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ORIGINAL PAPER

Muscle-strengthening and aerobic activities and mortality among 3+ year cancer survivors in the U.S.

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Abstract

Purpose This study examined the association between adherence to American College of Sports Medicine and American Cancer Society guidelines on aerobic and muscle-strengthening activities and mortality risks among 3+ year cancer survivors in the U.S.

Methods The observational study was based on 1999–2009 National Health Interview Survey Linked Mortality Files with follow-up through 2011. After applying exclusion criteria, there were 13,997 observations. The hazard ratios (HRs) for meeting recommendations on muscle-strengthening activities only, on aerobic activities only, and on both types of physical activity (i.e., adhering to complete guidelines) were calculated using a reference group of cancer survivors engaging in neither. Unadjusted and adjusted HRs of all-cause, cancer-specific, and cardiovascular disease-specific mortalities were estimated using Cox proportional hazards models.

Results In all models, compared to the reference group, cancer survivors adhering to complete guidelines had significantly decreased all-cause, cancer-specific, and cardiovascular disease-specific mortalities (HRs ranged from 0.37 to 0.64, p's < 0.05). There were no statistically significant differences between hazard rates of cancer survivors engaging in recommended levels of muscle-strengthening activities only and the reference group (HRs ranged from 0.76 to 0.94, p's > 0.05). Wald test statistics suggested a significant dose–response relationship between levels of adherence to complete guidelines and cancer-specific mortality.

Conclusions While muscle-strengthening activities by themselves do not appear to reduce mortality risks, such activities may provide added cancer-specific survival benefits to 3+ year cancer survivors who are already aerobically active.

Keywords Cancer survivor · Strength training · Exercise · Mortality · NHIS · Linked mortality files

Abbreviations

ACSM American College of Sports Medicine
ACS American Cancer Society

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Introduction

Due to the population aging and improvements in cancer survival from advances in cancer care, the population of cancer survivors in the United States is projected to grow from 15.5 million cancer survivors in 2016 to 20.3 million by 2026 [1]. Although these trends are positive, the surgeries and adjuvant therapies that accompany cancer diagnoses can precipitate a range of physical and psychosocial sequelae [2, 3]. Excess medical expenditures represent the largest share of the economic burden among cancer survivors [4, 5].

Engagement in physical activity (PA) and exercise (i.e., a planned, structured, and repetitive form of PA, aimed to improve fitness, performance, or health [6]) is an important determinant of beneficial health conditions among cancer survivors and therefore, is being recommended by the American College of Sports Medicine (ACSM) and American Cancer Society (ACS) to this population [7, 8]. Specifically, cancer survivors are encouraged to avoid inactivity and return to daily activities as soon as possible following diagnosis. For substantial health benefits, they should aim to engage in aerobic exercise for at least 150 min per week. To receive additional health benefits, cancer survivors are recommended to perform muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups at least 2 days per week [7, 8].

A vast majority of studies on the significance of PA for cancer survivors have focused on aerobic PA. Prior research has suggested that aerobic PA improves disease-free and overall survival [9–13] in addition to health-related outcomes of cancer survivors (e.g., quality of life, fatigue, psychosocial distress, depression, self-esteem, and cancer recurrence) [7, 8, 14]. Unlike aerobic exercise, strength training has only recently garnered attention for its benefits in regaining muscle mass and strength often depleted with age and disability [15]. In addition to positive effects of strength training on muscular function, a meta-analyses of randomized controlled trials comparing resistance training with an exercise or non-exercise control group in cancer survivors during and after treatment found improvements in body composition in patients undergoing treatment and in long-term follow-up [16]. Whether engagement in recommended levels of muscle-strengthening activity improves cancer survival remains uncertain. Furthermore, we currently lack evidence on the significance of adherence to recommended levels of both leisure-time muscle-strengthening and aerobic PA (hereinafter referred to as complete guidelines) for cancer survival on the population level.

Psychosocial, physical, and behavioral experiences unique to cancer patients and those transitioning to "persons with a history of cancer" may pose significant challenges to their engagement in PA [17]. Although research suggests exercise is safe during cancer treatment and can improve physical functioning and quality of life, cancer patients are recommended to exercise at a lower intensity and build up more slowly than people who are not receiving cancer treatment [8]. This study examined survival benefits of engaging in recommended levels of aerobic and muscle-strengthening PA among the U.S. cancer survivors after medical treatment completion (i.e., 2–3 years post-cancer diagnosis). The study findings will contribute to population-based evidence on the significance of adherence to complete PA guidelines post-cancer diagnosis for prolonging lives of cancer survivors and development and promotion of lifestyle programs for this population [14, 18].

Methods

Data source

The study is based on observational data with a longitudinal component: public-use 1999–2009 National Health Interview Survey (NHIS) Linked Mortality Files with follow-up through 2011—the most recent data available at the time of analyses [19]. The NHIS is an ongoing in-person household survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. The survey uses multistage sampling designed to produce nationally representative estimates of the civilian, non-institutionalized U.S. population. Sociodemographic information is collected from each sampled household, and one adult is sampled within each household to complete a more in-depth survey with questions on self-rated health status, health conditions, disabilities and limitations, access to care, and health care utilization. From 1999 to 2009, the NHIS final sample adult response rates ranged from 62.2 to 74.3% [20]. More information about the NHIS and linked mortality files can be found elsewhere [19, 20]. Given the public-use nature of the data, the study was exempted from full IRB/ethical review.

