DOI:10.1093/jnci/djs530
Advance Access publication January 7, 2013

ARTICLE

Prediagnosis Body Mass Index, Physical Activity, and Mortality in Endometrial Cancer Patients

Hannah Arem, Yikyung Park, Colleen Pelser, Rachel Ballard-Barbash, Melinda L. Irwin, Albert Hollenbeck, Gretchen L. Gierach, Louise A. Brinton, Ruth M. Pfeiffer, Charles E. Matthews

Manuscript received August 21, 2012; revised November 20, 2012; accepted November 21, 2012.

Correspondence to: Hannah Arem, MHS, 6120 Executive Blvd, EPS 3029, Rockville, MD 20852 (e-mail: aremhe2@mail.nih.gov).

Background Higher body mass index (BMI) and inactivity have been associated with a higher risk of developing endometrial cancer, but the impact on endometrial cancer survival is unclear.

Methods Among incident endometrial cancer case subjects in the National Institutes of Health–AARP Diet and Health Study, we examined associations of prediagnosis BMI (n = 1400) and physical activity (n = 875) with overall and disease-specific 5- and 10-year mortality. Using Cox proportional hazards regression, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for tumor characteristics, treatment, and other risk factors. All statistical tests were two-sided.

Results Compared with women with a BMI in the range of 18.5 to less than 25 kg/m^2, the hazard ratios for 5-year all-cause mortality were 1.74 (95% CI = 1.13 to 2.66) for BMI in the range of 25 to less than 30 kg/m^2, 1.84 (95% CI = 1.17 to 2.88) for BMI in the range of 30 to less than 35 kg/m^2, and 2.35 (95% CI = 1.48 to 3.73) for BMI greater than or equal to 35 kg/m^2 (P_{trend} < .001). Higher BMI was also statistically significantly associated with poorer endometrial cancer–specific but not cardiovascular disease 5-year mortality. Hazard ratio estimates for 10-year all-cause and endometrial cancer–specific mortality as related to BMI were similar to 5-year hazard ratio estimates, whereas 10-year cardiovascular disease mortality became statistically significant (HR = 4.08; 95% CI = 1.56 to 10.71 comparing extreme BMI groups). More physical activity was related to lower all-cause 5-year mortality (HR = 0.57, 95% CI = 0.33 to 0.98 for >7 hours/week vs never/rarely), but the association was attenuated after adjustment for BMI (HR = 0.64, 95% CI = 0.37 to 1.12). No association was observed between physical activity and disease-specific mortality.

Conclusions Our findings suggest that higher prediagnosis BMI increases risk of overall and disease-specific mortality among women diagnosed with endometrial cancer, whereas physical activity lowers risk. Intervention studies of the effect of these modifiable lifestyle factors on mortality are needed.

J Natl Cancer Inst;2013;105:342–349

Endometrial cancer survivors are the second largest group of female cancer survivors in the United States, estimated at 606 910 women in 2012 (1). The 5-year survival rate for endometrial cancer is 83% but varies by disease stage and grade (1–2). Higher body mass index (BMI) and inactivity are established risk factors for endometrial cancer incidence (2,3), although less is known about these factors and survival (4). A growing body of literature on cancer survival suggests higher overall and cancer-specific mortality for overweight/obese and physically inactive breast and colon cancer survivors (5). A recent study of Surveillance, Epidemiology and End Results (SEER) data with 33 232 endometrial cancer patients who died found that the most common cause of 5-year mortality was death due to endometrial cancer, whereas at 10 years and later intervals, death due to cardiovascular disease (CVD) was most common (6).

A recent systemic review of 12 studies of BMI and endometrial cancer survival (7) was inconclusive: Some studies reported an increased risk of all-cause mortality with higher BMI (8–11), whereas other studies showed no association (12–19). Of four studies with information on BMI and disease-specific mortality, three found no association (8,10,13) and a fourth reported more endometrial cancer deaths among morbidly obese women (11). An additional recent study in the Women's Health Initiative (WHI) found an association between BMI and overall and disease-specific mortality among endometrial cancer survivors (20). These inconsistent findings on BMI and mortality among endometrial cancer patients may be explained by small sample sizes, population differences across studies, choice of BMI categorization, time points of BMI measurement in relation to diagnosis, and an inability to adjust for cancer treatment. The WHI study is the only other study on physical activity and mortality among women with endometrial cancer, and it showed no association (20).

We assessed the associations among prediagnosis BMI and physical activity independently and jointly on total and common causes

of mortality among endometrial cancer patients in the National Institutes of Health (NIH)–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study Cohort.

Methods

Study Population

The NIH–AARP Diet and Health Study has been previously described (21). Briefly, the NIH–AARP cohort included 566 399 AARP members (aged 50–71 years) who completed a mailed baseline questionnaire in 1995–1996. Participants resided in six states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) or two metropolitan areas (Atlanta, Georgia; or Detroit, Michigan). Of the 226 732 women who completed baseline questionnaires, we excluded women whose questionnaires were completed by proxy, those diagnosed with cancer before study entry, those with self-reported poor health or end-stage renal disease at baseline, those whose cancer was identified on death certificate only, and those who reported a hysterectomy or had missing information on hysterectomy at baseline. After exclusions, 197 128 women were followed for endometrial cancer. In 1996–1997, an additional risk factor questionnaire was administered that queried in greater detail about physical activity (response rate = 67%). The NIH–AARP Diet and Health study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute, and all participants gave informed consent by virtue of completing and returning the questionnaire.

