Retrospective Cohort Study

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Joint association of physical activity and dietary quality with survival among US cancer survivors: a population-based cohort study

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Background: Limited studies have explored the joint effect of physical activity (PA) and dietary quality (DQ) on the mortality outcomes of the cancer population. The authors aim to investigate the separate and joint prognostic effect of PA and DQ on the survival of US cancer survivors.

Methods: Data of cancer survivors ($n = 3007$, representing 22 million cancer survivors) were from the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2018. PA was assessed using the self-reported Global Physical Activity Questionnaire (GPAQ) and DQ was evaluated through the Health Eating Index-2015 (HEI-2015). Kaplan–Meier (KM) curves and the Cox proportional hazard model were used to evaluate the associations between separate and joint prognostic effects of PA and DQ with mortality outcomes among cancer survivors.

Results: In the joint analyses, cancer survivors with sufficiently active PA ($\geq$ 600 MET-min/week) and qualified DQ ($\geq$ 60) presented reduced risks of all-cause mortality (HR 0.45, 95% CI: 0.35–0.59) as compared with each lifestyle intervention separately. Meanwhile, the joint effects of either insufficiently or sufficiently active PA (> 0 MET-min/week) and qualified DQ ($\geq$ 60) were associated with lower risks for cancer (HR 0.60, 95% CI: 0.40–0.90) and noncancer mortality (HR 0.43, 95% CI: 0.32–0.59).

Conclusions: Our study highlights the combination of active PA and qualified DQ was strongly associated with reduced mortality risk of cancer survivors. Our findings might help to refine the lifestyle intervention recommendations for this population.

Keywords: cancer survivors, cohort study, dietary quality, mortality outcome, physical activity

Introduction

To date, the global population of cancer survivors has been experiencing rapid growth[1], with 19.3 million new cases observed in 2020, and is estimated to increase to 28.4 million new cases by 2040[2]. Despite the gradually improved survival rate for all cancers during the past decades[3,4], cancer survivors still have shorter life expectancies compared to those without cancers.

HIGHLIGHTS

- This is the first study to explore the joint effects of physical activity (PA) and dietary quality (DQ) with mortality outcomes among cancer survivors.
- PA and DQ are separately associated with the all-cause mortality of cancer survivors.
- Joint effects of active PA and qualified DQ are associated with reduced mortality outcomes of cancer survivors.
- Cancer survivors with PA of 2000-3999 MET-min/week present the lowest mortality risk.
- Sensitive analysis supports the main findings.

Additionally, the life quality of cancer survivors is compromised, resulting in a significant burden on public health. Hence, it is important to develop effective strategies for enhancing the life quality and reducing mortality rates for cancer survivors in the current research.

As one of the well-known modifiable factors, adequate physical activity (PA) can enhance cardiopulmonary function, increase muscle mass, and reduce fat mass, thereby reducing the incidence of disease and subsequent complications[4]. More importantly, PA may improve the survival of cancer survivors by modulating insulin/glucose metabolism[5], enhancing immune function[6], regulating hormone metabolism[7], reducing inflammation[8], and inhibiting tumor growth and metastasis[9]. Meanwhile, emerging evidence shows that healthy dietary intakes can significantly reduce the mortality risk of cancer survivors[10–13]. Of note, recent epidemiological studies highlighted the importance of dietary

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patterns rather than individual foods or nutrients to evaluate the association between diet behaviors and clinical outcomes of cancer survivors[14,15]. Especially, the Health Eating Index-2015 (HEI-2015) is one of promising dietary quality (DQ) assessment tools to comprehensively reflect the healthy eating patterns of individuals. Moreover, The HEI-2015 would be optimal to meet the call for better nutritional management of cancer survivors from the American Cancer Society (ACS)[4]. Several studies have determined the prognostic effect of HEI-2015 among cancer survivors, with higher levels of HEI-2015 predicting better survival probabilities[15,16]. Previous works have demonstrated the tight correlations between PA and DQ. The inactive PA was associated with poor appetite, which could lead to unqualified DQ[17]. Alternatively, individuals with active PA tended to choose healthy diets, while those with inactive PA tended to choose unhealthy diets[18]. Nevertheless, to our knowledge, the evidence regarding the joint effect of PA and DQ on the mortality risks of cancer survivors remains limited.

To fill the mentioned research gaps, the primary goal of this study is to investigate the independent and combined associations between PA and DQ with all-cause, cancer, and noncancer mortality among US cancer survivors. The potential links between the joint effect of PA and DQ with the mortality risk of cancer survivors are expected to bring benefits to the development of evidence-based guidelines for designing rational PA and DQ for these populations.

Methods

Data source and study population

The data of this observational cohort study were extracted from six consecutive cycles of the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES): including waves of 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017-2018. The NHANES database systematically gathered nationally representative health-related data on noninstitutionalized general US civilians, utilizing a stratified, multistage probability sampling design, which has been conducted on 2-year cycles since 1999 to assess the health and nutritional status of the US population. All the NHANES protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and written informed consent was provided by all participants. The data analyzed in this study included demographic data, health conditions, examination data, and questionnaire data. Participants with missing cancer investigation, dietary recall, and incomplete follow-up information were excluded from this study. The detailed participant selection process is summarized in Figure 1. This work has been reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS, Supplemental Digital Content 1, http://links.lww.com/JS9/C758) criteria[19]. As a secondary analysis of anonymized data, this study did not involve human participants. Thus, informed consent and institutional review board approval were not required. This study has been registered on the website of ClinicalTrials.gov.

