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A prospective study of leisure-time physical activity and risk of incident epithelial ovarian cancer: impact by menopausal status

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Abstract

Despite multiple hypotheses for a protective effect, epidemiologic findings are inconsistent regarding the association between physical activity and risk of ovarian cancer. Considering physical activity assessment at different times of life, including pre- and postmenopause, may be important for explaining these discrepancies. Therefore, we examined the risk of ovarian cancer according to total, premenopausal and postmenopausal physical activity among 85,462 women from the Nurses' Health Study and 112,679 women from the Nurses' Health Study II. Leisure-time physical activity was prospectively assessed about every 2–4 years using validated questionnaires, and characterized as metabolic equivalent task hours per week (MET-hrs/week), which combines exercise duration and intensity. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for these associations. We identified 815 incident epithelial ovarian cancer cases during 24 years of follow-up. A modestly increased ovarian cancer risk was observed for high levels of total cumulative average physical activity and a suggestively increased risk for low activity. Compared with 3–9 MET-hrs/week, HRs (95% CIs) were 1.26 (1.02, 1.55) for ≥27 MET-hrs/week (equivalent to 1 hr/day of brisk walking) and 1.19 (0.94, 1.52) for <3 MET-hrs/week. This association was limited to premenopausal physical activity (comparable HR [95% CI] of 1.50 [1.13, 1.97] and 1.29 [0.95,

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1.75], respectively). Postmenopausal physical activity was not associated with risk. Our data do not support a protective role of physical activity for ovarian cancer. The increased risk associated with physical activity during premenopausal years and the underlying etiology require further investigation.

Keywords

physical activity; ovarian cancer; menopausal status; luteal progesterone; ovulation

Introduction

Epidemiologic data support the health benefits of physical activity for cardiovascular disease, diabetes, and several types of cancers, including breast, colorectal and endometrial cancer.[1, 2] However, findings for ovarian cancer from >20 studies have been inconsistent. Ovarian cancer is the most lethal gynecological malignancy and the fifth leading cause of cancer death among US women,[3] but the current strategies for prevention are limited. Since physical activity is a modifiable lifestyle factor that may be protective against carcinogenesis through different mechanisms, elucidating this association would be instrumental for understanding the prevention and etiology of ovarian cancer.

To date, eleven case-control studies and thirteen prospective studies have evaluated the association between physical activity and ovarian cancer risk,[4] with significant heterogeneity reported by a recent meta-analysis.[5] Inverse associations were observed in most, but not all case-control studies.[4] Results from prospective studies were inconsistent, with seven studies reporting null associations[6–12] and three larger cohorts[13–15] suggesting an increased risk with higher levels of activity. In addition to recall bias for case-control studies, most previous studies were limited by small case numbers, use of a single assessment of physical activity, and lack of details on the timing, type, and intensity of activity. Given the heterogeneity of ovarian cancer and changes in hormone levels over the life course, it is possible that physical activity may only be relevant for certain ovarian cancer subtypes or during specific life periods.

Despite inconsistent evidence, higher physical activity has been hypothesized to reduce ovarian cancer risk by decreasing circulating estrogen levels in postmenopausal women, reducing obesity and inflammation, and strengthening immunity.[2] Particularly, very vigorous activity may suppress ovulation, a key risk factor for ovarian cancer,[16] in premenopausal women, although recent evidence suggests that higher activity may increase fertility.[17] This apparent dichotomy may be clarified by evaluating the unclear association between physical activity and luteal progesterone,[18–21] which rises after ovulation. Importantly, progesterone has seemingly opposing roles in ovarian cancer. While exposure to progesterone may inhibit proliferation and induce apoptosis of ovarian epithelial cells,[22] higher luteal progesterone levels suggest a greater likelihood of a successful ovulation event.[23] Thus, it is unclear whether ovulation-related pathways can potentially explain the association between physical activity and ovarian cancer.

Therefore, we examined the associations between physical activity and ovarian cancer risk in two large cohorts of US women. Specifically, we calculated cumulative average activity levels in the premenopausal and postmenopausal period separately, since activity during these periods may have different biologic impacts on ovarian cancer development. We also explored the ovulation-related hypothesis by investigating the relationship of physical activity with luteal progesterone among a subset of premenopausal women.

Methods

Study population

The Nurses' Health Study (NHS) was comprised of 121,700 US female registered nurses aged 30–55 at study initiation in 1976. The Nurses' Health Study II (NHSII), a similar cohort of younger women, commenced in 1989 among 116,430 nurses, aged 25–42. All participants were prospectively followed by biennial questionnaires to update their information on disease diagnoses, health conditions and lifestyle factors.

For this study, the start of follow-up was 1986 in the NHS and 1989 in the NHSII, when comprehensive information on various leisure-time activities was first collected. Eligible women completed at least one physical activity assessment during follow-up. Women were excluded if they had a bilateral oophorectomy, pelvic irradiation, or a prior diagnosis of cancer, other than non-melanoma skin cancer, before the return of the first physical activity questionnaire, leaving 85,462 in the NHS and 112,679 in the NHSII for analysis.