Study population

In the 1999–2009 NHIS, cancer survivorship status and cancer site were assessed using participants' reports on whether they were ever told by a doctor or other health professional they "had cancer or a malignancy of any kind" and if so, what kind of cancer they had. Age at and time since cancer diagnosis were calculated using responses on how old participants were when a given type of cancer was first diagnosed and their reported age at the time of the survey.

There were 318,331 participants in 1999–2009 NHIS. Among them, 23,413 reported a cancer diagnosis. After excluding participants reporting only non-melanoma skin cancer ($n = 3{,}440$) and unknown age at cancer diagnosis ($n = 499$), mortality status was available for 18,796 cancer survivors in the Linked Mortality File [21]. We then excluded 124 observations who died of accidents/unintentional injuries, 71 observations who were first diagnosed with cancer and died in the same year, and 4,461 early cancer survivors (i.e., those diagnosed < 3 years ago). Among the remaining observations, data on PA levels were available for 13,997 cancer survivors (Fig. 1).

Measures

To examine all-cause mortality we used a final mortality status variable as the NCHS' final determination of vital status. Each survey participant who was eligible for mortality follow-up was assigned a vital status code (0 = assumed alive and 1 = assumed deceased). For analyses of cause-specific mortality, we used the NCHS' recode variable for the underlying cause of death. Among 3,528 cancer survivors assumed deceased, cause of death data were available for 3,512 observations. The two leading