PA assessment

The total time of PA was self-reported by the participants by using the Global Physical Activity Questionnaire (GPAQ), which was created by the WHO. The GPAQ was used to assess different domains of individuals' PA, such as occupation, transportation, and leisure-time PA (the detailed assessment for PA can be found on the website https://wwwwhoint/ncds/surveillance/steps/resources/GPAQ_Analysis_Guidepdf). Accordance to the WHO analysis guide, the PA of each participant was converted to metabolic equivalent (MET) minutes of moderate to vigorous PA per week. MET values vary with the type of exercise, and the NHANES provides the reference MET values for each type of PA. PA scores were calculated based on the MET values of type, frequency, and duration of activities per week, with the equation of MET × weekly frequency × duration of each PA[9]. According to the American Physical Activity guideline, moderate-intensity PA should be done for 150 min/week, or vigorous-intensity PA should be done 75 min/week for adults (all equivalent to 600 MET-min/week)[20]. To investigate the effect of PA on mortality risk among cancer survivors, we categorized PA into three levels: inactive (0 MET-min/week), insufficiently active (1-599 MET-min/week), and sufficiently active ($\geq$ 600 MET-min/week), based on the definition of American Physical Activity Guideline[20]. Additionally, to examine the dose-response relationship of PA with the mortality risk of cancer survivors, we established the following categories for PA: 0, 1–599, 600–1999, 2000–3999, and $\geq$ 4000 MET-min/week, based on previous research studies[21,22].

DQ assessment

The 24 h dietary recall was administered in person by a trained interviewer using the United States Department of Agriculture automated multiple-pass method[6]. DQ utilized in the analyses was derived from data obtained through two 24 h recalls of all food and drink consumed on the day before the interview (from midnight to midnight), with a time interval ranging from 3 to 10 days. We used the latest iteration of the HEI-2015, a comprehensive measurement of an individual's dietary pattern that adheres to the 2010 Dietary Guidelines for Americans[23]. It contains 13 types of nutrient-based and food-based components, including nine components for dietary adequacy assessment (including total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids) and four components for dietary moderation assessment (including refined grains, sodium, added sugars, and saturated fats). For the adequacy components, higher levels of intake are associated with higher scores, whereas for the moderation components, higher levels of intake are associated with lower scores. The total HEI-2015 score ranges from 0 to 100, with a higher score indicating greater overall DQ[23]. Participants with a 2-day HEI-2015 average score of more than 60 were considered to have observed the dietary guidelines[23,24]. Therefore, we classified DQ into two levels: unqualified ($<$ 60) and qualified ($\geq$ 60).

Diagnosis of cancer

Records on the cancer history of participants were obtained from the 'medical conditions' section of the NHANES database.

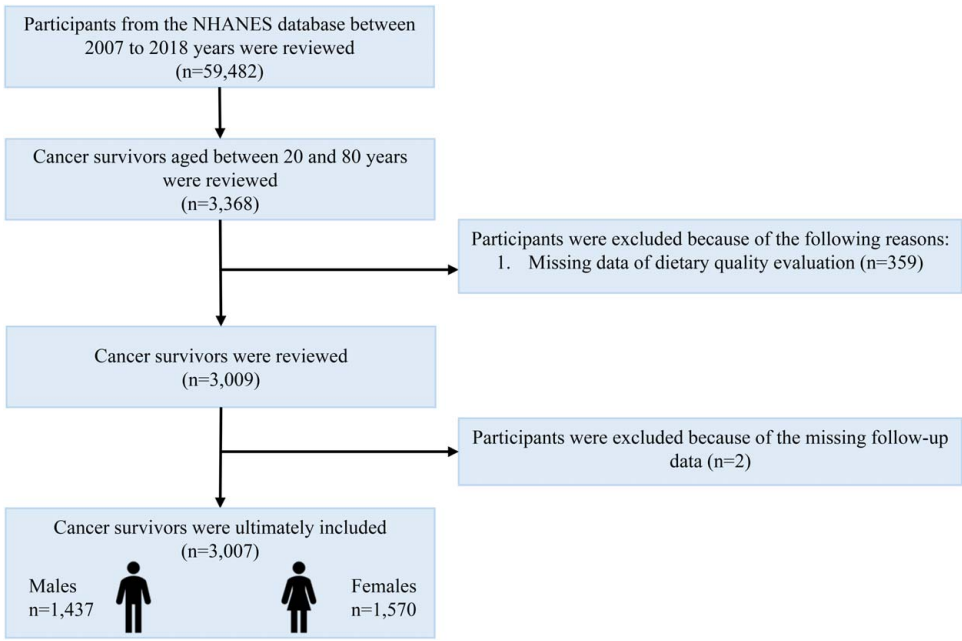

Figure 1. The participants' selection process in the present study. A total of 59 482 participants from six cycles of interviews between 2007 and 2018 years were reviewed and 3007 cancer survivors were ultimately included. NHANES, National Health and Nutrition Examination Survey.