Between 1996 and 1999, 18,521 premenopausal women who had not taken hormones, been pregnant or lactating within the previous 6 months provided a blood sample timed within the mid-luteal phase (estimated 7–9 days before the onset of the next cycle) of their menstrual cycle. Women returned a postcard with the date of their next menstrual period to accurately date the luteal sample. The current analysis included 1,475 women with physical activity assessments as well as timed luteal blood collections 5–12 days prior to the start of the next cycle, who were controls in nested case-control studies on plasma steroid hormones and breast cancer or endometriosis risk. The study protocol was approved by the institutional review board of the Brigham and Women's Hospital.

Physical activity assessment

Assessments of physical activity were administered about every 2–4 years. Women were asked about their average time per week spent in each of the eight common leisure-time activities, including walking, jogging, running, bicycling, swimming, tennis, squash/racquetball, and calisthenics/aerobics/rowing machine. We also collected information on women's usual walking pace and the number of flights of stairs they climbed daily. A metabolic equivalent task (MET) score was assigned to each activity to quantify its energy expenditure, and MET-hours per week (MET-hrs/week) were calculated for each activity by multiplying the corresponding MET score and the reported hours per week spent in that activity.[24] Total physical activity was assessed by summing MET-hrs/week over all activities. Activities with a MET score ≥6 were defined as vigorous; other activities, mainly walking, were considered to be moderate.

The physical activity questionnaire was validated in a representative sample of 147 women.[25] The physical activity levels reported by this questionnaire were highly correlated with those assessed by past-week recalls (r=0.79). The moderate/vigorous activity reported by questionnaire had a reasonable correlation compared to prospectively recorded activity diaries over a 1-year period (r=0.62).

Ovarian cancer and death assessment

Pathology reports and related medical records were obtained for all incident epithelial ovarian cancer cases reported on each biennial questionnaire. A gynecologic pathologist blinded to women's exposure status reviewed the pathology reports to confirm the diagnosis, as well as to identify tumor characteristics including morphology, stage, histology, and invasiveness. Deaths of cohort members and the related cause of death were identified by family members, the US Postal Service, or the National Death Index. In a subset of 215 ovarian cancer cases, concordance between reviews of pathology reports and surgical pathology slides was 98% for invasiveness and 83% for histologic type.[26]

Statistical analysis

Person-time was calculated from the return date of the first completed physical activity questionnaire to the date of any cancer diagnosis (except non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up (NHS: June 2010; NHSII: June 2011), whichever came first. Women only contributed person-time for follow-up periods in which they provided physical activity information. Activity data from the most recent assessment were carried forward when physical activity was not asked on certain questionnaires. As participation in leisure-time physical activity could be affected by preclinical symptoms of ovarian cancer, we included a latency period of 2–4 years between physical activity assessment and the disease follow-up period. For example, we used activity measures in 1986 to evaluate disease incidence in 1988–1990, measures in 1988 for incidence in 1990–1992, and so on.

We used Cox proportional hazards model with time-varying variables to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cancer according to various measures of physical activity, stratified by age and calendar years. In multivariable analysis, we adjusted for menopausal status, parity, duration of oral contraceptive (OC) use, duration of postmenopausal hormone (PMH) use by type, history of tubal ligation, history of hysterectomy, family history of breast cancer or ovarian cancer, caffeine intake, and lactose intake. Because physical activity may influence ovarian cancer through its strong correlation with body mass index (BMI), which is also a potential risk factor for ovarian cancer, we adjusted for BMI in a separate model. In pooled analyses combining NHS and NHSII, we additionally stratified by cohort. Random effects meta-analysis was used to assess heterogeneity between the two studies.

To assess the impact of timing of physical activity on ovarian cancer risk, we examined activity in various time periods, including baseline activity (i.e., the first reported physical activity), most recent activity, and cumulative average (i.e., average of all previous activity measures since baseline), with ovarian cancer. We further calculated cumulative average

activity during premenopausal and postmenopausal periods separately. Women who were postmenopausal at baseline or had no premenopausal activity assessment were excluded from the analysis of premenopausal activity; the follow-up for the postmenopausal activity analysis began at the time of menopause. Physical activity was assessed by MET-hrs/week in all analyses unless otherwise stated, and modeled in five categories to allow for nonlinear associations (<3, 3–<9 [reference], 9–<18, 18–<27 and ≥27 MET-hrs/week).