Cancer Incidence

Cancer case subjects were identified by linkage to the cancer registries of the eight states originally included in the study and to three additional states (Texas, Arizona, and Nevada) to capture cancer among participants who relocated during follow-up. Cancer registry incidence data is estimated to be about 90% complete (22). Information on date of cancer diagnosis, histology, stage, grade, and first course of treatment reported within 1 year of diagnosis was also gathered from registries. The American Joint Committee on Cancer Staging System was used.

We classified invasive epithelial endometrial carcinoma case subjects using histology codes from the *International Classification of Diseases for Oncology, Third Edition*, (ICD-O-3 code 54). Among 1466 incident invasive endometrial cancer case subjects identified, we excluded women who reported stopped menstruation due to radiation/chemotherapy (n = 1) or surgery (n = 13), women missing height or weight (n = 37) measurements, and women with BMI less than 18.5 kg/m^2 (n = 15). Thus, a total of 1400 endometrial cancer case subjects were available for the BMI analysis. Among these women, 886 also completed the secondary risk factor questionnaire. We excluded women missing information on physical activity (n = 11), leaving 875 case subjects for the physical activity analysis.

Mortality Ascertainment

Participants were followed for address changes using the US Postal Service's National Change of Address database, and vital status was ascertained annually by linkage to the Social Security Administration Death Master File through December 31, 2009 (all-cause mortality), and the National Death Index Plus through December 31, 2008 (cause-specific mortality). We used ICD-9 and ICD-10 codes to separately classify deaths due to CVD (IDC-9 codes 390–398, 401–404, 410–438, 440–448 and ICD-10 codes I00-I13, I20-I51, I60-I69, and I70-I78) and endometrial cancer (ICD-9 codes 179 and 182, and ICD-10 codes C54-C55).

Exposure Assessment

BMI was calculated as kilograms per meter squared using baseline self-reported height and weight. The baseline questionnaire also queried about demographic characteristics, diet, reproductive and medical history, and lifestyles factors. The subsequent risk factor questionnaire assessed leisure time moderate-to-vigorous-intensity physical activities (MVPAs) performed in the last 10 years. Example activities included tennis, golf, biking, swimming, heavy gardening, fast walking or dancing, aerobics, and jogging. Participants reported categorical duration of activities (never, rarely, <1 hour/week, 1–3 hours/week, 4–7 hours/week, and >7 hours/week). The NIH–AARP physical activity questionnaire has not been validated directly, but it has demonstrated expected inverse associations with risk for colon and endometrial cancer in this cohort (3,23).

Statistical Analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models in SAS version 9.2 (SAS Institute, Cary, NC). To adjust for age in the best possible way, we used age as the underlying time metric (age at diagnosis and age at death or censoring). This is considered to be a better approach for survival than calendar year because it compares women of similar age (eg, similar comorbidities) over a defined period of time. The proportional hazards assumption, which was evaluated by modeling interaction terms of the continuous main exposure with follow-up time for each model, was met. Follow-up started at endometrial cancer diagnosis and ended at death or end of follow-up, whichever occurred first. For cause-specific death outcomes, deaths from causes other than the one of interest were treated as censoring events. BMI was categorized into predefined groups according to World Health Organization classifications of normal weight (18.5 to <25 kg/m^2[reference]), overweight (25 to <30 kg/m^2), obese (30 to <35 kg/m^2), and very obese (≥35 kg/m^2) (24). Tests for linear trend in BMI models were performed with BMI categories coded in an ordinal fashion. Physical activity was categorized into never/rarely (reference), less than 1 hour/week, 1 to 3 hours/week, 4 to 7 hours/week, and more than 7 hours/week.

Because BMI was recorded at baseline and time from baseline to diagnosis (lag time) varied, we examined whether hazard ratios for BMI and survival differed by lag time, categorizing women into three time blocks for year at diagnosis (1995–1998, 1999–2002, and 2003–2006) and testing for interaction across four levels of BMI (Supplementary Table 1, available online). These test results indicated no heterogeneity for 5-year mortality models ($P_{interaction}$ = .15) and borderline nonsignificant heterogeneity for 10-year models ($P_{interaction}$ = .06).

