, parity, and tubal ligation were allowed to vary across subtypes[16].

Effect modification by BMI (<25, ≥25 kg/m^2), oral contraceptive use (never, <5 years, ≥5 years), and menopausal status (premenopausal, postmenopausal) was assessed using a likelihood ratio test comparing a model with interaction terms and main effects to a model with main effects only. All p-values were based on two-sided tests and were considered statistically significant if $p<0.05$. Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC) and Stata 9 (StataCorp, College Station, TX).

Results

The study population included 2041 epithelial ovarian cancer cases and 2100 controls. Cases were less likely than controls to have ever used oral contraceptives, and more likely to be nulliparous and have a family history of ovarian cancer. Cases and controls were similar with respect to menstrual cycle irregularity and PCOS (Table 1). One hundred fifty-one cases and 175 controls reported periods that were never regular, 18 cases and 26 controls reported an average menstrual cycle length of >35 days, and the mean cycle length was 28.4 days in cases and 28.6 days in controls. Among study phases 2 and 3, 41 cases and 37 controls self-reported a PCOS diagnosis. The overlap between menstrual cycle characteristics and self-reported PCOS are reported in Supplemental Table 1.

In the analyses examining all cases combined, we observed no difference in ovarian cancer risk in women who reported periods that were never regular compared to women who did not report menstrual cycle irregularity (multivariable OR=0.87; 95% CI=0.69-1.10). A similar risk was observed for those reporting an average menstrual cycle length of greater than 35 days with a multivariable OR of 0.83 (95% CI=0.44-1.54). Among women from phases 2 and 3, no association was observed with self-reported PCOS and ovarian cancer (multivariable OR=0.97; 95% CI=0.61-1.56) (Table 2). Further adjustment for BMI did not materially alter any of the associations (results not shown). When all three exposure categories were combined (any report of menstrual cycle irregularity, cycle length >35 days, or self-reported PCOS), we observed no association with ovarian cancer risk (OR=0.94; 95% CI=0.74-1.20).

When we examined the associations by histologic subtype, we observed significant differences in the association with menstrual cycle irregularity as the exposure ($p_{heterogeneity}=0.03$) but not for cycle length >35 days ($p_{heterogeneity}=0.89$) or self-reported PCOS ($p_{heterogeneity}=0.91$) (Table 2). Menstrual cycle irregularity was non-significantly positively associated with serous borderline tumors (OR=1.33; 95% CI=0.87-2.04) and was significantly protective for high grade serous tumors (OR=0.68; 95% CI=0.49-0.95).

The association between menstrual cycle irregularity and ovarian cancer varied by oral contraceptive use ($p_{interaction}=0.001$) (Table 3). Women reporting menstrual cycle irregularity who had used oral contraceptives for less than 5 years were at a decreased risk of ovarian cancer OR=0.60 (95% CI=0.41-0.90) while those who had never used oral contraceptives or used oral contraceptives for 5 or more years did not have a similar decrease in risk. When we examined oral contraceptive use categories more finely, we observed the reduced risk was strongest in women with menstrual cycle irregularity who had used oral contraceptives for less than two years (OR=0.49; 95% CI=0.29-0.89). In contrast, women

with irregular cycles who never used oral contraceptives had an increase in risk serous borderline ovarian cancer (OR=3.48; 95% CI=1.85-6.56). Similar effect modification by OC use was observed for self-reported PCOS ($p_{interaction}$=0.03), however, the confidence intervals were wider likely due to smaller numbers in these analyses (results not shown).

The association between menstrual cycle irregularity and ovarian cancer also differed by BMI ($p_{interaction}$=0.006) (Table 4). Women reporting menstrual cycle irregularity with a BMI <25 had a statistically significantly reduced risk of ovarian cancer (OR=0.62; 95% CI=0.44-0.88) while no association was observed among those with a BMI ≥25 . Lean women with irregular cycles had a reduced risk of high grade serous ovarian cancer (OR=0.58; 95% CI=0.35-0.95) with no association observed among heavier women. In contrast, lean women with irregular cycles had no significant risk of serous borderline tumors, while heavier women had a statistically significant increased risk (OR=2.29; 95% CI 1.32-3.98). No effect modification by menopausal status was observed ($p_{interaction}$=0.82) (results not shown).