We conducted several *post hoc* analyses to examine the association with cumulative average premenopausal activity in detail. First, we examined the relationship of premenopausal activity with ovarian cancer cases diagnosed during premenopause or postmenopause separately. Second, we evaluated whether the association differed by activity intensity (i.e., vigorous and moderate). Third, we examined whether the association differed by BMI (<25, ≥25 kg/m^2) or OC use (ever, never). Stratified analyses were performed within categories of BMI or OC use, and a likelihood ratio test comparing the models with versus without the interaction terms was used to assess statistical significance. Fourth, we assessed whether associations differed by histologic subtype (serous/poorly differentiated, endometrioid, other subtypes) or by tumor aggressiveness (fatal within 3 years of diagnosis or not) using competing risks Cox models.[27]

As progesterone data were pooled from seven assay batches, we recalibrated the levels using the average batch method to account for laboratory variation across studies,[28] adjusting for age, BMI, duration of OC use, parity, family history of breast or ovarian cancer, batch, and blood collection characteristics including luteal day of the blood draw, time of day and fasting status at blood collection. We used generalized linear models to evaluate the association of cumulative average premenopausal activity (through 1997) with luteal progesterone levels. Least squares means of progesterone levels were computed for each category, and median MET-hrs/week of the categories were modeled continuously to test for a linear trend. The multivariable model adjusted for the same set of covariates as in the batch recalibration. We also stratified our analyses by BMI (<25, ≥25 kg/m^2) and tested for interaction using multiplicative terms and a likelihood ratio test. All analyses were performed in SAS version 9.3 (Cary, NC, USA).

Results

A total of 815 histologically-confirmed ovarian cancer cases were identified during 24 years of follow-up (2,860,718 person-years). At the mid-point of follow-up, the mean age was 66 years in the NHS (97% postmenopausal) and 46 years in the NHSII (15% postmenopausal) (Table 1). Physically active women were more likely to have ever used OC or PMH, and have lower caffeine, but higher lactose, intake. There was a graded decrease in BMI with increasing activity levels.

In the pooled analysis, compared to women with 3–9 MET-hrs/week of total cumulative average activity, the multivariable-adjusted HRs (95% CIs) were 1.19 (0.94, 1.52) for inactive women with <3 MET-hrs/week, and 1.08 (0.88, 1.31), 1.22 (0.97, 1.52), and 1.26 (1.02, 1.55) for more active women with 9–18, 18–27 and ≥27 MET-hrs/week, respectively (Table 2). Twenty-seven MET-hrs/week is approximately equivalent to 1 hr/day of brisk

walking. This association appeared stronger in the NHSII, with HR (95% CI) of 1.55 (0.94, 2.55) for <3 and 1.76 (1.18, 2.62) for ≥27, compared to 3–9 MET-hrs/week (p-heterogeneity by cohort=0.13). Covariate adjustments for ovarian cancer risk factors or BMI had little influence on the risk estimates. For total baseline activity, we only observed an increased risk for higher, but not lower, levels of activity in both cohorts (pooled multivariable HR for ≥27 versus <3 MET-hrs/week: 1.39; 95% CI: 1.12, 1.72; p for trend<0.01). However, no clear associations were observed for total recent activity.

We then evaluated cumulative average physical activity during premenopausal and postmenopausal years separately in relation to ovarian cancer risk (Table 3). High levels of premenopausal activity were associated with significantly increased risk of ovarian cancer. Low activity levels were also associated with suggestively higher risk, although the association was not statistically significant. For example, compared to a premenopausal activity level of 3–9 MET-hrs/week, the multivariable-adjusted HRs (95% CIs) were 1.29 (0.95, 1.75) for <3 MET-hrs/week, and 1.24 (0.95, 1.63), 1.06 (0.76, 1.47) and 1.50 (1.13, 1.97) for 9–18, 18–27 and ≥27 MET-hrs/week, respectively, for all cases combined. Similar trends were observed when we examined the associations of premenopausal activity with premenopausal and postmenopausal cases individually. There was a significant positive association between premenopausal activity and premenopausal ovarian cancer risk (HR for ≥27 versus 3–9 MET-hrs/week: 1.66; 95% CI: 1.11, 2.49), while the positive association for premenopausal activity with postmenopausal ovarian cancer risk was weaker and did not reach statistical significance (comparable HR: 1.34; 95% CI: 0.91, 1.99). Postmenopausal physical activity was not significantly associated with ovarian cancer risk.

When further examining premenopausal activity, higher levels of both moderate and vigorous activity were suggestively associated with increased ovarian cancer risk, although the associations were weaker than that for total activity (Supplementary Table 1). We did not observe a statistically significant difference in the association across strata of BMI (p for interaction=0.12) or OC use (p for interaction=0.69), though the positive association for higher premenopausal activity was only apparent among overweight or obese women or among women who never used OCs (Supplementary Table 2). Furthermore, the association between premenopausal activity and ovarian cancer risk suggestively varied by histologic subtype (p for heterogeneity=0.06, Table 4). While a significantly increased risk for high activity level was observed for serous/poorly differentiated tumors (HR for ≥27 versus 3–9 MET-hrs/week: 1.50; 95% CI: 1.05, 2.15), low physical activity was only associated with a significantly higher risk of endometrioid tumors (HR for <3 versus 3–9 MET-hrs/week: 2.43; 95% CI: 1.17, 5.02). Other tumor subtypes were not significantly associated with risk, and there was no difference in association by tumor aggressiveness (p for heterogeneity=0.93).

