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Anthropometric measures and risk of epithelial ovarian cancer: results from the Nurses' Health Study

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Abstract

Epidemiologic evaluations of the relationship between anthropometry and ovarian cancer risk have not been conclusive. Using data collected from two large cohorts, the Nurses' Health Study (NHS) and NHSII, we prospectively evaluated the association between waist and hip circumference, the waist-to-hip ratio (WHR), and body mass index (BMI) with risk of epithelial ovarian cancer. Women completed biennial questionnaires assessing ovarian cancer risk factors beginning in 1976 (NHS) and 1989 (NHSII). For the WHR and BMI analyses, 333 and 862 confirmed cases were identified, respectively, through June 1, 2006 (NHS) and June 1, 2005 (NHSII). WHR and waist circumference were not associated with risk (*P*-trend=0.63 and 0.65, respectively). There was evidence for a decreased risk with increasing hip circumference among post-(*P*-trend=0.03), but a suggestive positive association among premenopausal women (*P*-trend=0.04) (*P*-interaction = 0.01). The hazard ratios comparing the highest versus lowest quintile of hip circumference among pre- and postmenopausal women were 1.54 (95% confidence interval [CI]=0.45–5.23) and 0.66 (95% CI=0.37–1.16), respectively. BMI was not clearly associated with risk in pre- or postmenopausal women. Results from this large prospective study suggest that hip circumference could be a possible risk factor for premenopausal ovarian cancer, but may reduce risk of postmenopausal ovarian cancer. The differential effect of hip circumference based on menopausal status requires further confirmation.

Keywords

cancer; BMI; waist circumference

Introduction

Anthropometry plays an important role in the etiology of hormone-related cancers (1), particularly breast and endometrial cancers (2). In postmenopausal women, higher adiposity, as measured by body mass index (BMI), is associated with a higher risk of breast and endometrial cancers (2). Interestingly in premenopausal women, higher adiposity is associated with a lower risk of breast cancer (2), possibly because in these women body fat is associated with lower estrogen levels (3). However, the association between adiposity and

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risk of ovarian cancer is unclear, with epidemiological studies generally reporting moderate positive associations (4,5). In a meta-analysis of 28 population-based studies of ovarian cancer risk, Olsen *et al.* reported a statistically significant, pooled relative risk (RR) of 1.2 for overweight women (body mass index [BMI]= 25–29.9) and 1.3 for obese women (BMI≥30) compared to women with a normal weight (BMI=18.5–24.9). A stronger effect was observed among case-control studies versus prospective cohort studies suggesting modest associations may be driven by the retrospective analyses. In a recent analysis of 12 prospective cohorts, Schouten *et al.* reported that a high BMI was positively associated with risk among premenopausal (RR=1.72; 95%CI=1.02–2.89) but not postmenopausal women (RR=1.07; 95%CI=0.87–1.33). Despite this, relatively little is known about relationships with other measures of body size, such as waist-to-hip ratio (WHR). The complexity in delineating a possible role of obesity may be attributed to the lack of specificity of BMI for central adiposity or effect modification by other factors.

Given the paucity of prevention strategies for ovarian cancer, along with the high case-fatality rate, it is important to clarify the role of modifiable risk factors. Further, adiposity can influence endogenous sex hormone levels, which may play a role in ovarian carcinogenesis (6). Thus, using data collected from two large cohort studies, the Nurses' Health Study (NHS) and NHSII, we prospectively evaluated the association between waist and hip circumference, WHR, and BMI with the risk of developing epithelial ovarian cancer.

Materials and Methods

Study Populations

The NHS cohort was established in 1976 when 121,700 US female nurses aged 30–55 years completed a questionnaire. The NHS cohort has been followed by questionnaire every 2 years since to update exposure variables, including reproductive and dietary factors, and ascertain disease. In 1989, the NHSII was established among 116,430 female nurses, aged 25–42 years. Questionnaires and follow-up were similar to those in the NHS. Women were considered to be postmenopausal if they reported having a natural menopause (e.g., no menstrual cycles during the previous 12 months) or had a bilateral oophorectomy. Women who had a hysterectomy but had at least one ovary remaining were considered postmenopausal at age 56 (for nonsmokers) or 54 (for smokers) years of age. These were the ages at which natural menopause occurred for 90% of the overall cohort. The follow-up rate for the NHS and NHSII through 2006 and 2005 was 90% and 94% of the potential person-years, respectively. These studies were approved by the Committee on Human Subjects, Brigham and Women's Hospital.