Cancer survivors were identified based on the response to ('yes') to the question: 'Have you ever been told by a doctor or other health professional that you had cancer or malignancy of any kind?'. Cancer types were confirmed by asking, 'What kind of cancer was it?' In our study, cancer types of the breast, colorectal, liver, pancreas, stomach, thyroid, ovary, uterus, brain, blood, gallbladder, kidney, and esophagus were classified as obesity-related cancers according to the previous literature, and other cancer types were classified as nonobesity-related cancers. To further explore the joint effect of PA and DQ on survivals of cancer survivors with different primary sites, we further divided the cancer types into nine categories: gynecologic tumors (breast, cervical, ovarian, and uterine), male urologic tumors (prostate and testicular), gastrointestinal tumors (colorectal, esophageal, gallbladder, hepatocellular, pancreatic, rectal, and gastric), respiratory system tumors (lung and laryngeal/tracheal), head and neck tumors (laryngeal/tracheal, oral/tongue/lip, and thyroid), urologic tumors (bladder and kidney), hematologic malignancies (leukemia, lymphoma, and other blood cancers), skin cancers (melanoma and nonmelanoma), and other types of cancers (bone, brain, nervous system, and soft tissue).

Mortality ascertainment

The death data for the follow-up population were obtained from the NHANES public-use linked death file, which was correlated with the NCHS using the National Death Index (NDI) through a probability matching algorithm. Additionally, the International Statistical Classification of Diseases, 10th revision (ICD-10), was utilized to identify the underlying causes of death. The primary study outcome in our study was all-cause mortality of the study population. Cancer and noncancer mortality were the secondary outcomes of the study. The duration of death follow-up was calculated from the date when interviews were initially taken until either the date of the patient's death or 31 December 2019[25].

Covariates assessment

The selection of potential covariates was based on prior knowledge regarding the relationship between lifestyle and the prognosis of cancer survivors. In the study, specific covariates were analyzed for descriptive and inferential statistics. i) Sociodemographic characteristics included age, sex (male or female), race (Hispanic, non-Hispanic white, non-Hispanic black, and others), marital status (not married and married/living with partner), educational level ($\leq$ high school, college, and $>$ college), and family income poverty ratio (<1.3, 1.3–3.5, and >3.5). ii) Personal behavioral variables included smoking status (never, now, and ever), alcohol use (never, now, and ever), sleep time (<7, 7–9, and >9 h/d), and sedentary behavior time (<4, 4–6, and >6 h/d). BMI (<25, ≥ 25 and <30, and ≥ 30 kg/m^2) was obtained when participants attended a physical examination at a mobile health center. iii) Factors associated with health conditions included hypertension, hyperlipidemia, diabetes mellitus, and cardiovascular disease (CVD), based on self-reported physician diagnoses obtained during an individual interview using a standardized medical condition questionnaire.

Study outcome

The primary study outcome of this study was to evaluate the association between different patterns of PA and DQ with the mortality risk of cancer survivors. Besides, we also evaluated the prognostic effect of the dose of PA on the mortality risk of cancer survivors.

Statistical analysis

According to the NHANES analytic tutorials for weights in making estimates that were representative of the US civilian noninstitutionalized population, all analyses in this study incorporated sample weights, clustering, and stratification to estimate appropriate variance and ensure national representation of the US population. The baseline characteristics were displayed according to PA classification (0, 1–599, and ≥600MET-min/week). The normally distributed variables were presented as mean (SD). The non-normally distributed variables were presented as median (interquartile range). The categorical variables were presented as numbers (percentage, %). Continuous variables with normal distribution were evaluated using Student's *t*-test, while continuous variables with non-normal distribution were tested using the Kruskal–Wallis test. Categorical variables were compared by using the χ^2 test. The Cox proportional hazards regression models were applied to ascertain the association of PA and DQ with all-cause, cancer, and noncancer mortality of cancer survivors, respectively. Model 1 served as the crude model with no adjustments. Subsequently, adjustments for age, sex, and race were made in Model 2. In the fully adjusted model, we accounted for age, sex, race, marital status, educational level, family poverty income ratio, smoking status, alcohol use, sleep time, sitting time, BMI, hypertension, hyperlipidemia, diabetes mellitus, and CVD. To investigate the joint effect, participants were categorized based on PA and DQ, and multivariable Cox proportional hazards regression models were used to estimate mortality risk. To analyze the association between PA and cancer and noncancer mortality of cancer survivors, PA categories were combined [inactive (0 MET-min/week) and active (insufficiently active or sufficiently active, >0 MET-min/week)] due to small case numbers for each outcome. All analyses were conducted in different subpopulations including overall, female, male, and obesity-related and nonobesity-related cancers. In addition, subgroup analyses of primary outcomes were performed among cancer survivors with gynecological tumors, male urologic tumors, gastrointestinal tumors, respiratory system tumors, head and neck tumors, urologic tumors, hematologic malignancies, skin cancers, and other cancers. Furthermore, Kaplan–Meier (KM) curves were utilized to display the different survival probabilities among cancer survivors with different PA-DQ phenotypes. Variables with missing data were imputed using multiple imputation methods. Last, sensitivity analysis was conducted by excluding participants who died during the first 24 months of follow-up to minimize the potential impact of reverse causation.

All statistical analyses were conducted using R software (version 4.3.2). A two-tailed *P*-value of <0.05 was considered as statistically significant.

