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Body size over the life-course and the risk of endometrial cancer: the California Teachers Study

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Abstract

Purpose—Obesity is a public health epidemic and a major risk factor for endometrial cancer. Here we identify key aspects of body size which jointly, over the life-course (since adolescence), are associated with endometrial cancer risk.

Methods—Among 88,142 participants in the California Teachers Study, 887 were diagnosed with invasive type 1 endometrial cancer between 1997–1998 and 2012. Multivariable Cox proportional hazards models provided estimates of hazard rate ratios (HR) and 95% confidence intervals (CI) for endometrial cancer associated with life-course body size phenotypes, which incorporated validated measures.

Results—Among women currently using hormone therapy, endometrial cancer risk was only associated with height (HR=1.78, 95% CI: 1.32–2.40 for ≥67 versus <67 inches). Among women not using hormone therapy, tall women who were overweight/obese in adolescence (HR=4.33, 95% CI: 2.51–7.46) or who became overweight/obese as adults (HR=4.74, 95% CI: 2.70–8.32) were at greatest risk.

Conclusions—Considering absolute body mass, changes in adiposity over time, and body fat distribution together, instead of each measure alone, we identified lifetime obesity phenotypes

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The authors declare they have no conflict of interest.

COMPLIANCE WITH ETHNICAL STANDARDS

All procedures performed in the California Teachers Study involving human participants were in accordance with the ethnical standards of the Institutional Review Boards of the Cancer Prevention Institute of California, City of Hope National Medical Center, the University of Southern California, the University of California at Irvine, and the California Health and Human Services Agency and were in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethnical standards. Informed consent was obtained from all individual participants included in the study.

associated with endometrial cancer risk. These results more clearly define specific risk groups, and may explain inconsistent findings across studies, improve risk prediction models, and aid in developing targeted interventions for endometrial cancer.

Keywords

body size; endometrial cancer; height; life-course; obesity

INTRODUCTION

One of the most serious public health crises worldwide over the last thirty years has been the rapidly increasing prevalence of overweight and obesity and the impact of this epidemic on the risk of many chronic diseases. It is well established that body size impacts endometrial cancer risk [1–3]. Overall, women are at greater risk of endometrial cancer if they are tall, obese, or have substantial adult weight gain or abdominal adiposity [4,5,1,2,6]. However, these associations are largely limited to women who have not used any form of hormone therapy (HT) [7–11]. With the substantial reduction in HT use since 2002 following the publicity surrounding the findings of increased breast cancer risk associated with estrogen plus progestin use in the Women's Health Initiative clinical trial [12], body size may have a greater impact on endometrial cancer risk than in past decades. Indeed, among white women the rates of uterine cancer have increased during this time [13].

Most epidemiologic studies have examined body size measures individually or as the joint association between two variables [7–10,4,11,1,2,6]. However, the interrelationships between various body measurements are complex. Individual body size measures are often correlated with one another and the associations with disease risk reflect confounding and interactions and vary over the life-course. Thus, our objective was to identify key aspects of body size over the life-course that are associated with endometrial cancer risk, jointly considering aspects of absolute obesity and stature, changes in adiposity over time, and body fat distribution using data from our large, diverse cohort of women prospectively followed for more than 10 years.

METHODS

The California Teachers Study recruited 133,479 active or retired female public school professionals in 1995–1996 [14]. At the time participants joined the cohort (baseline), they completed a self-administered questionnaire addressing health and medical history (including HT use and body size), lifestyle, and other exposures and behaviors. The second follow-up questionnaire, completed in 1997–1998, included self-measured waist and hip circumferences. The third (2000–2001) and fourth (2005–2006) questionnaires updated HT use.

The California Teachers Study was approved by the Institutional Review Boards of the Cancer Prevention Institute of California, City of Hope National Medical Center, the University of Southern California, the University of California at Irvine, and the California Health and Human Services Agency.

