Published in final edited form as:
Int J Cancer. 2010 January 15; 126(2): 490–499. doi:10.1002/ijc.24718.

Body Size, Adult BMI Gain and Endometrial Cancer Risk: The Multiethnic Cohort

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Abstract

The effect of body size and change in BMI on endometrial cancer risk across different racial/ethnic groups has not been studied. We examined the association between body size and endometrial cancer risk and potential effect modification of other risk factors among 50,376 women in the Multiethnic Cohort Study. During 10.3 years of follow-up, 463 endometrial cancer cases were identified. Epidemiologic data were collected from the baseline questionnaire. “BMI change” was defined as the percentage of body mass index change from age 21 to the time of recruitment. Women who were heavier at age 21 or at baseline (weight ≥ 53.5kg or ≥ 63.9 kg, respectively) had an increased endometrial cancer risk compared to the lowest quartile of weight during the respective periods. BMI gain ≥ 35% had a RR of 4.12 (95% CI: 2.69, 6.30) compared to the reference group (−5% ≤ BMI change <+5%). Women who averaged an annual BMI gain ≥ 1% had a >3.20-fold (95% CI: 2.37, 4.33) increased risk compared to women who maintained a stable adult BMI (−0.25 to <+0.25%). The highest risk associated with BMI gain was observed among nulliparous women and postmenopausal women who never used hormone therapy. While African Americans and Whites showed an increase in risk after ≥ 35% BMI gain, Japanese Americans showed an increase in risk with much smaller gain (≥ 5%). In conclusion, adult obesity and increase in adiposity are risk factors for endometrial cancer; and the risk associated with these factors may vary across racial/ethnic groups.

Keywords

Weight change; endometrial cancer; multiethnic populations

Introduction

Endometrial cancer is the fourth most common cancer among US females.[1] The role of obesity in endometrial cancer etiology is well established[2, 3]; prospective studies report obesity, defined as body mass index (BMI) ≥ 30 kg/m^2, is associated with a 1.7 to 4.5 fold increase in

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Novelty/Impact Statement: Obesity is a major risk factor for endometrial cancer, however, the effect of body size and BMI change on endometrial cancer risk across different racial/ethnic groups has not been previously studied. This is the first study, that we are aware of, which prospectively examines the association of body size measure over time with endometrial cancer risk across a multiethnic population in the United States.

risk.[4–12] Because substantial body weight gain can lead to obesity, it is believed that adult weight or BMI change, often a measure of increased adiposity, is associated with endometrial cancer risk.

Among five prospective studies,[5, 6, 8, 13, 14] all five reported a positive association between weight gain during the period of young adulthood (age 18 to 25) to age at study entry and endometrial cancer risk; however, none of these studies have investigated the role of anthropometric measures across racial/ethnic populations. The aim of this analysis was to examine the association of body size and its change over time with the risk of endometrial cancer in a multiethnic population, as well as the potential modifying effect of other risk factors on these relations.

Material and Methods

Study population

The Multiethnic Cohort Study (MEC) is a prospective cohort study established to investigate the association of lifestyle and genetic factors with chronic disease. Details of the study design, recruitment, response rates, and baseline characteristics of the MEC have been previously published.[15] Briefly, the cohort consists of 215,251 men and women between the ages of 45 to 75 selected from five racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites. Potential participants were identified through drivers' license files from the Department of Motor Vehicles, voter registration lists, and Health Care Financing Administration data files primarily from Los Angeles County, California and the state of Hawaii during the period of 1993–1996. Initially, for the purpose of study recruitment, racial/ethnic groups were identified by last name but the final determinant of race/ethnicity was through self-report. The response rates were highest in Japanese Americans (51.3%), Whites (47.0%), and Native Hawaiians (42.2%) and lowest in African Americans (25.5%) and Latinos (21.3%).[15] Each participant completed a mailed self-administered questionnaire regarding demographic and lifestyle factors, physical activity, tobacco smoking history, diet, anthropometric measures, personal history of medical conditions, family history of cancer, as well as reproductive history and hormone use (women only). The respective institutional review boards have approved of the study protocol.

Inclusion and exclusion criteria

Women were excluded from the present analysis if they *i*) were diagnosed with cancer (other than nonmelanoma skin cancer) before the date of the baseline questionnaire (n=6,734), *ii*) had missing menopausal information or reported a hysterectomy or bilateral oophorectomy on the baseline questionnaire (n=19,656), *iii*) had missing data on any of the following variables: education, height or weight at baseline, weight at age 21, age at menarche, age at menopause, parity, oral contraceptive (OC) use, postmenopausal hormone therapy (HT) use, smoking status, and physical activity (n=12,117). After all exclusions, 50,376 eligible women (14.7% African Americans, 32.4% Japanese Americans, 18.7% Latinas, 8.1% Native Hawaiians, and 26.2% Whites) were included in the analysis. Excluded women were approximately 3.5 years older than women retained for analysis, but the distribution of the remaining risk factors did not differ between the two groups.