We first built a parsimonious model adjusted for tumor characteristics and treatment using categorical variables for stage (localized, regional, distant), grade (well, moderately, poorly differentiated), surgery (yes/no), and chemotherapy (yes/no). Missing data were treated as separate categories for relevant variables. We explored all variables in Table 1 as confounders

Table 1. Baseline characteristics of 1400 women diagnosed with endometrial cancer by body mass index, NIH–AARP Diet and Health Study*

	Body mass index, kg/m²								
	18.5 to <25		25 to <30		30 to <35		≥35		
Characteristics	**No.**	**%‡**	**No.**	**%‡**	**No.**	**%‡**	**No.**	**%‡**	***P*†**
Total women	387	27.6	403	28.8	299	21.4	311	22.2	
Age at diagnosis, y									.09
<60	45	11.6	44	10.9	29	9.7	44	14.2	
60 to <70	204	52.7	194	48.1	150	50.2	172	55.3	
≥70	138	35.7	165	40.9	120	40.1	95	30.6	
Tumor summary stage									.24
Localized	207	53.5	201	49.9	155	51.8	173	55.6	
Regional	45	11.6	42	10.4	30	10.0	26	8.4	
Distant metastases	4	1.0	16	4.0	9	3.0	13	4.2	
Unknown	131	33.9	144	35.7	105	35.1	99	31.8	
Tumor grade at diagnosis									.002
Well differentiated	184	47.6	157	39.0	126	42.1	144	46.3	
Moderately differentiated	117	30.2	129	32.0	95	31.8	114	36.7	
Poorly differentiated	55	14.2	80	19.9	47	15.7	27	8.7	
Undifferentiated	4	1.0	15	3.7	6	2.0	5	1.6	
Unknown	27	7.0	22	5.5	25	8.4	21	6.8	
First course of cancer treatment§									
Surgery	346	89.4	350	86.9	258	86.3	265	85.2	.39
Chemotherapy	19	4.9	25	6.2	21	7.0	15	4.8	.55
Radiation	65	16.8	70	17.4	60	20.1	47	15.1	.13
Education									.03
Less than high school/high school graduate	91	23.5	131	32.5	99	33.1	103	33.1	
Post–high school/some college	137	35.4	130	32.3	94	31.4	109	35.1	
College or graduate degree	153	39.5	130	32.3	97	32.4	89	28.6	
Race/ethnicity									.17
Non-Hispanic white	371	95.9	371	92.1	273	91.3	286	92.0	
Non-Hispanic black	6	1.6	21	5.2	16	5.4	15	4.8	
Other	7	1.8	8	2.0	4	1.3	4	1.9	
Self-reported diabetes	6	1.6	38	9.4	45	15.1	33	17.7	<.001
Family history of breast cancer	35	9.0	50	12.4	32	10.7	35	11.3	.50
Age at menarche, y									<.001
≤12	162	41.9	200	49.6	177	59.2	177	56.9	
>13	224	57.9	203	50.4	120	40.1	134	43.1	
Parity									.08
Nulliparous	75	19.4	86	21.3	74	24.8	80	25.7	
1–2	166	42.9	147	36.5	95	31.8	97	31.2	
≥3	143	37.0	168	41.7	129	43.1	132	42.4	
Age at menopause									.25
Premenopausal	50	12.9	32	7.9	28	9.4	22	7.1	
<45, y	20	5.2	39	9.7	23	7.7	26	8.4	
45 to <49, y	83	21.5	84	20.8	62	20.7	64	20.1	
50 to <54, y	174	45.0	191	47.4	133	44.5	151	48.6	
≥55, y	58	15.0	56	13.9	53	17.7	48	15.4	
Oral contraceptive use, ever	148	38.2	125	31.0	66	22.1	86	27.7	<.001
Menopausal hormone therapy use, ever	258	66.7	174	43.2	72	24.1	30	14.2	<.001
Smoke									.01
Never	181	46.8	197	48.9	171	57.2	160	51.5	
Former	159	41.1	149	37.0	102	34.1	131	42.1	
Current	35	9.0	48	11.9	20	6.7	15	4.8	

* NIH = National Institutes of Health

† *P* values were calculated using the χ^2 test.

‡ Column percentages may not add up to 100% because of rounding or missing data.

§ Categories were not mutually exclusive. Data on radiation was missing for 255 women (18.2%), and data on chemotherapy was missing for 122 women (8.7%).

and retained factors that changed modeled estimates by more than 10% or that statistically significantly improved model fit as assessed by the likelihood ratio test. We also included race because previous research has shown black women to have poorer survival independent of comorbidities such as diabetes (25). Thus the final model included further adjustment for race (non-Hispanic white, non-Hispanic black, other), smoking (never, former, current), family history of breast cancer (yes/no), and diabetes (yes/no).

Table 2. Associations between body mass index (BMI) and 5- and 10-year mortality among 1400 women with endometrial cancer, NIH–AARP Diet and Health Study*