The mean age of 1,475 women with luteal progesterone data was 44 years. There was a significant positive trend between premenopausal physical activity and luteal progesterone (p for trend=0.01, Table 5), which was attenuated in multivariable analysis, particularly after adjusting for age and BMI (p for trend=0.29). Stratified analysis suggested a possible difference in the association by BMI (p for interaction=0.07). The positive trend was more

evident in normal or underweight women, who on average had significantly higher luteal progesterone levels than overweight or obese women ($p<0.0001$).

Discussion

In two large prospective cohort studies, women with very low or higher levels of leisure-time activity had a modestly increased risk of ovarian cancer. However, premenopausal, but not postmenopausal physical activity, was associated with risk. Interestingly, we observed a positive association of higher premenopausal activity with serous/poorly differentiated tumors, whereas premenopausal low physical activity levels were only significantly associated with increased risk of endometrioid tumors, even after adjustment of BMI. To our knowledge, this is one of the largest longitudinal studies to date on this relationship that assessed long-term physical activity patterns over different potential periods of susceptibility during the life course.

An earlier study examining this association in 377 cases in the NHS suggested a possible increased risk of ovarian cancer with higher physical activity.[13] With more cases, follow-up, and the addition of NHSII, we observed a modest elevation in risk not only for higher levels but also for very low levels of physical activity. More importantly, our results highlight that the association was specific to physical activity before menopause. This may explain the somewhat stronger positive association in our earlier study, which included a greater proportion of premenopausal cases. Results from two other prospective studies have also suggested a positive association between physical activity and ovarian cancer risk,[14, 15] although one of them was conducted among postmenopausal women.[14] By contrast, some prospective studies have reported no association.[6–11] This may be because many large cohort studies have primarily evaluated older or postmenopausal women,[8–11] which was not associated with risk in our study. No association was observed in several studies evaluating activities in adolescence, early adulthood and middle age;[6, 8, 9] however, these measures were assessed retrospectively by recalling early-life physical activity decades later.

Ovulation only occurs in premenopausal women, and factors leading to fewer ovulatory cycles (e.g., OC use) have been consistently associated with lower risk of ovarian cancer. It is thought that vigorous physical activity disrupts female reproductive function and suppresses ovulation, and therefore was hypothesized to be protective for ovarian cancer. However, these observations were based on women participating in very intense or frequent exercise (e.g., marathon runners),[29–33] which may not be generalizable to most US women. In fact, mechanistic studies suggest that energy restriction after extremely strenuous exercise may be responsible for exercise-induced menstrual disorders;[34–36] this is unlikely to occur in US women who generally have a caloric surfeit. Intervention studies also reported no menstrual cycle disturbances with recreational running for 4 months to 1 year.[37, 38] Further, in the NHSII, higher levels of vigorous physical exercise were associated with a significantly reduced risk of ovulatory infertility, which is consistent with our observation of a suggestive positive association between physical activity and luteal progesterone.[17] However, this association was modest and may be due to chance given that a single timed luteal progesterone measure may not reliably reflect anovulation over a longer period of time.[39] Previous studies with repeated progesterone measures observed a higher prevalence

of luteal phase deficiency and anovulation among recreational runners.[19–21] Also, recreational runners tended to revert back and forth frequently and intermittently between ovulatory and anovulatory cycles, which was likely to be modulated by changes in energy balance.[19] Of note, the activity level in our population was very modest compared to recreational running. For example, median level of our highest activity category was 38 MET-hrs/week, compared to 84 MET-hrs/week for 1-hr/day of recreational running. Additional studies are needed to understand the long-term impact of very moderate activity on reproductive function, which may help elucidate the mechanisms underlying the association between physical activity and ovarian cancer.

Our data also suggest that cumulative average, but not recent activity, was associated with ovarian cancer risk. This implies that the long-term physical activity measures are important for studying ovarian cancer risk. The cumulative effects of long-term activity on ovulation (e.g., lifetime ovulatory cycles) are more likely to be observable than short-term or recent activity. Also, there was some evidence for a suggestively positive association between premenopausal activity and postmenopausal risk of ovarian cancer. Although this association was weaker than the comparable association for premenopausal ovarian cancer risk, the results suggest that premenopausal physical activity may have a prolonged effect on postmenopausal risk of ovarian cancer that may wane with time; however we did not have power to assess this. This is consistent with previous findings that the protective effect of several ovulation-related factors during premenopausal period, such as OC use, parity and lactation, can persist into postmenopausal years.[16, 40] Further, although not statistically significant, the association was suggestively stronger among women who never used OCs. Since OCs suppress ovulation, activity in women who never used OCs may be more likely to influence risk through increasing ovulation. Finally, we observed a consistent positive association with baseline activity, which was more likely to reflect women's premenopausal activity.