Follow-up and case identification

Participants' follow-up time began at the completion of the baseline questionnaire and continued until they reach one of the following endpoints: 1) diagnosis of endometrial cancer, 2) death, or 3) end of follow up (December 31, 2004). All incident cases of endometrial cancer were identified through record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry. These cancer

registries participate in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program and have completeness > 99%.[16] Cases of endometrial cancer were defined by the International Classification of Diseases for Oncology (ICD-O-3) code C54 (uterine corpus). Uterine sarcomas (n=29) were excluded from the case group. Deaths within the cohort were determined through annual linkage to state death certificate files in California and Hawaii and periodically to the National Death Index. The follow-up rate in the cohort is 95%; National Death Index information was available for the remaining 5% of the cohort. Cohort participants were followed for an average 10.3 years, contributing to a total of 517,808 person-years of follow-up time. A total of 463 women with incident endometrial cancer were identified during the follow-up period.

Assessment of anthropometric measures

Measures of weight (at age 21 and baseline) and height (at baseline) were obtained by self-report from the baseline questionnaire. For cohort participants missing baseline weight data (6%), measures were imputed from their drivers' license files. The average correlation between self-reported weights (from questionnaire) and imputed weights (from drivers' license file) was 90%. If no source of information was available, participants were excluded from the analysis, as mentioned in the inclusion and exclusion criteria. The methodology of BMI (kg/m^2) calculations was previously reported.[17] Briefly, BMI at age 21 and at baseline was calculated using self-reported weights and height. To categorize BMI at baseline, we used cutpoints defined by World Health Organization standards.[18] Weight and height measures and BMI at age 21 were categorized according to quartile and tertile distributions of the eligible female population. We also examined all body size measures as continuous variables. Change in BMI (%) and change in weight (%) was calculated as [(measure at baseline minus measure at age 21) / measure at age 21]×100 and initially categorized using fine categories (intervals of 10% change); negative values denote loss, whereas positive values denote gain, and a value of "0" represents no change between reported body measure at age 21 to baseline. Percent change was utilized instead of absolute difference because it standardized the body weight variance of our study population. With regards to body size change over time, we opted to present percent BMI change instead of both weight and BMI change for the following reasons: *i*) percent BMI change accounts for potential associations related to height; *ii*) distribution and findings for BMI change and weight change were correlated (r=1.0) and nearly identical because there was only one measure of height. Average annual BMI change (%/year) was calculated as (change in BMI) / (age at cohort entry minus 21 years of age).

Statistical analysis

Relative risks (RR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. Age (in days) was the underlying time variable in the Cox regression, starting with a participants' age at entry to one of the endpoints. For the main effects of anthropometric measures, Cox models were adjusted for the following variables: race/ethnicity (African American, Native Hawaiian, Japanese American, Latina, and White), education (years), smoking status (never, past, current), age at menarche (≤ 12, 13–14, ≥ 15), menopausal status/age at natural menopause (premenopausal, <45, 45–49, 50–54, ≥ 55), parity (nulliparous, 1, 2–3, ≥ 4 children), duration/type of HT use (never, and per 5 years of past estrogen only therapy (ET), past estrogen-progestin therapy (EPT), current ET, and current EPT use), OC use (never, ≥ one month use), diabetes (yes, no), and hypertension (yes, no). For height, baseline weight in quartiles was added to the model and for percent BMI change, BMI at age 21 was adjusted for in the model. In addition, in our preliminary analyses we included in our models factors related to energy balance: total caloric intake (continuous) and physical activity [measured in metabolic equivalents of energy expenditure (METs)].[19, 20] We observed no change in our findings; therefore we kept these variables out of the model. In an earlier study we found differences in distribution of histological type 1 and 2 tumors by racial/ethnic groups primarily

among African Americans[9]. We attempted to control for these differences by adjusting for race/ethnicity in our model; further exclusion of type 2 tumors from the analyses did not change our results.

Linear trend tests were conducted by treating the categorical variable of interest as continuous in the model. The likelihood ratio test was used to test for statistical interactions between menopausal status, ethnicity, or BMI change and the covariates of interest with respect to endometrial cancer. The test compared the full model (main effect term and above mentioned covariates) to the full model including interaction terms. Interaction terms were created using the categories as described above. All statistical analyses were performed in SAS version 9.1 (SAS Institute, Cary, NC) and STATA version 10 (StataCorp, College Station, TX).

Results

Table 1 presents the baseline characteristics among eligible women by categories of BMI change. Overall, Japanese-American women had the least percentage BMI gain (<35%); whereas, African Americans and Latinas reported the greatest BMI gain (mean percent BMI change by racial/ethnic group: African Americans=36.0%, Japanese Americans=15.2%, Latinas=29.1%, Native Hawaiians=28.9%, and Whites=21.3%). The majority of women (76.1%) were postmenopausal at cohort entry. Women who had a BMI loss or least amount of BMI gain (category 1) were more likely to be heavier at age 21, nulliparous, physically active, current HT users, and current smokers. Women with the greatest BMI gain (category 3) were more likely to be never HT users, have an earlier age at menarche, higher BMI at baseline, and a history of diabetes and hypertension.

