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Body size and the risk of ovarian cancer by hormone therapy use in the California Teachers Study cohort

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Abstract

Objective—To investigate whether obesity and hormone therapy (HT) are associated with ovarian cancer risk among women in the California Teachers Study cohort.

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Methods—Of 56,091 women age ≥45 years, 277 developed epithelial ovarian cancer between 1995 and 2007. Multivariate Cox regression was performed.

Results—Among women who never used HT, greater adult weight gain, waist circumference and waist-to-height ratio, but not adult BMI, increased risk of ovarian cancer. Compared to women who never used HT and had a stable adult weight, risk of ovarian cancer was increased in women who gained ≥40 lb (relative risk (RR) 1.8, 95% confidence interval (CI): 1.0–3.0) or used HT for >5 years (RR 2.3 95% CI: 1.3–4.1). Having both exposures (RR 1.9, 95% CI: 0.99–3.5), however, did not increase risk more than having either alone. Results were similar for waist circumference and weight-to-height ratio; however, differences across HT groups were not statistically significant.

Conclusions—This study suggests that abdominal adiposity and weight gain, but not overall obesity, increase ovarian cancer risk and that there may be a threshold level beyond which additional hormones, whether exogenous or endogenous, do not result in additional elevation in risk. However, large pooled analyses are needed to confirm these findings.

Keywords

Ovarian cancer; Obesity; Abdominal adiposity; Hormone therapy

Introduction

The impact of obesity on the risk of ovarian cancer has not been established. Individual studies, pooled analyses and meta-analyses of ovarian cancer risk and obesity have yielded mixed results [1–4]. Conversely, long-term hormone therapy (HT) use has been positively associated with ovarian cancer risk [5–9]. The joint relationship between these factors remains unclear.

Obesity causes physiological changes that lead to perturbation of steroid hormone levels. When menstrual cycles cease, adipose tissue becomes a primary source of estrogens through the aromatization of adrenal androgens [10]. Greater overall and abdominal adiposity after menopause are independently associated with lower levels of sex hormone–binding globulin (SHBG) [11, 12], which resultsin higher levels of non-protein-bound, biologically available estrogen [12]. Hormone therapy (HT) also plays a role in the risk of hormone-related cancers by increasing circulating hormone levels [13].

Few studies have evaluated whether the effect of obesity on the risk of ovarian cancer varies by HT use, or whether these risk associations differ by various measures of overall and abdominal adiposity. If there is an interaction between HT use and obesity on ovarian cancer risk, the discrepant results between studies may be related to differences in the proportion and duration of HT use in the various populations studied. Therefore, we investigated the effects of obesity and HT use on the risk of epithelial ovarian cancer among women age ≥ 45 years in the large, prospective California Teachers Study (CTS) cohort.

Materials and methods

Study population

The CTS cohort was established in 1995–1996 and includes 133,479 active and retired female teachers and administrators recruited through the California State Teachers Retirement System [14]. Participants completed a baseline questionnaire that collected information on family history of cancer and other conditions, menstrual and reproductive history, a brief health history that included self-reported weight and height, living environment, diet, alcohol and tobacco use. Two years later, a follow-up questionnaire

collected self-reported measurements of waist and hip circumference; 99,529 participants (75%) completed the follow-up questionnaire.

The analytic subcohort for the present analysis was created after excluding, sequentially, women who at baseline did not live in California (n = 8,867); consented to participate only in breast cancer research (n = 18); did not provide adequate information on personal history of cancer (n = 662); had a history of ovarian cancer (identified by self-report or by linkage with the California Cancer Registry [CCR]) (n = 641); reported having had a bilateral oophorectomy (n = 14,422); were not between the ages of 45 and 84 years (n = 33,696 younger than age 45 years and n = 1,874 older than 84 years); had missing or unreliable data on height, weight or body mass index (BMI) (n = 3,490); had unknown HT use or duration (n = 6,201); reported using progestin-alone HT exclusively (n = 850: excluded due to an insufficient number of cases (n = 4) for stratified analysis); or had missing data for one or more of the confounding factors included in the analysis (n = 6,667). We restricted the analysis to women age ≥45 years so that all women were likely to be in or have passed through the peri- or postmenopausal period; thus, all women who were included could potentially have used HT. Of the 56,091 women eligible for analysis, 277 were diagnosed with incident invasive epithelial ovarian cancer after joining the cohort and on or before December 31, 2007. For waist and hip circumference analyses, we further excluded, sequentially, women who did not complete the follow-up questionnaire (n = 12,886); were diagnosed with ovarian cancer between baseline and completing the follow-up questionnaire (n = 37); moved out of California before completing the follow-up questionnaire (n = 409); or had missing or unreliable waist or hip circumference data (n = 4,600). Among the remaining 38,159 women, 166 were diagnosed with incident invasive epithelial ovarian cancer after completing the follow-up questionnaire and on or before December 31, 2007.

