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ORIGINAL PAPER

Mortality risk and physical activity across the lifespan in endometrial cancer survivors

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Abstract

Purpose Physical activity (pre- and post-diagnosis) has been studied in prevention and survivorship contexts for endometrial cancer. However, the association of physical activity (PA) across the lifespan on mortality risk among endometrial cancer survivors is understudied. The study's objective was to identify the association of lifetime PA on mortality risk in endometrial cancer survivors.

Methods Seven hundred forty-five endometrial cancer survivors drawn from a population-based cancer registry (diagnosed between 1991 and 1994) reported the frequency (sessions/week) of moderate- and vigorous intensity physical activity (MVPA) at age 12, age 20, and 5 years pre-interview (post-diagnosis). Cox proportional hazards were used to estimate hazard ratios (HR) and 95% confidence intervals for the association between PA, all-cause, and cardiovascular disease mortality as assessed in 2016. MVPA was modeled using natural cubic splines.

Results Diagnosis age, body mass index, and smoking (pack-years) were each positively associated with increased all-cause mortality risk. Those who did one session of MVPA 5 years pre-interview had a lower mortality risk (HR 0.61; 95% CI 0.41–0.92) compared to those with no MVPA. Those reporting one session of MVPA was similarly observed at age 12 (HR 0.95; 95% CI 0.86–1.06) and at age 20 (HR 0.87; 95% CI 0.65–1.16).

Conclusion Those who participated in PA, compared to those who did not, in the 5 years before diagnosis had a lower mortality risk. While PA was not independently protective against mortality risk at ages 12 or 20, PA is still important for endometrial cancer survivors for other non-mortality outcomes.

Keywords Physical activity · Mortality · Epidemiology · Measurement

Introduction

Regular physical activity is associated with physical and mental health benefits for cancer survivors, including improved cardiorespiratory fitness, [1, 2] greater muscular strength and endurance, improved mood, and lower anxiety and depression [1, 3]. Participation in physical activity also has been associated with lower mortality risk for post-diagnosis breast, colorectal, and prostate cancer survivors, but the relationship is understudied for those with endometrial cancer [4]. Endometrial cancer survivors have a high 5-year survival rate at 82%, with median age of 63 at diagnosis, yielding an increasing population of women who have survived their endometrial cancer diagnosis [5]. An emerging body of evidence shows that endometrial cancer survivors are more likely to die from cardiovascular disease than from any other cause, with the second as death

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from a non-endometrial cancer site [6, 7]. Physical activity is associated with lower risk of cardiovascular disease [8]; however, the relationship of physical activity and mortality risk in endometrial cancer survivors is unclear.

Few publications to date have examined the association of physical activity and mortality in women with endometrial cancer. Endometrial cancer survivors in the women's health initiative observational study with higher BMI had a greater mortality risk (HRR 1.86 for BMI > 35 kg/m^2). In that study, physical activity, measured via self-report over a 10-year period, was independently protective against all-cause mortality for endometrial cancer survivors, but the association was no longer present after adjustment for BMI [9]. In an analysis from the NIH-AARP cohort, self-reported physical activity captured at entry to the cohort showed no association between moderate-to-vigorous physical activity (MVPA) and mortality risk for endometrial cancer survivors (fully adjusted model HRR 0.87 NS; 95% CI 0.42–1.13). In a separate investigation using endometrial cancer survivors in the NIH-AARP cohort study, there was no independent relationship between physical activity and mortality risk; however, there was an association of TV viewing with elevated mortality risk in post-diagnosis endometrial cancer survivors [10].

A prospective cohort study in Canada recently evaluated the role of pre- and post-diagnosis physical activity in endometrial cancer survivors. Using data from the Alberta cancer registry, Friedenreich et al. found a reduced mortality risk for participants who reported high recreational physical activity, especially post-endometrial cancer diagnosis [11]. High levels of recreational physical activity were associated with mortality benefits pre-diagnosis (46% risk reduction), post-diagnosis (64% risk reduction), and with sustained high levels both pre- and post-diagnosis (67% risk reduction) [11]. This study used an assessment of lifetime physical activity recalling physical activity each year by domain [12]. These findings provide evidence for the role of physical activity improving survival, especially post-diagnosis physical activity.