The associations of anthropometric measures with endometrial cancer risk are shown in Table 2. Compared to women in the lowest quartile of weight, at either age 21 or at baseline, women in both the third and fourth quartiles had an increase in endometrial cancer risk. BMI at age 21 $\geq$ 21.897 kg/m^2 had a RR of 1.71 (95% CI: 1.31, 2.25) when compared to the lowest quartile. Women with a baseline BMI $\geq$ 30 kg/m^2 had a 3.5-fold increase in risk (95% CI: 2.70, 4.63) compared to those with a BMI <25 kg/m^2. A positive dose-response relation with BMI gain and the risk of endometrial cancer was observed, with a greater than four-fold increased risk associated with $\geq$ 35% BMI gain (Table 2). When BMI at baseline (categorical, WHO criteria) was included in the model, the RRs were slightly attenuated toward the null (for $\geq$ 35% BMI gain: RR=2.60, 95% CI: 1.54, 4.39). For average annual BMI change, women who averaged a weight gain $\geq$ 0.5% per year had an increase in risk (>1.5-fold) compared to those with average annual change between −0.25 to <0.25%.

Measures of weight, BMI, and BMI change were associated with an increased risk of endometrial cancer in all racial/ethnic groups (Table 3). Due to the limited number of Native Hawaiian cases (n=44), we did not include them in this analysis. Japanese Americans had a greater than four-fold risk at BMI $\geq$ 30kg/m^2. When using comparable categories, we found in Japanese Americans a smaller percentage of BMI gain ($\geq$ 5%) was associated with endometrial cancer risk (RR=2.17; 95% CI: 1.29, 3.67). Due to few number of cases in African Americans and Latinas in the referent group (n $\leq$ 7), we also presented results using ethnic-specific tertiles. Among Latinas, endometrial cancer risk increased in those who gained $\geq$ 18.46% BMI from age 21 compared to their lowest tertile. Among Japanese Americans, a smaller increase in BMI (8.18 to <20.10%), was associated with endometrial cancer risk (RR=1.99; 95% CI: 1.25, 3.17) when compared to their lowest tertile group; whereas, in Whites an association was not observed until BMI gain $\geq$ 26.19% and African Americans showed an increased risk only after a BMI gain $\geq$ 42.80%. Tests for heterogeneity showed weight at baseline, BMI change, and average annual BMI change in relation to endometrial cancer risk varied by ethnicity (p=0.002, 0.016, and 0.002, respectively); however, a significant difference

was only observed for weight at baseline between Whites and African Americans (p=0.024) and between Whites and Japanese Americans (p=0.007).

We also explored the potential modifying effects of other endometrial cancer risk factors on the association of BMI change and endometrial cancer (Table 4). The association between endometrial cancer and ≥ 35% BMI gain was strongest among women who never used HT (RR=5.33; 95% CI: 2.79, 10.2) or among nulliparous women (RR=7.05; 95% CI: 3.01, 16.5). The association between endometrial cancer and ≥ 35% adult weight gain was also stronger among non-smokers (RR=4.27; 95% CI: 2.61, 6.99) than among either past or current smokers. Tests for interaction, however, was only notable for HT use (p<0.001) and among nulliparous postmenopausal women (p=0.034, data not shown).

Discussion

In this large prospective multiethnic study, we confirmed that heavier weight and obesity (BMI ≥ 30 kg/m^2) increase endometrial cancer risk, as well as the presence of a dose-response relation with BMI. We also observed after adjusting for confounding variables, BMI at age 21 ≥ 21.897 kg/m^2 and adult BMI gain increase risk. Risk was greatest among women who had a ≥ 35% gain in BMI or women who averaged ≥ 1% annual increase in BMI during the period from age 21 to cohort entry. Among Japanese Americans, a 5% gain in BMI resulted in increased risk of endometrial cancer.

The association of BMI gain and obesity with endometrial cancer might be explained by the unopposed estrogen theory which suggests that elevated exposures to estrogen, particularly when not counterbalanced by progesterone, can result in increased mitotic proliferation of endometrial cells and greater likelihood for DNA replication errors and somatic mutations.[21] Obesity in postmenopausal women is associated with higher levels of circulating estrogens and lower levels of sex-hormone-binding globulins.[22] In premenopausal women, obesity results in chronic anovulation, a reduction of progesterone synthesis, and higher levels of free estrogen.[23]

