Body Mass and Endometrial Cancer Risk by Hormone Replacement Therapy and Cancer Subtype

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Abstract

Epidemiologic studies unequivocally show that greater body mass increases the risk of endometrial cancer, but whether risk varies by use of postmenopausal hormone therapy (HT), location of fat deposition, or cancer subtype is still unclear. We examined these associations among 33,436 postmenopausal women in the Cancer Prevention Study II Nutrition Cohort, who completed questionnaires on diet, lifestyle, and medical history at baseline in 1992. A total of 318 cases were eligible through June 2003. Cox-proportional hazards analyses were used to estimate multivariate-adjusted rate ratios (RR). As expected, adult body mass index (BMI) was a strong predictor of risk [RR, 4.70; 95% confidence interval (CI), 3.12-7.07 for BMI 35+ versus 22.5-25.0, *P* trend < 0.0001]. Use of estrogen plus progestin postmenopausal HT modified the association. Among never-users, risk was significantly linear across the entire range of BMI examined (RR, 0.51; 95% CI, 0.29-0.92 for <22.5 versus 22.5-25.0; RR, 4.41; 95% CI, 2.70-7.20 for ≥35 versus 22.5-25.0, *P* trend < 0.0001), but among ever estrogen plus progestin users, the association was not significant (*P* trend = 1.0; *P* interaction < 0.0001). We observed no difference in risk according to tendency for central versus peripheral fat deposition. Greater BMI (≥30 versus <25.0) increased risk of both ''type I'' (classic estrogen pathway, RR, 4.22; 95% CI, 3.07-5.81) and ''type II'' (serous, clear cell, and all other high grade) cancers (RR, 2.87; 95% CI, 1.59-5.16). The increased risk of endometrial cancer across the range of BMI in women who never used postmenopausal HT stresses the need to prevent both overweight and obesity in women. (Cancer Epidemiol Biomarkers Prev 2008;17(1):73–9)

Introduction

Endometrial cancer is the most common female gynecologic cancer in the United States, ranking fourth among all cancers in women in age-adjusted incidence (1). The large international variation in incidence rates indicates that much of the risk is modifiable (2). Most of the major known risk factors for endometrial cancer contribute to prolonged and excessive exposure of the endometrium to estrogens unopposed by progesterone, as occurs with unopposed postmenopausal estrogen therapy and obesity. Among women who do not use hormone therapy (HT), adipose tissue provides the major source of circulating estrogens through increased conversion of androstenedione to estrone, and decreased production of sex hormone–binding globulin by the liver (3, 4). Together, these increase the concentration and bioavailability of circulating estrogens.

Endometrial cancer was among the first cancers identified as being obesity-related. Although the relationship between excess body mass and endometrial cancer is well-established (5, 6), several unresolved questions remain. First is the extent to which HT modifies the association between body mass index (BMI) and endometrial cancer. Unopposed estrogen HT is contraindicated in women with an intact uterus. Previous studies suggest that progestins in estrogen plus progestin (E + P) attenuate risks associated with estrogen, but that this protection may vary by body fatness (7). A recent prospective study found that obese women who exclusively used E + P had a borderline, nonsignificant higher risk of endometrial cancer compared with normal weight women (8).

Second is whether the location of body fat influences the relationship between BMI and endometrial cancer. Recent data suggests an independent association between insulin resistance (for which waist size is an important independent predictor; ref. 9) and endometrial cancer (10), but results from studies examining central and peripheral fat deposition, independent of BMI, have been inconsistent (11-17).

Third is the question of whether BMI differentially affects the two main subtypes of endometrial cancer. Type I tumors are mostly endometrioid carcinomas, comprising ~80% of tumors, and are associated with endometrial hyperplasia; type II tumors are mainly serous and clear cell adenocarcinomas that arise from polyps or precancerous lesions in the vicinity of atrophic endometrium in older women (18-21). Other aggressive tumors (e.g., International Federation of Gynecology and Obstetrics grade 3) develop characteristics similar to type II

Received 9/14/07; revised 10/29/07; accepted 11/1/07.