Discussion

Overall, we observed no association between menstrual cycle characteristics or self-reported PCOS and ovarian cancer risk. However, we observed significant differences for the association between menstrual cycle irregularity and ovarian cancer risk by histologic subtype. In addition, there was the suggestion of differences in the associations when stratified by BMI and oral contraceptive use.

Few studies have examined the association between PCOS and ovarian cancer risk[18, 22-24, 26, 27] and only one study examined the association by histologic subtype[24]. A 2014 meta-analysis based on three studies reported a non-significant increased risk of ovarian cancer among women with PCOS (OR=1.41; 95% CI=0.93-2.15)[31]. More recently, a register-based study in Denmark compared the incidence of ovarian cancer between women diagnosed with PCOS and the general Danish female population observing a non-significant increased risk of ovarian cancer in women with PCOS (SIR=1.8; 95% CI=0.8-3.2), however these results were based on only 10 total ovarian cases[23]. Another recent study conducted using a health insurance database in Taiwan, reported no association between PCOS and ovarian cancer (HR=1.00; 95% CI=0.21-4.64) based on 11 cases of ovarian cancer[27]. Among the 1,483 cases and 1,578 controls from phases 2 and 3 of our study we did not observe an association between self-reported PCOS and ovarian cancer risk (OR=0.97; 95% CI=0.61-1.56). Differences in the definition of PCOS are likely in all of these studies since the diagnostic criteria for PCOS has changed over time and currently there is not one singular definition (Supplemental Table 2)[7-9]. Since some of these studies span decades, disentangling how the changing definition of PCOS might have influenced the results of these studies and thus differences between these studies is difficult.

Ovulatory dysfunction is one major component of each the three current definitions of PCOS. Approximately 75-85% of women with PCOS will have clinically evident menstrual dysfunction[32]. Thus, identifying women with long and/or irregular menstrual cycles may be an effective way to identify women with a PCOS phenotype in a population-based study[33].

In addition, longer menstrual cycle length and irregular cycles have been associated with higher androgen levels[10-12] and hyperandrogenism is a major component in all of the current PCOS definitions. Elevated androgen levels have been hypothesized play a role in the etiology of ovarian cancer[34]. Conversely, longer menstrual cycles are more likely to be anovulatory[35], which could reduce ovarian cancer risk. Previous studies that have examined menstrual cycle characteristics have produced conflicting results and used varying definitions of menstrual cycle dysfunction[13-21, 36]. We examined both menstrual cycle irregularity, defined as reporting periods that never became regular, and menstrual cycle length greater than 35 days. While we did not observe an association overall between either of these measures of menstrual cycle dysfunction and ovarian cancer risk, we did observe a significant inverse association between menstrual cycle irregularity and the high grade serous subtype and increased risks for the serous borderline subtypes in specific subgroups (BMI>25 and never users of oral contraceptives). Few previous studies have examined menstrual cycle irregularity by histologic subtype. Consistent with our results, Tung, et al. using a menstrual cycle irregularity definition of a period varying from cycle length by 2 or more days, observed an inverse association between cycle irregularity and ovarian cancer that was stronger for non-mucinous (OR=0.7; 95% CI=0.5-0.9; n=449 cases) vs. mucinous subtypes (OR=0.9; 95% CI=0.6-1.4; n=109 cases), and additionally was strongest among the invasive clear cell subtype (OR=0.3; 95% CI=0.1-0.7; n=48 cases), while a non-significant inverse association was observed for the serous invasive subtype (OR=0.7; 95% CI=0.5-1.1; n=220 cases)[21]. In contrast to our results, the Child Health and Development Studies (CHDS) cohort reported that irregular cycles (defined as cycles >35 days, irregular cycles, oligomenorrhea, or anovulatory cycles) were associated with a non-significant increase in risk of the high grade serous subtype (HR=2.1; 95% CI=0.9-5.0; n=30 cases), but did not report results for other subtypes, likely due to small numbers. Explanations for these differing results may include that the CHDS cohort was compromised of only parous women and few reported oral contraceptive use (4%) and we observed that both parity and oral contraceptive use were modifiers of the menstrual cycle-ovarian cancer association[13].