Five other prospective studies have investigated the association of weight or BMI gain with endometrial cancer risk.[5, 6, 8, 13, 14] Of which, Terry *et al.*[14] and Le Marchand *et al.*[13] found an association between weight change and endometrial cancer risk after adjusting for some comparable confounding variables to our study. In accord with our findings, Friedenreich *et al.*,[6] Schouten *et al.*,[5] and Chang *et al.*[8] observed a ≥ 1.75-fold increase in endometrial cancer risk among women in the highest category of weight or BMI change: ≥ 20 kg[6] ≥ 8 kg/m^2 5 (these two studies additionally adjusting for BMI at age 20), and ≥ 20 kg (additionally adjusting for weight at age 18 or baseline BMI).[8] When BMI at baseline was included in our model, the association between weight gain and endometrial cancer was attenuated suggesting that the association may in part be explained by BMI at baseline. Prior studies found that current BMI was more predictive of endometrial cancer risk than earlier BMI measures.[6, 7, 13, 14, 24–26] Our findings from stratified analysis are in accordance with this hypothesis. Among those with the BMI at age 21 <19.35 kg/m^2, a ≥ 35% BMI gain resulted in a 2-fold increased risk. However, among women in the second and highest tertiles of BMI at age 21, a ≥ 35% BMI gain resulted at least a 3-fold increased risk; perhaps because most women with very low BMI at age 21 do not gain enough weight to become overweight or obese later in life. Alternatively when stratified by baseline BMI, we found BMI gain is a risk factor for endometrial cancer, even when gain does not result in becoming overweight or obese (baseline BMI ≥ 25); suggesting both BMI gain and baseline BMI are risk factors for endometrial cancer development. Moreover, controlling for baseline BMI may possibly be an overadjustment since baseline BMI could be considered an intermediate[27] for BMI change, and in our population BMI change and BMI at baseline were highly correlated (r=0.74).

Prior studies[5–8, 13, 14, 25, 26, 28, 29] have investigated the role of weight change on endometrial cancer risk using the absolute difference in weight or BMI. Only two case-control studies and no prospective studies examined percentage change (weight only) in relation to endometrial cancer risk. In both studies, the authors found a slightly ≥ 2-fold increase in risk among women with an adult weight gain ≥ 40%.[25, 28] We observed no change in our findings when using this measure of weight change.

In our study population, Japanese-American women had the least weight gain and African Americans the greatest weight gain in adulthood. Among Japanese Americans, who are leaner than women of other racial/ethnic groups to begin with, we found that a smaller percentage of BMI gain (≥ 5%) was associated with an increase in endometrial cancer risk, unlike the other four racial/ethnic groups, where a greater weight gain was needed to observe similar effects. To distinguish whether our findings may be associated with baseline BMI, we investigated the association between BMI at baseline and endometrial cancer risk, stratified by race/ethnicity and found Japanese Americans with a BMI ≥ 30 kg/m^2 had the greatest (4-fold) increase in endometrial cancer risk. Although our findings could be due to chance, they could also suggest that a lower percentage of BMI gain in Japanese-American women may result in sufficient hormonal changes to influence their endometrial cancer risk. It has been observed that Asians have a slightly higher body fat percentage than Whites with comparable BMI,[30] and that Japanese-American women relative to White women in the MEC have higher circulating levels of estrogens independent of BMI.[31]

To our knowledge we are unaware of studies directly comparing the effect of BMI in endometrial or breast cancer incidence between Asians and Caucasians or other racial/ethnic groups. Studies specific to Asian populations showed conflicting findings regarding the role of BMI in endometrial cancer. In two case-control studies among Chinese women, one found BMI of 20.9 to 22.9 kg/m^2 or weight gain of ≥ 7.5 kg from ages 40–49 to ages 50–59[32] to be associated with endometrial cancer; however, Xu *et al.*, found an increase in risk only after a ≥ 30% weight gain.[28] Because the majority of our Japanese-American population were born in the United States, it is possible the variation of lifestyle and dietary factors in American born Asians may contribute to this difference. In a another hormone-obesity related cancer site, breast, Ziegler *et al.* observed among Asian Americans in their 50s, weight gain of ≥ 11 lbs. was associated with breast cancer.[33] Moreover, a meta-analysis by Renehan *et al.* found stronger associations in breast cancer risk per 5 kg/m^2 increase in BMI in postmenopausal women from the Asia-Pacific region than those from North American, European, and Australian regions.[34] Our findings in endometrial cancer risk by ethnicity merit corroboration in studies with larger sample size.

Consistent with results from two other prospective cohort studies,[6, 8] we found that postmenopausal HT modified the relation of weight gain to endometrial cancer risk; the risk associated with weight gain ≥ 35% was most apparent among never HT users, and was not observed in current ET or EPT users. It has been suggested that there is an upper limit beyond which unopposed estrogens do not induce further increase in the mitotic rate of endometrial cells.[23] ET use is a known and strong risk factor for endometrial cancer and thus the effect of weight gain is probably masked by its large effect on risk. For current EPT, it is possible that the added progestins counteract the effect of higher circulating estrogens from the increased adipose tissue mass.[23]

In accordance with our findings, another prospective study found an increased incidence among nulliparous women with a BMI ≥ 30 kg/m^2.[8] It has been previously observed that nulliparous postmenopausal women may have higher levels of FSH than parous ones[35] and FSH have been found to increase growth of endometrial cancer cell lines.[36] Thus, increased levels of FSH and estrogen as a result of nulliparity and BMI gain may play a multiplicative synergistic role in

increasing endometrial cancer risk, particularly in postmenopausal women. Our findings should be corroborated in other studies.

