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

Alison J. Canchola¹, Ellen T. Chang^{1,2}, Leslie Bernstein³, Joan A. Largent⁴, Peggy Reynolds^{1,2}, Dennis Deapen⁵, Giske Ursin^{5,6}, and Pamela L. Horn-Ross^{1,2}

¹ Cancer Prevention Institute of California (formerly the Northern California Cancer Center), Fremont, CA, USA

² Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA

³ Division of Cancer Etiology, Department of Population Sciences, City of Hope National Medical Center, Duarte, CA, USA

⁴ Department of Epidemiology, College of Health Sciences, University of California Irvine, Irvine, CA, USA

⁵ Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

⁶ Department of Nutrition, University of Oslo, Oslo, Norway

Abstract

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

Methods—Of 28,418 postmenopausal women, 395 developed type 1 endometrial cancer between 1995 and 2006. Multivariate Cox regression was performed to estimate relative risks (RR), stratified by HT use (never used, ever estrogen-alone (ET), or exclusively estrogen-plus-progestin (EPT)).

Results—Among women who never used HT, overall and abdominal adiposity were associated with increased risk; when evaluated simultaneously, abdominal adiposity was more strongly associated (RR 2.2, 95% confidence interval (CI): 1.1–4.5 for waist ≥ 35 vs. < 35 inches). Among women who ever used ET, risk was increased in women with BMI ≥ 25 kg/m² (RR 1.6, 95% CI: 1.1–2.3 vs. < 25 kg/m²). Neither overall nor abdominal obesity was associated with risk in women who exclusively used EPT (P -interaction < 0.001 for BMI by HT use).

Conclusions—Among women who never used HT, risk was strongly positively related to obesity and may have been influenced more by abdominal than overall adiposity; however, due to small numbers, this latter finding requires replication. Among women who ever used ET, being overweight at baseline predicted higher risk, whereas use of EPT mitigated any effect of obesity.

Keywords

endometrial cancer; obesity; abdominal adiposity; hormone therapy

Introduction

Consistent epidemiologic evidence has established that obesity and unopposed estrogen hormone therapy use are the strongest risk factors for endometrial cancer [1–3]. However, the joint relationship between these factors is less clear.

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 [4,5]. Greater overall and abdominal adiposity after menopause are independently associated with lower levels of sex hormone binding globulin (SHBG) [6,7], which results in higher levels of non-protein-bound, biologically available estrogen [2,4,7]. Endometrial cancer risk has been shown to be directly associated with circulating estrogen and androgen levels (possibly due to the conversion of the latter to estrogens, particularly in adipose tissue) and inversely associated with SHBG levels [8].

Hormone therapy (HT) also plays a role in the risk of hormone-related cancers. The positive association between estrogen-only hormone therapy (ET) and the development of endometrial cancer was first suggested in the early 1970's [9,10]. Subsequent case-control studies found a four- to eight-fold excess risk of endometrial cancer among ET users and a dose-response relationship between risk and number of years of use [11–13]. Therefore, for women with an intact uterus, the preparation of HT was modified to include a progestin to oppose the proliferative effect of estrogen on the endometrium. The association between estrogen-plus-progestin HT (EPT) and endometrial cancer risk has generally been null [14–16].

Based on pathological and clinical differences, endometrial cancer has been divided into two main types. Type 1, endometrioid adenocarcinoma, is the most common (about 80%) and typically develops from endometrioid hyperplasia in a setting of unopposed estrogen [17,18]. Risk factors for this estrogen-related type of endometrial cancer include obesity, early menarche and late menopause, nulliparity and use of unopposed exogenous estrogens. These carcinomas are usually diagnosed at an early stage and prognosis is excellent. Type 2 endometrial cancers, on the other hand, develop from atrophic endometrium, are aggressive with mostly high-grade or high-risk histology (serous-papillary or clear-cell carcinomas), have a poor prognosis and may not share the classical risk factors for type 1 cancers [17,18].