These studies have focused on self-reported physical activity measured around the time of a cancer diagnosis, both measured in the decade prior to diagnosis, with the few examining the years post-diagnosis. The recent publication from Friedenreich was the first to examine lifetime physical activity using a Canadian sample of endometrial cancer survivors [11]. It is possible that physical activity over the lifespan confers cumulative or long-term benefits. Physical activity tends to decline with age [13]. Physical activity during adolescence and young adulthood also predicts sustained physical activity in adulthood [14, 15]. Assessment of physical activity over a longer period, including during adolescence or early adulthood, is therefore important for a more comprehensive picture of its benefits and to identify critical periods for intervention. While there has been one previous study in endometrial cancer survivors, the association of lifetime physical activity and mortality risk in endometrial cancer survivors has not been done in a US sample. Additionally, due to the understudied relationship of physical activity and mortality risk in endometrial cancer survivors, replication is warranted. Therefore, the purpose of this investigation was to examine the relationship between self-reported physical activity (moderate and vigorous intensity) at different life stages and risk of mortality, both prior to and after cancer diagnosis.

Methods

Design

This study was approved by the University of Wisconsin's Health Sciences Minimal Risk Institutional Review Board, and informed consent was obtained from all participants. All women in this study were aged 40–79 years and had an incident diagnosis of endometrial cancer between 1991 and 1994 reported to the Wisconsin Cancer Reporting System, a statewide mandatory tumor registry.

Participants

Participants in this study were the cases for a parent case–control study described in greater detail elsewhere [16]. Briefly, histology reports confirming an incident cancer via the state cancer registry were linked to the physician of record for each case, who received a written letter requesting permission to approach the patient. Cases with a publicly available telephone number and without a previous endometrial cancer diagnosis prior to the incident endometrial cancer were eligible. Among the 856 eligible women approached for participation in the study, interviews were completed with 745 cases (87%). Data on cancer state, histologic type, and other tumor characteristics were collected from the state's cancer registry.

Exposure assessment

Study participants completed a 45-min telephone interview by trained study staff to collect relevant clinical and demographic information, including health practices (smoking, alcohol use), reproductive history, medication use, history of cancer, height, weight, education, marital status, and other sociodemographic and behavioral characteristics. Participants were asked to report on exposures approximately 5 years prior to the date of interview, with the interview occurring post-diagnosis inquiring about pre-diagnosis exposures. Body mass index (kg/m^2) was calculated using anthropometric data collected 5 years prior to interview. Smoking pack-years was calculated as the number of packs of cigarettes (20 cigarettes/pack) over the smoking time frame. Stage of disease (distant vs. all other stage) was included for certain models, as stage of disease could be a confounder or part of the causal pathway. Mortality data, including date of death and cause of death, were collected via linkage with the national death index through 2016. There were insufficient deaths attributable to endometrial cancer to analyze disease-specific mortality.

Physical activity assessment

Physical activity was assessed via self-report during the telephone interview. Participants were asked to recall only the frequency of physical activity at three different time points: age 12, age 20, and 5 years prior to interview date. Participants were asked to estimate the number of times they engaged in moderate and vigorous intensity activity per day, week, month, or year. There was no specification of duration for any activity or pattern beyond frequency which prevented any conversion to MET values. Vigorous activities were prompted as "running, basketball, lap swimming, or gymnastics." Moderate activities were prompted as "recreational volleyball, softball, brisk walking, or leisurely biking." Reports of both moderate and vigorous physical activity were combined into an aggregated MVPA variable at each age (12, 20, 5 years prior to reference).