Results

Baseline characteristics

A total of 3007 cancer survivors were ultimately included in this study (weighted population: 22 239 072, weighted median age: 65 years, and weighted female proportion: 56.2%). Among the total participants, 85.8% ($n=1998$) were non-Hispanic White, 34.7% ($n=793$) had more than a college education, 65.8% ($n=1796$) were married or living with partner, and 45.7% ($n=951$) lived in households with family poverty income ratio beyond 3.5. At the time of the interview, over half of the study population were still drinking ($n=1750$) and nearly 15% of them were still smoking ($n=473$). The prevalence rates of comorbidities were as follows: 59.1% ($n=1749$) for hypertension, 52.0% ($n=1553$) for hyperlipidemia, 16.2% ($n=625$) for diabetes mellitus, and 14.9% ($n=569$) for CVD. Overall, 57.1% (1538/3007) of the participants met the PA recommendation (≥600 MET-min/week), and 28.8% (920/3007) of participants scored at or above 60 on the HEI-2015. Participants with inactive PA (0 MET-min/week) were more likely to be older, female, non-Hispanic White, married or living with partner, obese, have a middle family poverty income ratio, have hypertension, hyperlipidemia, and had shorter sleep time, longer sitting time and unqualified DQ (<60). Moreover, there was a significant increasing trend in the level of DQ among cancer survivors as PA increased ($P<0.001$). The detailed information on the population with varied levels of PA was summarized in Table 1.

Relationship between PA, DQ, and mortality

During the follow-up median period of up to 69 months, 730 deaths occurred, including 255 participants died from cancer, 155 died from CVD, and 320 died from other causes. The fully adjusted model revealed that cancer survivors with sufficient PA (≥600 MET-min/week) had the lowest risks of all-cause (HR 0.57, 95% CI: 0.48–0.68), cancer (HR 0.64, 95% CI: 0.48–0.86), and noncancer mortality (HR 0.53, 95% CI: 0.43–0.66) when compared with other groups (Table 2). Meanwhile, cancer survivors with qualified DQ (≥60) had lower risks of all-cause (HR 0.84, 95% CI: 0.71–0.99) and noncancer mortality (HR 0.81, 95% CI: 0.66–0.99) than those with unqualified DQ (<60) (Table 2).

Joint association of PA and DQ with mortality

In the joint analyses, combinations of active PA and qualified DQ were associated with the lowest all-cause, cancer, and noncancer mortality risks. To be specific, cancer survivors with sufficiently active PA (≥600 MET-min/week) and qualified DQ (≥60) had the lowest risk of all-cause mortality (HR 0.45, 95% CI: 0.35–0.59) when compared to other groups in the fully adjusted model (Fig. 2, Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). Meanwhile, when compared with other groups, cancer survivors with active PA (>0 MET-min/week) and qualified DQ (≥60) had the lowest risks of cancer (HR 0.60, 95% CI: 0.40–0.90) and noncancer (HR 0.43, 95% CI: 0.32–0.59) mortality, respectively (Fig. 3, Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). Furthermore, the KM curves revealed that cancer survivors with sufficiently active PA (≥600 MET-min/week) and qualified DQ (≥60) showed the significantly highest overall survival probability (Supplementary Figure S1A, Supplemental Digital Content 2, http://links.lww.com/JS9/C759), while groups with active PA (>0 MET-min/week) and qualified DQ (≥60) showed the highest cancer-specific, and noncancer-specific survival probabilities when compared with other groups (Supplementary Figure S1B, Supplemental Digital Content 2, http://links.lww.com/JS9/C759, Supplementary Figure S1C, Supplemental Digital Content 2, http://links.lww.com/JS9/C759) (all $P<0.0001$). In the sensitivity analysis, the association remained robust, after excluding the participants who

Table 1

The demographic characteristics of the cancer survivors in the present study were stratified by physical activity classification.