Despite the considerable evidence implicating obesity and ET in the etiology of type 1 endometrial cancer, few studies have evaluated whether the effect of obesity varies by HT use, and furthermore how these risk associations differ by various measures of overall and abdominal adiposity. Therefore, we investigated the effects of obesity and other body size measures, stratified by HT use, on the risk of type 1 endometrial cancer among postmenopausal women 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 [19]. 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 this questionnaire.

The analytic cohort 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 endometrial cancer (identified by self-report or by linkage with the California Cancer Registry [CCR]) (N=1,619); reported having had a hysterectomy (N=27,798); were age 85 years or older (N=1,331); were pre- or peri-menopausal (N=50,482: see definition of menopausal status under *Data Analysis*); had unknown menopausal status due to being younger than age 56 and having started HT before experiencing menopause (N=4,790) or having missing or unreliable data (N=507); had missing or unreliable data on height, weight or body mass index (BMI) (N=2,162); had unknown HT use or type (N=2,701); reported using progestin-alone HT exclusively (N=384: excluded due to an insufficient number of cases (N=9) for stratified analysis); or had missing data for one or more of the confounding factors included in the analysis (N=3,740). Of the 28,418 postmenopausal women eligible for analysis, 395 were diagnosed with incident invasive type 1 endometrial cancer after joining the cohort and on or before December 31, 2006. For waist circumference analyses, we further excluded, sequentially, women who: did not complete the follow-up questionnaire (N=6,297); were diagnosed with endometrial cancer between baseline and completing the follow-up questionnaire (N=85); moved out of California before completing the follow-up questionnaire (N=215); or had missing or unreliable waist or hip circumference data (N=2,339). Among the remaining 19,482 women, 218 were diagnosed with incident invasive type 1 endometrial cancer after completing the follow-up questionnaire and on or before December 31, 2006.

The CTS study was approved by the Institutional Review Boards of the Cancer Prevention Institute of California (formerly the Northern California Cancer Center), 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 diagnosis, death, and change 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 [20]. 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 first occurrence of a first diagnosis of endometrial cancer (International Classification of Diseases for Oncology-3 (ICD-O-3) site code C54.1 or C54.9), death, or a permanent (over 4 months long) move out of California, or December 31, 2006. 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 first outcome/ censoring event as defined above. For analysis, cases were restricted to invasive type 1

endometrial cancers (ICD-O-3 histology codes 8010, 8140, 8210, 8255, 8260, 8380, 8480, 8570); 55 women with type 2 endometrial cancer, 19 with other histologic types of endometrial cancer, and 10 with in-situ endometrial cancer were censored on the dates of their diagnoses.

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) squared, and is a measure of overall adiposity that is independent of height (Pearson correlation coefficient of -0.05 in our study population). Women with extreme BMI values, defined as baseline BMI $<16 \text{ kg/m}^2$ or BMI at age 18 <15 or $\geq 54.9 \text{ kg/m}^2$, were considered unreliable and 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 was 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 was 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 [21]; these two ratios, along with waist circumference, were considered as measures of abdominal adiposity.

Data Analysis

We limited the analysis to invasive type 1 endometrial cancer, since type 1 and type 2 endometrial cancers may have different etiologies [17,18].

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: age at menarche (continuous from <9 to ≥ 17 years), parity (no, yes) and age at first full-term pregnancy (continuous), oral contraceptive (OC) use and duration (never used, <3 years, ≥ 3 years), average lifetime (high school to age 54 years) strenuous plus moderate physical activity (hours/week; <5.5 , ≥ 5.5), height at baseline (inches; continuous) and self-reported history of high blood pressure or use of hypertensive medications (no, yes) and its interaction with time-dependent age. These covariates were included based on their independent association with risk in our cohort and prior knowledge of endometrial cancer risk factors; variable definitions were chosen which best described the relationship with risk while preserving parsimony. We additionally investigated race, family history of

endometrial cancer, total daily caloric intake, percent of calories from fat, history of diabetes, smoking history and alcohol intake 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 modeled as a continuous variable.