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doi:10.1158/1055-9965.EPI-07-2567

tumors and have sometimes been considered in the definition of type II cancers (19, 21). Little is known about the etiology of the more aggressive type II tumors. Although these tumors are not thought to be related as strongly to estrogenic stimuli and, therefore, to obesity as the more indolent tumors (18-20, 22), the only prospective epidemiologic analysis to examine risks by type found an ~2-fold higher risk of both type I and type II cancers among obese versus normal weight women (23).

We prospectively examined the association between BMI and incident endometrial cancer in postmenopausal women from the United States, focusing on patterns of risk associated with never postmenopausal HT use and ever E + P use, location of weight deposition, and type I and type II cancers.

Materials and Methods

Study Population. Women in this study were participants in the Cancer Prevention Study (CPS) II Nutrition Cohort, a prospective study of cancer incidence and mortality among 86,404 men and 97,786 women (24). The Nutrition Cohort was begun by the American Cancer Society in 1992 to 1993, and is a subgroup of the ~1.2 million participants in CPS-II, a prospective study of cancer mortality established in 1982. In brief, Nutrition Cohort participants were members of the CPS-II cohort who resided in 21 states with population-based cancer registries (24). Participants were 50 to 74 years of age at enrollment in 1992 or 1993, when they completed a 10-page confidential, self-administered mailed questionnaire that included questions on demographic, medical, lifestyle, anthropometric, and dietary factors. Follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, and 2003 to update exposure information and to ascertain newly diagnosed cancers. The response rate among living cohort members for every follow-up questionnaire was at least 88% through 2003. The Emory University School of Medicine Institutional Review Board approved all aspects of the CPS-II Nutrition Cohort.

Anthropometric Measures. At baseline in 1992 to 1993, participants were asked to report their current weight and weight at age 18 years. BMI was calculated as current weight in kilograms divided by the square of height in meters (kg/m^2). BMI was categorized as <22.5, 22.5 to 25.0 (referent), 25.0 to <30, 30 to <35, and 35+. We coded the 1992 question ''when you gain weight, where on your body do you mainly add the weight?'' with possible responses: chest and shoulders, waist, hips and thighs, other part of body, equally all over, and don't gain weight. Because only 0.45% of women responded ''chest and shoulders'', this was combined with ''waist'', and categorized as a tendency for ''central'' weight gain. Weight gain in hips and thighs and/or ''equally all over'' were categorized as ''peripheral.'' We examined these exposures as independent risk factors for endometrial cancer.

Measures of Hormone Use and Physical Activity. Postmenopausal HT was assessed at enrollment in 1992 and on each follow-up questionnaire. The 1992 baseline questionnaire and the 1997 follow-up questionnaires included questions on current and past postmenopausal HT use as well as type and duration of use. Later follow-up questionnaires (1999 and 2001) included only questions regarding type of hormone use in the last 2 years. In addition, because all Nutrition Cohort participants were historically participants in the larger CPS-II cohort (25), information on prospectively collected hormone use was also available from the 1982 CPS-II questionnaire. Because we did not ask for the type of HT used in 1982, women who reported hormone use in the 1982 CPS-II questionnaire were considered former estrogen therapy users. Baseline recreational physical activity information was collected using the question ''During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?'' Response to each activity could be ''none'', ''1 to 3 h per week'', ''4 to 6 h per week'', or ''7+ h per week.'' Summary MET hours per week were calculated for each participant. A MET, or metabolic equivalent, is the ratio of metabolic rate during a specific activity to resting metabolic rate (26). Due to the older age of this population, MET hours per week were calculated using the lowest value of hours spent and moderate-intensity MET values for each activity such that summary measures would be estimated conservatively.

Analytic Cohort. We excluded from this analysis women who did not return any questionnaires after enrollment in 1992 to 1993 and were not known to be dead (n = 3,190), or who at baseline, reported a history of uterine cancer (n = 259) or other cancer except non–melanoma skin cancer (n = 11,794). Because few women were premenopausal (and thus could not be evaluated separately), we excluded women who were premenopausal or perimenopausal at baseline or with unknown menopausal status (n = 4,291). Women who reported on the baseline questionnaire that their uterus (and/or one or two ovaries) had been removed (n = 29,014) or those with unknown uterine status at baseline (n = 1,710) were excluded. We excluded women who reported current or past estrogen-only use in 1992 or 1982 (n = 11,622) and those for whom the type of hormone use was unknown (n = 1,763) to eliminate the powerful influence of estrogen-only postmenopausal hormone replacement on endometrial cancer, and to avoid the possibility that reports of such use were erroneous (because use of unopposed estrogen is contraindicated in women with an intact uterus).