		Physical activity			
Variable	**Total ($n=3007$)**	**0 MET-min/week ($n=1052$) Weighted %:28.9**	**1-599 MET-min/week ($n=417$) Weighted %:14.0**	**≥600 MET-min/week ($n=1538$) Weighted %:57.1**	***P***
Age, M (Q_1, Q_3)	65.00 (54.00,74.00)	70.00 (59.00,79.00)	64.00 (52.00,74.00)	63.00 (53.00,71.00)	<0.001
Sex, *n* (%)					<0.001
Male	1437 (43.8)	432 (37.2)	189 (42.9)	816 (48.3)	
Female	1570 (56.2)	620 (62.8)	228 (57.1)	722 (51.7)	
Race, *n* (%)					0.092
Hispanic	397 (5.0)	156 (6.2)	46 (3.8)	195 (4.8)	
Non-Hispanic white	1998 (85.8)	674 (83.3)	273 (86.3)	1051 (86.8)	
Non-Hispanic black	442 (5.4)	169 (6.7)	71 (5.9)	202 (4.6)	
Others	170 (3.8)	53 (3.8)	27 (4.0)	90 (3.8)	
Education level, *n* (%)					<0.001
≤High school	1298 (33.1)	566 (44.7)	167 (27.5)	565 (28.2)	
College	916 (32.2)	295 (30.6)	133 (32.7)	488 (31.9)	
>College	793 (34.7)	191 (24.7)	117 (39.8)	485 (39.9)	
Marital status, *n* (%)					<0.001
Not married	1211 (34.2)	485 (42.1)	181 (34.8)	545 (29.3)	
Married/living with partner	1796 (65.8)	567 (57.9)	236 (65.2)	993 (70.7)	
Family poverty income ratio, *n* (%)					<0.001
<1.3	696 (14.2)	307 (20.3)	91 (14.1)	298 (11.2)	
1.3–3.5	1360 (40.1)	516 (48.9)	193 (40.0)	651 (35.8)	
>3.5	951 (45.7)	229 (30.8)	133 (45.9)	589 (53.0)	
BMI, *n* (%), kg/m^2					<0.001
<25	785 (26.5)	231 (20.2)	99 (25.1)	455 (31.3)	
≥25 and <30	1091 (35.3)	400 (36.1)	144 (31.8)	547 (35.1)	
≥30	1131 (38.2)	421 (43.7)	174 (43.1)	536 (33.6)	
Smoking status, *n* (%)					0.360
Never	1367 (47.2)	476 (45.3)	175 (45.1)	716 (47.7)	
Now	473 (14.7)	156 (15.4)	79 (19.9)	238 (14.2)	
Ever	1167 (38.1)	420 (39.3)	163 (35.0)	584 (38.1)	
Alcohol use, *n* (%)					<0.001
Never	674 (18.0)	300 (24.4)	89 (16.1)	285 (15.1)	
Now	1750 (66.8)	473 (52.3)	264 (71.8)	1013 (72.7)	
Ever	583 (15.2)	279 (23.3)	64 (12.1)	240 (12.2)	
Hypertension, *n* (%)					<0.001
No	1258 (48.1)	350 (36.9)	165 (43.8)	743 (54.4)	
Yes	1749 (51.9)	702 (63.1)	252 (56.2)	795 (45.6)	
Hyperlipidemia, *n* (%)					0.037
No	1454 (48.0)	506 (46.3)	182 (41.9)	766 (49.8)	
Yes	1553 (52.0)	546 (53.7)	235 (58.1)	772 (50.2)	
Diabetes mellitus, *n* (%)					<0.001
No	2382 (83.8)	754 (76.8)	333 (84.2)	1295 (87.3)	
Yes	625 (16.2)	298 (23.2)	84 (15.8)	243 (12.7)	
CVD, *n* (%)					<0.001
No	2438 (85.1)	792 (77.1)	343 (84.8)	1303 (88.7)	
Yes	569 (14.9)	260 (22.9)	74 (15.2)	235 (11.3)	
Sleep time, *n* (%), h/d					0.032
<7	1852 (66.4)	614 (63.1)	251 (68.9)	987 (68.2)	
7–9	937 (27.4)	326 (28.6)	132 (24.4)	479 (26.8)	
>9	218 (6.2%)	112 (8.3)	34 (6.7)	72 (5.0)	
Sitting time, *n* (%), h/d					<0.001
<4	601 (18.1)	144 (10.1)	68 (12.2)	389 (22.1)	
4-6	760 (24.8)	217 (20.7)	83 (19.2)	460 (28.8)	
>6	1646 (57.1)	691 (69.2)	266 (68.6)	689 (49.1)	
Dietary quality, HEI-2015, *n* (%)					<0.001
<60	2087 (71.2)	768 (74.2)	310 (79.3)	1009 (66.9)	
≥60	920 (28.8)	284 (25.8)	107 (20.7)	529 (33.1)	

CVD, cardiovascular disease; HEI-2015, Health Eating Index-2015; M, median; n, number; Q1, 1st quartile; Q3, 3rd quartile.

*P-value <0.05 was considered significant.

Table 2

Association of physical activity and dietary quality with all-cause, cancer, and noncancer mortality among US cancer survivors.

		Model 1		Model 2		Model 3	
Mortality outcome	**Death/No.**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
All-cause mortality							
Physical activity							
Inactive	387/1052	Reference		Reference		Reference	
Insufficiently active	86/417	0.49 (0.39–0.62)	**< 0.001**	0.57 (0.45–0.72)	**< 0.001**	0.65 (0.51–0.82)	**< 0.001**
Sufficiently active	257/1538	0.39 (0.34–0.46)	**< 0.001**	0.43 (0.37–0.51)	**< 0.001**	0.57 (0.48–0.68)	**< 0.001**
Dietary quality, HEI-2015							
Unqualified	516/2087	Reference		Reference		Reference	
Qualified	214/920	0.88 (0.75–1.03)	0.101	0.69 (0.58–0.81)	**< 0.001**	0.84 (0.71–0.99)	**0.036**
Cancer mortality							
Physical activity							
Inactive	120/1052	Reference		Reference		Reference	
Insufficiently active	37/417	0.69 (0.48–1.00)	**0.048**	0.74 (0.51–1.07)	0.113	0.84 (0.58–1.22)	0.359
Sufficiently active	98/1538	0.49 (0.37–0.64)	**< 0.001**	0.50 (0.38–0.66)	**< 0.001**	0.64 (0.48–0.86)	**0.003**
Dietary quality, HEI-2015							
Unqualified	181/2087	Reference		Reference		Reference	
Qualified	74/920	0.87 (0.66–1.14)	0.308	0.72 (0.55–0.95)	**0.019**	0.89 (0.67–1.17)	0.396
Noncancer mortality							
Physical activity							
Inactive	267/1052	Reference		Reference		Reference	
Insufficiently active	49/417	0.40 (0.30–0.55)	**< 0.001**	0.49 (0.36–0.67)	**< 0.001**	0.55 (0.41–0.76)	**< 0.001**
Sufficiently active	159/1538	0.35 (0.29–0.43)	**< 0.001**	0.40 (0.33–0.49)	**< 0.001**	0.53 (0.43–0.66)	**< 0.001**
Dietary quality, HEI-2015							
Unqualified	335/2087	Reference		Reference		Reference	
Qualified	140/920	0.88 (0.72–1.07)	0.199	0.67 (0.55–0.82)	**< 0.001**	0.81 (0.66–0.99)	**0.047**

HEI-2015, Health Eating Index-2015; HR, hazard ratio.