	BMI, kg/m²									
	18.5 to <25		25 to <30		30 to <35		≥35			Continuous†
Mortality	No.	HR	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	P_{trend}	HR (95% CI)
5-year mortality										
All cause	32		73		56		55			
Model 1‡		1.00 (referent)		1.91 (1.25 to 2.91)		2.12 (1.37 to 3.29)		2.78 (1.78 to 4.34)	<.001	1.22 (1.12 to 1.34)
Model 2§		1.00 (referent)		1.74 (1.13 to 2.66)		1.84 (1.17 to 2.88)		2.35 (1.48 to 3.73)	<.001	1.17 (1.06 to 1.29)
Endometrial	16		40		36		28			
Model 1‡		1.00 (referent)		1.88 (1.04 to 3.39)		2.65 (1.46 to 4.82)		3.00 (1.59 to 5.67)	<.001	1.24 (1.10 to 1.40)
Model 2§		1.00 (referent)		1.62 (0.89 to 2.96)		2.25 (1.22 to 4.15)		2.39 (1.24 to 4.63)	.004	1.17 (1.03 to 1.34)
Cardiovascular	4		9		4		8			
Model 1‡		1.00 (referent)		2.14 (0.65 to 7.00)		1.02 (0.24 to 4.41)		3.02 (0.90 to 10.17)	.17	1.26 (0.98 to 1.61)
Model 2§		1.00 (referent)		2.06 (0.61 to 6.93)		0.82 (0.18 to 3.78)		2.78 (0.78 to 9.84)	.26	1.28 (0.98 to 1.68)
10-year mortality										
All cause	51		94		75		79			
Model 1‡		1.00 (referent)		1.73 (1.22 to 2.44)		1.98 (1.38 to 2.83)		2.56 (1.79 to 3.67)	<.001	1.22 (1.13 to 1.31)
Model 2§		1.00 (referent)		1.59 (1.12 to 2.25)		1.73 (1.20 to 2.50)		2.23 (1.53 to 3.23)	<.001	1.18 (1.09 to 1.27)
Endometrial	23		41		39		30			
Model 1‡		1.00 (referent)		1.44 (0.86 to 2.42)		2.19 (1.30 to 3.70)		2.22 (1.27 to 3.90)	.001	1.21 (1.07 to 1.35)
Model 2§		1.00 (referent)		1.26 (0.74 to 2.15)		1.80 (1.05 to 3.08)		1.79 (1.00 to 3.21)	.02	1.14 (1.01 to 1.29)
Cardiovascular	6		13		10		18			
Model 1‡		1.00 (referent)		2.09 (0.79 to 5.51)		2.11 (0.75 to 5.92)		4.77 (1.88 to 12.10)	<.001	1.36 (1.14 to 1.62)
Model 2§		1.00 (referent)		1.86 (0.69 to 5.00)		1.70 (0.59 to 4.93)		4.08 (1.56 to 10.71)	.004	1.35 (1.12 to 1.63)

* All models used age as the underlying time metric (age at diagnosis and age at death or censoring). CI = confidence interval; HR = hazard ratio; NIH = National Institutes of Health.

† Continuous models were scaled by a 5-unit change in BMI.

‡ Hazard ratios and 95% confidence intervals were adjusted for categorical variables tumor grade, tumor stage, surgery, and chemotherapy.

§ Hazard ratios and 95% confidence intervals were adjusted for categorical variables tumor grade, tumor stage, surgery, chemotherapy, race, family history of breast cancer, diabetes, and smoking status.

Physical activity models were adjusted for the same covariables and are presented with and without adjustment for BMI to address the possibility that BMI is in the causal pathway between physical activity and mortality.

In exploratory analyses, we stratified by stage, grade, and smoking status and created models restricted to type 1 endometrial cancers (n = 1251). Type 1 cases included endometrioid, mucinous, tubular, adenocarcinoma not otherwise specified, and adenocarcinoma with squamous differentiation (ICD codes 8380, 8382, 8383, 8480, 8481, 8482, 8210, 8140, 8560, and 8570). With only 108 type 2 tumors and 36 deaths (defined in Supplementary Methods, available online), we were unable to examine associations between BMI and mortality among these women. All statistical tests were two-sided, with *P* values less than .05 considered statistically significant.

Results

Our cohort consisted of 1400 women diagnosed with invasive epithelial endometrial cancer who were diagnosed a median of 5.1 years (range = 0–10.9) after baseline. We identified 312 total deaths through 2009. Cause-specific data through 2008 was used to identify top causes of death among these women: 133 deaths were due to endometrial cancer and 52 deaths were due to CVD. Median BMI at baseline was 28.9 kg/m² (range = 18.6–60.1).

Baseline characteristics by BMI category are presented in Table 1. Women with a higher BMI had fewer poorly differentiated tumors, less education, earlier age at menarche, and higher prevalence of diabetes, and they were less likely to use menopausal hormone therapy or oral contraceptives or to smoke.

Prediagnosis BMI was associated with a higher risk of all-cause 5-year mortality. Compared with normal weight women (BMI 18.5 to <25 kg/m²), women who were overweight (BMI 25 to <30) before cancer diagnosis had a 1.74 (95% CI = 1.13 to 2.66) times increased risk of all-cause 5-year mortality, women who were obese (BMI 30 to <35) before cancer diagnosis had a 1.84 (95% CI = 1.17 to 2.88) times increased risk of all-cause 5-year mortality, and women who were very obese (BMI ≥35) before cancer diagnosis had a 2.35 (95% CI = 1.48 to 3.73) times increased risk of all-cause 5-year mortality (Table 2). Similar results were observed when we restricted the analysis to type 1 endometrial cancer case subjects ($HR_{\text{very obese vs normal weight}}$ = 2.43, 95% CI = 1.45 to 4.05), to women without diabetes ($HR_{\text{very obese vs normal weight}}$ = 2.74, 95% CI = 1.69 to 4.43), and to women who had never used menopausal hormone therapy ($HR_{\text{very obese vs normal weight}}$ = 2.59, 95% CI = 1.31 to 5.10). Additional analyses of BMI and mortality stratified by tumor stage and grade did not indicate effect modification by those factors (Supplementary Table 2, available online). Sensitivity analyses to examine the impact of missing stage (Supplementary Table 3, available online) and missing chemotherapy information (data not shown) suggested that the estimates of the associations between BMI and mortality were not strongly affected by missing patterns of those two variables. Although the interaction between BMI and smoking was not statistically significant for all-cause mortality ($P_{\text{interaction}}$ = .39), we observed a stronger association among never smokers than in former or current smokers