For unverified self-reported cancers, we censored follow-up at the last cancer-free survey; when the last cancer-free survey was the baseline survey, these women were excluded from the analysis (n = 21). We also excluded women missing information on height (collected in 1982, n = 200) or weight in 1992 (n = 325), or those with extreme values (top/bottom 0.1%) of height (n = 92) or weight (n = 69). The final analytic cohort consisted of 33,436 women, among whom 318 incident endometrial cancers occurred between the date of enrollment in 1992 to 1993 and June 30, 2003.

Case Ascertainment. Endometrial cancers were defined as International Classification of Disease code C54.1 (27, 28) tumors diagnosed between the date of enrollment in 1992 to 1993 and June 30, 2003. Most incident cases of endometrial cancer were initially identified through a self-report of endometrial cancer on any of the questionnaires (n = 296) and subsequently verified by

medical records (n = 220) or by linkage with state cancer registries (n = 76). Eight additional cases were ascertained as deaths due to endometrial cancer through linkage with the National Death Index (29), and were subsequently verified through state cancer registries. Finally, 14 cases were identified as having endometrial cancer during verification of a different reported cancer, by medical record review (n = 4), or through linkage with state cancer registries (n = 10).

We conducted subanalyses of ''type I'' (endometrioid) cancers (n = 230), and ''type II'' (high grade, poor prognosis) cancers (n = 70). Type II cancers were defined as serous papillary, clear cell or squamous cell histology (n = 18), and any additional International Federation of Gynecology and Obstetrics grade 3 cancers (n = 52; ref. 21). For these analyses, cases with missing grade (n = 18) were excluded.

Follow-up. Follow-up ended at the date of diagnosis of endometrial cancer, death, or June 30, 2003, whichever came first. We censored women at the follow-up survey date of any other verified incident cancer (except non–melanoma skin cancer), the survey date of newly reported estrogen-only postmenopausal HT, and at the survey date of self-reported hysterectomy during follow-up. Cases with endometrial stromal sarcoma (histology code 8930), adenosarcoma (code 8933), Mullerian mixed tumor (code 8950), endometrial adenofibroma (code 8381), carcinosarcoma (code 8980), and missing histology (n = 20) were censored during follow-up and not considered cases because the etiology of these less common tumors is thought to be different from endometrial carcinomas.

Statistical Analysis. We used Cox proportional hazards models to estimate the endometrial cancer incidence rate ratio (RR) and 95% confidence interval (CI) in relation to BMI at baseline. Age-adjustment was accomplished by stratifying on single year of age within each Cox model. Covariates included age at menarche (<12, 12, 13, >13, and missing), age at menopause (<45, 45 to <50, 50 to <54, ≥54, and missing), combinations of number of live births (nulliparous, 1-2, 3+, and unknown), and age at first birth (<25, ≥25, or unknown), use of HT [never, current E + P, past E + P, or other (e.g., vaginal estrogen)], oral contraceptive use (never, ever, and unknown), smoking [never, past smoker according to years since quitting (<10, 10-19 and 20+, and unknown), current smoker by dose (<20, 20+, unknown number of cigarettes/d), and unknown smoking status], and recreational physical activity in MET hours per week (quartiles). HT use was modeled as a time-varying covariate using information from follow-up questionnaires in 1997, 1999, and 2001. Other potential covariates considered, but not included because they did not influence the effect estimates or were not risk factors in this cohort, were family history of endometrial cancer in a mother or sister, height, race (97.7% were white), education, energy intake, percentage of energy from fat, red and processed meat intake, and alcohol consumption. Trend variables for BMI were created by assigning the median value to each category.