There were some limitations in our study. Measures of height and weight were self-reported, possibly resulting in nondifferential misclassification. Nonetheless, such misclassification was not an important source of concern as some found self-reported height and weight are thought to be reasonably accurate[37]; and women 50 years of age were observed to recall their body weight at age 18 with a correlation of 0.88 to actual measures taken.[38] However, differential misclassification as a result of self perception or current weight[39] may play a factor in our findings. Selection bias as a result of varying response rates by racial/ethnic groups may limit external validity to general populations. Our estimation of average annual BMI change relies on the assumption that BMI or weight cycling does not play an important role in endometrial cancer risk; this association remains inconclusive.[7] Lastly, our study would have benefited from additional measures of weight during follow-up period and/or measures of central adiposity, such as waist-to-hip ratio which is reportedly a better predictor than BMI with regards to obesity-related diseases.[40] Additional weight measures closer to time of diagnosis would increase the predictability of risk modeling, however, if it is the case where recent weights or BMI gain measures are correlated with age stratums, we did not find a cohort effect within our population (data not shown). Strengths of the study include use of a prospective cohort design and the ability to control for a variety of potential confounders within a multiethnic population. Furthermore, measures of average annual BMI change in association with endometrial cancer risk may be beneficial to cancer prevention messaging. According to our findings, an average BMI increase of <0.5% per year, i.e. <5% per 10-year interval, does not increase endometrial cancer risk, thus weight control may be an effective mean of reducing risk of endometrial cancer.

In conclusion, our results show that adult BMI gain is a risk factor for endometrial cancer. Risk from BMI gain may differ somewhat by racial/ethnic groups, particularly among Japanese Americans, where a smaller percentage BMI gain appears to increase risk. Lastly, postmenopausal HT use and possibly parity modify endometrial cancer risk associated with adult BMI gain. The observed findings should be validated in other studies, and the role of genetic and other environmental factors as potential effect modifiers of BMI gain-related endometrial cancer risk should be evaluated as well.

Abbreviations used

RR	relative risk
CI	confidence intervals
BMI	body mass index
MEC	multiethnic cohort
OC	oral contraceptives
HT	hormone therapy
ET	estrogen-only therapy
EPT	estrogen-progestin therapy
METs	metabolic equivalents

Acknowledgments

The Multiethnic Cohort Study is supported by NCI grant CA54281. S.L.P is supported by NCI grant CA09142 and V.W.S is supported in part by NCI Career Development Award CA116543.

We would like the thank Dr. Lynne Wilkens, Dr. Kristine Monroe, and Ms. Peggy Wan for their assistance with the data management and analysis. Also, we are indebted to all the Multiethnic Cohort members for their participation and commitment.

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Table 1

BMI change by Baseline Characteristics on All Eligible Women in the Multiethnic Cohort[1]

Characteristics	BMI Change		
	Category 1 (<+5%)[2]	Category 2 (5% to <35%)	Category 3 (≥35%)
Total no. Women	9,012	28,864	12,500
Age at cohort entry, mean	59.1	57.8	57.7
Ethnicity %			
African American	6.0	12.0	27.3
Japanese American	46.1	36.2	13.7
Latina	11.1	18.1	25.5
Native Hawaiian	5.1	7.7	10.9
White	31.8	25.9	22.7
Postmenopausal %	77.6	75.1	77.2
Weight at age 21 (kg), mean	56.1	53.5	53.9
Weight at baseline (kg), mean	53.6	63.7	82.7
Height (m), mean	1.59	1.60	1.61
BMI at age 21 (kg/m^2), mean	21.8	20.6	20.3
BMI at baseline (kg/m^2), mean	20.9	24.5	31.1
METs, mean	1.63	1.59	1.55
Age at menarche %			
≤ 12	46.8	49.0	52.0
13–14	40.4	39.5	36.1
≥ 15	12.8	11.4	11.9
Age at menopause %[3]			
≤ 45	14.8	14.6	17.8
45–49	31.5	31.9	31.1
50–54	42.9	42.9	40.0
≥ 55	10.9	10.7	11.1
Nulliparous %	17.9	12.9	9.7
Postmenopausal hormone therapy use %[3]			
Never hormone therapy	49.4	50.8	60.2
Past hormone therapy	15.6	17.0	18.6
Current estrogen-only therapy	4.2	4.2	3.6
Current estrogen-progestin therapy	30.8	28.0	17.6
Ever oral contraceptive use	43.0	48.2	47.7
Smoking history %			
Never	57.5	57.7	53.2
Former	25.3	28.1	33.5
Current	17.2	14.2	13.3
Diabetes %	6.6	7.7	13.4
Hypertension %	22.7	30.9	46.0

Characteristics	BMI Change		
	Category 1 (<+5%)[2]	Category 2 (5% to <35%)	Category 3 (≥35%)
Family history of endometrial cancer %	1.3	1.3	1.5

[1] Percentages may not add 100% due to rounding.

[2] Category 1 includes weight loss.

[3] Among postmenopausal women only.