Assessment of anthropometric measures

Information on adult height and current weight was obtained at baseline in 1976 (NHS) and 1989 (NHSII). Participants also reported their current weight on each biennial questionnaire. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist and hip circumference were reported, to the nearest quarter inch, in 1986 and 2000 (NHS) and 1993 (NHSII), with waist to be measured while standing relaxed at the navel and hip to be measured at the largest circumference including the buttocks (women were asked not to wear bulky clothing while doing the measurements). These two measurements were used to compute WHR. Women without a tape measure were asked to skip this question, and were subsequently excluded from analyses of these exposures. The waist and hip analyses had 52,429 NHS and NHSII 44,291 women, who were classified into categories of BMI, waist circumference, hip circumference, and WHR using cut-points that have been shown

previously to be associated with the risk of cancer mortality in this cohort or in quintiles otherwise (7).

The validity of self-reported anthropometric measurements has been demonstrated among 140 women from the NHS cohort (8). The Pearson correlation coefficients of self-reported waist, hip, WHR, and weight with the average of two trained technician-measurements taken 6 months apart were 0.89, 0.84, 0.70, and 0.97, respectively.

Ascertainment of ovarian cancer cases

Incident cases of epithelial ovarian cancer were reported on biennial questionnaires from 1976–2006 in the NHS and 1989–2005 in the NHSII. For women reporting a new ovarian cancer or cases identified via death certificate, we obtained pathology reports and related medical records. A gynecologic pathologist, unaware of exposure status, reviewed the records to confirm the diagnosis and identify histologic type, morphology, and stage (9).

Exclusions

We excluded women at baseline from all of the analyses if they reported a previous cancer diagnosis except nonmelanoma skin cancer (n=3,358 NHS/1,050 NHSII), had a history of bilateral oophorectomy or pelvic irradiation (n=7,763 NHS/2,259 NHSII), and reported no year of birth (n=124 NHS/0 NHSII). The number of women remaining after exclusions and at the start of follow-up for each exposure is in Table 1. Exclusions were updated biennially. We also excluded women with missing data for the specific anthropometric measure of interest from that particular analysis. For example, women who were missing baseline waist measurements were excluded from the waist analyses as were women with implausible waist circumferences (<20 inches). Baseline was defined as the questionnaire year that the particular measure was first assessed. Since data on waist and hip were queried again in 2000 for the NHS, we updated the measures in 2000. We carried forward the last self-reported BMI for one cycle if the data were missing.

Statistical analysis

We examined the age-adjusted mean (for continuous variables) or percent (for categorical variables) of key ovarian cancer risk factors by our adiposity measures at the approximate mid-point of the study in 1990. For each analysis, participants contributed person-time from baseline until the date of ovarian cancer diagnosis, report of other cancer (except nonmelanoma skin cancer), death, or June 1, 2006 (NHS) or June 1, 2005 (NHSII), whichever occurred sooner. Cases and person-time were assigned to the appropriate category of each anthropometric measure. Cox proportional hazards models with age in months and 2-year questionnaire cycle as the time scale were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for known and suspected ovarian cancer risk factors (see Tables for detail). To reduce the influence of outlier values, tests for linear trend were conducted by modeling the category medians (i.e., the median of each quintile category) and calculating the Wald statistic.

Data analyses were conducted separately for each cohort and then pooled using a random effects model to test for heterogeneity (10). To assess if results varied by menopausal status (premenopausal vs. postmenopausal; women with an unknown status were excluded), age (<45, 45–55, >55 years) or PMH use (never/past vs. current), we ran multivariate models and tested interaction terms between the quintile medians of the binary exposure variables of WHR, BMI, waist and hip circumference with each potential modifier, using the Wald test. We also stratified our analyses by the major histologic subtypes of ovarian cancer (serous/poorly-differentiated, endometrioid, mucinous). In a secondary analysis, we excluded cases

diagnosed during the four years of follow-up after body measurement assessment (lagged analysis).