Analyses

Differences between those who died and those censored at the end of the follow-up period were assessed using *t* tests for continuous variables and chi-squared distribution tests for categorical. Hazard ratios (HR) and 95% confidence intervals were calculated using Cox proportional hazards regression models [17]. All-cause mortality was defined as death from any cause using linkages with the national death index. Women who were alive were censored at the study end date (December 31, 2016). Regression models were adjusted for age at diagnosis, BMI, and smoking pack-years (continuous). Due to the limited data available from the state cancer registry and parent investigation, other prognostic risk factors such as stage, treatment, alcohol use, and comorbid conditions were not available for this investigation. Age was divided (broken into quintiles) due to non-proportionality in the effects of age. There was no evidence of violations of the proportional hazards assumption for the other exposure variables.

Reported frequency of physical activity was modeled as a continuous exposure and was separated into moderate, vigorous, and MVPA variables independently at each assessment point. At each time point, regression models were constructed separately for moderate intensity, vigorous intensity, and MVPA. Associations between physical activity and all-cause mortality were estimated using natural cubic splines to allow for possible non-linear effects of physical activity [18]. Specific analyses were conducted to account for potential biases due to left truncation; neither the point estimates nor the confidence intervals changed appreciably (data not shown). All data were analyzed using SAS 9.4 (Cary, NC) and all *p* values are two-sided.

Results

Mean time from diagnosis to interview was 1.2 years (range 0.3–2.6). Of 745 participants with endometrial cancer, there were 450 (60.4%) deaths, with 102 deaths either primarily ($n=46$) or partially attributable ($n=63$) to endometrial cancer. Table 1 presents relevant clinical and demographic characteristics. Participants who died (of any cause) during the study follow-up period were more likely to be older at diagnosis, have less formal education, be a homemaker or not working full time, have more smoking pack-years, sit less, have fewer oral contraceptive pill use overall for less time, be postmenopausal, and use postmenopausal hormones.

Mean MVPA is also presented in Table 1 for each time point. There were no significant differences in physical activity between those who were censored and those who were deceased at the study's end. Participants reported the greatest frequency of moderate and vigorous intensity activity at age 12, with mean of 4.3 (SD = 3.0) sessions per week for moderate and 1.7 (SD = 2.7) sessions per week for vigorous intensity activity. Physical activity decreased over the lifespan, with the lowest frequency of moderate intensity activity reported at age 20 (mean of 2.6 sessions per week; SD = 2.8) and lowest vigorous physical activity at age 20 and 5 years prior to interview (mean of 0.4 sessions per week; SD = 1.4) (data not shown).

Risk of all-cause mortality was increased in women with older age (age HRR 1.10 (95% CI 1.07, 1.12) per year, results not shown], cases with obesity [BMI HRR 1.04 (95% CI 1.02, 1.07) per kg/m^2 results not shown), and smokers [HRR 1.30 (95% CI 1.26, 1.33) per pack-year results not shown]. In bivariate models, physical activity (isolating moderate, vigorous, and MVPA) was not independently associated with all-cause mortality at any time point (data not shown). Models with and without adjustment for distant disease were near identical, thus results for fully adjusted models including distant disease are presented in Table 2. The physical activity was not associated with risk of all-cause mortality at time point [age 12 MVPA HRR 1.00 (0.99–1.03)] nor at any intensity [5 years prior to reference vigorous intensity HRR 1.00 (0.93–1.09)] (Table 2). The point estimates presented for cardiovascular disease-specific

Table 1 Clinical and demographic characteristics for women who died during follow-up and those who were censored

