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Body mass index, physical activity, and television time in relation to mortality risk among endometrial cancer survivors in the NIH-AARP Diet and Health Study cohort

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Abstract

Purpose—Endometrial cancer (EC) survivors are the second largest group of female cancer survivors in the USA, with high prevalence of obesity and physical inactivity. While higher pre-diagnosis body mass index (BMI) has been associated with higher all-cause and disease-specific mortality, pre-diagnosis physical activity has shown mixed evidence of an association with mortality. However, the association between BMI, physical activity, and TV viewing measured after diagnosis and mortality risk among EC survivors is unknown.

Methods—We identified 580 women with EC in the NIH-AARP Diet and Health Study who completed a post-diagnosis questionnaire on BMI, leisure time moderate-to vigorous-intensity physical activity (MVPA), and TV viewing. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality.

Results—With a median follow-up time of 7.1 years, we observed 91 total deaths. We found a positive association between BMI ($HR_{35+vs.\ <25kg/m^2}$ = 2.14, 95% CI 1.08–4.24 and mortality, and no statistically significant association between TV viewing ($HR_{5+\ vs.\ <3\ h/day}$ = 1.46, 95% CI 0.86–2.46) and mortality nor MVPA with mortality ($HR_{15+\ vs.\ 0\ MET\ h/week}$ = 0.72, 95% CI 0.43–1.21) after adjusting for tumor characteristics and demographic factors. Further adjustment for lifestyle and health status attenuated BMI associations ($HR_{35+vs.\ <25kg/m^2}$ = 1.47, 95% CI 0.71–3.07), but

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Conflict of interest None.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

strengthened the association between TV viewing and mortality ($HR_{5+ \text{ vs. } <3 \text{ h/day}}$ = 2.28, 95% CI 1.05–4.95).

Conclusions—Our results suggest that higher post-diagnosis BMI and TV viewing may be associated with higher mortality risk among EC patients, but that there may be complicated interrelationships between lifestyle factors of BMI, PA, and TV viewing and the mediating role of health status that need to be clarified.

Keywords

Cancer survivorship; Endometrial cancer; Body mass index; Physical activity; Television; Mortality

Higher body mass index (BMI) and physical inactivity are established endometrial cancer risk factors [1, 2]. In a population-based sample of Canadian endometrial cancer survivors, over 70 % were obese (BMI ≥ 30 kg/m^2) and 70 % failed to meet exercise guidelines recommended for general health benefits and reduced mortality risks [3]. Endometrial cancer survivors are the second largest group of female cancer survivors in the USA, with good prognosis as represented by an average 5-year survival rate of 83 % [4]. These survivors, however, are at increased risk of health complications including recurrence, new primary cancers, heart disease, and death [5–7]. Improving health status in endometrial cancer survivors is thus an important public health objective.

The few studies that have examined associations between pre-diagnosis BMI and survival suggest that higher BMI is associated with worse survival, while prediagnosis physical activity has not shown an association with survival [8]. Post-diagnosis BMI and physical activity could influence mortality risk, but at present these associations are unexplored. Sedentary time, for which there is strong evidence of a positive association with all-cause and cardiovascular disease-related mortality independent of physical activity levels [9–11], also may affect mortality risk among endometrial cancer survivors.

Cancer diagnosis is frequently thought of as a “teachable moment, ” whereby survivors may have increased motivation to actively improve their health [7]. Building the evidence based on these post-diagnosis behaviors and survival provides information that supports the development of targeted interventions in this population to enhance survival and improve quality of life. We hypothesized that higher post-diagnosis BMI and more TV viewing time (the most prevalent leisure time sedentary behavior) would be associated with higher mortality and that higher physical activity levels would be associated with lower mortality in endometrial cancer survivors.