Assessment of body size

Body size measures included in the present analysis were: height (inches), body mass index (BMI; kg/m^2), weight change (pounds), and waist-to-height ratio (WHtR). Self-reported height at baseline and at age 18 years were highly correlated (r=0.97). Thus, if height at baseline was missing, we substituted height at age 18 years. BMI was calculated based on height and self-reported weight at age 18 years and at baseline. At the 2-year follow-up, women were provided a standard heavy-weight flexible paper tape measure (calibrated in inches on both sides with each side being a different color to prevent errors in measurement) and asked to measure their waist and hip circumferences following written, illustrated instructions. We chose to use WHtR instead of waist-to-hip ratio as a measure of abdominal adiposity as the former has been found to be a better predictor of visceral fat while the latter is more strongly correlated with subcutaneous fat [15,16]. Details on the measurement and validation of body measurements have been published elsewhere [7].

We used the following measures to identify lifetime body size phenotypes: adult height; BMI at age 18 years; BMI at baseline; weight change from age 18 years to baseline among women of normal weight (i.e., BMI<25) at baseline; and WHtR among women who were overweight (i.e., BMI 25.0–29.9) or obese (BMI≥30) at baseline. Based on *a priori* decisions, we evaluated weight change only among women of normal weight (BMI<25) (i.e., overweight/obese women were not further split into additional phenotypes based on degree of weight change) under the assumption that attained BMI among overweight/obese women was more important than the amount of weight gained. Similarly, body fat distribution (i.e., WHtR) was evaluated only among overweight/obese women under the assumption that in the absence of substantial adipose tissue among normal weight women the location of the adipose tissue had minimal influence. These assumptions also reduced the number of total phenotypes evaluated.

Follow-up for outcomes

The cohort was followed annually to ascertain cancer diagnoses, changes of address, and deaths. Cancer diagnoses were identified through linkage with the California Cancer Registry, a population-based cancer registry covering all of California and whose data are included in the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Since more than 99% of all cancer diagnoses among California residents are reported to the cancer registry [17], cohort members who continue to reside in California are all continually followed for cancer outcomes. Changes of address were obtained using annual mailings, notifications from participants, and record linkages with several sources including the United States Postal Service National Change of Address database. Linkages with California and national mortality files were used to ascertain date and cause of death.

Study population

We began follow-up for the present analysis on the date the 2-year questionnaire was completed (since this was when abdominal adiposity was reported). We excluded women who, at that time, did not live in California (n=10,230); had a prior history of endometrial cancer (identified by self-report or linkage with the cancer registry; n=1,791) or whose history of cancer prior to baseline was unknown (n=662); had a hysterectomy (identified by

selfreport or linkage with California hospital discharge files; n=29,120); or had died (n=498). We also excluded 1,330 women who were aged 85 years or older at baseline, one with invalid data overall, one who asked to be removed from the cohort, and 18 who requested that their data only be used for breast cancer research. Also excluded were 1,685 women who contributed person-time to the analysis past the 10-year follow-up but had missing data on HT use on all three assessments where it was collected (i.e., baseline, 5-year, and 10-year follow-ups). Thus, the analytic cohort included 88,143 women.

Statistical Analysis

Multivariable Cox proportional hazards regression was used to estimate hazard rate ratios (HR) and 95% confidence intervals (CI) relating endometrial cancer to measures of body size measures and lifetime phenotypes as a function of current HT use. Follow-up time was calculated as the number of days between completion of the 1997–98 follow-up questionnaire (or for those not completing this questionnaire, November 5, 1997, the median date the questionnaire was completed by those who submitted it) and the first of the following six events: diagnosis of invasive type I endometrial cancer (International Classification of Diseases for Oncology-3 site codes C54.1 or C54.9 and histology codes 8140, 8380–8383, 8560, and 8570; n=887), diagnosis of in-situ, type II or other specific or non-specified type of endometrial cancer (n=20, 113, and 115 respectively), a move outside of California lasting more than 4 months (n=7,751), death (n=8,615), a hysterectomy (n=6,508), or December 31, 2012.

HT use was collected at baseline and updated on the 5- and 10-year follow-up questionnaires. For each woman, current HT use was modeled as a time-varying covariate with three levels: using, not using, or unknown. The data were represented as a counting process, with transitions at the dates of the two follow-up questionnaires (or the median completion date for non-responders) for each subject whose status changed. Specifically, women were classified as using HT, not using HT or unknown HT use at the beginning of follow-up based on their responses to the baseline questionnaire and contributed person-time to that HT level until the 5-yr follow-up at which time they are "re-classified" into one of the same three categories based on their 5-yr questionnaire responses. The reclassification process was then repeated based on the 10-yr responses. Two subsets of the resulting counting process data were created for subsequent analyses (currently using HT and not using HT) and separate regression analyses were performed for each subset. Thus, in the context of the Cox regression model "current" HT refers to a given woman's use at the time an "event" (i.e., cancer diagnosis) is evaluated, given the caveat that this re-classification process occurred at only the 5- and 10-yr follow-ups rather than more frequently. 27,581 women contributed time to the current HT use subset and 66,392 women to the not using HT subset.