It is increasingly recognized that ovarian cancer is a group of molecularly and etiologically distinct diseases[37-40] which may explain the differing associations we observed for the high grade serous and serous borderline subtypes. Many high grade serous tumors likely arise from the fallopian tubes[37-40]. The origin of the serous borderline subtype of ovarian cancer is less understood but it has been proposed that some could originate from benign ovarian tumors[41]. The ovary is a major source of the increased androgen production in PCOS and androgen receptors levels have been shown to be higher in benign ovarian and serous borderline tumors compared to serous invasive[42]. In addition, the ovarian epithelial cells may be more exposed to paracrine ovarian androgens[34] than cells in the fallopian tubes. These differences may explain the increased risk found in those with the serous borderline subtype while other systemic effects of PCOS and fewer lifetime ovulatory cycles among women reporting menstrual cycle irregularity may play a role in the decreased risk of high grade serous tumors.

Oral contraceptives have a robust protective effect on ovarian cancer with longer use conferring greater reduction in ovarian cancer risk[43, 44]. This association has been shown to vary by histologic subtype. In a large collaborative analysis of 45 studies OC use was

significantly protective for serous malignant, endometrioid, and clear cell subtypes, was less pronounced and non-significant for the serous borderline subtype, and had little effect on the mucinous subtype[43]. The exact mechanism(s) through which oral contraceptives decrease ovarian cancer risk is not completely understood. However, reducing a women's lifetime ovulations, thus reducing the repeated trauma and repair to the ovarian surface, likely plays a role[45, 46]. Similar to women who use OCs, women with PCOS also have a reduced number of lifetime ovulations which may at least partially explain the inverse associations we observed. Further support for this shared mechanism includes that the histologic subtypes that we observed had the greatest risk reduction with menstrual cycle irregularity were the serous invasive, endometrioid, and clear cell subtypes which is consistent with the histologic subtypes associated with the greatest risk reductions for OC use.

One of the first line treatments for menstrual irregularities in women with PCOS who are not attempting to become pregnant is combined oral contraceptives[47]. We examined whether use of oral contraceptives modified the association between menstrual cycle irregularity and ovarian cancer risk and observed the most significant reduced risk among those who used oral contraceptives for <2 years. While it is not clear why this lower risk was observed among women who took oral contraceptives for a shorter period of time it may be that women who discontinued OC use did so because in these women the OCs were less effective in treating the menstrual cycle irregularities or other clinical features of PCOS (i.e. hirsutism), perhaps representing women with a different/more serious phenotype of the condition. The lack of association observed among those who used OCs for 5 or more years may reflect the strong protective effect of OC use among long-term users obscuring the influence of menstrual cycle irregularity among this group. In contrast, we observed an increased risk of the serous borderline subtype among women who had never used oral contraceptives. While these results are based on small numbers (n=94 cases), the data suggest that the influence of PCOS may be more apparent in the absence of exogenous hormones.

Differences in the association between menstrual cycle irregularity and ovarian cancer risk were also observed by BMI where women with a BMI <25 had an inverse association between menstrual cycle irregularity and ovarian cancer risk while a similar association was not observed among those who were overweight or obese. Some studies have suggested that testosterone levels increase with increasing BMI[48-50] thus the influence of elevated androgens in women with PCOS may be most apparent in thin women as overweight women may have higher levels of these hormones even in the absence of PCOS.