The CTS study was approved by the Institutional Review Boards of the Cancer Prevention Institute of Cal-ifornia, the California Health and Human Services Agency, the University of California, Irvine, the University of Southern California, and the City of Hope.

Follow-up

The CTS cohort is followed annually for cancer diagnoses, death, and changes of address. Annual linkage between the CCR and the cohort membership is used to identify incident cancer cases. The CCR is a population-based cancer registry that is anchored in state legislation that mandates reporting and is estimated to be over 99% complete [15]. The high standards maintained by the CCR ensure that follow-up for cancer outcomes are virtually complete as long as the cohort members reside in California. Linkage between the CTS cohort and the CCR database is based on full name, date of birth, address and Social Security number, and includes manual review of possible matches.

California and national mortality files are used to ascertain date and cause of death. Changes of address are obtained through annual mailings, responses from participants, and record linkages with multiple sources, including the US Postal Service National Change of Address database.

Follow-up time was calculated as the number of days between the date the baseline questionnaire was completed and the earliest occurrence of a first diagnosis of ovarian cancer (International Classification of Diseases for Oncology-3 (ICD-O-3) site code C56.9), death, a permanent (over 4 months long) move out of California or December 31, 2007. For waist circumference analyses, follow-up time was calculated as the number of days between the date the follow-up questionnaire was completed and the earliest outcome/censoring event as defined previously. For analysis, cases were restricted to invasive epithelial ovarian cancers (ICD-O-3 histology codes 8010, 8012, 8020, 8041, 8050, 8070, 8071, 8120, 8130,

8140, 8255, 8260, 8310, 8323, 8380, 8382, 8441, 8450, 8460, 8461, 8470, 8480, 8481, 8490, 8560, 9014) [16]; 23 women with other or unknown histologic types of ovarian cancer and 26 women with borderline ovarian cancer were censored at the time of their diagnoses. Analyses were limited to invasive epithelial ovarian cancer since over 90% of the invasive cases were this type.

Body size assessment

Height (in feet and inches) and weight (in pounds) were self-reported for age 18 and at the time of completing the baseline questionnaire. Body mass index (BMI) for both time periods was calculated as weight (converted to kilograms) divided by height (converted to meters and squared) and is a measure of overall adiposity that is independent of height (Pearson correlation coefficient of –0.04 in our study population). Extreme BMI values, defined as BMI at baseline <16 kg/m^2 or BMI at age 18 < 15 or ≥ 54.9 kg/m^2, were considered unreliable and these women were excluded from analysis. Weight change since age 18 was calculated as the absolute gain or loss of weight (in pounds) between age 18 and baseline.

In conjunction with the follow-up questionnaire, participants were provided with a standard heavy-weight flexible paper tape measure and written illustrated instructions on how to measure their waist and hip circumferences (in inches). Waist was measured as the circumference one inch above the navel. Hips were measured at the largest circumference between waist and thighs. Women were instructed to measure and record each circumference twice. For each circumference (waist or hips), if the two repeated measurements were within 3 inches of each other, the average was used in the analysis. If the two repeated measurements were over 3 inches apart or if either measurement was less than 20 inches, the data were considered unreliable and the woman was excluded from the analysis. In addition, if the final waist and hip circumference values were extreme in relation to each other [i.e., waist circumference less than 26.5 inches (10th percentile) and hip circumference greater than 45 inches (90th percentile) or waist circumference greater than 39.5 inches (90th percentile) and hip circumference less than 35.5 inches (10th percentile)], the data were considered unreliable and the woman was excluded from the analysis. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference, and waist-to-height ratio (WHtR) was calculated as waist circumference divided by height (in inches). WHR is a measure of body fat distribution (abdominal vs. hip) but reflects both fat and muscle, whereas WHtR is considered a measure of visceral fat that is independent of height/body stature (Pearson correlation coefficient of -0.14 in our study population) [17]; these two ratios, along with waist circumference, were considered as measures of abdominal adiposity.