Note: Model 1 served as the unadjusted analysis; Model 2: adjusted for age, sex, and race; Model 3: adjusted for age, sex, race, educational level, marital status, family income poverty ratio, BMI, smoking status, alcohol use, hypertension, hyperlipidemia, diabetes mellitus, CVD, sleep time, and sitting time.

Inactive PA: 0 MET-min/week; Insufficiently active PA: 1-599 MET-min/week; Sufficiently active PA: ≥600 MET-min/week.

Unqualified DQ: <60; Qualified DQ: ≥60.

*P-value <0.05 was considered significant.

died within 24 months (Supplementary Tables S4, S5, S6, Supplemental Digital Content 2, http://links.lww.com/JS9/C759).

Subgroup analysis

In sex-subgroup analyses, the association between PA and mortality was consistent in males and females, while the negative association between DQ and mortality was more pronounced in males (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). The joint effect of PA and DQ on mortality was consistent across the sex groups (Supplementary Table S3, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). In the age-subgroup analyses, the active PA and qualified DQ had a greater positive effect on 65-year-old and older cancer survivors than on those under 65 years (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). The results of the joint analysis of PA and DQ remained consistent with the above (Supplementary Table S3, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). In addition, we explored the effect of PA and DQ in different cancer types. To be specific, the separate and combined positive effects of PA and DQ were significantly associated with survival in both obesity-related and nonobesity-related cancers (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/C759, Supplementary Table S3, Supplemental Digital Content 2, http://links.lww.com/JS9/C759). The combined positive effect of active PA and qualified DQ on survival was pronounced in cancer survivors with gynecological tumors, male urologic tumors, respiratory system tumors, hematologic malignancies, skin cancers, and other cancers. By contrast, no such joint positive effect was observed in survivors with gastrointestinal tumors, head and neck tumors, and urologic tumors (Supplementary Table S3, Supplemental Digital Content 2, http://links.lww.com/JS9/C759).

Dose-response relationship of PA and mortality

As shown in Supplementary Table S7 (Supplemental Digital Content 2, http://links.lww.com/JS9/C759), while higher levels of PA predicted reduced risk for mortality in cancer survivors, the best gains occurred at the PA level of 2000-3999 MET-min/week for all mortality outcomes. Specifically, cancer survivors with PA level of 2000-3999 MET-min/week presented the lowest risks of all-cause (HR 0.46, 95% CI: 0.34–0.63), cancer (HR 0.52, 95% CI: 0.32–0.85), and noncancer (HR 0.43, 95% CI: 0.29–0.64) mortality when compared with the rest groups.

Discussion

In the present study, we preliminary explored the joint effect of PA and DQ on mortality risks of cancer survivors, based on a US nationally representative cohort. We observed that about 57.1% had sufficiently active PA, and 28.8% had qualified DQ among

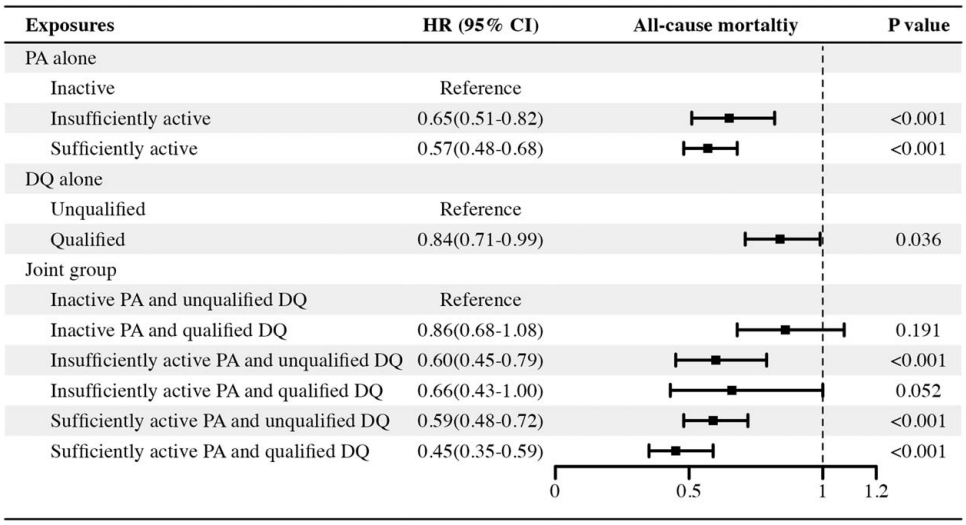

Figure 2. The forest plot shows the associations between PA and DQ and their joint effect on all-cause mortality among 3007 cancer survivors. The results were adjusted for age, sex, race, educational level, marital status, family income poverty ratio, BMI, smoking status, alcohol use, hypertension, hyperlipidemia, diabetes mellitus, CVD, sleep time, and sitting time. DQ, dietary quality; HR, hazard ratio; PA: physical activity. Inactive PA: 0 MET-min/week; Insufficiently active PA: 1-599 MET-min/week; Sufficiently active PA: ≥600 MET-min/week. Unqualified DQ: <60; Qualified DQ: ≥60.

these cancer survivors. During the 69-month median follow-up period, active PA was associated with decreased risks of all-cause, cancer, and noncancer mortality, while qualified DQ was associated with reduced risks of all-cause and noncancer mortality. In the combined analysis, the cancer survivors with inactive PA (0 MET-min/week) and unqualified DQ (<60) had higher risks of all-cause, cancer, and noncancer mortality than those with one risk factor. The association remained significant in sensitivity and subgroup analyses. According to our knowledge, this is the first study to investigate the joint effect of PA and DQ on mortality risks of US cancer survivors. Our findings highlighted the importance of the joint effect of PA and DQ for the follow-up management of the cancer population.