	Total $n = 745$ Mean (SD) or *n* (%)	Died (any cause) $n = 450$ Mean (SD) or *n* (%)	Alive $n = 295$ Mean (SD) or *n* (%)
Age at diagnosis*	63.0 (9.9)	67.3 (7.6)*	56.3 (9.4)*
BMI (kg/m^2)	29.3 (7.3)	29.4 (7.3)	29.1 (7.4)
Healthy (BMI < 24.9)	249 (33.4%)	141 (32.2%)	108 (37.2%)
Overweight (25–29.9)	209 (28.1%)	133 (30.4%)	76 (26.2%)
Obese I (30–34.9)	134 (18.0%)	83 (18.9%)	51 (17.6%)
Obese II (35–39.9)	71 (9.5%)	42 (9.6%)	29 (10.0%)
Obese III (40+)	65 (8.7%)	39 (8.9%)	26 (9.0%)
MVPA, age 12	5.8 (2.8)	5.7 (4.6)	6.0 (3.8)
MVPA, age 20	2.9 (3.4)	3.1 (3.6)	2.7 (3.0)
MVPA, 5 years prior	3.2 (3.1)	3.2 (3.1)	3.1 (3.1)
Married*	500 (67.6%)	271 (60.3%)*	229 (78.2%)*
Education*			
Less than HS	133 (17.8%)	110 (24.4%)*	23 (7.8%)*
HS diploma	362 (48.6%)	216 (48.0%)	146 (49.5%)
Some college	155 (20.8%)	80 (17.8%)	75 (25.4%)
College degree + Unknown	90 (12.1%)	41 (9.1%)*	49 (16.6%)*
	5 (0.7%)	3 (0.7%)	2 (0.7%)
Working status*			
Homemaker	167 (22.6%)	105 (23.5%)	62 (21.2%)
Full time	190 (25.7%)	66 (14.8%)*	124 (42.3%)*
Histology—adenocarcinoma	597 (80.1%)	355 (78.9%)	242 (82.0%)
Smoking			
Never	445 (60.1%)	264 (59.1%)	181 (61.8%)
Former	202 (27.3%)	132 (29.5%)	70 (23.9%)
Current	93 (12.6%)	51 (11.4%)	42 (14.3%)
Sitting hours/day			
1 h	20 (2.9%)	10 (2.5%)	10 (3.6%)
2–4 h	346 (50.7%)	219 (53.9%)	127 (45.9%)
5–8 h	237 (34.7%)	138 (34.0%)	99 (35.7%)
9–12 h	69 (10.1%)	35 (8.6%)	34 (12.3%)
More than 12 h	10 (1.5%)	4 (1.0%)	6 (2.2%)
None	1 (0.1%)	0 (0%)	1 (0.4%)
Ever use of oral contraceptive pills*	218 (29.5%)	72 (16.1%)*	146 (50.0%)*
Use in months*	13.7 (37.3)	8.1 (33.5)*	22.4 (40.9)*
Parity	2.6 (1.9)	2.6 (2.1)	2.6 (1.8)
Age at first birth	23.7 (4.0)	23.6 (4.2)	23.7 (3.5)
Age at menarche	12.6 (1.6)	12.7 (1.5)	12.6 (1.6)
Postmenopausal*	620 (83.2%)	430 (95.6%)*	190 (64.4%)*
Age at menopause	50.5 (5.1)	50.5 (5.1)	50.5 (5.1)
Use of postmenopausal hormones*			
Never	535 (72.7%)	331 (74.9%)	204 (69.4%)
Former	65 (8.8%)	46 (10.4%)*	19 (6.5%)*
Current	136 (18.5%)	65 (14.7%)*	71 (24.2%)*
Personal history of diabetes*	93 (12.6%)	72 (16.1%)*	21 (7.2%)*

Exposures are reported at reference (approximately 5 years before interview) unless otherwise indicated. Statistical differences between groups are indicated with an asterisk (*)

MVPA moderate–vigorous physical activity

Table 2 Hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards of all-cause mortality and cardiovascular diseases specific in endometrial cancer survivors ($n=745$)

