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OBESITY IN RELATION TO ENDOMETRIAL CANCER RISK AND DISEASE CHARACTERISTICS IN THE WOMEN'S HEALTH INITIATIVE

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Abstract

Objective—Obesity increases endometrial cancer risk, yet its impact on disease stage and grade is unclear. We prospectively examined the effects of body mass index (BMI) and waist-to-hip ratio (WHR) on incidence, stage, and grade of endometrial cancer.

Methods—We studied 86,937 postmenopausal women enrolled in the Women's Health Initiative. Height, weight, and waist and hip circumference were measured at baseline. Endometrial cancer cases were adjudicated by trained physicians and pathology reports were used to determine stage and grade. Cox proportional hazards models generated hazard ratios (HR) for associations between BMI and WHR and risk of endometrial cancer. Logistic regression was used to evaluate associations between BMI and WHR and disease stage and grade.

Results—During a mean 7.8 (standard deviation 1.6) years of follow-up, 806 women were diagnosed with endometrial cancer. Though incidence was higher among Whites, stage and grade were similar between Whites and Blacks. Elevated BMI (HR 1.76, 95% confidence interval [CI] 1.41-2.19) and WHR (HR 1.33, 95% CI 1.04-1.70) increased endometrial cancer risk when comparing women in the highest and lowest categories. No associations were observed between BMI or WHR and disease stage or grade.

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Conclusions—Obesity increases endometrial cancer risk independent of other factors, but is not associated with stage or grade of disease. These findings support and validate previous reports. Future research should evaluate the impact of obesity on racial disparities in endometrial cancer survival.

Keywords

Body Mass Index; Waist-Hip Ratio; Endometrial Neoplasms; African Americans; Caucasians

Introduction

Obesity is a well-established risk factor for endometrial cancer [1-3] and may contribute to 40% of the incident cases of this disease [4-6]. However, the impact of obesity on prognostic features of endometrial cancer, such as histologic grade and clinical stage, has not been extensively studied. Some studies have suggested that increased obesity is associated with a lower, and thus more favorable, grade of disease [7-9], though another reported no significant association [10]. Additionally, obesity was associated with earlier stage disease in some [7,8,11], but not all [9,12] previous studies.

Common to these studies, however, is that anthropometric measurements have only been measured at, or close to, the time of diagnosis. It is possible that the disease may have impacted the woman's body weight at this time, thus confounding any observed associations between obesity and prognostic features. Additionally, these studies have utilized the body mass index (BMI) as their only measure of obesity. Central adiposity, as measured by the waist-to-hip ratio (WHR), may pose a greater health risk, as abdominal fat tends to be more metabolically active than fat in other areas [13]. Data from the Nurses' Health Study document that WHR and BMI are not strongly correlated with one another [14]. Thus it is important to consider how additional measures of obesity, such as WHR, relate to prognostic features of endometrial cancer.

We utilized data from the Women's Health Initiative (WHI) to prospectively study associations between measures of obesity and endometrial cancer risk and prognostic features. Specifically, we hypothesized that increased pre-diagnosis BMI and WHR would be positively associated with endometrial cancer incidence and more favorable stage and grade. As an exploratory aim, we evaluated differences between Blacks and Whites.

Methods

Study Population

The WHI study design and methods have been described in detail [15]. Briefly, the WHI is comprised of an observational study (OS) (n=93,676) and three clinical trials (CT) (n=68,132) covering the components of dietary modification, hormone therapy, and supplementation of calcium/vitamin D. The combined WHI cohort consists of 161,808 postmenopausal women from various ethnic and racial backgrounds, including 14,618 (9%) Black participants. Women were recruited at 40 clinical centers nationwide between October 1, 1993 and December 21, 1998. Eligibility criteria for WHI were age 50-79 years, postmenopausal, no plans to move from the area, and an estimated survival ≥ 3 years. We included all WHI participants (Figure 1), except for those reporting cancer (n=14,849) or hysterectomy (n=67,696) prior to baseline or those missing data for either of these factors (n=1,401 cancer; n=86 hysterectomy). Women missing information for baseline BMI (n=799) or WHR (n=421) were excluded from analyses involving those variables. The final sample for analyses involving BMI was 86,228 (n=38,152 from CT and n=48,076 from OS), and the final sample for analyses of WHR was 86,606 (n=38,197 from CT and n=48,409

from OS). All procedures and protocols were approved by the Institutional Review Boards at each participating institution and all participants provided written informed consent.