Table 3. Associations between prediagnosis moderate-to-vigorous intensity physical activity (MVPA) and 5- and 10-year mortality among 875 women diagnosed with endometrial cancer, NIH–AARP Diet and Health Study*

	MVPA										
	Never/rarely		<1 hr/wk		1–3 hr/wk		4–7 hr/wk		>7 hr/wk		
Mortality	No.	HR	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	P_{trend}
5-year mortality											
All cause	34		21		26		32		24		
Model 1†		1.00 (referent)		0.62 (0.35 to 1.10)		0.40 (0.23 to 0.68)		0.55 (0.33 to 0.90)		0.52 (0.30 to 0.87)	.01
Model 2‡		1.00 (referent)		0.71 (0.40 to 1.26)		0.47 (0.27 to 0.81)		0.67 (0.40 to 1.13)		0.57 (0.33 to 0.98)	.06
Model 3§		1.00 (referent)		0.69 (0.39 to 1.23)		0.48 (0.28 to 0.83)		0.73 (0.43 to 1.23)		0.64 (0.37 to 1.12)	.17
Endometrial	17		15		11		17		15		
Model 1†		1.00 (referent)		1.11 (0.53 to 2.30)		0.36 (0.16 to 0.81)		0.73 (0.36 to 1.47)		0.78 (0.38 to 1.59)	.27
Model 2‡		1.00 (referent)		1.28 (0.61 to 2.72)		0.43 (0.19 to 0.997)		0.87 (0.42 to 1.82)		0.77 (0.37 to 1.62)	.33
Model 3§		1.00 (referent)		1.26 (0.59 to 2.70)		0.45 (0.19 to 1.040		0.96 (0.46 to 2.03)		0.91 (0.43 to 1.93)	.64
10-year mortality											
All cause	39		31		40		43		34		
Model 1†		1.00 (referent)		1.00 (0.62 to 1.63)		0.56 (0.35 to 0.88)		0.67 (0.43 to 1.04)		0.64 (0.40 to 1.02)	.02
Model 2‡		1.00 (referent)		1.16 (0.71 to 1.90)		0.64 (0.41 to 1.03)		0.83 (0.52 to 1.33)		0.72 (0.44 to 1.16)	.09
Model 3§		1.00 (referent)		1.16 (0.71 to 1.90)		0.68 (0.43 to 1.09)		0.92 (0.58 to 1.47)		0.83 (0.51 to 1.36)	.34
Endometrial	17		15		13		19		17		
Model 1†		1.00 (referent)		1.30 (0.63 to 2.67)		0.43 (0.20 to 0.94)		0.88 (0.45 to 1.75)		0.90 (0.45 to 1.80)	.51
Model 2‡		1.00 (referent)		1.50 (0.72 to 3.13)		0.52 (0.23 to 1.13)		1.05 (0.52 to 2.14)		0.87 (0.43 to 1.78)	.51
Model 3§		1.00 (referent)		1.51 (0.72 to 3.17)		0.54 (0.25 to 1.20)		1.16 (0.56 to 2.38)		1.01 (0.49 to 2.09)	.84

* All models used age as the underlying time metric (age at diagnosis and age at death or censoring). CI = confidence interval; HR = hazard ratio; NIH = National Institutes of Health.

† Hazard ratios and 95% confidence intervals were adjusted for categorical variables tumor grade, tumor stage, surgery, and chemotherapy.

‡ Hazard ratios and 95% confidence intervals were adjusted for categorical variables tumor grade, tumor stage, surgery, chemotherapy, race, family history of breast cancer, diabetes, and smoking status.

§ Hazard ratios and 95% confidence intervals were adjusted for categorical variables tumor grade, tumor stage, surgery, chemotherapy, race, family history of breast cancer, diabetes, smoking status, and continuous body mass index.

(Supplementary Table 4, available online). Compared with normal weight women, the hazard ratios for very obese women were 4.39 (95% CI = 2.00 to 9.62) among never smokers, 1.83 (95% CI = 0.90 to 3.74) among former smokers, and 2.18 (95% CI = 0.43 to 11.01) among current smokers.

High BMI was also associated with increased risk of 5- and 10-year disease-specific mortality (Table 2). Compared with normal weight women, very obese women had a statistically significant increased risk of endometrial cancer death within 5 years (HR = 2.39, 95% CI = 1.24 to 4.63; P = .01) and 10 years (HR = 1.79, 95% CI = 1.00 to 3.21; P = .05). Very obese women had a non-significantly elevated risk of CVD death after 5 years (HR = 2.78, 95% CI = 0.78 to 9.84), but they had a more than fourfold statistically significant increased risk of CVD death 10 years after diagnosis (HR = 4.08, 95% CI = 1.56 to 10.71).