	Modeling MVPA for all-cause mortality		Modeling MVPA for CVD-specific death	
	HR	(95% CI)	HR	(95% CI)
Age 12				
Moderate	1.02	(0.99, 1.06)	1.01	(0.95, 1.07)
Vigorous	1.01	(0.98, 1.05)	1.03	(0.97, 1.08)
MVPA[a]	1.01	(0.99, 1.03)	1.01	(0.97, 1.05)
Age 20				
Moderate	1.00	(0.97, 1.04)	0.99	(0.94, 1.05)
Vigorous	1.00	(0.94, 1.07)	0.96	(0.84, 1.10)
MVPA	0.99	(0.93, 1.07)	0.99	(0.95, 1.04)
5 years before interview				
Moderate	1.00	(0.96, 1.04)	1.03	(0.97, 1.10)
Vigorous	1.03	(0.95, 1.11)	0.96	(0.81, 1.13)
MVPA	1.00	(0.97, 1.04)	1.01	(0.96, 1.07)

[a]MVPA abbreviates moderate-to-vigorous intensity physical activity

death are comparable to all-cause mortality [age 12 MVPA HRR 1.01 (0.99–1.05), fully adjusted] for both time points and activity intensity [5 years prior to reference vigorous HRR 0.96 (0.81–1.13) Model 2] found in Table 2.

Table 3 shows estimated hazard ratios and confidence intervals for those who report increasing number of sessions of MVPA compared to no sessions of MVPA per week (p values MVPA: reference = 0.02, age 20 = 0.27, age 12 = 0.31). There was not a clear dose–response relationship between increasing reports of MVPA per week and all-cause mortality hazard at any time point. Those who reported at least one session of MVPA (compared to none) 5 years prior to interview had lower all-cause mortality risk (HR 0.61, 95% CI 0.41–0.92) after covarying for age, BMI, and smoking pack-years; however, this was the only significant finding. The p values in Table 3 show a non-significant dose–response relationship between sessions of MVPA per week against all-cause mortality. No other models showed a statistically significant association between physical activity and all-cause mortality.

Discussion

In this population-based sample of endometrial cancer survivors, moderate–intensity physical activity frequency 5 years before interview was associated with reduced mortality risk after adjustment for age, smoking, and BMI. Null associations were observed for both moderate and vigorous intensity frequencies at ages 12 and 20. Additional sensitivity testing which included modeling physical activity as a non-linear term also confirmed the null associations of physical activity at ages 12 and 20 but showed mortality risk reduction for activity in the years prior to interview, but consider this was mortality risk reduction was not consistent across time points or intensity It is important to note that results are limited by measurement error inherent in retrospective assessment, especially with the longer periods of recall [19, 20]. In this study, these reporting errors are presumed to be non-differential with respect to the outcome as all study participants have endometrial cancer.

Women who recalled doing at least one session of moderate intensity physical activity per week had a lower mortality risk as compared to those who reported none. This association was only observed at 5 years before interview and was not for seen at ages 12 or 20. Moreover, no dose–response relationship was observed, showing a lack of an increased benefit at higher frequency of exercise. The results should therefore be interpreted cautiously. Our study has the potential for survival bias, in that those who were diagnosed with but died before inclusion in our study were not included for analysis. However, findings are consistent with those from healthy populations, where similar reductions in mortality risk have been demonstrated for those who do some physical

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality in endometrial cancer survivors ($n=745$) according to moderate intensity physical activity frequency across the lifespan (age 12, 20, 5 years before interview)

Sessions per week	Age 12 HR (95% CI)	Deaths	Age 20 HR (95% CI)	Deaths	5 years pre-diagnosis HR (95% CI)	Deaths
0	1.00 (ref)	71	1.00 (ref)	166	1.00 (ref)	152
1	0.95 (0.86–1.06)	15	0.87 (0.65–1.16)	38	0.61 (0.41–0.92)	23
2	0.91 (0.74–1.11)	35	0.87 (0.63–1.19)	40	0.70 (0.50–0.98)	35
3	0.87 (0.65–1.17)	34	0.94 (0.73–1.21)	44	0.95 (0.69–1.29)	55
5	0.86 (0.60–1.24)	79	1.03 (0.80–1.33)	39	0.87 (0.65–1.18)	63
7	0.97 (0.70–1.30)	113	1.05 (0.82–1.34)	89	0.92 (0.70–1.26)	100
p for trend	$p=0.31$		$p=0.64$		$p=0.10$	