Case Determination

Adjudication and outcome ascertainment for the WHI have been described elsewhere [16]. Briefly, all outcomes were self-reported semi-annually in the CT and annually in the OS. Self-reported outcomes were confirmed by local physician adjudicators who examined the pathology report and any additional information regarding the cancer diagnosis. Trained SEER coders at the Clinical Coordinating Center examined the pathology reports and any additional relevant information on all primary occurrences of endometrial cancer to finalize each cancer outcome. Each case was centrally coded by tumor registry coders to determine grade and stage. Only endometrial cancer cases confirmed by adjudication were included in these analyses (n=806). Due to missing data, 801 cases were included in the analyses with BMI and 802 cases were included in the analyses with WHR. We coded the endometrial cancer cases into histopathological subtypes following World Health Organization and International Society of Gynecological Pathology guidelines [17]. Information on histopathological subtype was missing for 27 cases. The endometrioid subtype was the most frequent (N=639, 82.0%) and cases of other subtypes were too few for analysis: adenosquamous carcinoma, N=1, 0.1%; clear cell adenocarcinoma, N=9, 1.2%; mixed carcinoma, N=28, 3.6%; mucinous adenocarcinoma, N=25, 3.2%; papillary serous adenocarcinoma, N=61, 7.8%; other, N=16, 2.1%. Therefore, we coded histopathological subtype as endometrioid or other for our analyses.

Obesity Variables

Height, weight, and waist and hip circumference were measured according to a standard protocol at clinical center visits. Measurements were obtained by trained and certified clinic staff. Height and weight were measured without shoes or heavy clothing using a wall mounted stadiometer and a calibrated balance beam or digital scale. Waist and hip measurements were taken in light indoor clothing. Baseline values of BMI and WHR were used as measures of obesity in these analyses. BMI was calculated by dividing weight in kilograms by height in meters squared, and WHR was obtained by dividing waist circumference by hip circumference measurements.

Statistical Analysis

Baseline descriptive characteristics were examined separately by BMI category and WHR quartile. BMI was categorized as underweight/normal (<25 kg/m^2), overweight (25 - <30 kg/m^2), and obese (≥30 kg/m^2). Tests of association were conducted using Chi-square tests for categorical variables and two-sample t-tests for continuous variables.

Event rates adjusted to the overall WHI population age distribution were computed for absolute disease rate comparisons. Endometrial cancer rates, separately for BMI category and WHR quartile, were compared using time-to-event methods. Time to event was defined as days from randomization to first diagnosis of endometrial cancer. Follow-up time was censored at a woman's last known follow-up contact, date of hysterectomy, or date of death. Quantitative comparisons by BMI category and WHR quartile are presented as hazard ratios (HRs) with nominal 95% confidence intervals (CIs) from Cox proportional hazards analyses stratified by WHI study component and adjusted for age, race/ethnicity, income, education, physical activity, smoking, total energy intake, percent energy from fat, fiber intake, fruit and vegetable intake, grain intake, diabetes, history of hypertension, age at menarche, age at menopause, attempted to get pregnant for more than 1 year, age at last term pregnancy, duration of hormone use, duration of oral contraceptive use, NSAID use, and family history of endometrial and ovarian cancers; these covariates were chosen based upon past analyses

conducted within the WHI cohort and knowledge of potential associations with obesity and endometrial cancer. We performed separate regression with additional adjustment for BMI or WHR. Dietary variables were categorized into quartiles. These analyses were repeated separately for White and Black racial groups. We also repeated analyses among women with at least two years of follow-up in WHI prior to an endometrial cancer diagnosis in order to assess whether observed associations were influenced by undetected disease at baseline, and using only invasive cancer cases and then only cases of the endometrioid histopathological subtype.