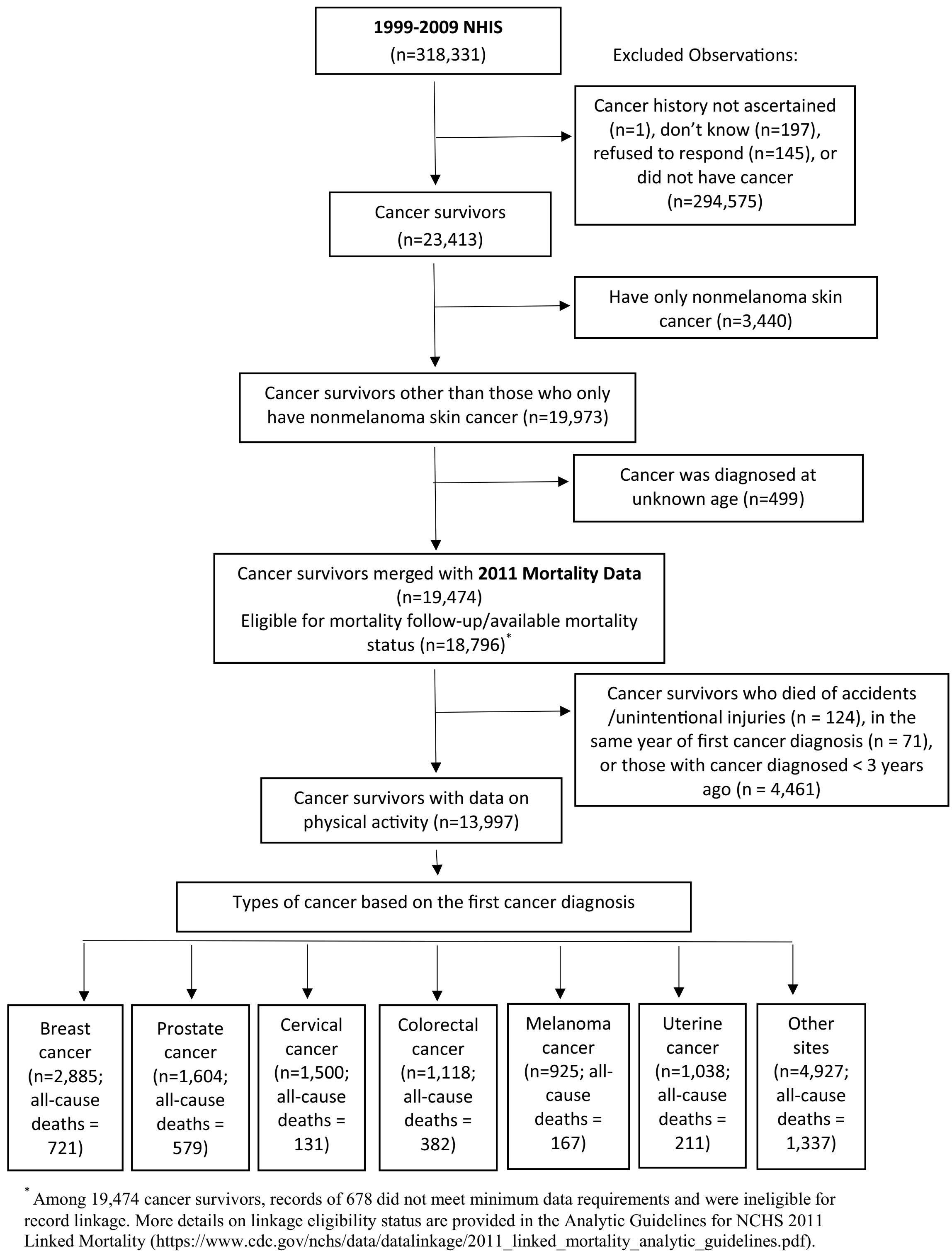

Fig. 1 Analytic sample selection

causes of death with sufficient number of observations for multivariable sub-analyses of cause-specific mortality were "malignant neoplasms" (i.e., cancer; $n=1,263$; 37.2%) and cardiovascular diseases (CVD) (i.e., "diseases of heart" and cerebrovascular; $n=799$ or 21.8%) [19]. The survival time was measured in years from the third year after a participant's first cancer diagnosis to the end of follow-up or the date of death.

Adherence to ACSM and ACS PA recommendations was operationalized using responses on weekly frequency and duration of moderate- and vigorous-intensity aerobic and muscle-strengthening activities. We assessed engagement in PA using two measures, the first captured the three levels of leisure-time aerobic PA: (1) inactive (≤ 1 weekly session of aerobic 10-min activity); (2) insufficiently active (≥ 1 session of weekly aerobic PA for 10–150 min), and (3) sufficiently active/meeting recommendations on aerobic PA (≥ 150-min weekly session of moderate-intensity PA, or 75-min weekly session of vigorous-intensity PA, or an equivalent combination). The second measure captured the four levels of adherence to guidelines on both leisure-time aerobic and muscle-strengthening activities (i.e., complete or full PA guidelines): (1) meeting neither of the recommendations; (2) meeting recommendations on muscle-strengthening activity only (strength training exercise ≥ 2 days per week); (3) meeting recommendations on aerobic activity only, or (4) meeting both recommendations [7, 8].

Other covariates identified by prior research as related to mortality and PA included socio-demographic and health-related characteristics [22, 23]. Variables operationalizing socio-demographic status were age at interview, sex, ethnicity and race, marital status, educational level, and insurance coverage. Health characteristics included age at first cancer diagnosis, Body Mass Index (BMI) categories, self-rated health, number of co-existing chronic conditions, functional status, measured using the activities of daily living (ADLs) and instrumental ADLs [24], and smoking status.

Statistical analyses

Weighted percentages of cancer survivors by levels of leisure-time aerobic and muscle-strengthening PA and socio-demographic and health-related characteristics were calculated to describe study population. Differences in the distribution of characteristics by PA levels were assessed using χ^2 test.

We used Cox proportional hazards models to examine the association between aerobic PA levels and survival, and then between adherence to complete guidelines and survival. The hazard ratios (HRs) for being sufficiently active (i.e., meeting guidelines on aerobic PA) and insufficiently active were calculated using a reference group of inactive cancer survivors. The HRs for adhering to complete guidelines were calculated using a reference group of cancer survivors engaging in neither aerobic nor muscle-strengthening activities. Models were estimated at varying levels of adjustment by first considering bivariate analysis and then successively controlling for only aforementioned socio-demographic characteristics and then including health characteristics. The multivariable analyses were conducted for all-cause mortality and then cause-specific mortality (mortality from CVD and cancer) via competing risk models by treating cause-specific mortality as events and others as censored times [25].

We conducted two types of sensitivity analyses. First, we examined potential confounding by alcohol. Research on dual effects of alcohol on survival is ongoing: some studies suggest its beneficial effects in terms of decreased CVD-specific and all-cause mortality, while other studies find adverse or no effects on cancer-specific mortality from alcohol consumption [26–29]. Because data on alcohol consumption were only available for 42.8% of the final analytic sample, we fit each of the fully adjusted models on only those with available data on alcohol (Supplementary Tables S2 and S3). All but one estimated HR were qualitatively similar to models not adjusting for alcohol consumption. Because the one dissimilar estimate was imprecise due to the small number of observations, we did not include alcohol consumption as a covariate in the reported multivariable analyses.

Second, several studies have suggested differential effects of physical activity on the survival for different types of cancer (e.g., reduced all-cause, breast cancer-specific, and colon cancer-specific mortality) and acknowledged insufficient evidence on survival benefits from physical activity for survivors of other cancers [9–13]. Hence, we performed site-specific analyses, and their results were qualitatively similar to those for all cancer survivors combined. Using the rule that Cox models should be used with a minimum of 10 events per independent variable [30], we report results from all-cause mortality models by cancer sites, including breast, prostate, and colorectal cancers (Supplementary Tables S4 and S5).

All analyses employed sample weights to adjust for the selection probabilities and non-response. To account for the stratified multistage sampling design of NHIS, variance estimates were calculated using the Taylor Series Method. Statistical significance was set at $\alpha = 0.05$. All test were two-sided. The analyses were conducted in R version 3.3.1 in 2016.