We also reported potential heterogeneity by histologic subtype - the increased risk for higher premenopausal activity was limited to serous/poorly differentiated tumors, while lower premenopausal activity was only associated with endometrioid tumors. Four previous prospective studies evaluated the association by histologic subtype.[9–11, 13] Of these, three examined the association specific to serous versus non-serous tumors,[9, 11, 13] with two suggesting an increased risk of serous ovarian cancer with higher levels of activity;[11, 13] only one study was able to evaluate endometrioid subtype individually, and observed no association.[10] Given the limited evidence available and the small number of endometrioid cases, further investigation is required to clarify these subtype-specific associations. However, our results for endometrioid tumors, which are histologically similar to endometrial tissue, are consistent with the well-established positive associations of physical inactivity with endometrial cancer.[41] Since the inclusion of BMI in the model did not substantially alter the risk estimates, other factors besides obesity, such as sedentary behaviors and inflammation,[8, 9, 42, 43] may also play a role in explaining this association.

This study has some limitations. Despite good reliability of our physical activity measure, non-differential measurement error may lead to underestimation of the association. Also, the assessment did not fully capture physical activity in occupational settings, potentially

leading to additional misclassification. Further, since some analyses (e.g., by histology) were based on a small number of cases, the possibility of chance findings cannot be ruled out. Future prospective studies or pooling projects with larger sample size are needed to confirm these findings. Finally, the generalizability of the results may be limited due to relatively homogeneous study population of predominantly white registered nurses.

The strengths of the study include very long follow-up, a population encompassing a wide age range, a substantial number of cases, and repeated measurements of physical activity, which allowed us to assess recent and long-term activity as well as activity during specific life periods. We were able to control for confounding and evaluate effect modification using detailed and regularly updated data on ovarian cancer risk factors and lifestyle factors. Furthermore, the timed luteal progesterone data available in a subset of premenopausal women lent support to our findings and provided insight into the ovulation-related hypothesis.

In summary, our data do not support a protective role of physical activity for ovarian cancer. Given the substantial health benefits for other more prevalent chronic diseases, the modestly increased ovarian cancer risk associated with higher physical activity observed in this study would have little impact on current exercise guidelines. However, our findings provide important etiologic insight regarding the potential interplay between physical activity and certain premenopausal factors, such as ovulation, on ovarian cancer risk, which needs further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What's new?

Previous studies reported mixed associations between physical activity and ovarian cancer, including positive associations in some prospective studies. In this study, which represents one of the largest investigations to date on this association, we observed an increased ovarian cancer risk for both low and high levels of premenopausal physical activity. Postmenopausal activity, however, was not associated with risk. Further analyses on histologic subtype and luteal progesterone suggest that obesity and ovulation may play a role in the associations for low and high activity, respectively.

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Table 1

Age-standardized characteristics of the study population at the midpoint of follow-up in the Nurses' Health Study (2000) and Nurses' Health Study II (2001)

	Nurses' Health Study (2000)			Nurses' Health Study II (2001)		
	Total cumulative average leisure-time physical activity, MET-h/week					
	<3	9 to <18	≥27	<3	9 to <18	≥27
Subjects (n)	4734	15378	9365	5124	19928	16567
Cumulative average activity, MET-h/week	1.8 (0.8)[1]	13.2 (2.6)	40.1 (12.5)	1.8 (0.8)	13.2 (2.6)	42.3 (14.2)
Recent activity, MET-h/week	1.7 (2.1)	13.5 (11.0)	39.9 (25.1)	2.1 (2.6)	15.0 (12.5)	40.0 (26.7)
Baseline activity, MET-h/week	1.9 (2.2)	11.0 (9.9)	33.4 (23.8)	2.7 (2.6)	15.6 (12.7)	43.7 (27.4)
Age, years	66.3 (7.2)	66.0 (7.1)	66.0 (7.0)	47.3 (4.6)	46.5 (4.6)	45.9 (4.7)
Ever OC use, %	47	49	50	85	85	85
Duration of OC use, months[2]	49.9 (45.9)	51.0 (46.1)	50.8 (46.7)	67.5 (60.3)	67.7 (59.2)	70.2 (62.3)
Postmenopausal, %	97	98	98	17	15	15
Ever estrogen PMH use, %[3]	19	20	21	5	4	4
Duration of estrogen-only PMH use, months[2]	86.6 (78.4)	93.8 (80.6)	94.0 (80.7)	2.1 (2.4)	1.9 (1.7)	2.0 (1.9)
Ever estrogen-progestin PMH use, %[3]	32	37	39	51	56	56
Duration of estrogen-progestin PMH use, months[2]	61.4 (47.6)	65.2 (48.2)	67.0 (48.7)	3.0 (2.4)	2.7 (2.3)	2.6 (2.3)
History of tubal ligation, %	20	21	21	26	24	22
History of hysterectomy, %	23	23	21	9	9	9
Family history of breast or ovarian cancer, %	19	20	20	13	14	14
Parous, %	95	95	94	85	84	77
Number of children in parous women	3.3 (1.6)	3.2 (1.5)	3.2 (1.5)	2.3 (1.0)	2.3 (0.9)	2.3 (0.9)
Caffeine, mg/day	233.3 (225.9)	208.8 (201.7)	203.9 (194.4)	234.5 (224.4)	226.6 (209.4)	226.9 (206.1)
Lactose, g/day	14.8 (12.6)	16.4 (12.1)	16.7 (12.1)	15.8 (13.2)	17.7 (13.1)	18.5 (13.4)
Body mass index, kg/m^2	28.9 (6.7)	26.7 (5.0)	25.0 (4.3)	29.5 (8.1)	26.8 (6.1)	25.1 (5.1)