Logistic regression analyses examined differences in grade, stage at diagnosis, and histopathological subtype of endometrial cancer separately by BMI category and WHR category. This analysis included only women who were diagnosed with endometrial cancer during follow-up. Stage of endometrial cancer was categorized as in situ or localized versus regional or distant. Grade of endometrial cancer was categorized as well or moderately differentiated versus poorly differentiated or anaplastic. Analyses were adjusted for age, race/ethnicity, prior hormone use, family history of endometrial cancer, and WHI study component. Odds ratios (ORs) with 95% CIs are reported. All statistical tests performed were two-sided with $\alpha \leq 0.05$ considered statistically significant and no adjustment made for multiple comparisons. All analyses were conducted using SAS for Windows, v9.1.3 (Cary, NC).

Results

Women self-reporting a hysterectomy at baseline were excluded from this analysis, as they would not be at-risk for endometrial cancer. Differences in the proportion of potentially eligible WHI subjects excluded for this reason were observed to vary by race (40.4% Whites, 55.6% Blacks, 44.8% Hispanics, and 34.9% Asian/Pacific Islander; $p<0.001$).

Table 1 describes the baseline characteristics with stratification by BMI category. Statistically significant differences were observed for nearly all characteristics. Noteworthy differences across BMI category include the increased percentage of Blacks in the obese category (12.2%) as compared to the underweight/normal (3.4%) and overweight (6.6%) groups ($p<0.0001$). Current hormone use was more frequent among underweight/normal (39.4%) compared to the overweight (31.0%) and obese (22.9%) groups. Family history of endometrial cancer was more frequent among the obese (6.3%) compared to the overweight (5.3%) and underweight/normal (4.7%) groups. Overweight (45.8%) and obese (54.2%) women were more likely to be enrolled in the CT as compared to underweight and normal weight women (35.5%; $p<0.0001$).

Women who developed endometrial cancer were more likely to be of White race/ethnicity (90.5%) than those who remained cancer-free (84.4%; $p<0.0001$). Total energy intake of ≥1972.1 kcal/day was more common among endometrial cancer cases (31.3%) compared to women without endometrial cancer (24.9%; $p<0.0001$). Strong associations were observed between exogenous hormone use and endometrial cancer. Women diagnosed with endometrial cancer were more likely to be current hormone therapy users at baseline (41.3%) than those not diagnosed with endometrial cancer (31.8%; $p<0.0001$). Further, increased duration of hormone therapy use was related to endometrial cancer status, with 22.7% of cases and 10.9% of endometrial cancer-free women reporting hormone use for ≥10 years ($p<0.0001$).

Average follow-up for this study population was 7.8 years (standard deviation 1.6). Of the 806 cases of endometrial cancer included in this analysis, there were 730 cases among Whites (age-adjusted rate 123.4 cases per 100,000 person-years) and 38 cases among Blacks

(age-adjusted rate 82.7 cases per 100,000 person-years, p=0.01). Table 2 reports age-adjusted rates of endometrial cancer among BMI categories and WHR quartiles. Incidence was highest among obese women (187.1 cases per 100,000 person-years) and in the highest WHR quartile (141.8 cases per 100,000 person-years). In adjusted Cox proportional hazards models a positive association was observed between both BMI (p<0.0001) and WHR (p=0.001) and endometrial cancer risk. Obese women had a 76% increased risk of endometrial cancer compared to underweight and normal weight women (HR 1.76, 95% CI 1.41-2.19). Endometrial cancer risk increased 33% among women with a WHR ≥0.8530 versus <0.7554 (HR 1.33, 95% CI 1.04-1.70). Further adjustment for WHR did not appreciably change the associations between BMI and endometrial cancer risk. Associations between WHR and endometrial cancer risk were attenuated and non-significant upon additional adjustment for BMI, however. Results were similar when restricting cases to invasive disease or to the endometrioid subtype and when restricted to follow-up after two years of WHI participation (data not shown).