Results

Slightly over one-third of 3+ year cancer survivors (34.8%) were sufficiently active. Most met neither of the guidelines on leisure-time aerobic nor muscle-strengthening activities (60.9%); 4.3% engaged only in strength training exercise at least 2 days per week, and 11.1% met complete guidelines. Among 3+ year cancer survivors, 22.2% died during the follow-up. The population mean time from the first cancer diagnosis to death (i.e., survival time) was 16.8 years (95% CI 16.5–17.0).

The distribution of demographic and health characteristics of the study population overall and by PA levels is presented in Table 1. With the exception of insurance coverage, distribution of all characteristics of cancer survivors significantly differed by adherence to aerobic and complete guidelines (p's < 0.001).

The results for the statistical effect of meeting guidelines on aerobic PA on all-cause, cancer-specific, and CVD-specific mortalities are shown in Table 2. In bivariate analysis, insufficiently active cancer survivors had lower hazards of all-cause mortality than inactive cancer survivors (HR_{unadj} 0.65, 95% CI 0.58–0.72). Sufficiently active cancer survivors had less than twice the hazards of all-cause mortality compared to inactive cancer survivors (HR_{unadj} 0.43, 95% CI 0.38–0.48). A similar dose–response pattern was observed at varying levels of adjustment, with HR 0.78 (95% CI 0.69–0.88) and HR 0.57 (95% CI 0.51–0.63) for insufficiently active and sufficiently active vs. inactive cancer survivors, respectively, in the model adjusted for sociodemographics. In the fully adjusted model, insufficient and sufficient PA remained statistically significant compared to being inactive: HR_{adj} 0.83 (95% CI 0.75–0.93) and HR_{adj} 0.62 (95% CI 0.52–0.69), respectively.

Cancer survivors adhering to guidelines on aerobic PA also had significantly lower cancer- and CVD-specific mortality risks. In the fully adjusted model, sufficiently active cancer survivors had significantly lower cancer-specific mortality rates compared to inactive cancer survivors (HR_{adj} 0.65, 95% CI 0.55–0.78). Sufficiently active cancer survivors also had lower CVD-specific mortality rates than inactive ones (HR_{adj} 0.60, 95% CI 0.55–0.78). The associations were not statistically significant for insufficiently active cancer survivors.

Results examining the association of adherence to complete guidelines with all-cause, cancer-specific, and CVD-specific mortalities are reported in Table 3. Cancer survivors only adhering to guidelines on muscle-strengthening activity (i.e., engaging exclusively in strength training ≥ 2 days per week) did not have significantly different hazards of all-cause or disease-specific mortalities than cancer survivors who did not adhere to either guideline. In fully adjusted models, cancer survivors who adhered only to guidelines on aerobic PA had lower hazards of all-cause mortality (HR_{adj} 0.66, 95% CI 0.59–0.74). Lower hazards were also observed among cancer survivors who adhered to recommendations on both aerobic and muscle-strengthening activities compared to cancer survivors who did not adhere to either guideline (HR_{adj} 0.60, 95% CI 0.50–0.73).

Cancer-specific mortality was significantly lower in cancer survivors meeting only guidelines on aerobic PA (HR_{adj} 0.71, 95% CI 0.60–0.85) and those meeting guidelines on both aerobic and muscle-strengthening activity (HR_{adj} 0.52, 95% CI 0.38–0.72) compared to those who met neither of the guidelines, respectively. Similar mortality benefits were observed for CVD-specific mortality in those who met guidelines on aerobic activity only (HR_{adj} 0.63, 95% CI 0.48–0.82) and those who met recommendations of both aerobic and muscle-strengthening PA (HR_{adj} 0.56, 95% CI 0.34–0.92).

To determine whether there was a dose–response between levels of adherence to complete guidelines and mortality, we formally tested differences in the coefficients associated with PA levels, specifically between those adhering to guidelines on aerobic PA only and those meeting guidelines on both aerobic and muscle-strengthening activity. For cancer-specific mortality, results of the corresponding Wald tests were ($z = 2.87$, $p = 0.004$), ($z = 2.12$, $p = 0.033$), and ($z = 1.83$, $p = 0.067$) for the bivariate, demographic, and fully adjusted models, respectively. Results for CVD-specific mortality indicated incorporation of muscle-strengthening activity did not have significant added survival benefits over recommended levels of aerobic activity alone (p values not shown).

Discussion

Using the 1999–2009 NHIS Linked Mortality Files, we found reduced all-cause mortality by levels of leisure-time aerobic PA among 3+ year cancer survivors. Compared to inactive cancer survivors, those engaging in some, albeit insufficient aerobic PA had 1.2 times lower hazards of death ($p = 0.002$); whereas sufficiently active cancer survivors had 1.6 times lower mortality hazards ($p < 0.001$). Our findings from the disease-specific analyses suggest the beneficial mechanism of adhering to guidelines on aerobic PA manifests through reduced CVD events as well as reduced cancer-specific mortality.