All tests of statistical significance were two-sided. The SAS version 9.1 (SAS Institute, INC., Cary, NC) was used for all statistical analyses.

Results

During 3,956,759 person-years of follow-up for the NHS and NHSII combined, we observed 862 incident cases of epithelial ovarian cancer for the BMI analysis. The corresponding numbers for WHR were 1,234,083 person-years and 333 cases. Women in the highest quintile of BMI had a shorter duration of oral contraceptive use, were less likely to use PMH and had a higher current BMI (Table 1). Furthermore, in the NHSII, a greater proportion of women in the highest quintile of BMI had a history of tubal ligation.

WHR was not associated with the risk of developing ovarian cancer in the NHS (HR, highest versus the lowest quintile=0.78; 95%CI=0.52–1.16; *P*-trend=0.58), NHSII (HR=1.08; 95%CI=0.46–2.55; *P*-trend=0.98), or pooled analysis (HR=0.81; 95%CI=0.56–1.16; *P*-trend=0.63) (Table 2). After combining both cohorts and stratifying by menopausal status, we found no clear differential in risk with WHR between pre- and postmenopausal women or by age (data not shown). Because ovarian cancer is often accompanied by weight loss and the presence of ascites, we excluded cases diagnosed during the four years of follow-up after body measurement assessment, which did not change the associations (data not shown).

We found no evidence of an association between waist circumference and ovarian cancer risk (*P*-trend. pooled=0.65). There was significant heterogeneity in the association between hip circumference and risk between cohorts (*P*-heterogeneity<0.01). Hip circumference was modestly inversely associated with risk of ovarian cancer in the NHS (*P*-trend=0.05), but suggestively positively associated with risk in the NHSII (*P*-trend= 0.05). In stratified analyses, there was evidence for a decreasing risk of ovarian cancer with increasing hip circumference among post- (*P*-trend=0.03), but an increasing risk among premenopausal, women (*P*-trend=0.04) (*P*-interaction=0.01) (Table 3). The HRs (95%CIs) comparing the highest versus the lowest quintile of hip circumference among pre- and postmenopausal women were 1.54 (95%CI=0.45–5.23) and 0.66 (95%CI=0.37–1.16), respectively. Stratification by age (<45, 45–55, >55 years) showed similar results (data not shown).

The associations between BMI and ovarian cancer risk differed significantly by cohort (*P*-heterogeneity=0.04) (Table 2). Increasing BMI was significantly associated with increasing risk in the NHSII (*P*-trend=0.01), but not the NHS (*P*-trend = 0.72). The results became stronger when we also adjusted for WHR (data not shown). However, there was only a modest suggestion of a positive association between BMI and risk of ovarian cancer among pre- (*P*-trend=0.22), and no association among postmenopausal, women (*P*-trend=0.75)(*P*-interaction=0.22)(Table 3). This interaction was strengthened when we evaluated the association between BMI and risk using a binary cut-point to increase power (*P*-interaction=0.08). Among premenopausal women, those with a BMI of ≥25 vs. <25 kg/m^2 had an 18% (95%CI=0.91–1.52) increased risk of developing ovarian cancer. There was no such association among postmenopausal women (comparable HR=0.94; 95%CI=0.80–1.11). There was no association in the lagged analysis for either pre- and postmenopausal women {comparable HR=1.03 (95%CI=0.76–1.39) and 0.89 (95%CI=0.75–1.05), respectively}.

We did not observe a differential effect of BMI among postmenopausal women based on PMH use (*P*-interaction=0.23). We also examined whether the associations between WHR, BMI, waist and hip circumference varied by histologic subtype. A positive association with

BMI appeared stronger for the endometrioid subtypes; we did not observe any other differences in risk by tumor subtype. Further, there was no association between weight change since age 18 and risk, irrespective of menopausal status or exclusion of first four years of follow-up (data not shown).