[1] Mean (SD) for all such values

[2] Duration among ever users

[3] Among postmenopausal women

Table 2

Hazard ratios and 95% confidence intervals for the association between physical activity and incident epithelial ovarian cancer in Nurses' Health Study (1986–2010) and Nurses' Health Study II (1989–2011)

	Total physical activity in MET-hours/week, HR (95% CI)				
	<3	**3 – <9**	**9 – <18**	**18 – <27**	**≥27**
Baseline activity[1]					
NHS (N=601 cases)					
Cases/person-years	142/328,234	164/329,409	121/240,787	66/137,509	108/187,308
Age-adjusted	0.87 (0.69, 1.09)	1.00 (ref)	0.99 (0.78, 1.25)	0.95 (0.71, 1.27)	1.14 (0.89, 1.45)
Multivariable[2]	0.87 (0.69, 1.09)	1.00 (ref)	0.98 (0.78, 1.24)	0.94 (0.71, 1.26)	1.13 (0.88, 1.44)
Multivariable + BMI[3]	0.87 (0.69, 1.09)	1.00 (ref)	0.98 (0.77, 1.24)	0.94 (0.70, 1.25)	1.12 (0.87, 1.43)
NHSII (N=214 cases)					
Cases/person-years	28/244,747	45/377,475	45/351,689	25/223,044	71/440,517
Age-adjusted	0.93 (0.58, 1.49)	1.00 (ref)	1.07 (0.71, 1.62)	0.94 (0.58, 1.54)	1.41 (0.97, 2.06)
Multivariable[2]	0.94 (0.59, 1.52)	1.00 (ref)	1.08 (0.71, 1.63)	0.91 (0.56, 1.49)	1.35 (0.92, 1.96)
Multivariable + BMI	0.92 (0.57, 1.47)	1.00 (ref)	1.11 (0.73, 1.68)	0.96 (0.59, 1.57)	1.46 (1.00, 2.13)
Pooled (N=815 cases)					
Age-adjusted	0.88 (0.72, 1.08)	1.00 (ref)	1.00 (0.82, 1.23)	0.94 (0.74, 1.21)	1.22 (1.00, 1.49)
Multivariable[2]	0.89 (0.72, 1.09)	1.00 (ref)	1.00 (0.82, 1.23)	0.94 (0.73, 1.20)	1.20 (0.98, 1.47)
Multivariable + BMI	0.88 (0.72, 1.08)	1.00 (ref)	1.01 (0.82, 1.24)	0.94 (0.74, 1.21)	1.22 (1.00, 1.50)
Recent activity[4]					
NHS (N=601 cases)					
Cases/person-years	133/267,401	149/292,538	120/255,470	76/157,266	123/250,572
Age-adjusted	0.97 (0.77, 1.23)	1.00 (ref)	0.90 (0.71, 1.15)	0.93 (0.71, 1.23)	0.95 (0.75, 1.21)
Multivariable[2]	0.98 (0.78, 1.24)	1.00 (ref)	0.91 (0.71, 1.15)	0.93 (0.70, 1.23)	0.94 (0.74, 1.20)
Multivariable + BMI	0.98 (0.77, 1.24)	1.00 (ref)	0.90 (0.71, 1.15)	0.92 (0.70, 1.22)	0.93 (0.73, 1.18)
NHSII (N=214 cases)					
Cases/person-years	39/278,823	45/376,775	42/353,913	34/221,238	54/406,722
Age-adjusted	1.11 (0.72, 1.70)	1.00 (ref)	1.01 (0.66, 1.54)	1.29 (0.82, 2.01)	1.13 (0.76, 1.69)
Multivariable[2]	1.10 (0.71, 1.69)	1.00 (ref)	0.99 (0.65, 1.51)	1.27 (0.81, 1.99)	1.09 (0.73, 1.62)