Table 2

Relative Risk (RRs) For Endometrial Cancer in Relation to Anthropometric Measures in the Multiethnic Cohort

	No. Cases	RR[1] (95%CI)	RR[2] (95%CI)
Weight at 21 (kg)			
Quartile 1: <48.0	92	1.00	1.00
Quartile 2: 48.0 to <53.5	89	1.06 (0.79, 1.42)	1.04 (0.78, 1.40)
Quartile 3: 53.5 to <57.6	121	1.39 (1.06, 1.82)	1.31 (0.98, 1.74)
Quartile 4: ≥ 57.6	161	1.96 (1.51, 2.53)	1.76 (1.33, 2.34)
*P*trend		<0.001	<0.001
Weight at baseline (kg)			
Quartile 1: <55.7	74	1.00	1.00
Quartile 2: 55.7to <63.9	93	1.22 (0.90, 1.66)	1.28 (0.94, 1.76)
Quartile 3: 63.9 to <74.8	87	1.33 (0.97, 1.81)	1.47 (1.05, 2.05)
Quartile 4: ≥ 74.8	209	2.98 (2.28, 3.90)	3.43 (2.50, 4.72)
*P*trend		<0.001	<0.001
Height at baseline (m)[3]			
1.57	111	1.00	1.00
1.57 to 1.60	81	1.44 (1.08, 1.92)	1.26 (0.94, 1.69)
1.60 to 1.651	130	1.49 (1.16, 1.93)	1.17 (0.88, 1.54)
>1.651	141	1.50 (1.17, 1.93)	0.97 (0.72, 1.32)
*P*trend		0.001	0.719
BMI at age 21 (kg/m^2)			
Quartile 1: <18.840	86	1.00	1.00
Quartile 2: 18.840 to <20.216	115	1.31 (0.99, 1.73)	1.27 (0.96, 1.68)
Quartile 3: 20.216 to <21.897	109	1.30 (0.98, 1.73)	1.24 (0.93, 1.65)
Quartile 4: ≥ 21.897	153	1.88 (1.44, 2.44)	1.71 (1.31, 2.25)
*P*trend		<0.001	<0.001
BMI at baseline (kg/m^2)[4]			
<25	175	1.00	1.00
25 to <30	119	1.29 (1.02, 1.62)	1.36 (1.06, 1.75)
≥ 30	169	3.25 (2.63, 4.02)	3.54 (2.70, 4.63)
*P*trend		<0.001	<0.001
BMI change (%)[4]			
<−5 (weight loss)	20	1.57 (0.88, 2.81)	1.37 (0.76, 2.46)
−5 to <+5	26	1.00	1.00
5 to <15	80	1.78 (1.14, 2.77)	1.83 (1.17, 2.85)
15 to <25	80	1.81 (1.16, 2.82)	1.92 (1.23, 2.99)
25 to <35	66	1.93 (1.23, 3.04)	2.09 (1.32, 3.31)
≥ 35	191	3.56 (2.36, 5.37)	4.12 (2.69, 6.30)
*P*trend		<0.001	<0.001
BMI change continuous (1%)		1.02 (1.01, 1.02)	1.02 (1.01, 1.02)
Average annual BMI change (%/year) [4]			

	No. Cases	RR[1] (95%CI)	RR[2] (95%CI)
< −0.25 (weight loss)	9	1.04 (0.52, 2.08)	0.91 (0.46, 1.83)
−0.25 to < +0.25	77	1.00	1.00
0.25 to <0.50	73	1.15 (0.84, 1.59)	1.21 (0.88, 1.67)
0.50 to <0.75	72	1.37 (0.99, 1.89)	1.51 (1.08, 2.09)
0.75 to <1.0	54	1.47 (1.04, 2.09)	1.68 (1.17, 2.42)
≥ 1.0%	178	2.69 (2.04, 3.54)	3.21 (2.37, 4.33)
*P*trend		<0.001	<0.001

[1] Age-adjusted RR.

[2] RRs were adjusted for age, ethnicity, education, age at menarche, menopausal status, age at menopause, duration and type of hormone therapy, oral contraceptive use, parity, smoking history, diabetes, and hypertension.

[3] Additionally adjusted for baseline weight (quartiles).

[4] Additionally adjusted for BMI at age 21 (quartiles).

Table 3

Relative Risks (RRs) For Endometrial Cancer in Relation to Anthropometric Measures Stratified by Race/Ethnicity in the Multiethnic Cohort[1]