We utilized two different definitions of menstrual cycle dysfunction in our analyses: women who never reported regular menstrual cycles and those reporting an average menstrual cycle length of greater than 35 days. We only observed significant associations among those never reporting regular cycles. Normal ovulation varies over a women's lifetime thus women who reported never having regular menstrual cycles may represent those with more severe cases of menstrual cycle dysfunction and this could explain the stronger associations observed with this definition.

Limitations of our study should be considered. As with any case-control study recall bias is a possibility. However, it is unlikely that participants would recall menstrual cycle characteristics differently by case or control status thus misclassification of these exposures is likely non-differential with respect to the outcome. In addition, recall bias is unlikely to explain the differing associations observed by histologic subtype. With an average time of nine months from cancer diagnosis to study enrollment women with the most aggressive disease may have died before they could be enrolled in the study. This would influence our results only if menstrual cycle characteristics and PCOS were associated with survival.

Our study has several strengths. With a large sample size, including 2041 cases and 2100 controls, we were able to evaluate overall ovarian cancer risk as well as histologic subtypes and potential effect modifiers. Additional strengths include detailed covariate information, high quality information on histologic subtypes, and population based controls.

In conclusion, our findings suggest while that menstrual cycle characteristics did not influence overall ovarian cancer risk they may influence risk of specific ovarian cancer subtypes. Future research in a large collaborative consortium will help clarify these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

PCOS	polycystic ovary syndrome
SHBG	lower sex hormone binding globulin levels
BMI	body mass index
NECC	New England Case-Control Study
OR	odds ratios
CI	confidence intervals
CHDS	Child Health and Development Studies

Novelty and impact

We investigated whether PCOS and related menstrual cycle characteristics were associated with ovarian cancer risk, overall and by histologic subtype. Few ovarian cancer studies of this size have examined these associations by histologic subtype, an important consideration since it is increasingly recognized that ovarian cancer subtypes represent a group of molecularly and etiologically distinct diseases. Our results suggest that menstrual cycle characteristics may influence risk of specific ovarian cancer subtypes.

Table 1

Descriptive characteristics of invasive ovarian cancer cases and controls in the New England Case-Control Study, 1992-2008

Characteristics	Cases (n=2041)	Controls (n=2100)
Study center, n (%)		
Massachusetts	1616 (79.2)	1709 (81.4)
New Hampshire	425 (20.8)	391 (18.6)
Age (years), mean (SD)	52.4 (12.3)	52.3 (12.6)
Age at menarche (years), mean (SD)	12.6 (1.5)	12.7 (1.6)
Oral contraceptive use, n (%)		
Never use	974 (47.7)	766 (36.5)
<5 years	663 (32.5)	703 (33.5)
≥5 years	404 (19.8)	631 (30.1)
Parity, n (%)		
Nulliparous	650 (31.9)	378 (18.0)
′1	289 (14.2)	267 (12.7)
′2	537 (26.3)	664 (31.6)
′3	325 (15.9)	418 (19.9)
4+	240 (11.8)	373 (17.8)
Duration of breastfeeding (months), mean (SD)	5.0 (10.8)	8.4 (14.1)
Premenopausal, n (%)	853 (41.8)	892 (42.5)
Age at menopause (years), mean (SD)	49.3 (5.1)	49.5 (4.8)
Tubal ligation, n (%)	277 (13.6)	419 (20.0)
Female infertility, n (%)	387 (19.0)	395 (18.8)
Number of ovulatory cycles, mean (SD)	373 (116)	348 (121)
BMI (kg/m^2), mean (SD)	26.5 (6.3)	26.0 (5.5)
Family history of ovarian cancer, n (%)	95 (4.7)	54 (2.6)
Self-reported PCOS,[1] n (%)	41 (2.8)	37 (2.3)
Hirsutism, n (%)[2]	153 (10.3)	168 (10.6)
Menstrual cycle length, mean (SD)	28.4 (2.4)	28.6 (2.6)
Menstrual cycle irregularity,[3] n (%)	151 (7.4)	175 (8.3)

[1] Phase 1 not included because question was not directly asked (only asked via infertility diagnoses).