	Total physical activity in MET-hours/week, HR (95% CI)				
	<3	**3 – <9**	**9 – <18**	**18 – <27**	**≥27**
Multivariable + BMI	1.04 (0.68, 1.61)	1.00 (ref)	1.05 (0.68, 1.60)	1.38 (0.88, 2.16)	1.23 (0.82, 1.84)
Pooled (N=815 cases)					
Age-adjusted	1.01 (0.82, 1.24)	1.00 (ref)	0.93 (0.75, 1.14)	1.02 (0.80, 1.29)	0.99 (0.81, 1.22)
Multivariable[2]	1.01 (0.82, 1.24)	1.00 (ref)	0.93 (0.75, 1.14)	1.02 (0.80, 1.29)	0.98 (0.80, 1.21)
Multivariable + BMI	1.00 (0.81, 1.23)	1.00 (ref)	0.94 (0.76, 1.16)	1.03 (0.81, 1.31)	1.01 (0.82, 1.24)
Cumulative average					
NHS (N=601 cases)					
Cases/person-years	79/177,319	147/326,958	163/325,827	105/182,010	107/211,133
Age-adjusted	1.09 (0.83, 1.44)	1.00 (ref)	1.07 (0.86, 1.34)	1.23 (0.96, 1.59)	1.10 (0.86, 1.41)
Multivariable[2]	1.11 (0.84, 1.46)	1.00 (ref)	1.07 (0.85, 1.33)	1.22 (0.95, 1.57)	1.09 (0.85, 1.40)
Multivariable + BMI	1.10 (0.83, 1.45)	1.00 (ref)	1.07 (0.85, 1.33)	1.21 (0.94, 1.56)	1.08 (0.83, 1.38)
NHSII (N=214 cases)					
Cases/person-years	26/159,552	41/383,431	49/424,901	33/264,760	65/404,827
Age-adjusted	1.64 (1.00, 2.69)	1.00 (ref)	1.08 (0.71, 1.63)	1.17 (0.74, 1.86)	1.63 (1.10, 2.42)
Multivariable[2]	1.62 (0.99, 2.65)	1.00 (ref)	1.06 (0.70, 1.60)	1.13 (0.71, 1.79)	1.55 (1.04, 2.29)
Multivariable + BMI	1.55 (0.94, 2.55)	1.00 (ref)	1.11 (0.73, 1.69)	1.22 (0.77, 1.94)	1.76 (1.18, 2.62)
Pooled (N=815 cases)					
Age-adjusted	1.20 (0.94, 1.52)	1.00 (ref)	1.07 (0.88, 1.30)	1.21 (0.97, 1.51)	1.24 (1.01, 1.53)
Multivariable[2]	1.21 (0.95, 1.54)	1.00 (ref)	1.06 (0.87, 1.30)	1.20 (0.96, 1.50)	1.22 (0.99, 1.51)
Multivariable + BMI	1.19 (0.94, 1.52)	1.00 (ref)	1.08 (0.88, 1.31)	1.22 (0.97, 1.52)	1.26 (1.02, 1.55)

[1] Defined as the first reported physical activity measure during the study follow-up

[2] Stratified by age, calendar years and cohort (for pooled analysis), and adjusted for menopausal status (premenopausal, postmenopausal), duration of oral contraceptive use (never, <1, 1–5, >5 years), parity (nulliparous, 1, 2, 3, >3 children), history of tubal ligation (yes, no), history of hysterectomy (yes, no), duration of postmenopausal hormone use by type (never, <5, 5–10, >10 years for estrogen only and estrogen plus progesterone separately), family history of breast or ovarian cancer (yes, no), cumulative average intake of lactose and caffeine (in quintiles plus a missing indicator)

[3] BMI was evaluated as <20, 20 to <25, 25 to <30, ≥30 kg/m^2

[4] Physical activity 2–4 years prior to ovarian cancer diagnosis

Table 3

Hazard ratios and 95% confidence intervals for the association between cumulative average physical activity during premenopausal and postmenopausal periods and incident epithelial ovarian cancer in Nurses' Health Study (1986–2010) and Nurses' Health Study II (1989–2011)

	Physical activity in MET-hours/week, HR (95% CI)				
	<3	**3 – <9**	**9 – <18**	**18 – <27**	**≥27**
	Premenopausal physical activity				
All cases (N=462)					
Cases, n	74	100	120	60	108
Age-adjusted	1.31 (0.97, 1.78)	1.00 (ref)	1.24 (0.95, 1.61)	1.07 (0.77, 1.47)	1.48 (1.12, 1.95)
Multivariable[1]	1.30 (0.96, 1.76)	1.00 (ref)	1.23 (0.94, 1.60)	1.04 (0.76, 1.44)	1.43 (1.09, 1.89)
Multivariable + BMI	1.29 (0.95, 1.75)	1.00 (ref)	1.24 (0.95, 1.63)	1.06 (0.77, 1.47)	1.50 (1.13, 1.97)
Premenopausal cases (N=209)					
Cases, n	30	42	52	26	59
Age-adjusted	1.35 (0.84, 2.18)	1.00 (ref)	1.19 (0.79, 1.79)	1.03 (0.63, 1.68)	1.60 (1.07, 2.39)
Multivariable[2]	1.34 (0.83, 2.16)	1.00 (ref)	1.16 (0.77, 1.75)	0.99 (0.61, 1.62)	1.51 (1.01, 2.26)
Multivariable + BMI	1.32 (0.81, 2.12)	1.00 (ref)	1.19 (0.79, 1.80)	1.04 (0.64, 1.71)	1.66 (1.11, 2.49)
Postmenopausal cases (N=253)					
Cases, n	44	58	68	34	49
Age-adjusted	1.29 (0.87, 1.92)	1.00 (ref)	1.29 (0.90, 1.84)	1.14 (0.74, 1.75)	1.38 (0.93, 2.03)
Multivariable[3]	1.26 (0.85, 1.88)	1.00 (ref)	1.28 (0.90, 1.83)	1.10 (0.72, 1.69)	1.35 (0.92, 1.99)
Multivariable + BMI	1.25 (0.84, 1.86)	1.00 (ref)	1.28 (0.89, 1.82)	1.09 (0.71, 1.68)	1.34 (0.91, 1.99)
	Postmenopausal physical activity				
Postmenopausal cases (N=574)					
Cases, n	77	138	148	101	110
Age-adjusted	1.07 (0.80, 1.41)	1.00 (ref)	1.02 (0.81, 1.29)	1.20 (0.93, 1.56)	1.04 (0.81, 1.34)
Multivariable[3]	1.07 (0.81, 1.42)	1.00 (ref)	1.01 (0.80, 1.28)	1.18 (0.91, 1.53)	1.03 (0.80, 1.33)
Multivariable + BMI	1.05 (0.79, 1.40)	1.00 (ref)	1.02 (0.80, 1.28)	1.18 (0.91, 1.53)	1.03 (0.80, 1.33)