Hazard ratios were similar when the analyses were restricted to White participants (HR 1.80, 95% CI 1.44-2.27 for BMI ≥30 versus <25; HR 1.33, 95% CI 1.03-1.71 for WHR ≥0.8530 versus <0.7554). Among Blacks the association between both BMI (HR 2.76, 95% CI 0.57-13.51 for BMI ≥30 versus <25) and WHR (HR 4.61, 95% CI 0.50-42.67 for WHR ≥0.8530 versus <0.7554) and endometrial cancer risk appeared to be stronger. There was no significant interaction between race and BMI (p=0.35) or race and WHR (p=0.32).

Among endometrial cancer cases, 13 (1.7%) had in situ, 645 (82.1%) localized, 88 (11.2%) regional, and 40 (5.1%) distant disease. Stage information was missing for 20 (2.5%) cases. Disease grade was well differentiated for 199 (26.6%), moderately differentiated for 309 (41.3%), poorly differentiated for 159 (21.3%), and anaplastic for 81 (10.8%) cases. Grade classification was missing for 58 (7.2%) cases. Stage (p=0.14) and grade were similar between Whites and Blacks (p=0.95; data not shown). BMI and WHR were not associated with higher grade or later stage disease (Table 3). Obese BMI (OR 0.65, 95% CI 0.39-1.08) and WHR ≥0.8011 (OR 0.76, 95% CI 0.50-1.15) were associated with non-significant decreased likelihood of non-endometrioid histopatholgical subtypes. The analyses reported in Table 3 were not repeated with stratification on race/ethnicity due to the small number of Black cases.

Discussion

We found that elevated pre-diagnosis BMI and WHR were both related to an increased risk of endometrial cancer, yet had no association with prognostic features. Specifically, obese women (BMI ≥30 kg/m^2) experienced a 76% increase in endometrial cancer risk, and women with a WHR ≥0.8530 experienced a 33% increase in endometrial cancer risk. BMI and WHR were not associated with disease stage or grade. Results were similar when restricted to invasive cases or to cases of the endometrioid subtype.

Our findings are consistent with previous reports of positive associations of both BMI and WHR with the incidence of endometrial cancer [2]. Friedenreich et al [3] found that women with a BMI of 30 – 40 kg/m^2 had a 1.78 times (95% CI 1.41 – 2.26) increased risk of endometrial cancer compared to those of normal BMI, similar to our estimated 76% increased risk. Their estimate for WHR (RR 1.58, 95% CI 1.19-2.10) for highest quartile versus lowest quartile [3] was slightly higher than the 33% increased risk we report, likely due to differences in cut-offs for WHR between the two studies. Interestingly, BMI remained significantly associated with risk upon adjustment for WHR, but WHR was no longer related to disease risk in models adjusted for BMI. Similar observations were noted in other recent studies of adiposity and endometrial cancer [3,18], though another recent study

found the WHR was a risk factor for endometrial cancer independent of BMI [19]. As summarized by Friedenreich [3], earlier studies also provide inconsistent evidence regarding whether or not WHR is an independent risk factor for endometrial cancer. Thus it is currently unclear whether general obesity or abdominal obesity, and their respective hormonal and metabolic consequences, is more relevant to endometrial cancer risk.

Current evidence relating body fatness to stage and grade of endometrial cancer is inconsistent [7-9,11,20]. We observed no association between BMI or WHR and stage or grade of disease, contrary to our hypothesis. The close monitoring of WHI participants, especially those in the clinical trials, may have biased our results. While 82.1% of our endometrial cancer cases had localized disease, nationally only 69% of endometrial cancer cases are diagnosed at this stage [21]. It is possible that body composition may be related to stage and/or grade of endometrial cancer in the general population, but this was not the case within the WHI.