Discussion

The results from this large prospective evaluation provides evidence that hip circumference and possibly BMI, but not waist circumference or WHR, are associated with the development of ovarian cancer. Furthermore, the associations for BMI appeared stronger for endometrioid subtypes with some heterogeneity by cohort, while hip circumference was differentially associated with risk by menopausal status. We recently reported heterogeneity by cohort and menopausal status in an analysis of body size in early life and risk of ovarian cancer, suggesting that body size over the lifespan may exert differential effects on risk earlier versus later in life (11). The attenuation of the results for BMI following exclusion of cases diagnosed during the first four years of follow-up after assessment suggests that the inclusion of women with subclinical disease may bias the findings even in a prospective study.

WHR is a measure of central adiposity and could influence ovarian cancer by affecting steroid hormones, IGF's, and insulin (6). With additional follow-up and including the NHSII, we confirmed no significant relationship between WHR and risk of ovarian cancer (12). Three studies have previously published positive associations with WHR and risk; however, the associations were modest or had no evidence of a dose-response (13–15).

Unlike colon and breast cancers, hip circumference was a stronger predictor of risk than waist circumference (16). There was suggestion of a decreased risk in the NHS and an increased the risk in the NHSII. After stratifying by menopausal status, it appeared that higher hip circumference was associated with an increase among pre- and decrease in risk among postmenopausal women. Both associations had a significant trend. Nevertheless, these results require replication given the relatively small sample size and what is, to our knowledge, the first prospective assessment of this association. Although the underlying mechanism of this potential association is unclear; it has been shown that higher hip circumference, which is thought to reflect lean mass, is independently associated with a favorable metabolic profile (lower glucose and triglycerides, higher HDL) (17,18). In a *post hoc* analysis, we found no significant association between lean mass and risk using total body water as a surrogate for lean mass (19). Further, the results for hip circumference did not change substantially when we adjusted for fat mass (equals weight–lean mass). Further, it is unclear as to why this association may differ by menopausal status, which should be further examined. There was no independent association of ovarian cancer risk with waist circumference in either pre- or postmenopausal women suggesting little or no role of central adiposity in the etiology of ovarian cancer. One case-control study reported no association between waist circumference and ovarian cancer risk (15); however, this could have been confounded by the disease in the cases.

We also found that BMI was modestly positively associated with premenopausal ovarian cancer, although the risk estimate was not significant; however, this association was attenuated after excluding cases in the first four years of follow-up after BMI assessment. The suggestion of effect modification by menopausal status is similar to that observed in prior studies (4,12,13,20–28). This is unlike breast cancer where obesity is an independent positive predictor of risk among postmenopausal women, but inversely related to risk among premenopausal women (29). A major limitation of prior ovarian cancer studies is that most did not exclude women with preclinical disease. Examining the effect of preclinical disease

should be re-evaluated in future studies with additional follow-up, given our results. The possible stronger association between BMI and risk of endometrioid tumors should be re-evaluated since obesity is a well-established risk factor for endometrial cancer (30).

Mechanisms by which obesity influences cancer development include metabolic consequences (i.e. hyperinsulinemia, insulin resistance), elevated levels of circulating growth factors (i.e. glucose, IGF-1), or altered sex hormone profiles (1). In our prior reports, we have shown that BMI is inversely associated with SHBG, androstenedione and progesterone, but positively associated with free testosterone levels in premenopausal women (3). Circulating testosterone levels have not been clearly associated with risk (31–34).

We did not find any evidence for effect modification by PMH use among postmenopausal women in the current or our prior analysis (12) as observed in breast cancer (35). Only two other studies have evaluated an interaction between BMI and PMH use (5,36). Among 1,580 cases and 1,509 controls, Olsen *et al.* reported no effect modification by PMH use (5). However, Rodriquez *et al.* observed an increase in ovarian cancer mortality (n=1,511 deaths) with increasing BMI among women who never used postmenopausal estrogens (RR=1.36) and no association among ever users (RR=0.93) in their prospective assessment (36). The differing results may be due to using ovarian cancer mortality as an endpoint rather than risk since BMI and PMH use may be associated with survival (37,38).