We examined potential effect modification of the association between BMI and endometrial cancer by E + P HT history (never use or exclusive use of E + P) and smoking status (never, past, current). We combined current and past exclusive users of E + P because numbers were too small to examine separately. In the ever E + P only strata, we additionally controlled for duration of use. To test the Cox proportional hazards assumption, we created interaction terms between main effects variables and time. Statistical interaction and the Cox proportional hazards assumption were assessed in multivariate models using the likelihood ratio test (30). We also evaluated effect modification by testing the heterogeneity of trends among strata by creating interaction terms between the modifying factor and the trend variable for BMI, and comparing the base model to the model with the interaction term using the likelihood ratio test (30). Two-sided tests were statistically significant if $P \leq 0.05$.

Results

During the 11-year follow-up period, 318 incident cases of endometrial cancer were eligible for analysis. All women were postmenopausal, with a median (10th-90th percentile distribution) age of 62 (55-70) years at baseline. The median (10th-90th percentile distribution) of BMI from 1992 to 1993 was 24.6 (20.5-31.8) kg/m^2. Women in the highest baseline BMI categories had gained the most weight over time, and were heavier at age 18 (Table 1). These women were also of shorter stature, were less likely to be current or former HT users, to be current smokers, to have a college education, or to be physically active.

In multivariate analysis, BMI at baseline was strongly related to endometrial cancer incidence (BMI, 35.0+; RR, 4.70; 95% CI, 3.12-7.07 versus BMI, 22.5-25.0, P < 0.0001; Table 2). These findings remained statistically significant after controlling for weight change since age 18 (RR, 3.02; 95% CI, 1.74-5.24, P trend < 0.0001) or BMI at age 18 (RR, 4.86; 95% CI, 3.14-7.54, P trend < 0.0001). Conversely, neither BMI at age 18 nor weight gain from age 18 to baseline were independently associated with endometrial cancer risk after adjusting for BMI at baseline: individuals who gained 30.0+ kg versus individuals with a stable weight had an increased risk of endometrial cancer (RR, 3.68; 95% CI, 2.48-5.47, P trend < 0.0001), but after adjusting for BMI in 1992, the association was attenuated, and no longer significant (RR, 1.41; 95% CI, 0.78-2.53, P trend = 0.10); individuals who had a higher BMI at age 18 (25.0+ versus 18.5 to <20.0 kg/m^2) had a higher risk of endometrial cancer (RR, 2.01; 95% CI, 1.34-3.01, P trend = 0.0003), but after adjusting for BMI at baseline, this association was null (RR, 0.93; 95% CI, 0.60-1.44, P trend = 0.6; not presented in the tables). Women who reported a tendency to gain weight centrally (versus peripherally) were not at a significantly higher risk of endometrial cancer in a model controlling for BMI (RR, 1.12; 95% CI, 0.80-1.56).

We observed no effect modification between BMI and endometrial cancer by smoking status. However, the relationship between BMI and endometrial cancer risk was modified by E + P use. Among never-users of postmenopausal HT, risk increased across the entire range of BMI and was not confined to women who were obese (Table 3). Conversely, among women who were ever-users of E + P, a higher BMI was not associated with a significantly increased risk of endometrial cancer.

Table 1. Baseline characteristics according to BMI at baseline, CPS-II Nutrition Cohort women (*n* = 33,436)

Characteristics	BMI (kg/m^2)				
	<22.5	22.5 to <25.0	25.0 to <30.0	30.0 to <35.0	≥35.0
n	9,480	8,523	10,323	3,619	1,491
Mean age (y)	62.0	62.0	62.1	62.0	61.2
Mean BMI in 1992 (kg/m^2)	20.7	23.7	27.1	32.0	38.6
Mean BMI at age 18 (kg/m^2)	19.6	20.3	21.0	22.4	24.4
Mean weight gain since age 18 (kg)	3.3	9.4	16.6	25.7	37.6
Mean height (cm)	164.6	164.0	163.9	162.9	162.6
Race (% white)	98.0	97.9	97.6	96.8	96.4
College graduate (%)	40.6	34.9	29.5	25.5	26.8
Smoking history					
Never smoker (%)	53.9	55.1	57.2	60.7	57.5
Former smoker (%)	34.3	35.9	34.5	32.8	36.5
Current smoker (%)	11.8	9.1	8.3	6.5	6.1
Hormone therapy					
Never-user (%)	67.0	71.4	76.3	82.1	84.8
Past E + P user (%)	5.2	5.7	5.0	4.4	4.1
Current E + P user (%)	23.1	18.7	14.6	10.2	7.0
Oral contraceptive use					
Never-user (%)	61.9	62.6	64.8	65.0	67.0
Ever-user (%)	37.1	36.5	34.0	33.8	31.4
Mean age at menarche (y)	13.0	12.8	12.7	12.5	12.3
Mean age at menopause (y)	50.3	50.4	50.3	50.5	50.4
Parity					
Nulliparous (%)	8.2	7.3	7.0	6.8	9.4
<25 years old, 1-2 live births (%)	14.6	13.8	13.5	12.9	13.6
<25 years old, 3+ live births (%)	34.6	37.7	41.7	44.0	44.5
25+ years old, 1-2 live births (%)	20.4	18.9	16.5	14.9	14.6
25+ years old, 3+ live births (%)	19.6	19.9	18.8	18.4	15.7
Mean exercise (MET h/wk)*	14.1	12.8	11.4	9.6	8.1