In the present study, there was a suggestion that the effect of BMI and WHR on endometrial cancer incidence was greater among Blacks; however, small numbers limited statistical significance. The lack of endometrial cancer cases among Blacks may be related to the increased prevalence of hysterectomy among Blacks (55.6%) in the WHI population. We observed no differences in either stage or grade of disease between racial groups. Other studies have reported that Blacks diagnosed with endometrial cancer often have advanced stage disease and a worse prognosis compared to Whites. This disparity may be due to different genetic etiologies and inequalities in treatment [22]. To the extent that such disparities may be related to differences in socioeconomic status, this effect may not be apparent in our study due to the higher socioeconomic status of Black WHI participants as compared to the general population of U.S. Blacks. Unfortunately, we were unable to examine associations between BMI or WHR and stage or grade separately by race due to the small sample of Black cases. Given that neither BMI nor WHR were associated with stage or grade among our full study population, however, it is unlikely that differences in obesity prevalence explain the racial disparity in endometrial cancer survival. Analyses of SEER data show that poorer endometrial cancer survival among Blacks has persisted over recent decades [23]. Future research, perhaps through pooled data analysis, is needed to determine the reasons for this racial disparity in survival.

The WHI is a well-conducted prospective cohort study of over 160,000 postmenopausal women from various racial and ethnic backgrounds with extensive follow-up. Further strengths include the adjudication and central coding of the endometrial cancer outcomes and the standardized measurement of BMI and WHR. Additionally, BMI and WHR measurements were taken well before participants were diagnosed with endometrial cancer. Previous research studies performed anthropometric assessments at, or close to, the time of diagnosis, thus raising the possibility that such measures were affected by undetected disease. We additionally performed a sensitivity analysis excluding cases diagnosed within two years of enrollment and obtained results similar to those observed among the full cohort. Thus we believe that undetected disease is unlikely to bias our observed associations between BMI and WHR and endometrial cancer incidence.

Unfortunately, our ability to examine racial differences in the association between BMI and endometrial cancer incidence, stage, and grade was limited by the small numbers of cases among racial/ethnic subgroups. Additionally, the external validity of our study may be somewhat limited. The lower prevalence of obesity among both Blacks and Whites in our study population compared to national estimates indicates that our population may have been healthier than the general population. Finally, we measured BMI and WHR at only a single point in time. Women’s BMI or WHR may have changed throughout their WHI

follow-up, and it is possible that such changes might be associated (either causally or non-causally) with risk of endometrial cancer.

Our results suggest that obesity may not be important to prognostic features of endometrial cancer, though it clearly has an impact on disease risk. Moreover, our findings suggest areas where prevention and more intense surveillance strategies could be implemented – namely among obese women, and perhaps especially among obese Black women. More research is needed among Black women, however, to more conclusively assess the impact of obesity on the incidence, stage, and grade of endometrial cancer as well as survival from this disease.

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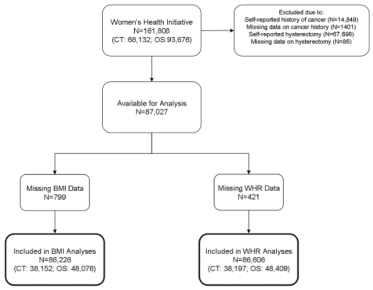

Figure 1.
Schematic of participants included in present analysis.

Table 1

Baseline Characteristics of WHI Women by Body Mass Index (kg/m^2) Category

	Body Mass Index, kg/m^2						
	Underweight/Normal <25		Overweight 25 - <30		Obese ≥30		
	N	%	N	%	N	%	P-value
Age at screening, mean years	32664	62.9	29509	63.3	24055	62.5	<.0001
50-59	11847	36.3	9761	33.1	8652	36.0	
60-69	13821	42.3	13283	45.0	11190	46.5	
70-79	6996	21.4	6465	21.9	4213	17.5	
Race/ethnicity							<.0001
White	28590	87.5	25035	84.8	19210	79.9	
Black	1097	3.4	1947	6.6	2931	12.2	
Hispanic	907	2.8	1269	4.3	1164	4.8	
American Indian	85	0.3	90	0.3	135	0.6	
Asian/Pacific Islander	1577	4.8	756	2.6	253	1.1	
Unknown	408	1.2	412	1.4	362	1.5	
Physical activity, METs/week							<.0001
None	3003	9.6	3815	13.6	5255	23.0	
<7.2	7221	23.0	8044	28.7	8181	35.8	
7.2 - <17.2	9406	29.9	8370	29.9	5568	24.3	
≥17.2	11791	37.5	7779	27.8	3875	16.9	
Smoking							<.0001
Never	16656	51.6	14594	50.0	11919	50.2	
Past	13042	40.4	12552	43.0	10478	44.1	
Current	2597	8.0	2014	6.9	1369	5.8	
Age at menarche, years							<.0001
<12	5404	16.6	6031	20.5	6494	27.1	
12	7956	24.4	7737	26.3	6404	26.7	
13	10287	31.6	8743	29.7	6487	27.0	