Methods

Study population

The National Institutes of Health (NIH)-AARP Diet and Health Study has been previously described [12]. Women with no history of cancer at baseline were eligible for this analysis. After excluding women who reported a hysterectomy at baseline (n = 37) and women who had periods stopped from radiation or surgery (n = 14), there were 1,491 incident

endometrial cancer cases with information from the baseline questionnaire. Of these women, 706 were diagnosed between baseline and the 2004 follow-up questionnaire. We excluded 126 women from the 706 eligible cases because they had no post-diagnosis information on weight; we thus had 580 endometrial cancer survivors for analysis. Of these survivors, only 17 died of endometrial cancer and only 20 died of cardiovascular disease, precluding analyses of our main exposures with cause-specific death. Those missing post-diagnosis BMI showed statistically significant differences from those with post-diagnosis BMI on the following variables: younger mean age (65.3 vs. 66.7 years), lower baseline BMI (29.1 vs. 29.6 kg/m^2), higher percentage of ever oral contraceptive users (39.7 vs. 32.4), lower MVPA levels (16.0 vs. 19.2 MET h/week), and more TV watching (3.8 vs. 3.6 h/day) (Supplemental Table 1).

The NIH-AARP 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 baseline questionnaire.

Cancer incidence

Information on date of cancer diagnosis, histology, stage, grade, and first course of treatment reported within 1 year of diagnosis was gathered from cancer registries [12]. We classified invasive, epithelial endometrial carcinoma cases using histology codes from the International Classification of Diseases for Oncology, *Third Edition*, (ICD-O-3 code 54).

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 and the National Death Index Plus through 12/31/2011.

Exposure assessment

Demographic characteristics and reproductive and medical history were collected from the 1994–1995 baseline questionnaire, while the 2004 follow-up questionnaire was used to calculate the post-diagnosis BMI, physical activity, TV viewing, and health status. BMI was calculated as kg/m^2 using self-reported height and weight; leisure time moderate- to vigorous-intensity physical activity (MVPA) was calculated as the sum of eight exercise and recreational activities such as walking, jogging, tennis, swimming, bicycling, or weight training over the prior year. Participants chose from 10 duration categories ranging from none to more than 10 h/week for each activity. This questionnaire was adapted from the Nurses' Health Study, which has been validated against physical activity diaries ($r = 0.62$) [13]. The energy cost of each activity was calculated by assigning a metabolic equivalent intensity (MET) value as determined in the Physical Activity Compendium [14] and then multiplying the MET value by reported duration (h/week) to yield expenditure values in MET h/week. Participants also reported time spent sitting watching television, videos, or DVDs, choosing from eight response categories ranging from 0 to >12 h/day.

Statistical analysis

Variables with more than 5 % missing are listed in Table 1 to show missing percentages. We used IVEware 2.0 (Ann Arbor, MI, 2002) to impute values for missing variables, using 10 iterations and five imputations. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) in SAS version 9.2 (PROC PHREG, SAS Institute Inc, Cary NC). PROC MIANALYZE was used to combine results from the five imputed datasets. The underlying time metric was calculated from age at post-diagnosis questionnaire to age at death or end of follow-up, whichever occurred first. We evaluated the proportional hazards assumption by modeling interaction terms of the continuous main exposure with follow-up time for each model; all p values were >0.1.

BMI was categorized into normal weight, overweight, class I obese, and class II obese [18.5 <25 (referent), 25–<30, 30–<35, 35 + kg/m^2] [15]. Physical activity was converted into categories of 0, 0.1–<15, and 15 + MET h/week to reflect US federal physical activity guidelines, whereby the recommended guidelines are to achieve at least 7.5–15 MET h/week. Television viewing time was divided into categories of <3, 3–4, and 5+ h/day to keep the distribution relatively even given our response categories on the questionnaire. Tests for linear trend were performed by coding main exposure categories in an ordinal fashion.