Race/Ethnicity	African American		Japanese American		Latina		White	
	No. Cases	RR[2] (95% CI)	No. Cases	RR[2] (95% CI)	No. Cases	RR[2] (95% CI)	No. Cases	RR[2] (95% CI)
Weight at 21 (kg)								
Tertile 1: <49.8	8	1.00	53	1.00	14	1.00	17	1.00
Tertile 2: 49.8 to <56.6	21	1.23 (0.54, 2.78)	48	1.29 (0.87, 1.91)	29	1.20 (0.63, 2.27)	55	1.38 (0.80, 2.39)
Tertile 3: ≥ 56.6	46	2.02 (0.95, 4.29)	30	2.04 (1.29, 3.24)	35	1.66 (0.89, 3.12)	63	1.44 (0.84, 2.48)
P Trend		0.024		0.004		0.089		0.244
Weight at baseline (kg)								
Tertile 1: <58.7	1	1.00	60	1.00	12	1.00	34	1.00
Tertile 2: 58.7 to <70.3	9	3.20 (0.41, 25.0)	39	1.47 (0.98, 2.22)	18	0.78 (0.38, 1.63)	37	0.77 (0.48, 1.23)
Tertile 3: ≥70.3	65	8.72 (1.20, 63.3)	32	3.50 (2.20, 5.57)	48	1.75 (0.92, 3.35)	64	1.42 (0.92, 2.19)
P Trend		0.001		<0.001		0.017		0.056
Height (m)[3]								
Tertile 1: <1.57	7	1.00	66	1.00	25	1.00	10	1.00
Tertile 2: 1.57 to <1.65	22	0.67 (0.28, 1.58)	57	1.11 (0.77, 1.62)	44	1.06 (0.64, 1.76)	65	1.88 (0.96, 3.69)
Tertile 3: ≥ 1.65	46	0.94 (0.41, 2.16)	8	0.95 (0.44, 2.05)	9	0.45 (0.21, 1.00)	60	1.42 (0.71, 2.84)
Ptrend		0.510		0.784		0.087		0.996
BMI at age 21 (kg/m^2)								
<19.35	18	1.00	38	1.00	16	1.00	43	1.00
19.25 to <21.23	24	1.51 (0.82, 2.80)	44	1.29 (0.83, 1.99)	17	0.88 (0.45, 1.75)	44	0.93 (0.61, 1.42)
≥ 21.23	33	1.66 (0.93, 2.98)	49	1.82 (1.18, 2.81)	45	1.67 (0.94, 2.99)	48	1.22 (0.80, 1.86)
P Trend		0.095		0.007		0.040		0.351
BMI at baseline (kg/m^2)								
<25	12	1.00	77	1.00	17	1.00	65	1.00
25 to <30	19	1.16 (0.55, 2.43)	30	1.30 (0.83, 2.04)	25	1.37 (0.72, 2.60)	33	1.22 (0.79, 1.89)
≥ 30	44	3.08 (1.51, 6.28)	24	4.60 (2.61, 8.11)	36	3.07 (1.59, 5.94)	37	2.75 (1.71, 4.43)
P trend		<0.001		<0.001		<0.001		<0.001
BMI change (%)[4]								

Race/Ethnicity	African American		Japanese American		Latina		White	
	No. Cases	RR[2] (95% CI)	No. Cases	RR[2] (95% CI)	No. Cases	RR[2] (95% CI)	No. Cases	RR[2] (95% CI)
< +5%	3	1.00	19	1.00	4	1.00	19	1.00
5% to <20%	6	0.77 (0.19, 3.08)	60	2.17 (1.29, 3.67)	13	1.45 (0.47, 4.46)	36	1.28 (0.73, 2.24)
20% to <35%	14	1.35 (0.38, 4.76)	34	2.15 (1.21, 3.83)	21	2.16 (0.74, 6.33)	34	1.67 (0.94, 2.96)
≥ 35%	52	3.08 (0.94, 10.1)	18	2.73 (1.40, 5.32)	40	3.82 (1.34, 10.9)	46	2.68 (1.53, 4.67)
P trend		<0.001		0.005		<0.001		<0.001
BMI change continuous (1%)[4]		1.02 (1.01, 1.03)		1.02 (1.01, 1.03)		1.02 (1.01, 1.03)		1.02 (1.01, 1.02)
Body weight change (%)[4], ethnic specific tertiles[5]								
Tertile 1	13	1.00	28	1.00	15	1.00	33	1.00
Tertile 2	20	1.62 (0.80, 3.29)	52	1.99 (1.25, 3.17)	23	1.67 (0.86, 3.21)	43	1.34 (0.84, 2.11)
Tertile 3	42	3.47 (1.81, 6.67)	51	2.02 (1.25, 3.26)	40	3.08 (1.66, 5.71)	59	1.83 (1.17, 2.86)
P trend		<0.001		0.005		<0.001		0.007
Average annual BMI change (%/year) [4]								
< +0.25 (weight loss)	4	1.00	41	1.00	7	1.00	33	1.00
0.25 to <0.50	8	1.88 (0.56, 6.28)	33	1.32 (0.83, 2.11)	7	0.98 (0.34, 2.81)	23	1.11 (0.65, 1.90)
0.50 to <0.75	10	1.96 (0.61, 6.29)	18	1.15 (0.65, 2.03)	15	2.15 (0.87, 5.31)	26	1.54 (0.91, 2.60)
0.75 to <1.0	9	2.02 (0.61, 6.67)	17	1.96 (1.08, 3.54)	13	2.45 (0.96, 6.22)	13	1.27 (0.66, 2.45)
≥ 1.0%	44	4.60 (1.59, 13.2)	22	2.33 (1.31, 4.14)	36	3.85 (1.66, 8.96)	40	2.40 (1.46, 3.93)
P trend		<0.001		0.003		<0.001		0.001

[1] Native Hawaiians excluded from analysis due to small sample size.