Furthermore, our study provides new epidemiologic evidence on contribution of adherence to complete PA guidelines to survival outcomes of the 3+ year cancer survivors in the U.S. In all adjusted analyses, engaging in recommended levels of muscle-strengthening activity alone did not appear to decrease all-cause, cancer-specific, and CVD-specific mortality in the study population. However, supplementation of recommended muscle-strengthening activity with aerobic activity appears to be associated with lower cancer-specific mortality risks, with HRs ranging from 0.39 to 0.52 (p's < 0.05) and the Wald tests significant for bivariate and demographically adjusted models. While the Wald test for the fully adjusted model does not meet the nominal significance level of 0.05, we hypothesize that this is likely because 262 observations and 25 events were excluded in the fitting procedure due to missing covariates.

Our findings on aerobic PA are consistent with those from prior studies. Although other studies have encompassed survivors of prostate, gastric, ovarian, and brain cancers, the epidemiologic evidence on the inverse

Table 1 Description of 3+ year cancer survivors by adherence to guidelines on aerobic and muscle-strengthening activities in the U.S., National Health Interview Survey 1999–2009 and 2011 mortality files

Characteristics	Total	Guidelines on aerobic activity only			Complete guidelines			
		Inactive	Insufficiently active	Sufficiently active	Met neither guideline	Met guidelines on muscle-strengthening activity only	Met guidelines on aerobic activity only	Met both guidelines
n[a] (weighted % [b])								
	13,997 (100)	6,873 (47.0)	2,555 (18.3)	4,569 (34.8)	8,797 (60.9)	598 (4.3)	3,129 (23.6)	1,421 (11.1)
Mortality status[***/***]								
Alive	10,469 (77.8)	4,561 (41.7)	2,011 (19.0)	3,897 (39.3)	6,093 (56.4)	451 (4.3)	2,622 (26.3)	1,260 (13.0)
Deceased	3,528 (22.2)	2,312 (65.3)	544 (15.6)	672 (19.1)	2,704 (76.7)	147 (4.3)	507 (14.5)	161 (4.5)
Age group[***/***]								
18–45	1,906 (14.4)	713 (36.5)	332 (17.7)	861 (45.8)	976 (50.7)	63 (3.4)	507 (26.1)	353 (19.8)
45–64	4,569 (35.7)	2,044 (42.7)	895 (19.6)	1,630 (37.7)	2,735 (58.0)	193 (4.3)	1,098 (25.4)	523 (12.3)
65–79	5,049 (34.5)	2,549 (48.4)	899 (17.7)	1,601 (34.0)	3,225 (62.0)	212 (4.1)	1,171 (25.0)	424 (9.0)
80+	2,473 (15.5)	1,567 (63.4)	429 (16.9)	477 (19.7)	1,861(74.9)	130 (5.5)	353 (14.5)	121 (14.5)
Sex[***/***]								
Male	4,900 (38.4)	2,307 (45.7)	799 (16.4)	1,794 (38.0)	2,887 (57.8)	208 (4.2)	1,215 (25.6)	57 (12.4)
Female	9,097 (61.6)	4,566 (47.8)	1,756 (19.4)	2,775 (32.8)	5,910 (62.9)	390 (4.4)	1,914 (22.4)	850 (10.4)
Race/ethnicity[***/***]								
Hispanic	910 (4.4)	511 (55.8)	159 (17.0)	240 (27.4)	636 (68.9)	33(3.7)	182 (20.9)	57 (6.42)
White non-Hispanic	11,576 (87.3)	5,492 (45.8)	2,127 (18.4)	3,957 (35.8)	7,083(59.8)	507 (4.4)	2,695 (24.2)	1,246 (11.6)
Black non-Hispanic	1,216 (6.2)	741 (58.0)	203 (16.3)	272 (25.8)	892 (71.0)	49 (3.3)	184 (17.2)	86 (8.5)
Other non-Hispanic[c]	295 (2.2)	129 (45.3)	66 (19.9)	100 (34.9)	186 (62.7)	9 (2.4)	68 (24.7)	32 (10.2)
Education level[***/***]								
< High School	2,884 (18.7)	1,973 (68.5)	401 (13.4)	510 (18.1)	2,293 (79.4)	77 (2.6)	411 (14.83)	96 (3.2)
HS Graduate/GED	4,264 (31.1)	2,301 (52.6)	789 (18.5)	1,174 (28.9)	2,905 (66.9)	170 (4.2)	890 (21.7)	278 (7.2)
> High School	6,781 (50.3)	2,545 (35.2)	1,363 (20.0)	2,873 (44.8)	3,545 (50.2)	351 (5.0)	1,820 (28.2)	1,043 (16.6)
Marital status[***/***]								
Not married/partnered	7,198 (37.0)	3,864 (53.6)	1,294 (17.5)	2,040 (28.9)	4,833 (67.1)	304 (4.0)	1,395 (19.6)	635 (9.3)
Married/partnered	6,781 (63.0)	2,999 (43.1)	1,259 (18.7)	2,523 (38.3)	3,953(57.3)	294 (4.4)	1,729 (26.0)	785 (12.2)
Health insurance coverage[*/]								
No	922 (6.7)	468 (51.1)	143 (14.7)	311 (34.2)	580 (62.8)	28 (3.0)	219 (23.9)	92 (10.3)
Yes	13,055 (93.3)	6,395 (46.7)	2,411 (18.5)	4,249 (34.8)	8,207 (60.8)	569 (4.4)	2,902 (23.6)	1,328 (11.2)
Years since cancer diagnosis[***/***]								
3–5	3,519 (25.6)	1,667 (45.2)	626 (17.9)	1,226 (36.9)	2,150 (59.6)	132 (3.4)	831 (24.7)	394 (12.4)
6–10	3,698 (27.1)	1,755 (44.8)	653 (17.8)	1,290 (37.4)	2,236 (58.1)	166 (4.5)	881 (25.5)	403 (11.9)
11+	6,780 (47.4)	3,451 (49.2)	1,276 (18.7)	2,053 (32.1)	4,411 (63.3)	300 (4.7)	1,417 (22.0)	624 (10.0)
Body Mass Index categories[d, ***/***]								
Underweight	5,250 (37.3)	2,445 (44.5)	938 (17.7)	1,867 (37.8)	3,133 (57.4)	239 (4.8)	1,204 (23.9)	656 (14.0)
Overweight	4,822 (34.6)	2,244 (44.1)	875 (18.1)	1,703 (37.8)	2,905 (58.2)	202 (4.0)	1,166 (26.0)	530 (11.8)
Obese	3,925 (28.2)	2,184 (53.8)	742 (19.2)	999 (27.0)	2,759 (69.1)	157 (3.9)	759 (20.5)	235 (6.6)
Self-rated health status[***/***]								
Fair or poor	4,173 (28.4)	2,905 (69.0)	602 (14.0)	666 (17.0)	3,355 (79.6)	142 (3.4)	521 (13.3)	141 (3.7)
Good	4,556 (32.6)	2,197 (45.9)	944 (20.9)	1,415 (33.1)	2,918 (62.2)	216 (4.7)	1,049 (24.8)	362 (8.3)