We first built a parsimonious model and then adjusted for tumor characteristics and treatment, as well as variables that showed significant differences by BMI category in Table 1. Thus, our final model included age at diagnosis, tumor stage and grade, treatment, diabetes, age at menarche, and hormone use. We did not adjust for smoking status in models because inclusion did not change parameter estimates. In additional analyses, we added self-reported health status to the models to address the possibility that health status is in the causal pathway between these lifestyle factors and mortality.

We also stratified by median time from diagnosis to questionnaire (i.e., lag time =4.1 years). We used an ordinal variable to create a single hazard ratio estimate for BMI, PA, and TV to maximize power in stratified analyses. We calculated p-interaction terms by multiplying lag category by the exposure of interest and using the Wald test for statistical significance.

All statistical tests were two-sided, with p values <0.05 considered statistically significant.

Results

Women who were class II obese at the time of the follow-up questionnaire were slightly younger, less likely to have had surgery as the first course of cancer treatment, more likely to have diabetes, a younger age at menarche, and have no history of menopausal hormone therapy use (Table 1). The obese survivors were also less likely to report excellent or very good health status and reported less MVPA and more daily TV watching than their normal weight counterparts.

In adjusted models, we found a nonsignificant associations comparing normal weight to overweight (HR = 1.19, 95% CI 0.66–2.14), or class I obese women (1.11, 0.57–2.16), but over a twofold, significant increased mortality risk among class II obese women (2.14, 1.08–

4.24; Model 2, Table 2). Once we further adjusted for physical activity levels and TV viewing, as well as health status, associations were attenuated and no longer statistically significant ($HR_{\text{Class II obese women vs. normal weight women}}$ = 1.47, 95% CI 0.71–3.07; Model 4, Table 2).

We observed no significant associations between post-diagnosis MVPA and mortality, although risk estimates were in the inverse direction for more active women. Compared to 0 MET h/week, those achieving 0.1–<15 MET h/week had a nonsignificant 17 % lower mortality risk (HR = 0.83, 95% CI 0.48–1.45) and women reporting 15+ MET h/week had a nonsignificant 28 % lower mortality risk (0.72, 0.43–1.21; Model 2, Table 2). When further adjusted for BMI, TV, and health status, associations were further attenuated (HR = 0.87, 95% CI 0.40–1.09; Model 4, Table 2).

For television viewing, compared to those watching <3 h/day, we found no associations for those watching 3–4 h/day (HR = 0.88, 95% CI 0.51–1.51) or 5+ h/day of TV (1.46, 0.86–2.46; Table 2). Associations grew stronger and were statistically significant when BMI, PA, and health status were added to the model (HR = 2.28, 95% CI 1.05–4.95); (Model 4, Table 2).

In stratified analyses, we used the ordinal trend variable for BMI, PA, and TV to maximize power. We observed no difference in the results for BMI in analyses stratified by median time from cancer diagnosis to follow-up questionnaire (lag time), (Table 3). For MVPA, we found that the inverse association was stronger among those who filled out the questionnaire ≥4.1 years after diagnosis ($HR_{\geq 4.1\text{ years}}$ = 0.62, 95% CI 0.41–0.95; $HR_{<4.1\text{ years}}$ = 0.99, 0.70–1.40). We observed qualitative differences for TV viewing as well, whereby the association was stronger for those who filled out the questionnaire closer to diagnosis ($HR_{\geq 4.1\text{ years}}$ = 0.90, 0.59–1.36; $HR_{<4.1\text{ years}}$ = 1.51, 1.04–2.20). Neither difference was statistically significant for multiplicative interaction. Also, when we stratified the baseline hazard by lag time quartiles, results did not change.

Discussion

Our findings provide some evidence that higher BMI and TV viewing after endometrial cancer diagnosis may be associated with higher all-cause mortality risk; however, it appeared that these associations were confounded by health status. MVPA measured after diagnosis was not associated with mortality risk.

Analyses stratified by lag time suggested that MVPA may be more protective farther out from cancer treatment and that television may be more detrimental closer to diagnosis. These findings may reflect true differences by time or may reflect post-treatment complications.

