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Body mass index, physical activity, and survival after endometrial cancer diagnosis: Results from the Women's Health Initiative

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Abstract

Objective—While low physical activity and high body mass index (BMI) have been associated with higher endometrial cancer incidence, no previous studies have evaluated the association between physical activity and survival after endometrial cancer diagnosis, and studies on BMI and survival have not been performed in a prospective cohort.

Methods—We examined pre-diagnosis BMI and moderate- to vigorous-intensity physical activity in relation to overall and disease-specific survival among 983 postmenopausal women who were diagnosed with endometrial cancer in the Women's Health Initiative Observational Study and Clinical Trials.

Results—Over a median 5.2 (max 14.1) years from diagnosis to death or end of follow-up, 163 total deaths were observed, 66 of which were due to endometrial cancer. We observed a higher all-cause mortality hazard ratio (HR)=1.85 (95% CI 1.19–2.88) comparing women with a BMI ≥35 kg/m² to women with BMI <25 kg/m². For endometrial cancer-specific mortality the HR=2.23 (95% CI 1.09–4.54) comparing extreme BMI categories. To examine histologic subtypes we analyzed type I endometrial tumors separately and found a HR=1.20 (95% CI 1.07–1.35)

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associated with all-cause mortality for each 5-unit change in BMI. Moderate- to vigorous-intensity physical activity was not associated with all-cause or endometrial cancer-specific mortality.

Conclusions—Pre-diagnosis BMI, but not physical activity, was associated with survival among women with endometrial cancer. Future studies should investigate mechanisms and timing of BMI onset to better understand the burden of disease attributable to BMI.

Keywords

endometrial carcinoma; survivorship; body mass index; physical activity

Introduction

High body mass index (BMI) and low physical activity have consistently been associated with higher risk of developing endometrial cancer [1]. In a recent study, 93% of endometrial cancer survivors had abdominal obesity and 12% met the U.S. government physical activity recommendation of 150 minutes of moderate to vigorous physical activity per week [2]. Despite this high prevalence of overweight and inactivity, the relationship between BMI, physical activity and survival after endometrial cancer diagnosis is unclear. A recent systematic review of BMI and survival after endometrial cancer diagnosis showed mixed results [3], with some studies showing no association after multivariate adjustment [4–11] and others suggesting worse survival associated with higher BMI [12–15]. Of the studies summarized in the review, none stratified by tumor type, none were performed in a prospective cohort setting, and most utilized BMI data abstracted from medical charts. To our review no previous studies address the association between physical activity and mortality among women with endometrial cancer. We hypothesized that BMI would be associated with a decreased risk of mortality, and that physical activity would show a protective association. With this background, we examined associations between pre-diagnosis, baseline BMI and physical activity with survival among endometrial cancer patients in the Women's Health Initiative (WHI).

Methods

Study population

Eligibility criteria and recruitment methods have been published [16]. In short, between October 1993 and December 1998, 161,808 women were enrolled in the WHI Observational Study (OS) (n=93,676) or Clinical Trial (CT) (n= 68,132) from 40 U.S. clinical centers. Eligible women were between 50 and 79 years of age, postmenopausal, had an anticipated survival of >3 years and were accessible for follow up. The institutional review boards at all institutions approved the protocol and all participants provided informed consent. Outcome data for this analysis were updated through August of 2009.

Exposure assessment

Height and weight were measured at baseline. Weight was measured using a calibrated balance beam or digital scale and height was measured using a wall-mounted stadiometer; both were recorded to nearest the one-tenth kilogram, rounded up. BMI was categorized as <25 kg/m² (normal), 25–<30 (overweight), 30–<35 (obese class I), and 35+ (obese classes II and III) [17].

Participants completed baseline questionnaires on medical history, reproductive factors, diet, lifestyle and physical activity. Participants reported “usual” frequency of walking outside the home for > 10 minutes without stopping. Six categories of frequency ranged from never to daily. Duration categories were < 20 minutes, 20–39 minutes, 40–59 minutes, and 1

hour. Four speed categories were created: < 2 mph (strolling), 2–3 mph (average/normal walking), 3–4 mph (fairly fast walking), and >4 mph (very fast walking). Women were also asked how often they usually exercised at moderate (not exhausting) or vigorous levels (that increased heart rate and produced sweating) by checking Likert scale categories [18] ranging from never to 5+ days/wk, and how long they exercised at each session to measure recreational physical activity. Vigorous activities included aerobics, jogging, tennis, and swimming laps and moderate-intensity physical activities included biking outdoors, exercise machines, calisthenics, easy swimming, and dancing.