Women were classified as postmenopausal at baseline if: they reported experiencing natural menopause or that their menstrual periods had stopped more than six months ago; both ovaries had been removed; or they were age 56 years or older at baseline. Women who were younger than age 56 at baseline and had started using HT prior to the cessation of menses, and women who had missing or inconsistent data for the variables used to define menopausal status, HT use or HT type were considered to have unknown data and were excluded from the analysis.

Women were stratified by their history of HT use at baseline: never used HT, ever used ET, or exclusively used EPT. This classification was chosen because unopposed estrogen has been more strongly associated with endometrial cancer risk than EPT [1–3]. The sample size was too small to further stratify by HT duration; however, analyses among HT users were additionally adjusted for total duration of HT use (≤ 5 years, > 5 years) and its interaction with time-dependent age.

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 above and main effects were categorized as presented in the tables. Hypertension and total duration of HT, separately, had significant interactions with time-dependent age in the entire cohort and in the subsets who used HT, respectively. Thus, these interaction terms were included as adjustment factors. There were no violations of the proportional hazards assumption for any of the main effects.

When baseline BMI and BMI at age 18 were assessed simultaneously, follow-up time began at baseline and those with missing data for BMI at age 18 were excluded. When baseline BMI and different measures of abdominal adiposity (waist, waist-to-hip ratio and waist-to-height ratio) were assessed simultaneously, follow-up time began at the 1997 follow-up questionnaire.

Likelihood ratio tests for trend across body measurement categories were conducted using an ordinal variable coded as the median value of each category. If the trend test was statistically significant ($P < 0.05$), we conducted a likelihood ratio test for non-linearity of the trend, comparing models with the body measurement coded as an ordinal versus a categorical variable [22]. Likelihood ratio tests for interaction across levels of HT use and type (never used HT, ever used ET or used EPT exclusively) were computed based on cross-product terms with body size measures categorized as presented in the tables, with the exception of weight change since age 18, which was modeled per 10-pound increase.

Results

The median age at baseline was 61 years (interquartile range (IQR) 55 to 68 years; $< 0.2\%$ of women were under age 40). The median follow-up was 11.1 years for analyses using baseline measures and 9.1 years for the waist circumference analyses. Compared to women of normal weight, women who were obese at baseline were more likely to have had high blood pressure, never used HT, 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 type 1 endometrial cancer was substantially higher among those who ever used ET (RR 2.2, 95% CI: 1.7–2.9) and slightly higher among those who used EPT exclusively (RR 1.4, 95% CI: 1.1–1.8). Among women who never used HT (N=10,168), the median age at baseline was 64 years (IQR 57 to 71 years). Among women who ever used ET (N=4,951), the median age at baseline was 68 years (IQR 62 to 75 years); 54% used HT (any type) for >5 years; 59% used ET exclusively; and at baseline 17% were currently using ET, 30% were currently using EPT, 53% were past users, and <1% had unknown current HT use. Among women who exclusively used EPT (N=13,299), the median age at baseline was 58 years (IQR 54 to 63 years); 42% used HT for >5 years; and at baseline 82% were currently using EPT and 18% were past users.

Obesity was associated with a higher risk of endometrial cancer in postmenopausal women overall (RR 1.9, 95% CI: 1.5–2.5 for BMI ≥ 30 vs. <25 kg/m²). This association was especially pronounced among postmenopausal women who never used HT (RR 3.5, 95% CI: 2.2–5.5) (Table 2). Risk in never HT users was also elevated among women who were overweight in young adulthood, had significant weight gain since age 18, and those with greater abdominal adiposity. For women who ever used ET, elevated risk was statistically significantly associated only with being overweight at baseline; however, the magnitude of effect was similar for overweight and obese women. The RR combining these two groups was 1.6 (95% CI: 1.1–2.3 compared to <25 kg/m²). No association was observed for overall obesity, abdominal adiposity or weight gain among women who exclusively used EPT. The associations for BMI, waist circumference, WHR and WHtR differed significantly by HT use (P -interaction <0.05).