NOTE: All variables except age are standardized to the age distribution of the entire cohort. Values are presented as mean (SD) unless otherwise noted.
*METs are defined for each type of exercise-related physical activity as a multiple of metabolic equivalent of sitting quietly for 1 h.

BMI at baseline predicted risk of both type 1 and type 2 endometrial cancers (Table 4). The association between BMI and type II cancer was driven by the higher grade tumors. RRs for type II cancers defined on the basis of International Federation of Gynecology and Obstetrics grade 3 tumors alone, excluding histologic definition for a BMI of 25.0 to <30.0 and 30.0+ were RR = 1.42 (95% CI, 0.72-2.80; 16 cases) and RR = 3.19 (95% CI, 1.61-6.29; 18 cases) versus reference (<25.0; 18 cases), *P* trend = 0.001. The number of cases defined only by histology were limited (*n* = 18). For these tumors, the risk associated with a BMI of 25.0 to <30.0 and 30.0+ was RR = 1.07 (95% CI, 0.34-3.34; 5 cases) and 2.17 (95% CI, 0.67-7.05; 5 cases) versus referent (8 cases), *P* trend = 0.2. Results were similar after removing E + P users from these analyses. Additionally, interactions between BMI and HT were significant among type I cancers (*P* interaction = 0.001) but not type II cancers (*P* interaction = 0.09).

Discussion

This prospective study examined several aspects of the relationship between BMI and endometrial cancer in postmenopausal women from the United States. First, among never-users of postmenopausal HT, the positive association between body mass and endometrial cancer was monotonic across the entire range of BMI examined, with a 51% reduction in risk among the leanest women and a 441% increase in risk among the heaviest women.

Table 2. RRs and 95% CI between BMI in 1992 and endometrial cancer risk, CPS-II Nutrition cohort women (1992-2003)

	Cases (*n*)	Person-years	Age-adjusted RR (95% CI)	Multivariate RR (95% CI)*
BMI in 1992 (kg/m^2)				
<22.5	54	84,838	0.93 (0.63-1.35)	0.92 (0.63-1.34)
22.5 to <25.0 (ref)	53	76,695	1.00 (—)	1.00 (—)
25.0 to <30.0	91	92,735	1.43 (1.02-2.01)	1.40 (0.99-1.96)
30.0 to <35.0	76	31,802	3.45 (2.43-4.90)	3.27 (2.29-4.67)
35.0+	44	13,019	4.99 (3.34-7.45)	4.70 (3.12-7.07)
P for trend †			<0.0001	<0.0001

*Multivariate model was adjusted for age, age at menarche, age at menopause, parity and age at first birth, HT use, smoking history, exercise METs, and oral contraceptive use.
†*P* for trend was calculated using the median for each category and modeled as a continuous variable.