We calculated the midpoint of the reported frequency and duration of exercise and multiplied the values to create a measure of “h/wk.” Corresponding intensity values were assigned using metabolic equivalent task (MET) values for walking (average, 3 METs; fast, 4 METs; and very fast 4.5 METs), moderate-intensity recreational (4 METs), and vigorous-intensity recreational (7 METs) activities based on the most recent compendium of physical activity [19]. We multiplied MET intensity by h/wk to compute a moderate- to vigorous-intensity physical activity variable (MET h/wk), excluding walking at or slower than an average/normal pace to better capture recreational physical activity. To categorize MET h/wk we identified those who performed no moderate to vigorous intensity physical activity (n=314) as one group and split the remaining women on the median MET value (MET h/wk= 11.26) to maintain similar size between groups.

Ascertainment of endometrial cancer outcomes

Participants completed annual (OS) or semi-annual (CT) health assessment questionnaires for self-reported health outcomes including cancer. Endometrial cancer diagnosis was verified by centrally trained physician adjudicators at the clinical centers after medical record and pathology report review, and coded according to National Cancer Institute Surveillance, Epidemiology, and End Results guidelines at the coordinating center [20]. Stage was based on the American Joint Committee on Cancer (AJCC) Staging Atlas. Vital status of participants was collected through clinical center follow-up of participants and surrogates, with death certificates obtained. In addition, periodic searches of the National Death Index (NDI) were conducted. Cause of death was determined by medical record and death certificate review by the clinical adjudicators with cause of death coded at the coordinating center; agreement rates between locally and centrally determined cause of death was 94% for cancer-related deaths [21]. Participants lost to follow up were matched to the NDI to confirm cause of death or otherwise unreported deaths [21]. To assess prognosis differences we stratified analyses by endometrial tumor types I and II using International Classification of Diseases for Oncology (ICD-O) morphology codes. Endometrial adenocarcinomas, adenosquamous carcinomas, mucin-producing adenocarcinoma and adenocarcinoma squamous metaplasia were categorized as type I and clear cell adenocarcinoma, papillary serous cystadenocarcinoma, adenosarcoma, mullerian mixed tumor, mesodermal mixed tumor, carcinosarcoma, and serous cystadenocarcinoma were categorized as type II.

Of the 161,808 women enrolled in WHI, 1,362 were diagnosed with endometrial cancer before August 2009. Exclusion criteria for this analysis included previous cancer diagnosis (n = 102), incomplete data on physical activity (n=65), BMI (n=9), or stage and grade (n=203). We excluded women without stage and grade since endometrial cancer survival is closely linked to these tumor characteristics [22–23]. We compared these 203 women missing stage and grade with the women retained in analysis on known risk factors for endometrial cancer, finding that excluded women did not significantly differ from those included in the analysis, although women with missing stage and grade seemed to have higher, although not statistically different, BMI (chi-squared p-value=0.06). All included women were able to walk more than 10 minutes outside. After exclusions, 983 women with

endometrial cancer remained in the study cohort. We observed 163 deaths from all causes and 66 deaths due to endometrial cancer.