In adjusted models, prediagnosis MVPA was associated with a 43% lower risk of 5-year all-cause mortality in a comparison of never/rare exercisers to women who reported more than 7 hours of MVPA per week (HR = 0.57, 95% CI = 0.33 to 0.98; Table 3). After further adjustment for BMI, the association was attenuated (HR = 0.64, 95% CI = 0.37 to 1.12). Prediagnosis MVPA was not related to endometrial cancer mortality. We found no association between MVPA and 10-year all-cause and endometrial cancer–specific mortality. Few cardiovascular deaths (n = 16 at 5 years, n = 30 at 10 years) precluded analysis of MVPA and CVD death.

We also assessed the joint effect of BMI and physical activity (Figure 1). Although the interaction term was not statistically significant ($P_{interaction}$ = .14), compared with women who were non-obese (BMI < 30 kg/m^{2}m) and reported some activity (>1 hour/week MVPA), we observed an increased risk of 5-year mortality for nonobese women who were inactive (HR = 2.28, 95% CI = 1.28 to 4.05) and obese women who reported some activity (HR = 1.70, 95% CI = 1.13 to 2.56) or were inactive (HR = 2.05, 95% CI = 1.11 to 3.77).

Discussion

In our study of women with endometrial cancer, higher prediagnosis BMI was associated with an increased risk of overall and endometrial cancer–specific 5- and 10-year mortality and an increased risk for 10-year CVD mortality. More MVPA was related to lower overall 5-year mortality but not disease-specific mortality or 10-year mortality. In joint effect analysis, even among nonobese women, those who were inactive had an increased risk of 5-year mortality compared with nonobese, active women.

BMI and physical activity may affect endometrial cancer survival through various pathways. Obesity may affect tumorigenesis and tumor progression through insulin resistance and hyperinsulinemia, increased bioavailability of steroid hormones, and localized inflammation (26). In 11 randomized controlled trials among breast, prostate, gastric, and colorectal cancer survivors, associations between physical activity and biomarkers of the insulin pathway, inflammation, and cell-mediated immunity showed mixed results, reporting changes in the insulin pathway but not of a consistent magnitude (27). Changes in the insulin pathway appeared to be strongest among obese and sedentary patients, and other studies also suggested that

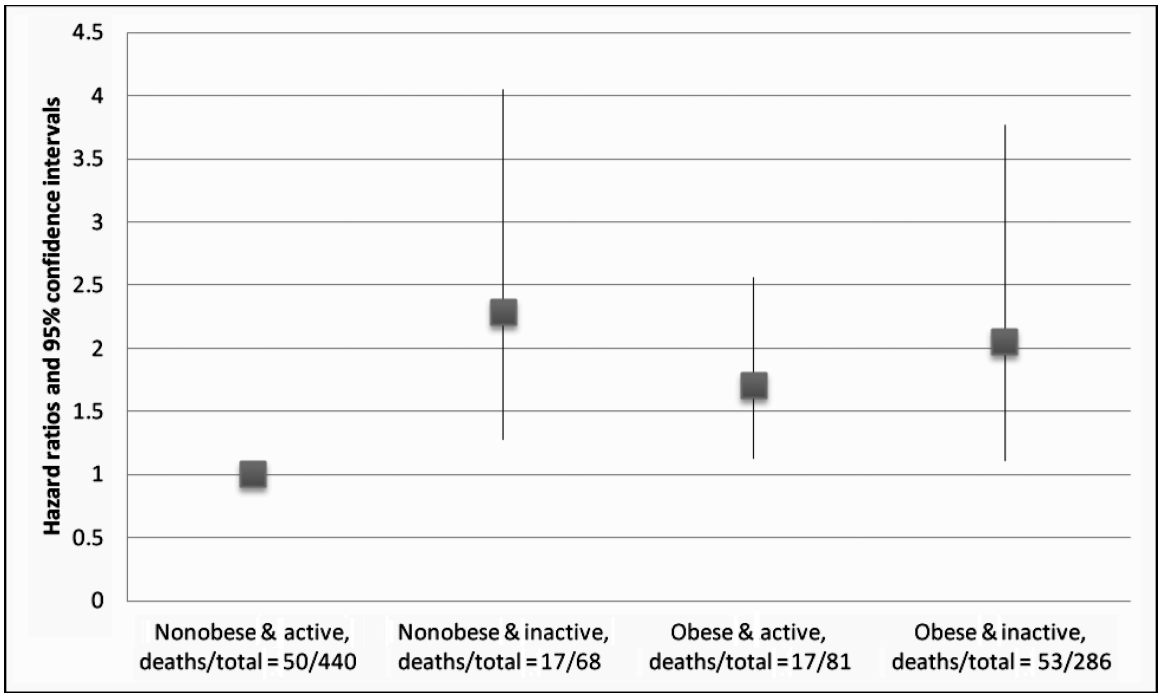

Figure 1. Joint effects of prediagnosis physical activity and obesity (n = 875) on 5-year all-cause mortality in the National Institutes of Health–AARP Diet and Health Study. Cox proportional hazards models were used with age as the underlying time metric (age at diagnosis and age at death or censoring). Nonobese was defined as a body mass index less than 30 kg/m^2, and active was defined as more than 1 hour/week of moderate to vigorous physical activity. $P_{interaction}$ = .14 for obesity and physical activity. Models were adjusted for categorical variables of tumor grade, tumor stage, surgery, chemotherapy, race, family history of breast cancer, diabetes, and smoking status.