All regression models were stratified by age (in years) at baseline to adjust for calendar effects. We evaluated covariates separately for each HT subset. For women not using HT, covariates included: age at menarche (in years from ≤9 to ≥17) and its interaction with time-dependent age, gravidity (yes, no) and among gravid women, age at last pregnancy (in years), duration of oral contraceptive use (none, <3 years, ≥3 years), self-reported history of

hypertension or use of hypertensive medications (yes, no) and its interaction with time-dependent age, self-reported history of diabetes (yes, no), and average daily caloric intake (kcal). For women currently using HT, covariates included: duration of oral contraceptive use and self-reported history of hypertension or use of hypertensive medications and its interaction with time-dependent age. These covariates were included based on prior knowledge and their independent association with endometrial cancer risk within each subset in our cohort.

Model selection—For each HT subset, our approach for identifying the lifetime body size phenotypes of importance proceeded in three steps. First, we examined the association of each body size variable separately, collapsing each variable, when possible, into two or three categories based on the observed hazard ratios and confidence intervals, with the goal of maintaining prediction while achieving the most parsimonious model. Second, we used the categories from step one to create and evaluate a full model obtained by partitioning the data set into a set of disjoint phenotype categories based on the joint consideration of height, BMI at age 18 years, BMI at baseline, weight change among those with a normal BMI at baseline, and site of adiposity (abdominal versus gluteal) among those who were overweight or obese, as described above. Finally, we repeatedly collapsed categories created in step two to achieve a final parsimonious model that maximized prediction. Collapsing categories was based on sample size (precision) within each phenotype and comparisons of between-phenotype differences using two-sided Wald tests.

Women with missing data for the covariates included in each HT-specific subset were omitted from the analyses reported in Tables 3 and 4. Women with missing data on any of the body size measures needed to define a specific phenotypic category in a given model were put together into a single 'missing' category for that model. As categories were collapsed, women could reenter the phenotypic analyses, hence the number of cases reported in the tables do not necessarily sum over the collapsed categories.

RESULTS

At the start of follow-up, 65,341 women were not current HT users and 19,926 were using HT (Table 1). HT users were confined to those who were peri- or postmenopausal while non-users included premenopausal women as well. As a result, non-users were on average younger (median=45 versus 56 years). Women using HT were more likely to have a history of hypertension (23% versus 14%).

The most parsimonious version of each of the variables of interest which, when considered separately, was associated with endometrial cancer risk in each of the HT subsets is shown in Table 2. Among women not using HT, endometrial cancer risk was associated with all of the variables of interest, including height; adolescent and adult BMI; weight change in adulthood; and abdominal (WHtR≥0.48) as opposed to gluteal (WHtR<0.48) adiposity. Only adult height was positively associated with risk among women currently using HT (HR=1.78, 95% CI: 1.32–2.40 for ≥67 versus <67 inches).

For each HT group, we evaluated the association between endometrial cancer risk and the full spectrum of 16 body size phenotypes, defined by height, adolescent BMI, adult BMI, weight change between age 18 years and joining the cohort, and abdominal adiposity (Table 3). Among women not using HT, overweight/obesity in adolescence, in adulthood, and throughout a woman's lifetime were associated with increased risk of endometrial cancer with taller women who experienced lifetime overweight/obesity having the greatest risk (HR=5.99, 95% CI: 3.03–11.82). Also at increased risk were tall women with normal adult BMI but who had gained 25 or more pounds since adolescence (HR=2.90, 95% CI: 1.45–5.79). Among women currently using HT, only tall women, regardless of body fatness, were at increased risk.