Previous studies[21,26,27] have demonstrated the potential benefits of PA in cancer prevention and improving the clinical outcomes of cancer survivors. Most recently, Cao *et al*.[26] observed that cancer survivors aged over 40 years old with active leisure-time PA presented reduced all-cause and cancer mortality risks when compared with those with inactive leisure-time PA. Of note, our study provided additional evidence for supporting the protective role of PA in cancer survivors, regardless of the types of PA and age. By contrast, our study determined that active PA was also significantly associated with a reduced noncancer mortality risk which was partially different from Cao's work. This difference might contribute to the different selection of age ranges in the study population, as previous evidence has shown that young cancer survivors were more likely to die from noncancer-related causes, such as cardiac/pulmonary disease, and psychological disorders like worry and anxiety[28]. PA could reduce these risk factors. Furthermore, some previous studies have explored the relationship between PA and breast cancer[29], endometrial cancer[30], colon cancer[31], skin cancer[32], and hematologic cancer[33], respectively. However, fewer studies concentrated on the association between PA and the mortality risk of all types of cancers. Thus, our study further validated the beneficial role of PA in the reduction of mortality risk of general cancer survivors,

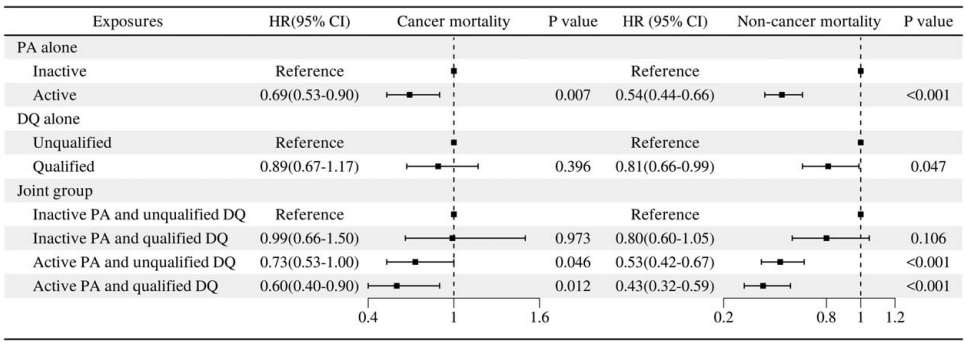

Figure 3. The forest plots show the associations between PA and DQ and their joint effect on cancer, and noncancer mortality among 3007 cancer survivors. The results were adjusted for age, sex, race, educational level, marital status, family income poverty ratio, BMI, smoking status, alcohol use, hypertension, hyperlipidemia, diabetes mellitus, CVD, sleep time, and sitting time. Active PA: Including Insufficiently active PA and Sufficiently active PA. DQ, dietary quality; HR, hazard ratio; PA, physical activity. Inactive PA: 0 MET-min/week; Active PA: ≥0 MET-min/week. Unqualified DQ: <60; Qualified DQ: ≥60.

which might provide additional insights for the update of PA recommendations. Notably, the dose-response relationship analysis revealed that cancer survivors with PA above 600 MET-min/week showed better survival probability when compared with those with inactive PA. Interestingly, we observed that cancer survivors with PA of 2000-3999 MET-min/week presented the lowest mortality risks when compared with other subgroups but the protective effect of PA was relatively compromised in cancer survivors with vigorous-intensity PA ($\geq$4000 MET-min/week). Our finding was consistent with one previous study focusing on the general population[22]. Therefore, these findings indicated maintaining moderate-intensity PA would bring superior benefits to reducing mortality risk among cancer survivors.

Meanwhile, the association between DQ and mortality has been explored in cancer populations[34–36]. The HEI-2015 has been selected as the assessment tool for DQ in this study, as analyzing dietary patterns is widely acknowledged to be a more comprehensive approach compared to focusing solely on individual nutrients or foods[37]. The dietary guidelines issued by the ACS and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) for cancer prevention advocate for the consumption of plant-based foods, including a variety of fruits and vegetables, as well as whole grains, limiting intake of red and processed meats, along with refined grains[4]. The healthy eating patterns defined by HEI-2015 are consistent with what these guidelines advocate. However, previous evidence on the association between healthy eating patterns and cancer mortality remains sparse[38]. Our data support that healthy eating patterns assessed by HEI-2015 might be associated with reduced all-cause and noncancer mortality risks, which were similar to some previous findings[14–16,39,40]. Based on a comprehensive dietary pattern rather than a single food or nutrient evaluation might provide stronger evidence of the rational dietary recommendation for cancer prevention.