Models are adjusted for age (years), BMI (kg/m^2), and smoking (lifetime pack-years). Numbers of deaths used for each analysis, those who reported physical activities at each time point, are listed for each model activity, as compared to none [21]. This is also consistent with the recent publication from Friedenreich showing a mortality risk reduction in endometrial cancer survivors with those with pre-diagnosis physical activity [11]. Our results are also consistent with other studies showing a protective effect of pre-diagnosis physical activity in endometrial cancer survivors [9]. These comparisons of any compared to no activity not only provide interpretable public health guidance, but also these discrete comparisons (some versus none) help to reduce some of the measurement errors associated with retrospective reporting.

While consistent associations between physical activity reports per week and risk for mortality were not seen in this study, it cannot conclusively identify the importance of physical activity to endometrial cancer survivors' health, as this investigation only focused on all-cause mortality. Endometrial cancer survivors face many health challenges beyond cancer, including metabolic syndrome, diabetes, heart disease, and hypertension [22, 23]. Many of these conditions contribute to morbidity and mortality; in fact, large cohort studies have demonstrated that endometrial cancer survivors are most likely to die from cardiovascular disease, a consequence of other morbidities [6, 24]. Regular physical activity confers many physiological benefits to the cardiovascular system [1, 25]. There is still a need for interventions to reduce cardiovascular death morbidity and mortality in this patient group. Several studies, including this one, are showing the mortality benefits for pre-diagnosis physical activity [9, 11]. However, strategies for identifying those most at risk for endometrial cancer and who are willing to participate in a physical activity prevention-focused trial need to be identified.

While advantageous to use self-report to examine exposures at different points in time, measurement error remains a limitation. Furthermore, our measure of physical activity was quite limited, including missing data on duration, modality, and intensity (other than moderate, vigorous descriptors). These assessments were isolated in time, and we are unable to report on habitual physical activity behavior, no can we describe pre-or post-diagnosis physical activity changes. Additionally, these data were collected almost 30 years ago. Since that time there have been improvements in diagnosis and treatment of endometrial cancer which limit the generalizability of our findings. Furthermore, the cultural attitudes and expectations around physical activity have shifted which may limit the generalizability of our findings to contemporary women diagnosed with endometrial cancer. We were limited by the data available from a state cancer registry including missing information on diagnostic, treatment, and lifestyle information beyond what was presented here, which would have strengthened this investigation. Finally, given the timing of the interview to diagnosis date, this sample may survival bias in that those who died before interview timing were excluded from diagnosis. Strengths of our study include the multiple periods of retrospective reporting allowing for investigation of physical activity across the lifespan. This study also includes death certificate data allowing for precise measurement of date of death; however, these certificates may have incomplete or erroneous data on cause or contributing factors to death [26–28].

Our findings show a small reduction in mortality risk for those who do some physical activity prior to diagnosis. Regular physical activity is associated with many health benefits beyond lowering mortality risk. Further investigation into the role of physical activity and mortality is warranted, but future investigations should include a device-based measurement of physical activity wherever possible to counteract some of the measurement limitations of this and other epidemiologic investigations. Due to the other health threats faced by endometrial cancer survivors including cardiovascular disease, diabetes and obesity, potential physical activity interventions, and their appropriate timing should be considered to counteract these threats to endometrial cancer survivorship. Future research is warranted to identify how and when is best to intervene with physical activity-promoting interventions in endometrial cancer survivors.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JG, supervised directly by LC-B. The first draft of the manuscript was written by JG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

Code availability N/A.

Declarations

Conflict of interest The authors have no conflict of interest to declare that are relevant to the content of this article.

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. This study was approved by the University of Wisconsin-Madison's Health Sciences Institutional Review Board (Protocol #2015-1492).

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent for publication N/A.

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