Table 3. RRs and 95% CI between BMI and endometrial cancer stratified by never and ever E + P use, CPS-II Nutrition Cohort (1992-2003)

	Never HT use*			Ever E + P use*			P interaction[†,‡]
	Cases	Person-years	RR (95% CI)[§]	Cases	Person-years	RR (95% CI)[§]	
BMI in 1992 (kg/m^2)							
<22.5	17	51,402	0.51 (0.29-0.92)	35	28,374	1.60 (0.90-2.87)	
22.5 to <25.0 (ref)	33	50,017	1.00 (—)	17	22,363	1.00 (—)	
25.0 to <30.0	59	65,576	1.32 (0.86-2.02)	27	21,950	1.56 (0.85-2.87)	
30.0 to <35.0	65	24,218	3.73 (2.44-5.70)	10[‖]	8,101	1.49 (0.68-3.28)	
35.0+	33	10,234	4.41 (2.70-7.20)				<0.0001/<0.0001
P trend[¶]			<0.0001			1.0	

*Never users of any type of postmenopausal hormone use. E + P users were exclusive current or past users of estrogen + progestin hormone therapy.
†P interaction based on heterogeneity of RRs.
‡P interaction based on heterogeneity of trends.
§Multivariate model contains age, age at menarche, age at menopause, parity and age at first birth, smoking history, exercise METs, oral contraceptive use, and duration of E + P use (time-dependent).
‖Among E + P ever users, the two highest BMI categories were combined due to small numbers. There were $n = 4$ individuals in the 35.0+ BMI category.
¶P for trend within each HT strata.

Secondly, use of E + P HT modified the association between BMI and endometrial cancer. BMI was not significantly related with risk among women who had used E + P. Obesity was associated with a greater risk of both type I and type II endometrial cancers, although the association with type II cancers was driven by high-grade endometrioid tumors; the small number of cases with serous, clear cell, and papillary histology precluded meaningful analysis using this stricter definition.

Most of the 57 case-control and 24 prospective cohort analyses published to date (6, 8, 31-33) show an unequivocal association between BMI and endometrial cancer. As indicated in a comprehensive review (5), whether the positive relationship between BMI and endometrial cancer exists at lower BMI levels has been unclear. In the European Prospective Investigation on Cancer study (31), obesity (BMI $\geq$ 30) was associated with increased risk but overweight (BMI, 25-29 versus <25) was not, whereas in the NIH-AARP Diet and Health Study (8), overweight women (BMI, 25-29 versus <25) were at increased risk. Our results for the overweight category were of borderline significance (BMI, 25-29.9; RR, 1.40; 95% CI, 0.99-1.96) compared with healthy weight women (defined as BMI of 22.5-25). Had we used <25 BMI as the referent category, as in these other studies, our multivariate RRs for BMI would have been: 25 to <30, 1.46 (1.10-1.94); 30 to <35, 3.41 (2.52-4.62); and >35, 4.90 (3.40-7.07). An earlier publication from the parent CPS-II mortality cohort (25) reported that women in the ''lean normal'' (18.5 to <22.9) BMI category were at a lower risk of fatal endometrial cancer than women in the ''heavy normal'' (23.0 to <24.9) category. In the current study, we found similar results for incident endometrial cancer, but only among never-users of postmenopausal HT.

The interaction by history of HT use may help explain inconsistencies in the dose-response relationship between BMI and endometrial cancer. The association between BMI and risk of endometrial cancer among women who never used HT was linear across the entire range of BMI examined. Although these findings are generally similar to other studies that examined risk among never-users (8, 31, 34), these studies did not examine the finer strata of normal weight women or the interactions by HT were not obvious (32). In contrast, BMI was not clearly related to endometrial cancer risk among ever E + P users. In the other study that examined E + P users exclusively, no elevated risk was observed in the 25 to 29.9 BMI category, but an association of similar magnitude to ours was observed among obese (BMI $\geq$ 30) women, which did not reach statistical significance (8).

The absence of an association in E + P users in our study may also be due to the limited power to detect an association in this group. None of the studies that

Table 4. RRs and 95% CI between BMI in 1992 and endometrial cancer incidence by subtype, CPS-II Nutrition Cohort (1992-2003)

	Type I*		Total type II*	
	Cases (n)	Multivariate RR (95% CI)[†]	Cases (n)	Multivariate RR (95% CI)[†]
BMI in 1992 (kg/m^2)				
<25.0 (ref)	75	1.00 (—)	26	1.00 (—)
25.0 to <30.0	65	1.51 (1.08-2.11)	21	1.33 (0.74-2.38)
30.0+	90	4.22 (3.07-5.81)	23	2.87 (1.59-5.16)
P for trend[‡]		<0.0001		0.0006