the beneficial effects of physical activity were more pronounced in overweight or obese individuals (28). Still, our findings on joint effects of BMI and physical activity suggest that despite no multiplicative interaction, even those who are normal weight and inactive may be at increased mortality risk compared with those who are normal weight and active. Also, overweight and inactive individuals are more likely to develop diabetes (29), and diabetics with cancer have higher overall mortality than nondiabetics with cancer (30). Physical activity has been shown to be protective against diabetes (29).

Other suggested explanations for the association between BMI and mortality include surgical complications, tumor characteristics, or the role of menopausal hormone therapy. However, a recent study comparing surgical staging outcomes between nonobese and obese women showed that primary surgical treatment operative complications did not vary by BMI (31). Although some studies have shown that higher BMI is associated with better endometrial tumor characteristics (9,10,12–14,16,17,19), our study does not support this association. Also, among those who never used menopausal hormone therapy, the magnitude of association between BMI and 5-year mortality was similar to that observed among all women, lessening the likelihood that our results were confounded by menopausal hormone therapy.

Evidence on physical activity and endometrial cancer survival is sparse. The only previous study on physical activity and endometrial cancer survival found no association between prediagnosis MVPA and all-cause or endometrial cancer-specific mortality in the WHI (20). Different results may be explained by the specifics of the physical activity questionnaires, timing of MVPA assessment relative to diagnosis, health differences between populations, or differences in adjustment factors.

Strengths of our study include the prospective nature of the cohort and standardized mortality ascertainment. To our knowledge, this is the first prospective cohort to assess prediagnosis BMI, physical activity, and endometrial cancer survival with information on treatment and to assess joint effects of BMI and physical activity. We also stratified by various mortality risk factors, such as tumor characteristics, treatment, diabetes, and smoking, to explore possible effect modification. In addition, we were able to examine the effect of BMI on CVD mortality, an important cause of death among endometrial cancer survivors.

This study is limited by few deaths among endometrial cancer patients, particularly in the subset of the population used for analysis of physical activity. The few deaths attributable to CVD in our study may also explain the lack of a statistically significant association between BMI and 5-year CVD mortality. Whereas in the SEER study of endometrial cancer patients, 40.6% of deaths 10 years after diagnosis were due to CVD (6), in our study, approximately 16% of deaths were attributable to CVD at 10 years in both the BMI and MVPA analytic cohorts. It is possible that because our study participants had more education than the general population (21), they may also have had better access to healthcare.

Other limitations of the study include that we had only self-reported, prediagnosis BMI and physical activity measures. Still validation studies have shown high correlations ($r > 0.9$), between self-report and measured BMI and self-reported BMI is widely accepted as a measure of adiposity in epidemiologic studies (32). Although this MVPA questionnaire has been shown to have construct validity in cancer studies with other outcomes, measurement error may have resulted in attenuation of the risk estimates, and fewer deaths in the MVPA analysis could have limited our

ability to detect statistically significant associations. Also, the time from baseline measures to cancer diagnosis was not uniform, and both BMI and MVPA may have changed over time (33,34). We did not assess BMI or physical activity after diagnosis and thus were not able to examine postdiagnosis measures and mortality. Although models accounted for age and we performed sensitivity analyses stratified by median age at diagnosis, the aging effect in a study of mortality cannot be eliminated. Another limitation is that we had information on tumor stage and grade and first course of treatment only as reported by cancer registries. However, stratification by cancer stage and grade did not show statistically significantly different results for those missing data, and additional sensitivity analyses to assess confounding by missing tumor characteristics and treatment did not change our observed associations.

In summary, in this study of women with endometrial cancer, prediagnosis BMI was related to an increased risk of 5- and 10-year all-cause and endometrial cancer–specific mortality and 10-year CVD mortality. We also observed a suggested protective association of physical activity with mortality. Future research is needed to understand the importance of both pre- and postdiagnosis obesity or physical activity and biological mechanisms underlying the observed association.