Although previous studies, including our earlier analysis, have evaluated how weight or BMI change might affect subsequent risk ovarian cancer, the majority have failed to report any significant associations (5,12,15,25). In the current analysis, we similarly found no association with weight gain/loss since age 18. Nevertheless, two studies reported non-significant positive associations with weight change since age 18/20 (39,40) that appeared stronger among nulliparous women (39). Conversely, Dal Maso *et al.* reported a lower increase in BMI from age 30 to the year prior to diagnosis/interview among cases versus controls (13). However, most of these were case-control studies that included retrospective assessment of body measures, possibly introducing bias, and fairly small sample sizes.

A major limitation of our study was the exclusion of a large number of potential participants due to missing data because the measurements of waist and hip circumference were only asked of women with a tape measure. Because ovarian cancer is a rare disease, we had limited statistical power to detect modest associations in stratified analyses. Nevertheless, with 333 incident cases, and 1,234,083 person-years of follow-up this is the largest prospective analysis of these adiposity measures and risk of ovarian cancer to date. Another potential drawback of our study was the use of self-reported anthropometry; however, this has previously been validated in our cohort (8). A major strength of our study was the prospective assessment of weight and WHR, especially since cachexia and ascites frequently occur in patients with ovarian cancer. We also controlled for the majority of the known or suspected risk factors for ovarian cancer thus decreasing the influence of confounding.

Overall, our findings do not support a strong role of adiposity measures in ovarian carcinogenesis. However, we did observe a differential association with hip circumference based on menopausal status, and BMI was not clearly associated with risk in pre- or postmenopausal women after accounting for preclinical disease. Considering adiposity is a modifiable risk factor, further evaluation of different adiposity measures on risk is important in light of the global increase in obesity. Future prospective studies with larger samples and additional follow-up should continue to examine a role of weight change overtime, early lifetime obesity, and hip circumference, as well as differences in risk by histologic subtype and menopausal status.

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Table 1

Age-standardized[a] characteristics of participants in the Nurses' Health Study (NHS) in 1986 and NHSII in 1993 by WHR, BMI and study population.

	NHS				NHSII			
	WHR (n = 41,531)		**BMI (n = 77,264)**		**WHR (n = 47,590)**		**BMI (n = 105,524)**	
Quintile	1	5	1	5	1	5	1	5
Sample size	9,248	7,234	12,019	11,180	9,980	9,321	22,284	17,604
Means								
Age (years)	50.7	55.3	51.2	52.8	38.2	38.5	37.2	39.0
Age at menarche (years)	12.5	12.4	12.8	12.1	12.4	12.3	12.8	11.9
Parity (among parous women)	3.0	3.3	3.0	3.3	2.2	2.2	2.2	2.2
Duration of oral contraceptive use (mo)	25.1	22.2	26.8	21.0	51.0	46.2	45.6	42.3
Current body mass index (kg/m^2)	22.7	27.6	19.9	34.4	22.4	27.7	19.8	35.5
Current hip circumference (inches)	39.1	40.6	36.2	46.5	38.7	41.1	36.0	47.6
Current waist circumference (inches)	27.5	36.1	27.2	38.4	26.9	36.8	27.1	40.0
Height (meters)	1.6	1.6	1.6	1.6	1.7	1.7	1.7	1.6
Caffeine intake (mg/day)	292.0	267.5	297.5	253.6	247.0	227.0	228.4	242.0
Percentages								
Parous	92.2	93.3	91.7	92.6	72.3	76.7	72.0	72.0
Premenopausal	36.5	34.7	38.0	37.8	97.7	97.5	92.3	92.1
Postmenopausal	63.4	65.2	61.0	61.2	1.2	1.4	1.0	1.0
Family history of ovarian cancer[c]	2.8	2.7	2.2	2.9	1.9	2.1	1.3	2.0
History of tubal ligation	16.6	16.3	16.8	17.7	20.0	22.8	17.9	23.3
Current postmenopausal hormone user (among postmenopausal women)	24.2	13.7	22.0	10.0	75.9	59.5	65.0	50.3

[a] All factors except age were age-standardized in five-year intervals for each cohort.