Among women who never used HT, we further assessed the independent effects of BMI and other measures of obesity. In this group, BMI at baseline was moderately correlated with waist circumference and WHtR (Pearson correlation coefficients 0.73 and 0.74, respectively) but was not correlated with BMI at age 18 or WHR (correlations 0.26 and 0.31, respectively). In those who never used HT, baseline BMI was positively associated with endometrial cancer risk among participants who completed the follow-up questionnaire (where waist circumference was reported) (RR 2.7, 95% CI: 1.4–5.3 for BMI ≥ 30 vs. <25 kg/m²). This association was greatly reduced in models that included baseline BMI and either waist circumference or WHtR, whereas the risk associated with these abdominal measures remained statistically significantly increased (Table 3). Both WHR and baseline BMI were independently associated with risk. In contrast, when simultaneously adjusting for both BMI at age 18 and BMI at baseline, the positive association with risk remained for baseline BMI, but was diminished for BMI at age 18.

Discussion

Results from our prospective cohort demonstrate that the association between obesity and type 1 endometrial cancer risk in postmenopausal women differs by HT use and type. Among women who never used HT, risk was strongly positively related to obesity and may have been influenced more by abdominal than overall adiposity; however, the latter finding should be interpreted with caution due to small numbers. Among women who ever used ET, being overweight at baseline predicted higher risk, while use of EPT mitigated any effect of obesity.

The associations between endometrial cancer risk and HT use and type in our study were consistent with results from a more detailed analysis of specific HT preparations in a subgroup of the CTS [23]. Only a few studies have investigated the joint effects of obesity and HT use on endometrial cancer risk. Recently, three cohort studies found results similar to ours. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort,

several measures of obesity (weight, BMI, waist circumference, hip circumference and WHR) were positively associated with endometrial cancer risk in postmenopausal women who never used HT, but were not associated with risk in those who ever used HT; however, the investigators did not stratify risk associations by HT type [24]. In the Cancer Prevention Study II Nutrition Cohort (CPS II), BMI was significantly associated with increased endometrial cancer risk in postmenopausal women who never used HT (RR 3.7, 95% CI: 2.4–5.7 for BMI 30.0–34.9 kg/m² and RR 4.4, 95% CI: 2.7–7.2 for BMI ≥35.0 kg/m² each compared to 22.5–24.9 kg/m²), but not among those who ever used EPT (RR 1.5, 95% CI: 0.68–3.3 for BMI ≥30.0 vs. 22.5–24.9 kg/m²) [25]. In the NIH-AARP Diet and Health Study Cohort, obesity was strongly associated with increased endometrial cancer risk in postmenopausal women who never used HT (RR 5.4, 95% CI: 4.0–7.3 for BMI ≥30 vs. <25 kg/m²) [26]. The obesity association was diminished in those who formerly used HT (RR=2.5, 95% CI: 1.2–8.3) and was only marginally significant in those who currently used HT (RR=1.4 95% CI: 1.0–2.1) (*P*-interaction<0.001). Within a subgroup who filled out a later questionnaire with information about HT formulation, overall obesity (RR 1.6, 95% CI: 0.69–3.8 and RR 1.4, 95% CI: 0.66–2.8, respectively) was not associated with endometrial cancer risk among women who exclusively used ET or continuous EPT, but risk was significantly elevated (RR=2.2, 95% CI: 1.0–4.8) among obese women who used a sequential EPT regimen. A similar pattern was seen for weight gain since age 18, i.e., a positive association in those who never used HT and no association in those who ever used HT. Taken together, the results of these cohort studies and our own suggest that the addition of progestin as part of HT can mitigate the effects of obesity on endometrial cancer risk, perhaps because progestins suppress endometrial proliferation that occurs as a result of higher circulation of estrogens in overweight and obese women. In addition, our study, which investigated HT type, showed the obesity effect in those who used ET was less strong than in those who never used HT. This suggests a threshold (rather than a multiplicative) effect beyond which additional exogenous and endogenous estrogens did not continue to increase risk. This could also imply that obesity and ET promote carcinogenesis through the same mechanism [27]. However, these results must be interpreted with caution, as the ever ET group contained both past users (53%) and users who at one time used EPT (41%).