Table 1 (continued)

Characteristics	Total	Guidelines on aerobic activity only			Complete guidelines			
		Inactive	Insufficiently active	Sufficiently active	Met neither guideline	Met guidelines on muscle-strengthening activity only	Met guidelines on aerobic activity only	Met both guidelines
Excellent or very good	5,245 (39.0)	1,753 (31.7)	1,008 (19.2)	2,484 (49.1)	2,506 (46.3)	240 (4.6)	1,556 (30.2)	917 (18.9)
Number of chronic conditions[e], ***/***								
0	5,168 (39.2)	1,998 (36.8)	986 (18.8)	2,184 (44.4)	2,766 (51.5)	201 (4.0)	1,379 (27.7)	797 (16.8)
1	4,786 (33.6)	2,383 (48.0)	938 (19.6)	1,465 (32.4)	3,084 (63.0)	228 (4.6)	1,063 (23.5)	397 (8.8)
≥ 2	3,922 (27.3)	2,421(60.2)	610 (15.6)	891 (24.2)	2,864 (71.7)	161 (4.2)	664 (18.0)	222 (6.1)
Need help with personal care***/***								
No	13,309 (95.3)	6,298 (45.2)	2,487 (18.6)	4,524 (36.2)	8,185 (59.6)	568 (4.2)	3,104 (24.7)	1,401 (11.6)
Yes	686 (4.7)	573 (83.1)	68 (10.8)	45 (6.1)	610 (88.5)	30 (5.4)	25 (3.3)	20 (2.8)
Need help with routine needs***/***								
No	12,311 (89.6)	5,569 (43.5)	2,333 (18.8)	4,409 (37.7)	7,349 (58.1)	523 (4.2)	3,015 (25.6)	1,375 (12.1)
Yes	1,679 (10.4)	1,297 (76.4)	222 (13.7)	160 (9.9)	1,441 (85.5)	75 (4.6)	114 (7.2)	46 (2.7)
Smoking***/***								
Never	6,121 (43.3)	2,931(44.8)	1,153 (19.2)	2,037 (36.0)	3,828 (60.0)	242 (4.1)	1,352 (23.6)	674 (12.4)
Former smoker	5,160 (37.7)	2,419 (44.8)	971 (18.7)	1,770 (36.5)	3,108 (58.4)	267 (5.1)	1,211 (25.1)	554 (11.5)
Current smoker	2,692 (19.0)	1,507 (56.0)	429 (15.4)	756 (28.6)	1,844 (68.2)	88 (3.2)	561 (21.0)	192 (7.6)

Differences in characteristics between cancer survivors by physical activity levels; guidelines on aerobic activity only/complete guidelines, $^{*}p = 0.032$, $^{***}p$'s < 0.001

[a] Unweighted number of observations

[b] Weighted percentages to reflect national estimates are reported

[c] Other includes non-Hispanic Asian; race group not releasable, and multiple race

[d] BMI was categorized as underweight or normal (BMI ≤ 24.9), overweight (25.0 ≤ BMI ≤ 29.9), and obese (BMI ≥ 30.0)