Statistical Analysis

We compared baseline characteristics of the included women by BMI category using the chi-squared distribution for categorical variables and the Kruskal Wallis test for continuous variables. To account for the influence of multiple variables, we used Cox proportional hazards modeling to estimate the association between the exposures of interest and all-cause and endometrial cancer-specific mortality. We calculated person years using time from diagnosis to death or end of follow-up. Follow-up was terminated at death or administrative censoring at August, 2009. To account for the lag time between baseline BMI and physical activity measures and endometrial cancer diagnosis we created a categorical variable (0–<3.5, 3.5–<7, 7–<10.5, 10.5+ years). We first examined unadjusted models, and then built adjusted models, including variables that changed the log hazard ratio by >10% and were associated with both exposure and outcome. Contribution to model fit was assessed using the likelihood ratio test. In model building we considered all variables in Table 1 as possible covariates and confounders. To create parsimonious models, variables not meeting statistical criteria were excluded from final models. Final models included age (continuous), lag time interval, tumor stage (in situ/localized, regional/distant), tumor grade (well, moderately, poorly differentiated), and age at menarche (<12, ≥12). To test the proportional hazards assumption we created an interaction term between the continuous exposure and time. We also stratified by types I and II endometrial cancer defined by histologic code and given the importance of stage and grade in endometrial cancer survival, we also performed analyses stratified by these factors. We tested for interaction by diabetes and race to assess the possibility of differential associations across these parameters. We performed an analysis limited to women who were part of the observational study to assess if participation in the clinical trial influenced the observed association. A two sided p-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Among the 983 women included in analysis, BMI, physical activity and other characteristics were measured at baseline a median of 5.1 years (max 13.5 years) before diagnosis, and women were followed a median of 5.2 years (max 14.1 years) from diagnosis to death or end of follow up. Overweight or obese women tended to be African American ($p<0.001$), had higher rates of diabetes ($p<0.001$), menarche age ≥12 ($p=0.022$) and lower moderate to vigorous intensity physical activity levels ($p<0.001$) (Table 1). Normal weight women were more likely to be using menopausal hormone therapy (any) at baseline compared to their overweight counterparts ($p<0.001$).

We observed a HR=1.85 (95% CI 1.19–2.88, p -trend=0.003) for all-cause mortality comparing women with a baseline BMI ≥35 kg/m² to those with a BMI <25 (Table 2). For endometrial cancer-specific mortality, the HR=2.23 (95% CI 1.09–4.54, p -trend=0.017) comparing extreme BMI categories. For a 5-unit BMI increase the HR (95% CI) was 1.20 (1.08–1.33) all-cause mortality and 1.18 (1.01–1.38) for endometrial cancer-specific mortality.

Although the HR for baseline moderate to vigorous intensity physical activity, adjusted for age only, suggested a lower risk of total death comparing some activity to none, after adjustment for BMI and other risk factors the association was no longer significant for all-cause mortality (HR=0.93, 95% CI 0.77–1.13) or endometrial cancer mortality (HR=1.05, 95% CI 0.79–1.38) comparing those who reported ≥11.26 MET h/wk to those who reported

no moderate to vigorous physical activity (Table 3). Our MET calculation did not include average speed walking, but additional analyses including average walking did not change the association.

When we stratified by tumor type we observed an all-cause mortality HR=1.20 (95% CI 1.07–1.35) for a 5-unit BMI increase among n=830 type I cases but no association among the n=127 type II cases (Table 4). For endometrial cancer-specific mortality the HR=1.17 (95% CI 0.98–1.40) for type I cases was suggestive of an association, although it was not statistically significant. We observed no association between BMI and endometrial cancer-specific mortality among type II cases. When we stratified the women with type I tumors by tumor grade, among women with type I well-differentiated and moderately differentiated tumors the all-cause mortality associations were not significant. Among women with type I poorly differentiated tumors, however, the all-cause mortality HR=1.36 (95% CI 1.09–1.69) per 5-unit BMI increase. In analyses stratified by tumor grade, the associations between BMI and endometrial cancer-specific mortality were not significant for women with well or moderately differentiated tumors, but a 5-unit BMI increase was associated with a HR=1.39 (95% CI 1.04–1.85) for women with poorly differentiated tumors. Type II tumors demonstrate heterogeneous characteristics and we had insufficient power to further subcategorize these women.

In analyses restricted to the 805 women (137 deaths) with in-situ/localized disease we observed a HR=2.03 (95% CI 1.26–3.26) comparing severely obese to normal weight women. We had too few deaths to separately estimate HRs for women with regional/distant disease (26 deaths). In sensitivity analyses we restricted analyses to women without diabetes, and found that the association between BMI and higher mortality persisted (HR=1.78, 95% CI 1.11–2.86 comparing severely obese to normal weight women). We did not observe an interaction between BMI and physical activity, and the association between physical activity and mortality was similar when stratified by obesity (BMI ≥ 30 kg/m²) (data not shown). Analyses restricted to the 570 women in the OS showed a stronger association between BMI and mortality, while the association for physical activity and mortality remained null. An additional physical activity analysis including walking at an average/normal pace (median MET h/wk=11.5) showed similar results. Exclusion of women who were diagnosed within one year of the end of follow-up also did not alter results. Although we had additional exposure information at year 3 of follow-up, because there were only 283 women diagnosed with endometrial cancer and 54 deaths before year 3 we were unable to assess post-diagnosis BMI or physical activity.