	Body Mass Index, kg/m^2						
	Underweight/Normal <25		Overweight 25 - <30		Obese ≥30		
	N	%	N	%	N	%	P-value
≥14	8938	27.4	6911	23.5	4604	19.2	
Age at menopause, mean years	31412	50.3	28017	50.3	22608	50.3	0.40
Tried becoming pregnant >1 year	5352	16.5	4698	16.0	3561	14.9	<.0001
Hormone use							<.0001
Never	15358	47.1	15991	54.2	15423	64.1	
Past	4435	13.6	4346	14.7	3114	13.0	
Current	12848	39.4	9144	31.0	5507	22.9	
E+P use							<.0001
Never	17634	54.0	18135	61.5	16953	70.5	
Past	3066	9.4	2868	9.7	2024	8.4	
Current	11948	36.6	8490	28.8	5071	21.1	
Unopposed estrogen use							<.0001
Never	28514	87.3	25989	88.1	21745	90.4	
Past	3258	10.0	2880	9.8	1888	7.9	
Current	879	2.7	627	2.1	416	1.7	
Non-aspirin NSAID use	29007	88.8	25459	86.3	19552	81.3	<.0001
Family history of endometrial cancer	1430	4.7	1472	5.3	1411	6.3	<.0001
Family history of ovarian cancer	660	2.2	616	2.2	538	2.4	0.13
Observational Study participant	21066	64.5	15996	54.2	11014	45.8	<.0001
Clinical Trial participant	11598	35.5	13513	45.8	13041	54.2	<.0001

Table 2

Multivariate associations of body mass index and waist-to-hip ratio with incidence (age-adjusted rate/100000 PY) of endometrial cancer during WHI

	N	Age-adjusted Rate/100000 PY*	Model 1† HR (95% CI)	P-value‡	Model 2§ HR (95% CI)	P-value‡
All endometrial cancers (in situ & invasive)						
Body Mass Index, kg/m^2				<0.0001		<0.0001
<25	264	107.3	1.00		1.00	
25 - <30	207	92.6	0.86 (0.69-1.07)		0.84 (0.67-1.05)	
≥30	334	187.1	1.76 (1.41-2.19)		1.68 (1.33-2.13)	
Waist-to-hip ratio quartiles				0.001		0.54
<0.7554	182	113.4	1.00		1.00	
0.7554 - <0.8011	193	117.0	0.96 (0.75-1.22)		0.93 (0.73-1.19)	
0.8011 - <0.8530	198	120.3	1.12 (0.88-1.43)		1.04 (0.80-1.33)	
≥0.8530	233	141.8	1.33 (1.04-1.70)		1.12 (0.86-1.47)	
Invasive endometrial cancers						
Body Mass Index, kg/m^2				<0.0001		<0.0001
<25	260	105.5	1.00		1.00	
25 - <30	202	90.4	0.84 (0.68-1.05)		0.82 (0.65-1.03)	
≥30	312	175.9	1.67 (1.33-2.09)		1.59 (1.25-2.02)	
Waist-to-hip ratio quartiles				0.001		0.41
<0.7554	180	112.0	1.00		1.00	
0.7554 - <0.8011	186	113.0	0.94 (0.73-1.21)		0.92 (0.72-1.18)	
0.8011 - <0.8530	186	113.1	1.06 (0.83-1.36)		1.00 (0.77-1.29)	
≥0.8530	223	137.0	1.32 (1.03-1.70)		1.15 (0.88-1.50)	
Endometrioid histopathological subtype						
Body Mass Index, kg/m^2				<0.0001		<0.0001
<25	212	86.0	1.00		1.00	
25 - <30	163	73.0	0.84 (0.65-1.07)		0.81 (0.63-1.04)	
≥30	262	147.1	1.69 (1.32-2.17)		1.60 (1.23-2.09)	
Waist-to-hip ratio quartiles				0.001		0.33
<0.7554	148	93.2	1.00		1.00	