To obtain the most parsimonious predictive models, rare phenotypic combinations (i.e., those with <10 cases) were collapsed into single groups as were groups with similar risk estimates using an iterative process. The final model for women not using HT is presented in Table 4 and includes expanded risk categories to illustrate the trends in risk observed with increasing height and adult BMI. Women who had maintained a normal weight (BMI<25) throughout life were not at increased risk of endometrial cancer, regardless of stature, nor were short women who became overweight (BMI 25.0–29.9) during adulthood. Women of average or tall stature who had gained 25 or more pounds during adulthood or become overweight were at increased risk (HR=1.87, 95% CI: 1.21–2.89 for average height women and HR=2.23, 95% CI: 1.36–3.64 for tall women). These estimates were not statistically different from each other (p=0.42), suggesting weight gain, not height, was driving risk for these women. Similarly, adult obesity increased risk (HR=2.39, 95% CI: 1.24–4.60, HR=2.93, 95% CI: 1.82–4.73, and HR=4.74, 95% CI: 2.70–8.32 for short, average, and tall women, respectively). The first two estimates did not differ from each other (p=0.41) but the association for tall women was greater than for women of short (p=0.03) or average (p=0.09) height. Finally, adolescent overweight/obesity increased risk, regardless of height. Among women currently using HT, only greater height was associated with increased risk (HR=1.78, 95% CI: 1.32–2.40).

DISCUSSION

Our analyses suggest that the relationships between life-course body size phenotypes and type 1 endometrial cancer incidence are complex. Among women not using HT, greater body size, both in terms of height and weight increased risk. Overweight/obesity in adolescence, even among those who were of normal body size in adulthood, was associated with increased risk, as was adult weight gain and overweight/obesity. Among women currently using HT, only height was positively associated with risk.

Our findings for the associations between single body size measures and endometrial cancer risk (Table 2) were consistent with the general consensus in the literature and confirmed that some of the heterogeneity in results between studies is likely due to lack of control for HT use [7–11,1–3]. Our life-course approach also highlights the complexity of associations between individual body size measures and endometrial cancer risk among women not using HT, a growing segment of the US population, and suggests that simple models using individual measures may be inadequate, even when adjusted for confounding. Most studies

that have included adolescent obesity and current BMI in the same model have found that only current BMI was associated with risk [7,8,18,2,19] leading to the conclusion that only current obesity plays a critical role in endometrial cancer risk. Our life-course approach, which essentially examines interactions rather than confounding, suggests that adolescent obesity also contributes to endometrial cancer risk, even among women who are of normal weight as adults. Life-long obesity, however, appears to be most detrimental, particularly among tall women. It is of note that many of the possible phenotypes were not commonly observed and those phenotypes which are most common differed somewhat by HT use. We were unable to evaluate whether body fat distribution was associated with endometrial cancer risk within specific body size phenotypes since a large proportion of the overweight/obese women with endometrial cancer had abdominal (as opposed to gluteal) adiposity. Thus, our results for BMI generally apply to adult abdominal adiposity.

HT use increases the risk of endometrial cancer [20,21] and, among postmenopausal women, those who report using estrogen alone or estrogen plus progestin therapy have serum estrogen levels that are 3 to 4 times higher than non-users [18,22]. In contrast, obesity alone increases serum estrogen levels by only 50% [18,23]. Thus, one would expect to see no added risk of obesity on endometrial cancer risk in the presence of exogenous estrogens which is what we observed in this study.

Apart from single measures assessed at different ages and reported separately, few studies have evaluated lifetime body size and endometrial cancer risk. One study found that women who were overweight or obese throughout adulthood had a 4.8-fold grater increase risk of endometrial cancer than women who maintained a normal weight [24]. In addition, they found that the increased risk associated with overweight/obesity lessened the older a women was when she became overweight/obese. Another study looked at body shape trajectories from age 5 to 60 years based on Sørensen's pictograms [25]. Among women who never used HT, those with moderate or marked increases in body size over time or who were heavy throughout life had greater risk of endometrial cancer than women reporting the leanest body shapes throughout life. While these findings are not directly comparable to ours, they are generally consistent with the patterns of risk we observed.