Arem et al. [8] previously published evidence of an association between higher pre-diagnosis BMI and worse endometrial cancer survival in NIH-AARP (comparing 35 + BMI to 18.5–<25 kg/m^2: HR= 2.35, 95% CI 1.48–3.73) and in the WHI (HR = 1.85, 95% CI 1.19–2.88). In NIH-AARP, the association between MVPA measured before diagnosis and mortality was significant only before adjusting for BMI ($HR_{>7\text{ h/week vs. never/rarely}}$ = 0.57,

95% CI 0.33–0.98), while no association was observed in WHI ($HR_{11.26–0\ MET\ h/week}$ = 0.93, 95% CI 0.77–1.13) [8]. In these previous studies, sedentary time and television viewing were not analyzed.

A 2014 report from the World Cancer Research Fund summarizing the scientific literature on diet, nutrition and physical activity in breast cancer survivors (also a BMI-related cancer) found that body fatness measured both pre-and post-diagnosis were independently associated with increased mortality risk, and that physical activity both pre-and post-diagnosis were associated with lower mortality [16]. However, the significant findings for post-diagnosis BMI and mortality among breast cancer survivors were observed only for BMI measured >12 months after diagnosis. Although women with endometrial cancer have different weight trajectory patterns than breast cancer survivors, the strength of associations for these lifestyle factors and mortality may also differ by timing of these measurements in relation to diagnosis and by cause of death. Thus, more research is needed to fully understand our observed associations.

Study strengths include the long-term follow-up of the cohorts with information collected at multiple time points. We also had access to data on first course of cancer treatment, as well as information on potential confounders and risk factors. Limitations of the study include the inability to further delve into stratified analyses by potential effect modifiers such as histologic sub-types or cause-specific death due to insufficient sample size and statistical power. For BMI, we had 87 % power to detect a HR of 2.35 comparing the highest to the lowest BMI category using a type I error of $p = 0.05$ (Power 3.0, NCI). For physical activity, we used the estimate from a previous study in this cohort, which shows a $HR_{>7\ h/week\ vs.\ never/rarely} = 0.57$, before adjusting for BMI [8]. With this HR and our sample size, we only had 44 % power to detect this difference between the highest and lowest PA group. For TV viewing time, we did not have HR estimates from previous studies of endometrial cancer survivors to use in power calculations. A previous study that we performed of post-diagnosis TV viewing and mortality among colorectal cancer survivors showed a HR = 1.25 [17]. We had only 13 % power to detect a difference of this magnitude in our population of endometrial cancer survivors.

Our findings suggest that endometrial cancer survivors who have BMI levels of 35 kg/m^2 or higher may be at increased mortality risk compared to those with BMI's in the normal range. Although the directions of our observed associations (positive for TV watching and inverse for MVPA) were consistent with our hypotheses, risk estimates were not statistically significant. Given the limited evidence on these modifiable lifestyle factors after endometrial cancer diagnosis and subsequent survival, these findings highlight the need for additional research in larger studies to clarify the nature of these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of women diagnosed with endometrial cancer in the NIH-AARP study population by BMI (kg/m^2; $n = 580$)