[e] Other chronic conditions were measured by the number of commonly reported chronic conditions and diseases (categorized as 0, 1, and 2+), which included heart disease, stroke, hypertension, emphysema, chronic bronchitis, diabetes, liver disease, and weak/failing kidneys

relationship between engagement in PA and mortality has been mostly based on studies of breast and colorectal cancer survivors [9–13]. While we examined all cancer survivors combined, our study population primarily included representation of breast (19.3%), prostate (12.1%), cervical (10.5%), colorectal (7.5%), and uterine (6.7%) cancers. The observational research suggests PA, both pre- and post-diagnoses, is associated with reduced risk of all-cause and cancer-specific deaths among breast and colorectal cancer survivors [9, 11, 12]. The higher levels of exercise tend to exert better survival benefits (10). Significant risk reduction for all-cause and breast cancer-related death was observed for more recent (i.e., ≤ 12 years) compared to lifetime pre-diagnosis and post-diagnosis recreational PA [11]. Greater protective effect of PA undertaken post-diagnosis rather than pre-diagnosis was confirmed in meta-analyses of both large and small studies, and studies from different regions: North America, Australia, and Europe [10, 12].

The effects sizes reported in our study are comparable to those based on a population-level study conducted in Scotland—the only other study which used a data source similar to the NHIS Linked Mortality Files [31]. The Scottish Health Surveys (1995, 1998, 2003) linked to a national database of cancer registration and deaths were analyzed to examine association between different types of PA (domestic, walking, sports) and mortality among 293 cancer survivors. Participation in more than three sessions of vigorous exercise per week for at least 20 min/session was associated with the lowest risk of all-cause mortality post-diagnosis. The mortality risk was the lowest for those engaging in the sports activity sessions (HR_{adj} 0.47, 95% CI 0.23–0.96) and those combining walking with sports activity at least three times/week (HR_{adj} 0.48, 95% CI 0.24–0.99), compared to inactive survivors [31].

Various biological mechanisms potentially explain the observed protective statistical effect of PA on all-cause, cancer-specific, and CVD-specific mortality among cancer

Table 2 Levels of leisure-time physical activity based on guidelines for aerobic activity only and mortality among the 3+ year cancer survivors in the U.S.

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
All-cause[d]	(Events = 3,528)		(Events = 3,501)		(Events = 3,424)	
Inactive	1.0	Referent	1.0	Referent	1.0	Referent
Insufficiently active	0.65	0.58, 0.72	0.78	0.69, 0.88	0.83	0.75, 0.93
Sufficiently active	0.43	0.38, 0.48	0.57	0.51, 0.63	0.62	0.55, 0.69
Cancer-specific[e]	(Events = 1,263)		(Events = 1,256)		(Events = 1,238)	
Inactive	1.0	Referent	1.0	Referent	1.0	Referent
Insufficiently active	0.75	0.63, 0.90	0.86	0.71, 1.04	0.92	0.76, 1.10
Sufficiently active	0.52	0.44, 0.61	0.61	0.52, 0.72	0.65	0.55, 0.78
Cardiovascular disease-specific[f]	(Events = 799)		(Events = 792)		(Events = 773)	
Inactive	1.0	Referent	1.0	Referent	1.0	Referent
Insufficiently active	0.67	0.54, 0.84	0.84	0.68, 1.06	0.84	0.67, 1.06
Sufficiently active	0.43	0.35, 0.54	0.62	0.50, 0.77	0.63	0.50, 0.79

Events = deaths

[a] Unadjusted

[b] Adjusted for age (continuous), sex, race/ethnicity, education level, marital status, and insurance status

[c] Adjusted for age (continuous), sex, race/ethnicity, education level, marital status, and insurance status, self-rated health, activity limitations, smoking status, BMI categories, number of comorbid conditions, and age at first cancer diagnosis (continuous)

[d] Unweighted $n = 13{,}997$

[e] $n = 13{,}896$

[f] $n = 13{,}730$

survivors. For example, intervention studies in breast cancer survivors show exercise lowers C-reactive protein and blood pressure, facilitates weight loss, and improves immune function. Additionally, PA lowers endogenous estrogen levels among healthy postmenopausal women, and an etiologic pathway involving decreased levels of endogenous estrogens among physically active women may also be operative after breast cancer diagnosis [11].

More recently, PA has been shown to lead to epigenetic modifications of DNA via the process of methylation. Although DNA methylation does not directly alter sequences of nucleotides, expression of certain genes may be switched on or off when methyl groups attach to the promoter regions of DNA. In a study of breast cancer, participants engaged in PA had significantly reduced methylation levels, and hence increased expression, of a known tumor suppressor gene, L3MBTL1. The PA group experienced significant reductions in breast cancer risk [32]. Another study, investigating associations between PA and epigenetic modification, showed endurance training that resulted in significant methylation changes across the genome [33].