	N	Age-adjusted Rate/100000 PY*	Model 1† HR (95% CI)	P-value‡	Model 2§ HR (95% CI)	P-value‡
0.7554 - <0.8011	148	90.1	0.89 (0.67-1.17)		0.87 (0.66-1.15)	
0.8011 - <0.8530	153	92.9	1.06 (0.81-1.39)		0.99 (0.75-1.32)	
≥0.8530	189	116.3	1.32 (1.01-1.74)		1.13 (0.85-1.52)	

*Adjusted to the overall WHI age distribution. PY = person years.

†Adjusted for age, race/ethnicity, income, education, physical activity, smoking, total energy intake, percent energy from fat, fiber intake, fruit and vegetable intake, grain intake, diabetes, history of hypertension, age at menarche, age at menopause, tried getting pregnant for >1 year, age at last term pregnancy, duration of hormone use, duration of oral contraceptive use, NSAID use, and family history of endometrial and ovarian cancers and stratified on study component.

‡Additionally adjusted for BMI or WHR.

§Tested using the continuous form of the log-transformed values of body mass index and waist-to-hip ratio.

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Table 3

Multivariate associations of body mass index and waist-to-hip ratio with grade, stage and histology of invasive disease*

	Well/Moderately Differentiated Grade	Poorly Differentiated/Anaplastic Grade	OR (95% CI) *
Body Mass Index, kg/m^2			
<25	169	74	1.00
25 - <30	128	65	1.05 (0.68, 1.62)
≥30	205	97	0.77 (0.50, 1.19)
Waist-to-hip ratio quartiles			
<0. 8011	246	99	1.00
≥0.8011	254	140	1.23 (0.87, 1.74)
	Localized Stage	**Regional/Distant Stage**	**OR (95% CI)***
Body Mass Index, kg/m^2			
<25	223	35	1.00
25 - <30	164	37	1.40 (0.82, 2.39)
≥30	255	54	1.05 (0.61, 1.79)
Waist-to-hip ratio quartiles			
<0. 8011	312	51	1.00
≥0.8011	329	77	1.23 (0.80, 1.88)
	Localized Stage Adjusted for Grade	**Regional/Distant Stage Adjusted for Grade**	**OR (95% CI)***
Body Mass Index, kg/m^2			
<25	210	32	1.00
25 - <30	161	32	1.32 (0.73, 2.38)
≥30	249	51	1.26 (0.70, 2.25)
Waist-to-hip ratio quartiles			
<0. 8011	298	46	1.00
≥0.8011	321	71	1.20 (0.75, 1.92)
	Endometrioid Histopathological Subtype	**Other Histopathological Subtype**	**OR (95% CI)***
Body Mass Index, kg/m^2			

	Well/Moderately Differentiated Grade	Poorly Differentiated/Anaplastic Grade	OR (95% CI) *
<25	211	48	1.00
25 - <30	163	39	1.04 (0.63, 1.73)
≥30	261	50	0.65 (0.39, 1.08)
Waist-to-hip ratio quartiles			
<0. 8011	295	70	1.00
≥0.8011	341	67	0.76 (0.50, 1.15)

*Odds ratios and 95% confidence intervals are from multinomial logistic regression models adjusted for age, ethnicity, prior hormone use, family history of endometrial cancer, and WHI study component.

*Numbers do not sum to 809 due to missing data for BMI, WHR, stage, grade, and/or histopathological subtype