Body mass index (BMI)	**18.5 ≤ 25**		**25 ≤ 30**		**30 ≤ 35**		**35+**		***p* value**
Deaths/*n*	21/172		26/160		21/133		23/115		0.358
Age at diagnosis, years (mean, SD)	67.3	(0.4)	67.4	(0.5)	67.2	(0.5)	64.4	(0.5)	<0.001
Pre-diagnosis BMI, kg/m^2(mean, SD)	22.8	(2.8)	27.2	(3.4)	32.5	(4.0)	39.9	(6.5)	<0.001
	n	%	*n*	%	*n*	%	*n*	%	
Tumor summary stage									0.245
Localized	105	61.1	96	60.0	91	68.4	61	53.0	
Regional/distant	17	9.9	14	8.8	6	4.5	11	9.6	
Unknown	50	29.1	50	31.3	36	27.1	43	37.4	
Tumor grade at diagnosis									0.105
Well differentiated	84	51.5	69	45.1	67	54.9	68	61.3	
Moderately differentiated	59	36.2	56	36.6	43	32.3	37	33.3	
Poorly differentiated	18	11.0	24	15.7	11	9.0	4	3.6	
First course of treatment									
Surgery									0.006
Yes	160	93.0	142	88.8	115	86.5	91	79.1	
No	12	7.0	18	11.3	18	13.5	24	20.9	
Radiation									0.191
Yes	25	14.5	32	20.0	18	13.5	13	11.3	
No	116	67.4	104	65.0	87	65.4	72	62.6	
Missing	31	18.0	24	15.0	28	21.1	30	26.1	
Chemo									0.077
Yes	7	4.1	6	3.8	3	2.3	1	0.9	
No	151	87.8	144	90.0	117	88.0	95	82.6	
Missing	14	8.1	10	6.3	13	9.8	19	16.5	
Education									0.401
<High school/high school graduate	43	25.0	39	24.4	43	32.3	28	24.4	
Post-high school/some college	53	30.8	55	34.4	46	34.6	42	36.5	

Body mass index (BMI)	18.5 ≤ 25		25 ≤ 30		30 ≤ 35		35+		*p* value
College or graduate degree	73	42.4	61	38.1	39	29.3	44	38.3	
Race/ethnicity									0.299
Non-Hispanic White	165	95.9	157	98.1	126	94.7	107	93.0	
Other	6	3.5	1	0.6	5	3.8	7	6.1	
Self-reported diabetes									<0.001
No	170	98.8	151	94.4	114	85.7	97	84.4	
Yes	2	1.2	9	5.6	19	14.3	18	15.7	
Age at menarche									0.011
≤12 years old	76	44.2	83	51.9	69	51.9	74	64.4	
13+ years old	96	55.8	77	48.1	64	48.1	41	36.7	
Parity									0.077
Nulliparous	36	20.9	31	19.4	35	26.3	38	33.0	
1–2	68	39.5	64	40.0	43	32.3	31	27.0	
3–4	56	32.6	51	31.9	44	33.1	37	32.3	
5+	9	5.2	14	8.8	11	8.3	9	7.8	
Age at menopause									0.252
Pre-menopausal	20	11.6	19	11.9	5	3.8	11	9.6	
<49	45	26.2	42	26.3	46	34.6	34	29.6	
50 ≤ 54	73	42.4	77	48.1	59	44.4	56	48.7	
55+	33	19.2	22	13.8	23	17.3	14	12.2	
OC use									0.203
Never	110	64.0	102	63.8	101	75.9	78	67.8	
Ever	61	35.5	58	36.3	32	24.1	37	32.2	
Hormone use at baseline									<0.001
Never	56	32.6	76	47.5	100	75.2	93	80.9	
Ever	116	67.4	84	52.5	33	24.8	22	19.1	
Smoke									0.707
Never	84	48.8	80	50.0	80	60.2	64	55.7	
Former	68	39.5	63	39.4	44	33.1	42	36.5	
Current	16	9.3	13	8.1	7	5.3	6	5.2	
Health status									<0.001

Body mass index (BMI)	18.5 ≤ 25		25 ≤ 30		30 ≤ 35		35+		*p* value
Excellent/very good	105	61.1	63	39.4	42	34.4	23	21.7	
Good	44	25.6	76	47.5	63	51.6	51	48.1	
Fair/poor	13	7.6	18	11.3	17	12.3	32	27.8	
Marital status									0.611
Married or living as married	88	51.2	92	57.5	76	57.1	62	53.9	
Not married	82	47.7	68	42.5	56	42.1	53	46.1	
MET h/week (mean, SD)	29.5	(2.7)	17.1	(1.5)	13.7	(1.5)	13.0	(1.9)	<0.001
TV h/day (mean, SD)	2.9	(0.2)	3.3	(0.2)	4.3	(0.3)	4.5	(0.3)	<0.001