*Type I cancers include grade 1 or 2 endometrioid cancers. Type II cancers include those with an aggressive histology (8310, 8460, 8461, 8462, and 8560), and endometrioid International Federation of Gynecology and Obstetrics grade 3.
†Adjusted for age at interview, age at menarche, age at menopause, parity, age at first birth, smoking status, physical activity METS, oral contraceptive use, and HT use.
‡P for trend was calculated using the median for each category and modeled as a continuous variable.

presented an interaction between BMI and HT used a BMI category lower than <25, so we were unable to compare our findings for lean E + P users to other studies. In the Million Women Study, cyclic (but not continuous) progestin E + P regimens increased endometrial cancer risk in lean women, whereas both E + P regimens seemed to act therapeutically in heavier women, possibly by counteracting both exogenous and endogenous estrogens (7). Thus, residual confounding by some unopposed exposure to estrogen in cyclic E + P regimens or other unmeasured factors may explain the absence of a strong association with obesity among E + P users.

Endometrial cancers have distinct histopathologic features with varying prognoses: type I cancers are associated with hyperplasia, are considered to be in the classic estrogen-driven pathway, and are associated with a better prognosis. Type II cancers have a poorer prognosis and are more often accompanied by p53 mutations (19, 22). Type II endometrial cancers develop from the atrophic endometrium of older women and rarely express functional estrogen and/or progestin receptors (19). Little is known about the etiology of the relatively less common type II cancers, and few epidemiologic studies have had enough cases to examine these categories separately. A case-control study in 1997 found that risk factors (including BMI) differed, and that sex hormone levels were lower in patients with serous compared with endometrioid carcinoma (35).

A recent large prospective analysis from a health survey in Norway (23), found that both type I and type II endometrial cancer incidence (using a broader definition for type II, including papillary, serous, and clear cell adenocarcinomas, and some poorly differentiated carcinomas, similar to the definition we used) was significantly associated with overweight and obesity (23). Although poorly differentiated (grade 3) tumors could acquire some molecular characteristics typical of type II tumors (21), they are not always included in this group (22). We had a limited number of cases to examine the relationship between BMI and histologically defined type II tumors alone. Additional studies should seek to clarify this relationship, and determine whether any associated risk is mediated by estrogen, or through modulation of peptide hormones, insulin resistance, inflammation, or oxidative pathways (10, 36-38).

The limitations of our analysis are the reliance on self-reported measures of anthropometry and the absence of measurements of waist and hip size at baseline. In a validation study of 4,808 participants in the European Prospective Investigation into Cancer, Spencer et al. (39) showed that women tend to underestimate their weight by an average of 1.4 kg (range, 1.31-1.49 kg), or ~3.1 pounds, with a tendency for heavier women to underestimate weight more than lean women. However, the measurement error from self-reported weight and recall of weight from age 18 should have little effect on our results because correlations between measured and self-reported weight typically are >0.95 (5), and correlations between recalled and measured weight over several decades have been between 0.80 and 0.87 in several studies (40). Height was assessed 10 years before baseline as part of the CPS-II mortality cohort, and participants are likely to have lost some height over that time, which would artificially increase BMI slightly (41). These sources of misclassification would be expected to attenuate relative risks. Finally, several self-reported anthropometric measures have strongly predicted cancer risk in this cohort (42-44).

The strengths of this analysis include detailed information on endometrial cancer risk factors, including history of hormone replacement therapy use over time, and detailed assessment of cancer outcomes. All medical records were reviewed by a pathologist (T. Gansler) and American Cancer Society nosologists. We were able to censor women who reported a hysterectomy during the study using three follow-up questionnaires.

These data contribute to the accumulating evidence that among never postmenopausal HT users, greater BMI is associated with a particularly elevated risk of postmenopausal endometrial cancer, even in the high-normal reference range for BMI. Among women who have used E + P, the association with greater BMI was not significant. These findings may help explain why the BMI threshold for the association with endometrial cancer has been inconsistent in previous studies. A tendency for central adiposity was not related to risk. Together, these findings support a central role of estrogen in endometrial cancer. Although our report found a positive association between BMI and type II tumors using a broad definition of type II cancers, further study is needed to clarify these relationships and the mechanisms involved. Avoidance of overweight and obesity remains a top priority for endometrial cancer prevention.

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