[1] Stratified by age, calendar years and cohort, and adjusted for menopausal status at ovarian cancer diagnosis, duration of OC use, parity, history of tubal ligation, history of hysterectomy, duration of PMH use by type, family history of breast or ovarian cancer, cumulative average intake of lactose and caffeine

[2] Accounted for the variables in 1 except menopausal status at ovarian cancer diagnosis and duration of PMH use by type

[3] Accounted for the variables in 1 except menopausal status at ovarian cancer diagnosis

Table 4

Hazard ratios and 95% confidence intervals for the association between premenopausal physical activity and incident epithelial ovarian cancer by ovarian tumor histologic subtype and aggressiveness

	Premenopausal physical activity in MET-hours/week, HR (95% CI)					*p for heterogeneity*
	<3	**3 – <9**	**9 – <18**	**18 – <27**	**≥27**	
Histologic subtype						
Serous or poorly differentiated (N=265)						
Cases, n	34	60	81	29	61	
Multivariable HR[1]	0.96 (0.63, 1.46)	1.00 (ref)	1.46 (1.04, 2.04)	0.91 (0.59, 1.42)	1.50 (1.05, 2.15)	
Endometrioid (N=75)						
Cases, n	17	13	15	12	18	0.06
Multivariable HR[1]	2.43 (1.17, 5.02)	1.00 (ref)	1.19 (0.56, 2.50)	1.63 (0.74, 3.57)	1.84 (0.90, 3.78)	
Other subtypes (N=122)						
Cases, n	23	27	24	19	29	
Multivariable HR[1]	1.64 (0.94, 2.87)	1.00 (ref)	0.90 (0.52, 1.56)	1.21 (0.67, 2.19)	1.39 (0.82, 2.36)	
Tumor aggressiveness						
Rapidly fatal tumors (N=116)						
Cases, n	22	25	28	13	28	
Multivariable HR[1]	1.44 (0.81, 2.57)	1.00 (ref)	1.23 (0.72, 2.11)	1.01 (0.52, 1.97)	1.72 (1.00, 2.96)	
Less fatal tumors (N=346)						0.93
Cases, n	52	75	92	47	80	
Multivariable HR[1]	1.26 (0.88, 1.80)	1.00 (ref)	1.27 (0.94, 1.73)	1.12 (0.78, 1.62)	1.45 (1.06, 2.00)	

[1] Stratified by age, calendar years and cohort, and adjusted for menopausal status, duration of oral contraceptive use, parity, history of tubal ligation, history of hysterectomy, duration of postmenopausal hormone use by type, family history of breast or ovarian cancer, cumulative average intake of lactose and caffeine, and body mass index

Table 5

Luteal phase progesterone levels according to premenopausal physical activity levels among premenopausal women in the Nurses' Health Study II

	Premenopausal physical activity in MET-hours/week					p for trend
	<3	**3 – <9**	**9 – <18**	**18 – <27**	**≥27**	
N	122	361	390	267	335	
	Least squares means of progesterone[1] (ng/mL)					
Unadjusted	14.7	15.9	16.1	17.0	16.9	0.01
Multivariable[2]	13.6	14.3	14.4	15.1	14.6	0.29
BMI<25kg/m^2	14.1	14.9	15.5	17.0	16.2	0.04
BMI≥25kg/m^2	12.9	14.2	13.7	12.6	13.3	0.42
p for interaction			0.07			

[1] Recalibrated using the average batch method

[2] Adjusted for age, BMI, time of the day at blood collection, fasting status, luteal days at blood collection, duration of past oral contraceptive use, parity, family history of breast or ovarian cancer, and assay batch