Discussion

In this prospective analysis of BMI, physical activity and survival among women diagnosed with endometrial cancer, we found that higher BMI, measured a median of 5.1 years before diagnosis, was associated with higher all-cause and endometrial cancer-specific mortality. The association between BMI and overall mortality was most apparent in women with type I tumors, particularly among women with poorly differentiated tumors. Moderate to vigorous intensity physical activity was not associated with all-cause or endometrial cancer mortality after multivariate adjustment.

A recent systematic review identifying 12 published studies on BMI and mortality among endometrial cancer patients provided evidence consistent with our findings [3]. Four of the reviewed studies showed that higher BMI was associated with all-cause mortality among the women with endometrial cancer [12–15]. Although some studies included in the review reported that higher BMI was associated with more favorable tumor characteristics [4–9, 13–14], none showed an association between BMI and overall mortality after multivariate

adjustment. Our results thus clarify previous clinical findings and given our larger sample size and prospective cohort setting, provide evidence of a more definitive role for BMI in endometrial cancer survival. Also, our finding on BMI and endometrial cancer-specific mortality provides a provocative suggestion of a disease specific impact of BMI on survival.

Our all-cause mortality results are similar to analyses conducted in large, prospective cohorts of individuals healthy at baseline such as the NIH-AARP study and the Cancer Prevention Study-II (CPS-II) that show an approximate two-fold increased risk of all-cause mortality comparing healthy women with a BMI ≥ 35 kg/m² to normal weight, similarly aged women [24–25]. Results for cancer specific-mortality in CPS-II were also similar, showing a nearly three-fold increased risk of endometrial cancer death observed comparing BMI 35–39.9 to BMI 18.5–24.9 kg/m² in a cohort of women healthy at baseline [26].

Published studies report a protective association between physical activity and endometrial cancer incidence [1, 27–28]. We did not observe a difference in survival associated with higher physical activity. This lack of association could be due to insufficient power, measurement error in physical activity reporting, or the single physical activity measure that could have changed over time. Still, as physical activity is an established component of weight loss and maintenance, it may be indirectly associated with survival through prevention of weight gain.

The geographic diversity of the cohort, prospective study design, and centralized adjudicated outcomes each contribute to study strengths. WHI staff performed standardized collection of measured height and weight, lessening measurement error from self report or lack of anthropometry protocols. Previous studies were based on data abstracted from charts for patients who sought treatment at specified hospitals [4–9, 11, 29], were identified through state registries [12], or participated in select treatment trials [13]. In comparison, our prospective cohort included women who were healthy at baseline. Sensitivity analyses limited to those who were enrolled in the observational study supported an even stronger role for BMI in mortality compared to women in the clinical trial, suggesting that clinical trial participation may have attenuated results.

Limitations of our study include that our analytic data was only from study baseline and BMI or physical activity levels could have changed over time. We thus accounted for time from baseline measure to diagnosis in models. To address concerns about length of follow up after diagnosis we performed additional analyses excluding those who were diagnosed < 1 year from end of follow-up. Other limitations of the study include the lack of treatment data. Nevertheless, stage system is the strongest prognostic parameter for women with endometrial carcinoma [23, 30–31]. We excluded the 203 women missing data on tumor stage and grade from our analytic population as these characteristics may act as a proxy for treatment. Surgery (hysterectomy and bilateral salpingo-oophorectomy) is the most common treatment method when the cancer is confined to the uterus and primary radiation therapy without surgery is considered only for high stage tumors or under rare circumstances when women have a very high operative risk [32]. Among women with surgical stage I–II endometrial cancers adjuvant therapy or chemotherapy has not been shown to improve outcomes, thus lessening the significance of chemotherapy treatment data for assessing survival [22, 33]. High grade, type II endometrial cancers such as papillary serous carcinoma or clear cell carcinoma may involve more extensive surgery, followed by radiation and chemotherapy [32], and we analyzed these women separately to assess different patterns of survival.