Sex steroid hormones, inflammation, and glucose/insulin have been suggested as the mechanisms most likely to be involved in anthropometric-related carcinogenesis [26–28,5,1]. These same pathways have been implicated in endometrial carcinogenesis [29]. The prevailing theory regarding steroid hormones suggests that excess bioavailable estrogen, due to a disruption in the estrogen-progesterone balance related to either elevated estrogen levels or reduced progesterone levels, plays an important role [26,30]. A woman's maximum height is usually established by mid-adolescence and may reflect the influence of early life nutrition, environmental exposures, the rate of sexual maturation, hormone profiles, and genetics on fetal and childhood linear growth [1,31]. Adolescent obesity is often associated with early menarche and irregular or anovulatory menstrual cycles resulting in altered profiles of ovarian hormones (including a reduction in progesterone exposure and unopposed estrogen), androgens, sex hormone binding globulin, and insulin-like growth factor-1 [18,1]. Weight gain is an indicator of sustained positive energy balance and, along with adult obesity, affects circulating hormones, growth factors, insulin, and inflammatory cytokines

which together can reduce apoptosis and stimulate low-grade chronic inflammatory responses [28,1,32]. Adult weight gain primarily reflects the disposition of fat mass with abdominal fat associated with impaired glucose metabolism, increased insulin resistance, and in postmenopausal women, altered estrogen synthesis [4,28]. Abdominal, as opposed to gluteal, adiposity is more closely correlated with visceral adipose tissue, which is more metabolically active, secreting more cytokines and hormones than subcutaneous adipose tissue [5,33,28]. Finally, exogenous HT use may mask any association of adiposity with endometrial cancer risk by increasing circulating estrogens levels beyond that of the adipose tissue.

The present analysis has several limitations. First, while determined *a priori*, our approach to and interpretation of the analysis is somewhat agnostic with a certain degree of subjectivity, involves multiple comparisons, and for some subgroups is based on small numbers of cases. However, we used quantitative methods (Wald tests) to determine whether associations between specific subgroups differed from each other. Collapsing subgroups having few cases may have masked some associations. Second, we included only 16 body size phenotypes in our analysis. Examining additional phenotypes, such as absolute weight gain among women with adult or life-long overweight/obesity or body fat distribution among women of normal BMI, may be possible in larger datasets, such as the pooled datasets available from the Epidemiology of Endometrial Cancer Consortium (E2C2) or the Harvard Diet Pooling Project. Third,, data on HT use were updated only twice (i.e., at the 5- and 10-year questionnaires) and we did not distinguish between estrogen-only (ET) and estrogen-plus-progestin (EPT) HT types, both of which may have introduced some misclassification. The largest change in HT use, a major reduction in use, would have occurred when the results of the Women's Health Initiative were released around 2002 [12]. This event fell between these two follow-up questionnaires administered in 2000–2001 and 2005–2006, respectively. Thus, women who quit HT use around 2002 would have contributed person-time and events to the current HT group for a few "extra" years as opposed to being moved to the "not currently using HT" group immediately. While data on ET vs EPT use were available, evaluation by type of HT use was precluded by the relatively small number of cases which would have occurred in each body size phenotype if separate regression analyses had been performed for each HT type. In addition, of the 66,392 women contributing time to the "not using HT" analysis, 49,377 (74%) never reported using HT. To the extent that data on HT use over time or specific HT preparations are available, analyses in large pooled datasets would be ideal for evaluating the effects of body size among never and former HT users separately. Finally, the anthropometric data used were self-reported which could have introduced measurement error due to the inability to accurately recall weight at age 18 or a desire to report socially more normative values. However, our validation study suggested valid reporting of current measures and excellent reproducibility of all measures, minimizing such concerns [7].

Notable strengths of this analysis include the unique conceptual approach taken to assess the impact of body size over the life-course and the conduct of these analyses in a large cohort of women who had detailed anthropometry data and a large number of endometrial cancer diagnoses over the more than 15 years that the women were followed. We included both dynamic body size measures (e.g., weight change) which reflect age-related metabolic

changes and static measures (e.g., BMI and height) which reflect the influence of absolute size [34]. In addition, when assessing abdominal (android) versus gluteal (gynoid) obesity, we used WHtR which is a better predictor of visceral fat rather than the more commonly used measures of waist circumference or waist-to-hip ratio [15].