[2] Phase 1 not included because question was not asked.

[3] If periods were reported as never becoming regular.

Table 2

Odds ratios (OR) and 95% confidence intervals (95% CI) of the association between menstrual cycle characteristics and ovarian cancer, overall and by histologic subtype, in the New England Case-Control Study, 1992-2008

	Number of cases	Menstrual cycle irregularity[2]	Cycle length >35 days	Self-reported PCOS[3]
Overall age adjusted	2041	0.88 (0.70-1.10)	0.71 (0.39-1.30)	1.16 (0.74-1.83)
Overall multivariable[1]		0.87 (0.69-1.10)	0.83 (0.44-1.54)	0.97 (0.61-1.56)
Serous borderline	250	1.33 (0.87-2.04)	1.47 (0.50-4.37)	1.19 (0.51-2.77)
Low grade serous invasive	49	0.71 (0.22-2.32)	--[4]	1.09 (0.14-8.29)
High grade serous invasive	846	0.68 (0.49-0.95)	0.94 (0.41-2.13)	0.71 (0.34-1.46)
Mucinous borderline	147	1.51 (0.90-2.52)	--[4]	0.82 (0.24-2.78)
Mucinous invasive	91	1.02 (0.48-2.14)	--[4]	--[4]
Clear cell	116	0.39 (0.14-1.07)	0.80 (0.10-6.13)	1.23 (0.41-3.64)
Endometrioid	331	0.87 (0.56-1.36)	0.87 (0.26-2.97)	0.98 (0.46-2.12)
$P_{heterogeneity}$		0.03	0.89	0.91

[1] Multivariable models adjusted for age, center, study, parity, oral contraceptive use, tubal ligation, and family history of ovarian cancer.

[2] If periods were reported as never becoming regular.

[3] Phase 1 (n=558 cases) not included because question was not directly asked (only asked via infertility diagnoses).

[4] No exposed cases in this subgroup so the effect estimate could not be calculated.

Table 3

Association between menstrual cycle irregularity[1] and ovarian cancer stratified by oral contraceptive use in the New England Case-Control Study, 1992-2008

	Oral Contraceptive use			
	Never	**<5 years**	**≥5 years**	**$P_{interaction}$**
N (cases/controls)	974/766	663/703	404/631	
Overall[2]	1.21 (0.82-1.77)	0.60 (0.41-0.90)	0.90 (0.56-1.44)	0.001
High grade serous invasive[2]	0.92 (0.56-1.51)	0.47 (0.25-0.89)	0.71 (0.33-1.50)	0.06
Serous borderline[2]	3.48 (1.85-6.56)	0.49 (0.20-1.20)	1.14 (0.44-2.91)	0.0003

[1] If periods were reported as never becoming regular.

[2] Models adjusted for age, center, study, parity, tubal ligation, and family history of ovarian cancer.

Table 4

Association between menstrual cycle irregularity[1] and ovarian cancer stratified by body mass index in the New England Case-Control Study, 1992-2008

	Body Mass Index		
	<25	**≥25**	**$P_{interaction}$**
N (cases/controls)	1024/1074	1017/1026	
Overall[2]	0.62 (0.44-0.88)	1.17 (0.85-1.62)	0.006
High grade serous invasive[2]	0.58 (0.35-0.95)	0.85 (0.53-1.37)	0.50
Serous borderline[2]	0.62 (0.29-1.35)	2.29 (1.32-3.98)	0.0008

[1] If periods were reported as never becoming regular.

[2] Models adjusted for age, center, study, parity, oral contraceptive use, tubal ligation, and family history of ovarian cancer.