[b] WHR = waist to hip ratio; BMI = body mass index.

[c] Mother or sister had ovarian cancer according to participant's response on questionnaire; family history was evaluated using data from 1992 for NHS and 1993 for NHS II because it was not available in previous cycles.

Table 2

Multivariate relative risks (RR) and 95% confidence intervals (CI) of epithelial ovarian cancer according to WHR, BMI, waist and hip circumference in the NHS, NHSII and pooled analysis.

	NHS			NHS II			NHS and NHS II		
	Cases	**Person-years**	**Multivariate[a] RR (95% CI)**	**Cases**	**Person-years**	**Multivariate[a] RR (95% CI)**	**Cases**	**Person-years**	**Multivariate[a] RR (95% CI)**
WHR									
< 0.73	54	138418	1.0 (REF)	11	112377	1.0 (REF)	65	253759	1.0 (REF)
0.73-≤0.75	35	121977	0.70 (0.45–1.07)	9	102586	0.99 (0.41–2.40)	44	227280	0.74 (0.50–1.09)
0.76-≤0.79	70	153879	1.06 (0.74–1.52)	13	128547	1.04 (0.46–2.36)	83	285718	1.04 (0.75–1.45)
0.80-≤0.83	65	122078	1.23 (0.85–1.79)	6	85560	0.70 (0.25–1.91)	71	209960	1.13 (0.80–1.61)
≥ 0.84	57	151189	0.78 (0.52–1.16)	13	103364	1.08 (0.46–2.55)	70	257367	0.81 (0.56–1.16)
P trend[b]			0.58			0.98			0.63
					P-heterogeneity[c]=0.82				
Waist, inches									
< 28	55	135883	1.0 (REF)	12		1.0 (REF)	67	292656	1.0 (REF)
28-<30	57	143263	0.91 (0.62–1.33)	8	115526	0.86 (0.35–2.14)	65	261747	0.91 (0.64–1.29)
30-<32	52	121716	0.94 (0.62–1.41)	4	86734	0.52 (0.16–1.66)	56	210725	0.89 (0.61–1.30)
32-<35	52	142957	0.76 (0.49–1.18)	16	81892	2.15 (0.91–5.05)	68	227091	0.90 (0.61–1.33)
≥ 35	67	149534	0.99 (0.59–1.64)	12	97929	1.12 (0.35–3.57)	79	250087	1.00 (0.62–1.58)
P trend[b]			0.35			0.27			0.65
					P-heterogeneity[c]=0.16				
Hip, inches									
< 37	64	130343	1.0 (REF)	10	145488	1.0 (REF)	74	279831	1.0 (REF)
38-<38.5	61	146285	0.78 (0.54–1.12)	7	117248	0.86 (0.35–2.13)	68	266595	0.80 (0.57–1.12)
38.5-<40.5	59	158808	0.66 (0.45–0.97)	8	104826	0.52 (0.16–1.66)	67	266310	0.71 (0.50–1.03)
40.5-<43	42	120409	0.57 (0.36–0.90)	15	70997	2.14 (0.91–5.04)	57	193259	0.74 (0.49–1.12)
≥43-≤65	55	132718	0.67 (0.39–1.17)	12	94309	1.12 (0.35–3.57)	67	229565	0.76 (0.46–1.26)
P trend[b]			0.05			0.05			0.33
					P-heterogeneity[c]<0.01				