The three recent cohort studies also examined the independent effects of BMI with other measures of obesity on endometrial cancer risk in women overall, but not within strata of HT use (and the EPIC cohort included women who were not postmenopausal). The EPIC cohort found that waist circumference remained significantly associated with increased risk after adjustment for BMI, but hip circumference and WHR did not [24]. In the CPS II, BMI at age 18, weight gain and tendency to gain weight centrally were not significantly associated with risk when adjusted for BMI [25]. In the NIH-AARP Diet and Health Study Cohort, BMI at age 50 remained significantly positively associated with risk after adjustment for baseline BMI, but BMI at age 18 and 30 and weight gain did not [26]. In our cohort, among postmenopausal women who never used HT, we found the positive associations with waist circumference, WHtR (a measure of visceral adiposity independent of height) and WHR (a measure of the distribution of muscle and adipose tissue) were independent of BMI, consistently suggesting that abdominal adiposity is an important risk factor for type 1 endometrial cancer in the absence of HT use. Furthermore, we observed the effects for BMI to be substantially diminished in models that included waist circumference or WHtR, suggesting that abdominal adiposity may be a more important indicator of risk than overall obesity. However, some care must be taken in interpreting these results, as waist and WHtR were moderately correlated with BMI, and thus these models could have collinearity problems. On the other hand, WHR was not correlated with BMI, yet is not strictly an indicator of abdominal adiposity. In addition, the sample size was limited for these analyses, as reflected in the wide confidence intervals. The number of cases was too small to assess the joint effects of BMI and abdominal adiposity and restricted the

interpretation of their simultaneous assessment. Finally, BMI was not reassessed on the follow-up questionnaire, and thus its value was from approximately two years before the waist circumference measure, which could have played a role in the relative strength of the later measure. Nonetheless, of the four cohort studies, ours provides the strongest evidence for the possible relative importance of abdominal versus overall obesity in the absence of HT use and thus, the importance of the aromatization of androgen precursors to estrogens in abdominal adipose tissue [4,6,28]. Similar to the CPS II and NCI-AARP cohorts, we did not find an association with BMI at age 18 independent of BMI at baseline. This finding implies a late-stage (promotional) effect, since it is later life obesity, rather than early obesity, that is important.

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, it was unlikely to differ systematically between cases and non-cases. Also, 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 relatively small sample size which prohibited analyses further stratified by duration of use or current use of each HT type and limited our ability to assess the joint effects of different aspects of body size. In addition, a large number of women were excluded due to missing data. However, in a comparison of the 28,418 women included in the present analysis with the 8,987 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, in this prospective cohort we found that obesity was strongly positively associated with an increased risk of type 1 endometrial cancer in postmenopausal women who never used HT, and that abdominal obesity may be more important to risk than overall obesity; however, due to small numbers, this latter finding requires replication. Among postmenopausal women who used ET, recently being overweight was a significant risk factor. In contrast, obesity was not associated with risk of endometrial cancer in women who exclusively used EPT. Given the epidemic of obesity in the United States and the recent cessation of HT use by many women resulting from the widely-publicized Women's Health Initiative results, understanding the associations between various aspects of obesity, modifying factors, and endometrial cancer risk is important. Furthermore, understanding the differential impact of abdominal versus overall obesity on endometrial cancer risk and how these associations differ by type of HT can provide insight into the etiology of this malignancy.