In summary, taking into account absolute body mass, changes in adiposity over time, and body fat distribution, we identified lifetime obesity phenotypes which were associated with endometrial cancer risk in our large cohort. These findings may aid in improving risk prediction models and developing targeted interventions, and may clarify inconsistent findings across studies to the extent that the study populations differ in composition as regards important anthropometric indicators and HT use. To the extent that equally detailed anthropometry is available in other studies, similar analyses conducted in large consortial data sets, such as E2C2 or the Harvard Diet Pooling Project, are needed to confirm our findings and improve statistical power for evaluating heterogeneity across rare body size phenotypes.

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Table 1

Baseline characteristics of the analytic cohort, California Teachers Study, 1995.

	Not using HT (n=65,341)				Current HT use (n=19,926)			
	N	**%**	**median**	**IQR**	**N**	**%**	**median**	**IQR**
Age (years)			45	37–53			56	52–63
Age at menarche (years)			13	12–13			13	12–13
missing	658	1.0%			482	2.4%		
Gravid	49,031	75.0%			16,092	80.8%		
missing	1,008	1.5%			530	2.7%		
Age at last pregnancy (among gravid)[a]			31	28–35			30	27–34
missing	182	0.4%			1	0.0%		
Duration of oral contraceptive use (years)								
none	17,499	26.8%			5,724	28.7%		
<3	12,605	19.3%			3.173	15.9%		
≥3	32,384	49.6%			9,636	48.4%		
missing	2,853	4.4%			1,393	7.0%		
Menopausal status								
premenopausal	46,097	70.5%			0			
postmenopausal	19,244	29.5%			19,926	100%		
Ever use of HT								
never	58,555	89.6%			0			
former	6,786	10.4%			0			
current	0				19,926	100%		
History of hypertension	9,030	13.8%			4,534	22.8%		
missing	0				0			
History of diabetes	1,517	2.3%			441	2.2%		
missing	0				0			
Average daily caloric intake (kcal)			1,564	1,233–1,951			1,472	1,178–1,822
missing	5,723	8.8%			1,507	7.6%		

Abbreviations: HT: hormone therapy; IQR: interquartile range; N: number.

[a]Age at most recent pregnancy among premenopausal women.

Table 2

Individual associations between body size variables and risk of type I endometrial cancer by HT use, California Teachers Study, 1995–2012.

	Not using HT					Currently using HT			
	Cases	Person-years	HR[a]	95% CI		Cases	Person-years	HR[b]	95% CI
Height (inches)									
<63	59	103,432	1.0			131	128,704	1.0	
63–66	188	285,585	1.29	0.96–1.73					
≥67	106	136,302	1.75	1.26–2.42	[c]	67	41,732	1.78	1.32–2.40
missing	1	1,256				0	305		
			p_{trend}=0.0005						
BMI at age 18 (kg/m^2)									
<25	269	454,597	1.0			173	151,357	1.0	
≥25	67	54,392	1.77	1.34–2.33		18	13,767	1.06	0.64–1.75
missing	18	17,586				7	5,616		
BMI at baseline (kg/m2)									
<25	134	325,310	1.0			122	108,264	1.0	
25–29	97	119.747	1.51	1.16–1.97		69	58,048	100	0.74–1.35
≥30	110	67,501	2.67	2.04–3.50					
missing	13	14,018				7	4,428		
			p_{trend}<0.0001						
Weight change (pounds) (age 18 to baseline)									
loss ≥10	40	56,578	1.69	1.16–2.44		128	104,603	1.0	
stable	95	267,152	1.00						
gain ≥25	203	185,307	2.20	1.72–2.83		62	60,519	0.83	0.61–1.13
missing	16	17,538				8	5,618		
Waist-to-height ratio									
<0.48	65	195, 604	1.0			75	64,317	1.0	
≥0.48	204	206,120	1.91	1.43–2.54		91	71,962	0.87	0.64–1.19
missing	85	124,852				32	34,461		

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio; HT: hormone therapy.

[a]Adjusted for the interaction between age at menarche and time-dependent age, gravidity, age at last pregnancy, duration of oral contraceptive use, the interaction between history of hypertension and time-dependent age, history of diabetes, and average daily caloric intake; age was the time metric and the model was stratified by age at baseline.

[b]Adjusted for duration of oral contraceptive use, and the interaction between history of hypertension and time-dependent age; age was the time metric and the model was stratified by age at baseline.