Data analysis

Relative risks (RR; hazard rate ratios) and 95% confidence intervals (CI) were estimated using multivariate Cox proportional hazards regression models with age (in days) as the time-scale. Models were stratified by age (in years) at baseline and adjusted for race/ethnicity (non-Hispanic white, non-white including Hispanic), oral contraceptive (OC) use and duration (never used, <5 years, ≥5 years), number of full-term pregnancies (0, 1, ≥2), wine consumption in the year preceding baseline (grams per day; continuous), strenuous and moderate physical activity in the 3 years before baseline (hours/week; both strenuous and moderate activities <0.5, intermediate, either ≥3.01), smoking history at baseline (never, former, current), history of tubal ligation (no, yes) and height at baseline (inches; continuous). These covariates were included based on their independent association with risk in our cohort and prior knowledge of ovarian cancer risk factors [18, 19]. We additionally investigated HT type, total daily caloric intake, history of simple hysterectomy and family history of ovarian cancer as potential confounding variables, but they were not

independently associated with risk in multivariate models and were therefore not included in the final models reported here. When included as a potential confounder, weight at age 18 was included as a continuous variable.

Women were classified by their history of HT use at baseline as follows: never used HT, total HT duration ≤5 years or total HT duration >5 years. We classified by short- and long-term HT as risk of ovarian cancer is positively associated with long-term HT, both in the literature [7–9] and in our data. The sample size was too small to further classify by HT type.

We tested the assumption of proportional hazards for each adjustment variable and main effect using a likelihood ratio test of interaction with the time-scale (continuous) based on cross-product terms. Adjustment variables were coded as defined previously, and main effects were categorized as presented in the tables. There were no violations of the proportional hazards assumption.

Likelihood ratio tests for interaction across HT use and duration (never used HT, total HT duration ≤5 years, total HT duration >5 years) were computed based on cross-product terms with body size measures categorized as presented in the tables.

Because early symptoms of ovarian cancer can include abdominal fullness or bloating, difficulty eating, anorexia or weight loss [20–23], we conducted a secondary analysis in which we excluded the first 3 years (and additionally the first 5 years) of follow-up to remove the possibility that body size measures were affected by early symptoms. For these analyses, follow-up began at 3 years and 1 day (or 5 years and 1 day) after the baseline questionnaire was completed (n = 202 cases and n = 169 cases, respectively) or the follow-up questionnaire was completed (for waist circumference analyses; n = 122 cases and n = 90 cases, respectively).

Since particular subtypes of epithelial ovarian cancer may be more related to weight gain or loss [24], where feasible, we examined the association of BMI with risk of subtypes of epithelial ovarian cancer (n = 136 serous, n = 16 mucinous, n = 34 endometrioid, n = 20 clear cell and n = 37 adenocarcinoma NOS cases); these analyses, however, were not stratified by HT use.

Results

The median age at baseline was 55 years (interquartile range (IQR) 49–64 years). The median follow-up was 12.1 years for analyses using baseline measures and 10.1 years for the waist circumference analyses. Compared to women of normal weight, women who were obese at baseline were more likely to have had lower levels of physical activity in the 3 years before baseline, been overweight at age 18, gained 40 or more pounds since age 18 and had a waist circumference of 35 or more inches (Table 1).