[2] Multivariate RRs were adjusted for age, education, age at menarche, menopausal status, age at menopause, duration and type of hormone therapy, duration and oral contraceptive use, parity, smoking history, diabetes, and hypertension.

[3] Additionally adjusted for baseline weight (quartiles).

[4] Additionally adjusted for BMI at age 21 (quartiles).

[5] Tertile distribution for African Americans: <23.59%, 23.59% to <42.80%, and ≥ 42.80%; Japanese Americans: <8.18%, 8.18% to <20.10%, ≥ 20.10%; Latinas: <18.46%, 18.46% to <35.45%, ≥ 35.45%; Whites: <10.00%, 10.00% to 26.19%, ≥ 26.19%

Table 4

Relative Risks (RRs) for Endometrial Cancer in Relation to BMI Change Stratified by Other Risk Factors in the Multiethnic Cohort

	BMI Change						
	Category 1 (<5%)[1]		Category 2 (5%to <35%)		Category 3 (≥35%)		
	No. cases	RR[2]	No. cases	RR[2]	No. cases	RR[2]	*P*trend
BMI at 21 (kg/m^2)							
Tertile 1: <19.35	10	1.00	66	1.49 (0.76, 2.92)	49	2.23 (1.09, 4.58)	0.013
Tertile 2: 19.35 to <21.23	17	1.00	65	1.30 (0.76, 2.23)	54	3.36 (1.86, 6.06)	<0.001
Tertile 3: ≥ 21.23	19	1.00	95	2.02 (1.23, 3.34)	88	4.55 (2.69, 7.70)	<0.001
P interaction= 0.136							
BMI at baseline (kg/m^2)							
<25	40	1.00	126	1.58 (1.07, 2.31)	9	2.39 (1.08, 5.32)	0.008
≥25	6	1.00	100	1.26 (0.55, 2.88)	182	2.73 (1.19, 6.28)	<0.001
P interaction= 0.523							
Postmenopausal hormone therapy use[3]							
Never hormone therapy	11	1.00	71	1.95 (1.03, 3.70)	107	5.33 (2.79, 10.2)	<0.001
Past hormone therapy	7	1.00	35	1.19 (0.52, 2.70)	30	1.67 (0.71, 3.96)	0.146
Current estrogen-only therapy	5	1.00	14	0.97 (0.34, 2.76)	5	1.08 (0.28, 4.11)	0.919
Current estrogen-progestin therapy	17	1.00	68	1.60 (0.94, 2.74)	13	1.32 (0.63, 2.79)	0.320
P interaction < 0.001							
Smoking history							
Never smoker	22	1.00	144	2.34 (1.49, 3.69)	96	4.27 (2.61, 6.99)	<0.001
Past smoker	15	1.00	62	1.21 (0.68, 2.14)	80	3.20 (1.78, 5.77)	<0.001
Current smoker	9	1.00	20	0.98 (0.43, 2.22)	15	1.99 (0.80, 4.94)	0.110
P interaction= 0.125							
Parity							
Nulliparous	7	1.00	43	2.58 (1.15, 5.78)	35	7.05 (3.01, 16.5)	<0.001
Parous[4]	39	1.00	183	1.54 (1.08, 2.19)	156	3.14 (2.15, 4.57)	<0.001
P interaction= 0.175							

	BMI Change						
	Category 1 (<5%)[1]		Category 2 (5%to <35%)		Category 3 (≥35%)		
	No. cases	RR[2]	No. cases	RR[2]	No. cases	RR[2]	*P*trend
Oral contraceptive use							
Never	31	1.00	146	1.70 (1.14, 2.51)	122	3.58 (2.34, 5.49)	<0.001
Ever	15	1.00	80	1.72 (0.99, 3.01)	69	3.73 (2.07, 6.71)	<0.001
P interaction= 0.964							
Physical activity (METs)							
Quartile 1: <1.4015	7	1.00	59	2.31 (1.05, 5.09)	58	4.81 (2.14, 10.8)	<0.001
Quartile 2: 1.4015 to <1.5900	11	1.00	50	1.53 (0.79, 2.98)	56	4.31 (2.16, 8.61)	<0.001
Quartile 3: 1.5900 to <1.7576	12	1.00	63	1.86 (0.99, 3.50)	34	2.61 (1.28, 5.31)	0.008
Quartile 4: ≥ 1.7576	16	1.00	54	1.37 (0.77, 2.43)	43	3.06 (1.62, 5.78)	<0.001
P interaction= 0.441							

[1] Category 1 includes weight loss.

[2] RRs were adjusted for age, ethnicity, education, age at menarche, menopausal status, age at menopause, duration and type of hormone therapy, oral contraceptive use, parity, smoking history, BMI at age 21, diabetes, and hypertension.

[3] Among postmenopausal women only.

[4] RRs were adjusted for age, ethnicity, education, age at menarche, menopausal status, age at menopause, duration and type of hormone therapy, oral contraceptive use, number of children, smoking history, BMI at age 21, diabetes, and hypertension.