[c]Indicates cells which were collapsed for analysis.

Table 3

Full models reflecting body size over the life-course and risk of type 1 endometrial cancer by HT use, California Teachers Study, 1995–2012.

					Not using HT			Currently using HT		
Height[a]	**BMI (age 18)**	**BMI (baseline)**	**Weight change**	**Adiposity**	**Cases**	**HR**[b]	**95% CI**	**Cases**	**HR**[c]	**95% CI**
Short	Normal	Normal	Loss		3	1.96	0.55–6.94	67	1.0	
			Stable		12	1.0				
			Gain		2	1.62	0.36–7.23	4	0.47	0.17–1.29
		Overweight/ obese		Abdominal	19	2.35	1.14–4.85	31	1.07	0.69–1.65
				Gluteal	0			1	0.49	0.07–3.55
	Overweight/ obese	Normal			4	2.88	0.93–8.95	6	1.17	0.50–2.70
		Overweight/ obese		Abdominal	5	3.93	1.38–11.22	6	1.62	0.70–3.77
				Gluteal	0			0		
Tall	Normal	Normal	Loss		12	2.00	0.90–4.46	32	1.82	1.19–2.78
			Stable		57	1.40	0.75–2.62			
			Gain		25	2.90	1.45–5.79	11	2.46	1.30–4.68
		Overweight/ obese		Abdominal	86	3.22	1.75–5.91	14	1.85	1.04–3.31
				Gluteal	3	1.32	0.37–4.70	1	1.00	0.14–7.22
	Overweight/ obese	Normal			15	2.94	1.37–6.29	1	0.60	0.08–4.33
		Overweight/ obese		Abdominal	30	5.99	3.03–11.82	1	1.03	0.14–7.47
				Gluteal	0			0		

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio; HT: hormone therapy.

[a]Body size cut-points: height <63,≥63 (for women not using HT) and <67,≥67 (for women currently using HT); BMI (age 18) and BMI (baseline) <25,≥25; weight change: loss >10 pounds, loss <10 pounds or gain <25 pounds (stable), gain ≥25 pounds (for women not using HT) and loss or gain <25 pounds, gain ≥25 pounds (for women currently using HT); adiposity ≥0.48 (abdominal),<0.48 (gluteal).

[b] Adjusted for the interaction between age at menarche and time-dependent age, gravidity, age at last pregnancy, duration of oral contraceptive use, the interaction between history of hypertension and time-dependent age, history of diabetes, and average daily caloric intake; age was the time metric and the model was stratified by age at baseline.

[c] Adjusted for duration of oral contraceptive use, and the interaction between history of hypertension and time-dependent age; age was the time metric and the model was stratified by age at baseline.

Table 4

Best fitting models describing the association between life-course body size and risk of type 1endometrial cancer among women not using HT, California Teachers Study, 1995–2012.

Height[a]	BMI (age 18)	BMI (baseline)	Weight change	Cases	HR	95% CI
short	normal	normal/ overweight		31	1.0[b]	
		obese		13	2.39	1.24–4.60
	overweight/obese			11	2.27	1.13–4.54
average	normal	normal	<25 lbs	48	1.04	0.66–1.64
		normal BMI with weight gain ≥25 lbs *or* overweight		60	1.87	1.21–2.89
		obese		40	2.93	1.82–4.73
	overweight/obese	normal/ overweight		14	1.98	1.05–3.74
		obese		18	3.83	2.11–6.95
tall	normal	normal	<25 lbs	21	1.17	0.67–2.04
		normal BMI with weight gain ≥25 lbs *or* overweight		34	2.23	1.36–3.64
		obese		21	4.74	2.70–8.32
	overweight/obese			24	4.33	2.51–7.46

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio; HT: hormone therapy.

[a]Body size cut-points: height <63 (short), 63–66 (average), ≥67 (tall); BMI (age 18) and BMI <25 (normal), 25–29 (overweight), ≥30 (obese).

[b]Adjusted for the interaction between age at menarche and time-dependent age, gravidity, age at last pregnancy, duration of oral contraceptive use, the interaction between history of hypertension and time-dependent age, history of diabetes, and average daily caloric intake; age was the time metric and the model was stratified by age at baseline.