Compared to women who never used HT, the risk of epithelial ovarian cancer was significantly increased among women who used HT for >5 years (RR 1.6, 95% CI: 1.2–2.2), but not among short-term HT users (RR = 1.0, 95% CI: 0.75–1.4). Risk did not differ by HT type. Among women who never used HT (n = 26,954), the median age at baseline was 50 years (IQR 47–61 years). Among women who used HT for ≤5 years (n = 15,655), the median age at baseline was 54 years (IQR 51–61). Thirty percent of these women used estrogen-alone therapy (ET) exclusively, 69% used combined estrogen-plus-progester-one therapy (EPT) exclusively and 1% used both types. At baseline, 14% were currently using ET, 57% were currently using EPT, and 30% were past users. Among women who used HT for >5 years (n = 13,482), the median age at baseline was 62 years (IQR 57–69). Thirty-

three percent of these women used ET exclusively, 45% used EPT exclusively, and 23% used both types. At baseline, 34% were currently using ET, 54% were currently using EPT, 12% were past users, and <1% had unknown current HT use.

In this subcohort of women age ≥45 years, obesity was not associated with risk of epithelial ovarian cancer overall (RR 0.85, 95% CI: 0.58–1.2 for BMI ≥ 30 vs.<25 kg/m^2) or among subgroups defined by HT use (Table 2). Among women who never used HT, greater weight gain since age 18 (RR 1.8, 95% CI: 1.0–3.0 for ≥40 lb vs stable weight), a larger waist circumference (RR 1.8, 95% CI: 1.1–3.0 for ≥35 vs. <35 inches), and a larger waist-to-height ratio (RR 1.8, 95% CI: 1.1–3.1 for ≥0.55 vs. <0.55) were signifi-cantly associated with higher risk of ovarian cancer.

Long-term HT use increased epithelial ovarian cancer risk among non-obese women (RR 1.8, 95% CI: 1.2–2.6 for BMI < 25 kg/m^2 and HT use >5 years and RR 1.7, 95% CI: 1.1–2.8 for BMI 25–29 and HT use >5 years, both compared to BMI < 25 and never used HT) (Table 2). No increase in risk associated with HT use was observed among those who were obese (RR 1.1, 95% CI: 0.53–2.5 for BMI > 30 and HT use >5 years); although, the latter estimate was based on small numbers.

Compared to women who never used HT and had a stable adult weight, risk of epithelial ovarian cancer was increased in women who gained ≥40 lb (RR 1.8, 95% CI: 1.0–3.0) or used HT for >5 years (RR 2.3 95% CI: 1.3–4.1) (Table 2). Having both exposures (RR 1.9, 95% CI: 0.99–3.5) did not increase risk more than having either alone (*P*-interaction = 0.05). Similar patterns were observed for waist and WHtR. Differences across HT groups, however, were not statistically significant for these other body measures (*P*-interaction > 0.05). In addition, compared to women who never used HT and had a stable adult weight, there was a suggestion of an increased risk of ovarian cancer among women who lost >10 lb, regardless of HT use (RR1.8, 95% CI: 0.94–3.5 for never HT, RR 2.0, 95% CI: 0.90–4.4 for HT ≤ 5 years and RR 2.9, 95% CI: 1.4–6.1 for HT > 5 years), although the number of cases was small.

Excluding the first 3 years of follow-up, results for Table 2 were similar. For example, compared to women who never used HT and had a stable adult weight, women who gained ≥40 lb or used HT for >5 years or both, had an increased risk of epithelial ovarian cancer (RR 1.9, 95% CI: 1.0–3.6; RR 2.3, 95% CI: 1.1–4.5; and RR 1.7, 95% CI: 0.76–3.6, respectively). With the same comparison group, for women who lost >10 lb since age 18, there was a statistically significant increased risk of ovarian cancer among those who had never used HT (RR 2.2, 95% CI: 1.0–4.5; *n* = 13 cases) and those with long-term HT use (RR 3.3, 95% CI: 1.4–7.6; *n* = 9 cases), but not among those who had used HT for ≤5 years (RR 1.2, 95% CI: 0.40–3.7; *n* = 4 cases). Excluding the first 5 years of follow-up, results were attenuated for every measure given the small number of cases in each subgroup.