Mechanisms linking BMI and physical activity to endometrial cancer survival are scarce in the published literature. Still, a recent study showed that cardiovascular disease is the

leading cause of death among endometrial cancer survivors [34]. It is well established that obesity is associated with a higher risk of death from cardiovascular disease [24, 35], and that this risk can be attenuated through physical activity and weight loss [36]. Another concern among obese women is perioperative morbidity and postoperative complications [37], but studies of obese women with endometrial cancer do not indicate poorer surgical outcomes [5, 38]. Women with a high BMI have more adipose tissue, which leads to greater synthesis and bioavailability of endogenous sex steroids such as estrogens, androgens and progesterone [39]. High levels of these sex steroids have consistently been associated with increased endometrial cancer risk and may play a role in survival [40]. Weight loss and physical activity trials among breast and colon cancer survivors show improvements in insulin, sex hormones, growth factors, adipokines and inflammatory biomarkers, which are suggested intermediaries on the pathway to improved survival [41]. To our knowledge there have not been randomized controlled trials measuring biomarkers among endometrial cancer survivors.

In conclusion, our study showed a higher risk of death among endometrial cancer survivors with higher pre-diagnosis BMI, while reported pre-diagnosis physical activity was not associated with endometrial cancer survival. More research is needed to understand how endometrial cancer patients may differ from the general population, and whether an association exists between physical activity and mortality. As endometrial cancer survivors are a growing population in the U.S. and previous surveys show high rates of overweight and obesity among these women, it is important to better understand the role of obesity and physical activity in survival. Future studies should investigate both pre and post-diagnosis BMI and physical activity with overall and cause-specific mortality.

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Research Highlights

- We examined pre-diagnosis body mass index and physical activity with mortality among women diagnosed with endometrial cancer.
- Risk of all cause and endometrial cancer specific mortality was higher among heavier women.
- No association was observed for pre-diagnosis physical activity and survival.

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Table 1
 Characteristics of endometrial cancer patients in the WHI study by level of BMI (kg/m²) (N=983)

BMI (kg/m ²)	<25	25–<30	30–<35	35+	P value ^a
N	314	271	212	186	
Age at enrollment, mean (SD)	63.55 (7.22)	64.16 (6.89)	63.55 (6.68)	62.72 (6.48)	0.190
Years from enrollment to diagnosis, mean (SD)	5.39 (3.38)	5.32 (3.51)	5.72 (3.42)	5.76 (3.27)	0.335
Years from diagnosis to death or end of follow up, mean (SD)	5.71 (3.29)	5.63 (3.59)	5.57 (3.64)	5.41 (3.30)	0.803
High school graduate, %	96.50	97.79	96.70	95.16	0.650
Race/ethnicity, %					<0.001
African American	1.59	1.48	4.72	12.90	
Non-Hispanic White	92.04	94.10	91.51	83.33	
Hispanic/Latino	1.59	1.85	1.89	1.61	
Other	4.14	2.58	2.89	2.15	
Disease stage, %					0.577
In Situ	0.00	0.74	0.47	0.54	
Local	85.67	84.50	79.72	82.80	
Regional	12.10	10.70	15.57	13.98	
Distant	2.23	4.06	4.25	2.69	
Age at menarche, % 12 yr old	83.44	76.38	73.58	74.19	0.022
Pregnancy (% ever)	87.54	87.04	83.96	88.17	0.583
Age at first birth, %					0.531
Never to term	4.14	4.06	2.36	2.15	
<20	6.05	6.27	8.02	10.75	
20–29	61.15	61.25	53.77	57.53	
30+	8.92	8.86	11.79	9.14	
Missing	19.75	19.56	24.06	20.43	
OC use (% ever)	42.99	34.69	40.57	35.48	0.145
Hormone use at baseline (%)					<0.001
Never	15.92	28.41	41.04	60.22	
Past	13.69	23.99	26.89	20.97	
Current	69.11	46.13	31.60	16.67	

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BMI (kg/m ²)	<25	25–<30	30–<35	35+	P value ^a
Missing	1.27	1.48	0.47	2.15	
Smoke (% current)	4.78	4.06	7.55	3.76	0.257
Diabetes (% diagnosed)	1.59	4.06	9.00	11.29	<0.001
MVPA, mean (SD) ^b	11.41 (13.62)	9.99 (15.20)	7.42 (9.83)	6.09 (9.94)	<0.001

^aP-values were calculated using the Kruskal Wallis test for continuous variables and the χ^2 distribution for categorical variables

^bModerate to vigorous physical activity (MVPA) was calculated as the sum of fast, very fast walking, and moderate and hard intensity recreational activities reported at baseline

Table 2
Hazard ratios and 95% confidence intervals for pre-diagnosis body mass index (BMI) and endometrial cancer outcomes (n=983)