Column percentages may not add up to 100 % due to rounding or missing data

p values were calculated using the Chi-squared test for categorical variables and the *t* test for continuous variables

Table 2

Hazard ratios and 95% CI for lifestyle factors and mortality risk among endometrial cancer survivors in NIH-AARP (n = 580)

	Deaths/total *n*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
BMI (kg/m^2)					
18.5–<25	21/172	1.00	1.00	1.00	1.00
25–<30	26/160	1.33 (0.75, 2.37)	1.19 (0.66, 2.14)	1.10 (0.61, 2.01)	0.98 (0.53, 1.81)
30–<35	21/133	1.30 (0.71, 2.39)	1.11 (0.57, 2.16)	0.97 (0.49, 1.92)	0.89 (0.45, 1.79)
35+	23/115	2.26 (1.23, 4.12)	2.14 (1.08, 4.24)	1.83 (0.90, 3.71)	1.47 (0.71, 3.07)
p-trend		0.021	0.057	0.172	0.404
MVPA (MET h/week)					
0	36/174	1.00	1.00	1.00	1.00
0.1–<15	24/162	0.69 (0.42, 1.13)	0.83 (0.48, 1.45)	0.86 (0.49, 1.51)	0.93 (0.54, 1.62)
15+	31/244	0.70 (0.42, 1.15)	0.72 (0.43, 1.21)	0.74 (0.43, 1.24)	0.87 (0.40, 1.09)
p-trend		0.042	0.220	0.345	0.721
TV time (h/day)					
<3	31/240	1.00	1.00	1.00	1.00
3–4	25/182	0.94 (0.56, 1.60)	0.88 (0.51, 1.51)	1.25 (0.74, 2.10)	1.21 (0.70, 2.10)
5+	35/158	1.61 (0.97, 2.65)	1.46 (0.86, 2.46)	2.69 (1.28, 5.65)	2.28 (1.05, 4.95)
p-trend		0.057	0.168	0.026	0.082

Model 1 was adjusted for the factor of interest only

Model 2 was additionally adjusted for age at diagnosis, tumor stage (localized, regional/distant), tumor grade (well, moderately, poorly differentiated), first course of treatment (yes/no for surgery, chemotherapy, and radiation), diabetes (yes/no), age at menarche (≤12, >12 years old), and hormone use at baseline (ever/never)

Model 3 was additionally adjusted for the other main exposures of interest (BMI, MVPA, and TV)

Model 4 was additionally adjusted for self-reported health status (excellent/very good, good, fair/poor)

Table 3

Hazard ratios and 95% CI for lifestyle factors and mortality risk among endometrial cancer survivors in NIH-AARP, stratified by median time from diagnosis to follow-up questionnaire (n = 580)

	BMI	MVPA	TV viewing
Overall	1.25 (0.99, 1.57)	0.85 (0.66, 1.10)	1.21 (0.92, 1.59)
Dx to FUQ <4.1 years	1.27 (0.93, 1.74)	0.99 (0.70, 1.40)	1.51 (1.04, 2.20)
Dx to FUQ ≥4.1 years	1.28 (0.90, 1.82)	0.62 (0.41, 0.95)	0.90 (0.59, 1.36)
p-interaction	0.420	0.314	0.082

BMI body mass index, *MVPA* moderate- to vigorous-intensity physical activity, *Dx* diagnosis, *FUQ* follow-up questionnaire

Models were adjusted for age at diagnosis, tumor stage (localized, regional/distant), tumor grade (well, moderately, poorly differentiated), first course of treatment (yes/no for surgery, chemotherapy and radiation), diabetes (yes/no), and hormone use at baseline (ever/never)

BMI, MVPA, and TV categories were treated as ordinal