Overall obesity decreased risk of serous tumors (RR 0.53, 95% CI: 0.28–0.99 for BMI ≥ 30 vs. <30 kg/m^2), but increased risk of clear cell tumors (RR 2.7, 95% CI: 0.99–7.3). No association with risk was observed for the other histologic subtypes, although statistical power was low due to the small number of cases.

Discussion

Results from our prospective cohort suggest that abdominal adiposity and weight gain, but not overall obesity, increased epithelial ovarian cancer risk in HT non-users. In addition, long-term HT use increased risk; however, risk was not further increased among women with both exposures. Interestingly, adult weight loss was associated with increased ovarian cancer risk, and this finding persisted when the first 3 or 5 years of follow-up were

excluded. The association between overall obesity and ovarian cancer risk may vary by histologic subtypes; however, larger studies or pooled analyses are needed to adequately address this issue.

The association between ovarian cancer and obesity in postmenopausal women in the recent literature is mixed. Consistent with our study, most studies, including a pooled analysis of 12 cohort studies, have found no association in postmenopausal women [2, 4, 25–31], although a few earlier studies did find a positive association for one or more of the obesity measures assessed [3, 25, 31].

Three recent cohort studies investigated the relationship between obesity and risk of epithelial ovarian cancer by HT use, two in postmenopausal women and one in women age 50–71. The European Prospective Investigation into Cancer and Nutrition (EPIC) found that higher BMI and larger hip circumference increased risk of epithelial ovarian cancer in postmenopausal women, but waist circumference, WHR and adult weight change were not associated with risk [32]. The Nurses' Health Study found evidence for the decreased risk of epithelial ovarian cancer with larger hip circumference in postmenopausal women, but no association with risk for BMI, waist circumference or WHR [33]. In both studies, the results for BMI did not differ by HT use. In contrast, the National Institutes of Health AARP Diet and Health Study found that BMI was significantly associated with increased risk in women who never used HT (RR 1.8, 95% CI: 1.2–2.8 ≥ 30 vs. <25 kg/m^2), but not among those who ever used HT (RR 0.96, 95% CI: 0.65–1.4) (*P*-interaction = 0.02) [34]. Findings were similar for BMI at age 18 (*P*-interaction = 0.02), but there was no association with adult weight gain in either group.

By comparison, our study found a positive association between risk of epithelial ovarian cancer and adult weight gain, waist circumference and WHtR in women who never used HT. However, among HT users, substantial weight gain had no impact on risk. Thus, while substantial abdominal weight gain and long-term HT use each increased the risk of epithelial ovarian cancer, having both exposures did not increase risk more than either alone. This pattern implies a threshold (rather than a multiplicative) effect beyond which additional exogenous and endogenous hormones did not continue to increase risk.

A pooled analysis of case–control studies reported differences by histologic subtypes of epithelial ovarian cancer [24]. Higher BMI was associated with a non-significant increased risk for endometrioid and mucinous tumors and decreased risk for serous tumors. However, the EPIC study found no association between BMI and subtypes of epithelial ovarian cancer [32]. Consistent with the pooled analysis, we found that higher BMI decreased the risk for serous tumors, while conversely, increased the risk for clear cell tumors, but was not associated with other histo-logic subtypes, including endometrioid and mucinous.

A potential limitation of our study is the possibility of error in self-reported anthropometric measurements. Such error could be the result of lack of knowledge, the desire to report a socially more normative value or measurement error (for waist and hip circumferences). However, to improve the accuracy of measured waist and hip circumferences, participants were provided with specific written and pictorial instructions and a standard tape measure and were asked to take and record their measurements twice. In addition, the prospective study design eliminated recall bias and, thus, if measurement error occurred in the self-reports, it was unlikely to differ systematically between cases and non-cases. However, socially desirable responses would have been likely to attenuate elevated risk estimates. Finally, in an ancillary validation study conducted within the cohort, comparison of the self-reported measurements to measurements taken by trained interviewers suggested excellent validity, with Pearson correlation coefficients of 0.87, 0.93, 0.85, and 0.87 for weight,