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Table 1

Characteristic	BMI (Body mass index)					
	<25			>25		
	Median (IQR)	N	(%)	Median (IQR)	N	(%)
BMI (kg/m ²)		16,350	57.5		7,986	28.1
Age (years)	61 (55–69)			62 (56–69)		
Age at menarche (years)	13 (12–13)			12 (12–13)		
Height (inches)	64 (63–66)			64 (63–66)		
Age at first full term pregnancy (years)	25 (23–29)			25 (23–28)		
Parity						
Nulliparous		3,729	22.8		1,681	21.1
Parous		12,621	77.2		6,305	79.0
Oral contraceptive duration (years)						
None		7,682	47.0		4,098	51.3
<3		2,381	14.6		1,178	14.8
>3		6,287	38.5		2,710	33.9
Lifetime strenuous plus moderate physical activity (hours/week)						
<5.5		12,205	74.7		6,116	76.6
>5		4,145	25.4		1,870	23.4
History of hypertension						
No		12,987	79.4		5,503	68.9
Yes		3,363	20.6		2,483	31.1
Hormone therapy history						
Never hormone therapy		5,320	32.5		2,967	37.2
Ever estrogen alone		2,901	17.7		1,454	18.2
E + P combination exclusively		8,129	49.7		3,565	44.6
BMI at age 18 (kg/m ²)						
<25		14,792	92.1		7,288	92.7
≥25		1,271	7.9		571	7.3
Missing or unreliable		287			127	

Characteristic	BMI (Body mass index)							
	<25				25–29			
	Median (IQR)	N	(%)	Median (IQR)	N	(%)	Median (IQR)	N (%)
Weight change (pounds) since age 18								
Loss, > 10 pounds		2,426	15.0		179	2.3		20 0.5
Stable, ± 10 pounds		6,862	42.5		486	6.2		68 1.7
Gain, 11–24 pounds		4,646	28.8		1,420	18.0		103 2.6
25–39 pounds		1,962	12.2		2,986	37.8		268 6.6
≥40 pounds		241	1.5		2,826	35.8		3,587 88.7
Missing or unreliable		213			89			36
Waist (inches) *								
<35		10,303	86.6		2,268	42.8		167 7.3
≥35		1,600	13.4		3,030	57.2		2,114 92.7
Waist-to-hip ratio *								
<0.80		6,231	52.4		1,504	28.4		362 15.9
≥0.80		5,672	47.7		3,794	71.6		1,919 84.1
Waist-to-height ratio *								
<0.55		10,704	89.9		2,709	51.1		223 9.8
≥0.55		1,199	10.1		2,589	48.9		2,058 90.2

* Available only among participants who completed the 1997 follow-up questionnaire.

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

Table 2

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

	Never used HT			Ever used estrogen alone ^c			Used E+P exclusively ^c		
	Cases	Person-years	RR ^a	95% CI	Cases	Person-years	RR ^a	95% CI	P-inter
BMI (kg/m ²)									
<25	34	52,324	1.0		60	28,011	1.0		
25–29	26	29,372	1.2	0.74, 2.1	46	14,087	1.6	1.1, 2.4	0.86, 1.7
≥30	48	18,272	3.5	2.2, 5.5	16	5,672	1.6	0.88, 2.8	1.0 0.63, 1.7 <0.001
<i>P</i> _(trend)			<0.001				0.03		0.61
<i>P</i> _(non-linearity)			0.17				0.15		
Per unit increase			1.07	1.04, 1.09			1.04	1.00, 1.08	1.03 0.99, 1.06
BMI at age 18 (kg/m ²)									
<25	84	86,815	1.0		110	43,032	1.0		
≥25	23	11,137	1.8	1.1, 2.9	11	3,907	1.2	0.64, 2.3	1.4 0.89, 2.3 NS
Per unit increase			1.07	1.03, 1.12			1.03	0.97, 1.09	1.02 0.97, 1.07
Weight change (since age 18) ^b									
Loss, >10 pounds	14	9,569	1.7	0.73, 3.9	5	3,879	0.32	0.12, 0.87	1.2 0.61, 2.3
Stable, ± 10 pounds	12	24,107	1.0		43	13,196	1.0		1.0 36,903
Gain, 11–24 pounds	7	19,159	0.81	0.32, 2.1	28	11,041	0.88	0.54, 1.4	1.2 0.79, 1.9
25–39 pounds	23	18,571	2.6	1.3, 5.3	22	8,971	0.91	0.54, 1.5	0.93 0.56, 1.6
≥40 pounds	52	26,990	3.7	2.0, 7.1	23	10,061	0.85	0.50, 1.4	1.5 0.93, 2.3
<i>P</i> _(trend)			<0.001				0.51		0.25
<i>P</i> _(non-linearity)			0.006						
Per 10-pound increase			1.10	1.05, 1.14			1.05	0.98, 1.13	1.04 0.99, 1.10 NS
Waist circumference (inches)									
<35	18	32,431	1.0		40	18,174	1.0		1.0 56,237
≥35	39	22,290	2.7	1.5, 4.8	26	9,681	1.3	0.78, 2.2	1.3 0.85, 2.0 <0.05
Per inch increase			1.09	1.05, 1.13			1.02	0.97, 1.08	1.02 0.98, 1.06
Waist-to-hip ratio									
<0.80	9	19,708	1.0		17	9,965	1.0		1.0 38,756