Limitations

There are several limitations that must be acknowledged in this study. Among them are our reliance on self-reported data and the inability to verify engagement in PA. Also, because the data are from cross-sectional surveys, it is not possible to determine if PA behaviors changed over time. This limitation is not unique to this study. Based on a systematic review and meta-analyses, an increase in recommended PA levels from pre- to post-diagnosis was associated with reduced risk of all-cause mortality in studies using self-reported and interview-based PA assessments [11]. Furthermore, the NHIS does not capture the extent of cancer at diagnosis (i.e., stage), which affects treatment options and long-term health with related challenges to engagement in PA. To mitigate this limitation we restricted our study to 3+ year cancer survivors. Although our study may be overrepresented by survivors with less severe cancer diagnoses, the association between PA and mortality benefits was reported in prior studies with and without adjustments for tumor stage, cancer treatment, as well as smoking and adiposity [12].

Additionally, although in our multivariable analyses, we adjusted for self-rated health, activity limitations, number of comorbid conditions, and BMI, we did not control directly for diet quality, medication, and supplement use. Based on a recently published systematic review and meta-analysis of 117 cohort studies enrolling 209,597 cancer survivors, higher intakes of vegetables and fish were inversely associated with all-cause mortality; whereas higher alcohol

Table 3 Adherence to guidelines on aerobic and muscle-strengthening activities and mortality among the 3+ year cancer survivors in the U.S.

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
All-cause [d]	(Events = 3,519)		(Events = 3,493)		(Events = 3,417)	
Met neither guideline	1.0	Referent	1.0	Referent	1.0	Referent
Met guidelines on muscle-strengthening activities only	0.83	0.69, 1.01	0.88	0.72, 1.07	0.94	0.78, 1.14
Met guidelines on aerobic activities only	0.52	0.46, 0.58	0.62	0.55, 0.70	0.66	0.59, 0.74
Met both guidelines	0.37	0.31, 0.44	0.53	0.45, 0.63	0.60	0.50, 0.73
Cancer-specific [e]	(Events = 1,260)		(Events = 1,253)		(Events = 1,235)	
Met neither guideline	1.0	Referent	1.0	Referent	1.0	Referent
Met guidelines on muscle-strengthening activities only	0.78	0.56, 1.10	0.80	0.57, 1.13	0.89	0.63, 1.25
Met guidelines on aerobic activities only	0.62	0.52, 0.73	0.68	0.58, 0.81	0.71	0.60, 0.85
Met both guidelines	0.39	0.29, 0.52	0.48	0.36, 0.65	0.52	0.38, 0.72
Cardiovascular disease-specific [f]	(Events = 796)		(Events = 789)		(Events = 770)	
Met neither guideline	1.0	Referent	1.0	Referent	1.0	Referent
Met guidelines on muscle-strengthening activities only	0.80	0.54, 1.17	0.84	0.57, 1.24	0.76	0.50, 1.13
Met guidelines on aerobic activities only	0.50	0.39, 0.62	0.64	0.51, 0.80	0.64	0.50, 0.80
Met both guidelines	0.38	0.25, 0.57	0.60	0.40, 0.89	0.64	0.42, 0.98

Events = deaths

[a] Unadjusted

[b] Adjusted for age (continuous), sex, race/ethnicity, education level, marital status, and insurance status

[c] Adjusted for age (continuous), sex, race/ethnicity, education level, marital status, and insurance status, self-rated health, activity limitations, smoking status, BMI categories, number of comorbid conditions, and age at first cancer diagnosis (continuous)

[d] Unweighted $n = 13{,}945$

[e] $n = 13{,}847$

[f] $n = 13{,}683$

consumption was positively associated with overall mortality. Adherence to the highest category of diet quality and of a prudent/healthy dietary pattern was inversely associated with all-cause mortality; whereas the Western dietary pattern was associated with increased risk of overall mortality among cancer survivors [29]. The use of dietary supplements and medication is widespread among cancer survivors. Studies suggest that individuals tend to increase their use of vitamins and mineral supplements after cancer diagnosis, often without their physician's knowledge [34].

Lastly, recognizing the complexity of cancer as a disease with a variety of treatment options, we have attempted cancer site-specific exploratory analyses but had insufficient sample sizes. Results of stratified analyses would have allowed us to provide insights on the relative importance of aerobic and muscle-strengthening activities for mortality of specific group of cancer survivors. Both observational and interventional studies to-date have demonstrated the effect of physical activity in cancer survivorship with a majority of them based on data from breast, colorectal, and prostate cancer survivors—individuals with high 5-year survival rates [1, 34]. As studies examining survival and exercise for gynecologic, lung, and other cancers are ongoing, adherence to the ACSM and ACS PA guidelines should be encouraged by all cancer survivors [7, 8]. Despite beneficial effects of PA on weight gain, quality of life, cancer recurrence or progression, and other aspects of cancer survivorship, less than half of cancer survivors engage in recommended PA levels [35].

In conclusion, our study provides new population-based evidence on the relationships between survival benefits and adherence to complete PA guidelines among 3+ year cancer survivors in the United States. While engagement in recommended levels of aerobic PA is associated with substantial survival benefits, supplementation of such activity with strength training may provide added cancer-specific survival benefits to this population.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest disclosures.

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