height, waist circumference, and hip circumference, respectively. Another limitation of the study was the small number of cases, particularly when stratified by duration of HT use; the small sample size resulted in limited power to detect differences within and across these strata. However, since HT use and duration may have been relevant to disentangling the mixed results observed to date, we presented the data accordingly. Nevertheless, combining different HT types together within strata of HT duration may have obscured effects, if different preparations have differential impact on the association between obesity and risk. However, HT type was not related to ovarian cancer risk in our subcohort (data not shown). An additional limitation was the relatively large number of women excluded due to missing data. However, in a comparison of the 56,091 women included in the present analysis with the 17,208 women excluded from analyses for missing data, none of the body size measures differed (data not shown); thus, there was no evidence of inclusion bias. Finally, we were unable to update cohort members' anthropometric and HT data during the decade-long follow-up period included in this analysis.

Strengths of our study include the prospective design minimizing recall bias, detailed exposure information, and virtually complete case ascertainment minimizing selection bias due to loss to follow-up.

In conclusion, our findings show that either substantial abdominal weight gain or long-term HT use increased the risk of epithelial ovarian cancer, emphasizing the importance of weight control and HT cessation in ovarian cancer prevention. Having both exposures, however, did not increase risk more than either alone. This pattern suggests a threshold effect of hormonal exposures, such that after a certain level is achieved, regardless of its source, no additional risk is incurred.

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Table 1

Selected baseline characteristics of women age ≥45 years in the California Teachers Study (CTS) cohort by body mass index (BMI)

Characteristic	BMI (Body mass index)								
	<25			25–29			≥30		
	Median (IQR)	*n*	(%)	Median (IQR)	*n*	(%)	Median (IQR)	*n*	(%)
BMI (kg/m^2)		32,941	58.7		14,980	26.7		8,170	14.6
Age (years)	54 (49–64)			56 (50–66)			55 (49–64)		
Wine g/d	3.3 (0–3.3)			3.3 (0–3.3)			3.3 (0–3.3)		
Height (inches)	65 (63–66)			65 (63–66)			64 (63–66)		
Race									
White		29,790	90.4		13,354	89.2		7,136	87.3
Non-white		3,151	9.6		1,626	10.9		1,034	12.7
Strenuous and moderate physical activity (hours/week) in the 3 years before baseline									
Both < 0.5 h/week		7,305	22.2		4,320	28.8		3,444	42.2
Intermediate		14,820	45.0		6,879	45.9		3,471	42.5
Either ≥3.01 h/week		10,816	32.8		3,781	25.2		1,255	15.4
Total number of full-term pregnancies									
None		7,140	21.7		2,945	19.7		1,917	23.5
1		4,945	15.0		2,015	13.5		1,146	14.0
≥2		20,856	63.3		10,020	66.9		5,107	62.5
Oral contraceptive duration (years)									
Never used		11,031	33.5		5,918	39.5		3,119	38.2
<5		9,899	30.1		4,179	27.9		2,504	30.7
≥5		12,011	36.5		4,883	32.6		2,547	31.2
Smoking history									
Never		20,048	60.9		9,065	60.5		5,040	61.7
Former		10,911	33.1		5,036	33.6		2,752	33.7
Current		1,982	6.0		879	5.9		378	4.6
History of tubal ligation									
No		27,684	84.0		12,524	83.6		6,822	83.5
Yes		5,257	16.0		2,456	16.4		1,348	16.5

Characteristic	BMI (Body mass index)								
	<25			25–29			≥30		
	Median (IQR)	*n*	(%)	Median (IQR)	*n*	(%)	Median (IQR)	*n*	(%)
Hormone therapy use (years)									
Never used		15,651	47.5		6,937	46.3		4,366	53.4
≤5		9,164	27.8		4,235	28.3		2,256	27.6
>5		8,126	24.7		3,808	25.4		1,548	19.0
BMI at age 18 (kg/m^2)									
<25		29,918	92.2		13,668	92.5		6,278	77.7
≥25		2,536	7.8		1,104	7.5		1,804	22.3
Missing or unreliable		487			208			88	
Weight change (pounds) since age 18									
Loss, >10 lb		4,823	14.8		355	2.4		55	0.7
Stable, ±10 lb		13,566	41.6		864	5.8		146	1.8
Gain, 11–39 lb		13,705	42.0		8,128	54.8		739	9.1
≥40 lb		511	1.6		5,493	37.0		7,174	88.4
Missing or unreliable		336			140			56	
Waist (inches)[a]									
<35		21,087	88.7		4,509	46.1		409	8.9
≥35		2,687	11.3		5,272	53.9		4,195	91.1
Waist-to-height ratio[a]									
<0.55		21,834	91.8		5,445	55.7		527	11.5
≥0.55		1,940	8.2		4,336	44.3		4,077	88.6
Waist-to-hip ratio[a]									
<0.80		13,900	58.5		3,086	31.6		783	17.0
≥0.80		9,874	41.5		6,695	68.5		3,821	83.0