To our knowledge, this is the first study to investigate the joint effect of PA and DQ on mortality outcomes based on a nationally representative sample of cancer survivors. Previous studies frequently investigated the independent effect of PA and DQ among cancer survivors with little consideration of their joint effect. The joint association of PA and DQ has been explored in general populations. A prospective study of 346 627 UK adults revealed that higher PA and better DQ were associated with reduced all-cause, CVD, and diet/adiposity-related cancer mortality risks[41]. Meanwhile, Abdelmawgoud *et al.*[42] determined that PA was associated with reduced risks of mortality and heart failure, regardless of healthy eating, among community older adults. The joint analysis allowed us to explore the unique and combined contribution of each factor to mortality outcomes, providing cancer survivors with more comprehensive survival guidance. Specifically, our findings indicated that increased PA along with improvements in DQ could significantly decrease the risks of all-cause, cancer, and noncancer mortality among cancer survivors as compared with each lifestyle intervention separately. Furthermore, the current findings revealed the importance of cancer types in evaluating the joint effect of PA and DQ on mortality outcomes. To be specific, the significant association between active PA and reduced mortality risk observed in gynecologic tumor survivors might be explained by the effect of estrogen metabolism[43], while the potential mechanisms of diet in improving survival of those populations might include reduction of weight and waist circumference, amelioration of blood glucose and insulin levels, and improvement of antioxidant capacity[44]. The lack of a significant association between the joint effect of PA and DQ with the survival of head and neck tumor survivors might be due to other factors not considered in the study, such as smoking, alcohol consumption, and viral infections[45]. The differences highlight the need for individualized lifestyle recommendations based on cancer types.

The importance of PA and DQ in reducing cancer incidence and mortality as well as improving the quality of life for cancer survivors was initially emphasized by the ACS in 2002[46]. During the past years, researchers have committed to investigating the potential connections between PA and DQ with the prognosis of cancer survivors. Notably, the 2022 ACS nutrition and PA guideline[4] for cancer survivors strongly recommended further exploration into the relationship between dose of PA, dietary patterns (rather than individual nutrients or foods), and risk for mortality among cancer survivors in future studies. From this perspective, a joint investigation of PA based on dose as well as DQ based on dietary patterns among cancer survivors is needed. This motivation led us to conduct this new study. The current findings contribute to filling previously existing knowledge gaps in the literature regarding cancer survival by providing direct evidence of an association between active PA and qualified DQ (defined by the HEI-2015) with improved survival after a diagnosis of cancer.

Several potential biological pathways might explain our findings. PA can modulate insulin/glucose metabolism[5], enhance the immune function[6], regulate hormone metabolism[7], reduce inflammation[8], and affect tumor growth and metastasis[47], thereby increasing the completion rate of treatment and improving the efficacy of treatment. Meanwhile, accumulating evidence suggests that diet can modulate the mechanisms of cancer development and progression, including inflammation and immune system, hormone metabolism, antioxidation, inhibition of proliferation, and so on[10–13]. For instance, the intake of polyphenols and fiber from grains has been shown the ability of reducing the cancer mortality risk[48,49]. Of note, PA and DQ might share the similar biological pathways to influence the prognosis of cancer survivors, which could explain the joint effect of these two factors.

Our study has several strengths. Initially, this is the first study to explore the joint effects of PA and DQ with mortality outcomes among cancer survivors. Second, we utilized the sample weights, clustering, and stratification to estimate appropriate variance and ensure national representation of the US population. The nationally representative sample of US cancer survivors in this study encompassed multiple races to enhance the generalizability of our findings to other cancer populations. Third, we controlled a series of covariates including the demographic characteristics, socioeconomic factors, comorbidities, and individual lifestyles of cancer survivors, which would help to reduce the potential confounding bias. Besides, we conducted sensitive and stratified analyses to validate the robustness of the main findings and determine the high-risk subgroups. Last, we further explored the relationship between the dose of PA with mortality risk among cancer survivors, which provided new insights into the optimal PA ranges for cancer survivors.

Admittedly, our study has some limitations which need to be addressed in the following works. First, the data on PA and DQ were self-reported and were subject to recall biases. Second, the diagnoses and types of cancers were self-reported. Although some

studies have indicated a good agreement between self-reported cancer history and medical records, self-reported data may be influenced by recall bias and misclassification during the data recording process[50,51]. Therefore, our findings need to be interpreted cautiously. Future studies with specific cancer-associated features are warranted to evaluate the impact of PA and DQ on the prognosis of cancer survivors with different cancer stages or treatment modalities. Third, the study only measured PA and DQ at baseline without collecting information on dynamic changes in these factors during the follow-up period. Last, the data regarding cancer stages and treatments were not collected in NHANES. However, the consistent results observed after excluding deaths occurring within the first 24 months follow-up period lessen the probability of reverse causation.

Conclusions

In summary, this population-based cohort study demonstrates that cancer survivors with characteristics of active PA and qualified DQ are associated with significantly reduced all-cause and cancer as well as noncancer mortality risks. A combined evaluation of PA and DQ may provide an additional understanding of the prognostic effects of lifestyle interventions on survival rates among cancer survivors.

Ethical approval

As a secondary analysis of anonymized data, this study did not involve human participants. Thus, informed consent and institutional review board approval were not required. This study has been registered on the website of ClinicalTrials.gov (NCT06350214, https://register.clinicaltrials.gov).

Consent

Informed consent was not required.

Source of funding

None.

Author contribution

L.L. and X.W.: conception and design; L.L. and Y.M.: administrative support; X.W., Y.M., Z.X., Y.Z., and J.W.: provision of study materials or patients; X.W., Y.M., Z.X., and Y.Z.: collection and assembly of data; X.W., Y.M., Z.X., Y.Z., and J.W.: data analysis and interpretation. All authors contributed in manuscript writing and final approval of manuscript.

Conflicts of interest disclosure

The authors declare no conflict of interest.

Research registration unique identifying number (UIN)

As a secondary analysis of anonymized data, this study did not involve human participants.

Guarantor

Lei Liu.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. Data described in the manuscript, code book, and analytic code will be made available upon request pending approval.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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