References

1. American Cancer Society. *Cancer Treatment and Survivorship Facts and Figures 2012–2013*. Atlanta: American Cancer Society; 2012.
2. Amant F, Moerman P, Neven P, et al. Endometrial cancer. *Lancet*. 2005;366(9484):491–505.
3. Gierach GL, Chang SC, Brinton LA, et al. Physical activity, sedentary behavior, and endometrial cancer risk in the NIH–AARP Diet and Health Study. *Int J Cancer*. 2009;124(9):2139–2147.
4. Fader AN, Arriba LN, Frasure HE, et al. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. *Gynecol Oncol*. 2009;114(1):121–127.
5. Demark-Wahnefried W, Platz EA, Ligibel JA, et al. The role of obesity in cancer survival and recurrence. *Cancer Epidemiol Biomarkers Prev*. 2012;21(8):1244–1259.
6. Ward KK, Shah NR, Saenz CC, et al. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol*. 2012;126(2):176–179.
7. Arem H, Irwin ML. Obesity and endometrial cancer survival: a systematic review. *Int J Obes*. 2012; doi:10.1038/ijo.2012.94
8. Chia VM, Newcomb PA, Trentham-Dietz A, et al. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. *Int J Gynecol Cancer*. 2007;17(2):441–446.
9. Modesitt SC, Tian C, Kryscio R, et al. Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and cisplatin: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2007;105(1):59–65.
10. Mauland KK, Trovik J, Wik E, et al. High BMI is significantly associated with positive progesterone receptor status and clinico-pathological markers for non-aggressive disease in endometrial cancer. *Br J Cancer*. 2011;104(6):921–926.
11. von Gruenigen VE, Tian C, Frasure H, et al. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma. *Cancer*. 2006;107(12):2786–2791.
12. Anderson B, Connor JP, Andrews JI, et al. Obesity and prognosis in endometrial cancer. *Am J Obstet Gynecol*. 1996;174(4):1171–1178; discussion 1178–1179.
13. Everett E, Tamimi H, Greer B, et al. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. *Gynecol Oncol*. 2003;90(1):150–157.
14. Jeong NH, Lee JM, Lee JK, et al. Role of body mass index as a risk and prognostic factor of endometrioid uterine cancer in Korean women. *Gynecol Oncol*. 2010;118(1):24–28.
15. Kodama J, Seki N, Ojima Y, et al. Correlation of presenting symptoms and patient characteristics with endometrial cancer prognosis in Japanese women. *Int J Gynaecol Obstet*. 2005;91(2):151–156.
16. Temkin SM, Pezzullo JC, Hellmann M, et al. Is body mass index an independent risk factor of survival among patients with endometrial cancer? *Am J Clin Oncol*. 2007;30(1):8–14.
17. Munstedt K, Wagner M, Kullmer U, et al. Influence of body mass index on prognosis in gynecological malignancies. *Cancer Causes Control*. 2008;19(9):909–916.
18. Studzinski Z, Zajewski W. Factors affecting the survival of 121 patients treated for endometrial carcinoma at a Polish hospital. *Arch Gynecol Obstet*. 2003;267(3):145–147.
19. Gates EJ, Hirschfield L, Matthews RP, et al. Body mass index as a prognostic factor in endometrioid adenocarcinoma of the endometrium. *J Natl Med Assoc*. 2006;98(11):1814.
20. Arem H, Chlebowski R, Stefanick ML, et al. Body mass index, physical activity, and survival after endometrial cancer diagnosis: results from the Women's Health Initiative. *Gynecol Oncol*. 2012; doi:10.1016/j.ygyno.2012.10.029
21. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health–American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001;154(12):1119–1125.
22. Michaud D, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH–AARP Diet and Health Study. *J Registry Manage*. 2005;32(2):70–75.
23. Howard RA, Freedman DM, Park Y, et al. Physical activity, sedentary behavior, and the risk of colon and rectal cancer in the NIH–AARP Diet and Health Study. *Cancer Causes Control*. 2008;19(9):939–953.
24. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic*. Geneva, Switzerland: World Health Organization; 2000.
25. Olson SH, Atoria CL, Cote ML, et al. The impact of race and comorbidity on survival in endometrial cancer. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):753–760.
26. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer*. 2004;4(8):579–591.
27. Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012;104(11):815–840.
28. Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: current evidence and research issues. *Med Sci Sports Exerc*. 1999;31(11 Suppl):S646–S662.
29. Helmrich SP, Ragland DR, Leung RW, et al. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1991;325(3):147–152.
30. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA*. 2008;300(23):2754–2764.
31. Pavelka JC, Ben-Shachar I, Fowler JM, et al. Morbid obesity and endometrial cancer: surgical, clinical, and pathologic outcomes in surgically managed patients. *Gynecol Oncol*. 2004;95(3):588–592.
32. Spencer EA, Appleby PN, Davey GK, et al. Validity of self-reported height and weight in 4808 EPIC–Oxford participants. *Public Health Nutr*. 2002;5(4):561–565.
33. Pinto BM, Trunzo JJ. Health behaviors during and after a cancer diagnosis. *Cancer*. 2005;104(S11):2614–2623.
34. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409–1426.

Funding

This work was supported in part by a Yale–National Cancer Institute predoctoral training grant (T32 CA105666). This research was also supported in part by the Intramural Research Program of the National Cancer Institute at the National Institutes of Health.

Notes

The authors of this manuscript take sole responsibility for the study design, data collection, analysis, interpretation, writing of the manuscript, and the decision to submit the manuscript for publication. The authors have no conflicts of interest.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract with the Florida Department of Health. The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, State of Nevada Department of Health and Human Services.

We are indebted to the participants in the NIH–AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

Affiliations of authors. Yale School of Public Health (HA, MLI) and Yale Cancer Center (MLI), New Haven, CT; Division of Cancer Epidemiology and Genetics (HA, YP, CP, GLG, LAB, RMP, CEM) and Division of Cancer Control and Population Sciences (RBB), National Cancer Institute, Bethesda, MD; AARP, Washington, DC (AH).