IQR interquartile range, BMI body mass index, E estrogen, P progestin

[a]Available only among participants who completed the 1997 follow-up questionnaire

Table 2

Body size and hormone therapy use and risk of epithelial ovarian cancer in women age ≥ 45 years in the California Teachers Study cohort

	Never used HT				HT ≤ 5 years				HT > 5 years			
	Cases	**Person-years**	**RR[a]**	**95% CI**	**Cases**	**Person-years**	**RR[a]**	**95% CI**	**Cases**	**Person-years**	**RR[a]**	**95% CI**
BMI (kg/m^2)												
<25	57	175,216	1.0	Reference	41	101,462	1.2	0.76, 1.8	64	88,130	1.8	1.2, 2.6
25–29	29	77,031	1.1	0.71, 1.8	21	46,700	1.3	0.74, 2.1	30	41,282	1.7	1.1, 2.8
≥30	21	48,237	1.2	0.72, 2.0	6	24,856	0.65	0.28, 1.5	8	16,507	1.1	0.53, 2.5
BMI at age 18 (kg/m^2)												
<25	90	263,607	1.0	Reference	57	154,751	1.0	0.71, 1.4	91	132,900	1.6	1.1, 2.2
≥25	16	32,733	1.4	0.82, 2.4	7	16,074	1.1	0.52, 2.5	9	10,986	1.9	0.94, 3.9
Weight change (since age 18)[b]												
Loss, >10 lb	15	29,294	1.8	0.94, 3.5	9	15,187	2.0	0.90, 4.4	12	12,446	2.9	1.4, 6.1
Stable, ±10 lb	22	78,662	1.0	Reference	28	43,887	2.2	1.2, 3.9	31	38,541	2.3	1.3, 4.1
Gain, 11–39 lb	31	117,098	0.96	0.55, 1.7	17	71,428	0.81	0.42, 1.5	37	62,356	1.7	0.98, 3.0
≥40 lb	38	72,570	1.8	1.0, 3.0	13	41,293	1.0	0.51, 2.1	20	31,092	1.9	0.99, 3.5
Waist circumference (inches)												
<35	32	113,564	1.0	Reference	29	69,763	1.4	0.83, 2.4	41	60,898	2.2	1.3, 3.6
≥35	29	52,592	1.8	1.1, 3.0	13	31,086	1.4	0.69, 2.6	22	28,210	2.4	1.3, 4.3
Waist-to-height ratio												
<0.55	35	120,779	1.0	Reference	33	74,915	1.5	0.88, 2.4	42	65,405	2.0	1.2, 3.3
≥0.5 5	26	45,378	1.8	1.1, 3.1	9	25,935	1.1	0.52, 2.4	21	23,703	2.7	1.5, 4.9
Waist-to-hip ratio												
<0.80	29	80,796	1.0	Reference	23	48,774	1.2	0.69, 2.2	25	38,331	1.6	0.88, 2.9
≥0.80	32	85,360	0.95	0.56, 1.6	19	52,076	0.90	0.49, 1.7	38	50,777	1.7	0.96, 2.9

HT hormone therapy, BMI body mass index, RR relative risk, CI confidence interval

[a] Adjusted for race, oral contraceptive use and duration, number of full-term pregnancies, wine consumption, physical activity, smoking history, history of tubal ligation and height; age was the time-scale, and analyses were stratified by age at baseline

[b] Additionally adjusted for weight at 18