BMI (kg/m ²)	<25		25–<30		30–<35		35+		P trend	Continuous BMI ^a
	N	HR	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)		
Person-years	1786		1526		1180		1007			
All-cause mortality										
Deaths	41		44		38		40			
Age adjusted		1.00		1.19 (0.78–1.83)		1.43 (0.92–2.22)		1.86 (1.20–2.88)	0.004	1.19 (1.07–1.32)
Multivariable-adjusted ^b		1.00		1.21 (0.78–1.85)		1.57 (1.00–2.45)		1.85 (1.19–2.88)	0.003	1.20 (1.08–1.33)
Endometrial cancer mortality										
Deaths	14		18		17		17			
Age adjusted		1.00		1.52 (0.76–3.06)		1.91 (0.94–3.87)		2.15 (1.06–4.37)	0.024	1.17 (0.99–1.37)
Multivariable-adjusted ^b		1.00		1.54 (0.76–3.13)		2.06 (1.01–4.20)		2.23 (1.09–4.54)	0.017	1.18 (1.01–1.38)

^aContinuous BMI was scaled per 5 unit (kg/m²) change.

^bMultivariable models were adjusted for age, tumor grade, tumor stage, and age at menarche (<12 years old, 12 years old, and time from baseline measures to endometrial cancer diagnosis (0–<3.5, 3.5–<7, 7–<10.5, 10.5+ years)).

Table 3

Hazard Ratios and 95% Confidence Intervals for pre-diagnosis moderate to vigorous intensity physical activity (MVPA)^a and endometrial cancer outcomes (n=983)

		0 MET hr/wk		0–<11.26 MET hr/wk		11.26+ MET hr/wk		P trend
		N	HR	N	HR(95% CI)	N	HR(95% CI)	
Person years		2038		1770		1691		
All-cause mortality								
Deaths		74		45		44		
Age adjusted			1.00		0.73 (0.50–1.06)		0.88 (0.73–1.06)	0.142
Age and BMI adjusted			1.00		0.80 (0.55–1.16)		0.93 (0.77–1.13)	0.418
Multivariable-adjusted ^b			1.00		0.75 (0.51–1.10)		0.93 (0.77–1.13)	0.403
Endometrial cancer mortality								
Deaths		31		12		23		
Age adjusted			1.00		0.45 (0.23–0.88)		0.94 (0.72–1.23)	0.546
Age and BMI adjusted			1.00		0.49 (0.25–0.95)		0.99 (0.75–1.31)	0.830
Multivariable-adjusted ^b			1.00		0.51 (0.26–1.01)		1.05 (0.79–1.38)	0.872

^aMVPA was calculated as the sum of fast, very fast walking, and moderate and hard intensity recreational activities reported at baseline.

^bMultivariable models were adjusted for age, BMI, tumor grade, tumor stage, and age at menarche (<12 years old, 12 years old, and lag time from baseline measure to endometrial cancer diagnosis (0–<3.5, 3.5–<7, 7–<10.5, 10.5+ years).

Table 4

Associations between pre-diagnosis body mass index (kg/m²) and endometrial cancer outcomes, stratified by tumor type and grade

	Deaths/Person-years	Continuous BMI ^a
All-cause mortality		
Type I HR (95% CI) ^b	134/4614	1.20 (1.07–1.35)
Well differentiated	33/1220	1.09 (0.81–1.45)
Moderately differentiated	61/2127	1.14(0.97–1.34)
Poorly differentiated	31/918	1.36(1.09–1.69)
Type II HR (95% CI) ^b	22/727	1.05 (0.74–1.48)
Endometrial cancer mortality		
Type I HR (95% CI) ^b	51/4614	1.17 (0.98–1.40)
Well differentiated	13/1220	1.19 (0.79–1.80)
Moderately differentiated	19/2127	0.99 (0.72–1.36)
Poorly differentiated	16/918	1.39 (1.04–1.85)
Type II HR (95% CI) ^b	12/727	1.10 (0.69–1.76)

^aContinuous BMI was scaled per 5 unit (kg/m²) change.

^bMultivariable models were adjusted for age, tumor stage, and age at menarche (<12 years old, 12 years old, 12 years old, 12 years old), and lag time from baseline measure to endometrial cancer diagnosis(0–<3.5, 3.5–<7, 7–<10.5, 10.5+ years).