	Never used HT				Ever used estrogen alone ^c				Used E+P exclusively ^c				
	Cases	Person-years	RR ^a	95% CI	Cases	Person-years	RR ^a	95% CI	Cases	Person-years	RR ^a	95% CI	P-inter
≥0.80	48	35,013	2.7	1.3, 5.6	49	17,890	1.5	0.83, 2.6	54	41,065	1.1	0.70, 1.6	<0.05
Per 0.1-unit increase			1.31	1.02, 1.68			1.10	0.85, 1.43			1.01	0.78, 1.31	
Waist-to-height ratio													
<0.55	21	34,709	1.0		44	19,145	1.0		69	60,432	1.0		
≥0.55	36	20,013	2.8	1.6, 4.8	22	8,709	1.3	0.78, 2.3	26	19,389	1.1	0.71, 1.8	<0.01
Per 0.1 unit increase			1.72	1.33, 2.23			1.16	0.82, 1.63			1.13	0.86, 1.48	

^a Adjusted for age at menarche, parity and age at first full term pregnancy, oral contraceptive use and duration, physical activity, height, hypertension and its interaction with time-dependent age; age was the time-scale and analyses were stratified by age at baseline.

^b Additionally adjusted for weight at 18.

^c Additionally adjusted for duration of HT and its interaction with time-dependent age.

HT: hormone therapy, E: estrogen, P: progestin, BMI: body mass index, RR: relative risk, CI: confidence interval, NS: non-significant

Table 3

Independent effects of obesity measures on endometrial cancer risk in postmenopausal women who never used HT

	RR ^a	95% CI
Model 1^b		
BMI (kg/m ²)		
<25	1.0	
25–29	1.3	0.76, 2.2
≥30	3.4	2.1, 5.4
P(trend)	<0.001	
P(non-linearity)	0.23	
BMI at age 18 (kg/m ²)		
<25	1.0	
≥25	1.5	0.93, 2.4
Model 2^c		
BMI (kg/m ²)		
<25	1.0	
25–29	1.3	0.63, 2.6
≥30	1.5	0.67, 3.5
P(trend)	0.33	
Waist circumference (inches)		
<35	1.0	
>35	2.2	1.1, 4.5
Model 3^c		
BMI (kg/m ²)		
<25	1.0	
25–29	1.6	0.85, 3.0
≥30	2.2	1.1, 4.4
P(trend)	0.03	
P(non-linearity)	0.60	
Waist-to-hip ratio		
<0.80	1.0	
≥0.80	2.2	1.1, 4.7
Model 4^c		
BMI (kg/m ²)		
<25	1.0	
25–29	1.3	0.65, 2.6
≥30	1.5	0.62, 3.4
P(trend)	0.41	
Waist-to-height ratio		
<0.55	1.0	

	RR^a	95% CI
≥0.55	2.3	1.1, 4.6

^a Adjusted for age at menarche, parity and age at first full term pregnancy, oral contraceptive use and duration, physical activity, height, and hypertension and its interaction with time-dependent age; age was the time-scale and analyses were stratified by age at baseline.

^b Follow-up time began at the baseline questionnaire. Excluding those with missing data for BMI at age 18.

^c Follow-up time began at the 1997 follow-up questionnaire.

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