	NHS			NHS II			NHS and NHS II		
	Cases	**Person-years**	**Multivariate[a] RR (95% CI)**	**Cases**	**Person-years**	**Multivariate[a] RR (95% CI)**	**Cases**	**Person-years**	**Multivariate[a] RR (95% CI)**
BMI, kg/m^2									
< 21.0	102	383568	1.0 (REF)	23	301288	1.0 (REF)	125	696833	1.0 (REF)
21.0-<23	138	470735	1.03 (0.80–1.33)	17	314319	0.67 (0.36–1.26)	155	798639	0.97 (0.77–1.23)
23-<25	156	458994	1.12 (0.87–1.44)	12	268800	0.51 (0.25–1.03)	168	739738	1.02 (0.81–1.29)
25-<30	204	661749	0.96 (0.75–1.22)	38	366831	1.13 (0.66–1.92)	242	1047619	0.96 (0.77–1.19)
≥30	132	370816	1.11 (0.85–1.45)	40	285650	1.36 (0.80–2.33)	177	673930	1.12 (0.89–1.42)
P trend[b]			0.72			0.01			0.29
					P-heterogeneity[c]=0.04				

[a]Multivariate analyses adjusted for age at menarche (continuous), parity (continuous), duration of oral contraceptive use (continuous), tubal ligation history (yes, no), height (< 1.6, 1.6-<1.65, 1.65-<1.7, 1.7-<1.75, and ≥ 1.75 meters), family history of breast or ovarian cancer (yes, no), caffeine intake (quintiles in mg/day), hysterectomy (yes, no), postmenopausal hormone use/menopausal status (premenopausal, postmenopausal/never PMH use, postmenopausal/past PMH use, postmenopausal/current PMH use, postmenopausal/missing PMH use, and missing/unknown menopausal status) and BMI (continuous) in the WHR analysis, waist (continuous) and BMI (continuous) in the hip analysis, and hip (continuous) and BMI (continuous) in the waist analysis.

[b]*P* value from multivariate model with WHR, BMI, waist or hip using the quintile median a continuous variable.

[c]*P*-heterogeneity by cohort assessed using the DerSimonian and Laird random effects model.

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Table 3

Multivariate relative risks (RR) and 95% confidence intervals (CI) of epithelial ovarian cancer according to hip circumference or BMI, by menopausal status, pooling the NHS and NHSII.

	Premenopausal			Postmenopausal		
	Cases	**Person-years**	**Multivariate[a] RR (95% CI)**	**Cases**	**Person-years**	**Multivariate[a] RR (95% CI)**
Hip, inches						
<37	12	148475	1.0 (REF)	59	118167	1.0 (REF)
38-<38.5	12	124457	1.09 (0.48–2.49)	56	131380	0.78 (0.53–1.13)
38.5-<40.5	15	110243	1.52 (0.66–3.48)	51	145767	0.60 (0.40–0.91)
40.5-<43	18	72864	2.60 (1.07–6.36)	37	113162	0.51 (0.32–0.83)
≥ 43-≤65	12	90832	1.54 (0.45–5.23)	54	127344	0.66 (0.37–1.16)
P-trend[b]			0.04			0.03
P-interaction			0.01			
<40.5	39	383175	1.0 (REF)	166	395314	1.0 (REF)
≥40.5	30	163696	1.86 (0.95–3.63)	91	240506	0.81 (0.58–1.14)
P-interaction			0.06			
BMI, kg/m^2						
<21.0	44	459209	1.0 (REF)	79	216024	1.0 (REF)
21.0-<23	45	485819	0.84 (0.55–1.28)	108	287208	1.03 (0.77–1.38)
23-<25	43	398029	0.94 (0.61–1.43)	120	317031	1.05 (0.78–1.39)
25-<30	66	499993	1.03 (0.70–1.53)	168	509654	0.90 (0.69–1.18)
≥30	52	338193	1.15 (0.76–1.75)	115	302032	1.10 (0.82–1.48)
P-trend[b]			0.22			0.75
P-interaction			0.22			
<25	132	1343056	1.0 (REF)	307	820263	1.0 (REF)
≥25	118	838186	1.18 (0.91–1.52)	283	811685	0.94 (0.80–1.11)
P-interaction			0.08			

[a]Multivariate analyses adjusted for age at menarche, parity, duration of oral contraceptive use, tubal ligation history, height, family history of breast or ovarian cancer, caffeine intake, hysterectomy, and waist and BMI in the hip analysis. Postmenopausal analysis also adjusted for postmenopausal hormone use (never, past, current use).

[b]*P*-value from multivariate model with hip or BMI using the quintile median as a continuous variable.