Published in final edited form as:

J Geriatr Oncol. 2016 March ; 7(2): 108–115. doi:10.1016/j.jgo.2016.01.009.

Patient-Reported versus Objectively-Measured Physical Function and Mortality Risk among Cancer Survivors

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Abstract

Introduction—This study characterized the relationship of patient-reported functional limitations, gait speed, and mortality risk among cancer survivors.

Materials and Methods—This study included cancer survivors from the Third National Health and Nutrition Survey. Patient-reported functional limitations were quantified by asking participants to assess their ability to complete five tasks: (1) walking ¼ mile, (2) walking up 10-steps, (3) stooping, crouching, kneeling, (4) lifting or carrying an object of 10 pounds, and (5) standing up from an armless chair. Gait speed was quantified using a 2.4-meter walk. Vital status was obtained through the United States National Center for Health Statistics.

Results—The study sample included 428 cancer survivors who averaged 72.1 years of age. The average number of patient-reported functional limitations was 1.8 (out of 5) and 66% of participants reported 1 functional limitation. Patient-reported functional limitations and gait speed were related, such that each functional limitation associated with a -0.08 meter/second slower gait speed (95% Confidence Interval: -0.10 to -0.06 ; $P<0.001$). During a median follow-up of 11-years, 329 (77%) participants died. In multivariable-adjusted analysis, patient-reported functional limitations and survival were related, such that each additional reported functional limitation was associated with a 19% increase in the risk of death (95% Confidence Interval: 9 to 29%; $P<0.001$).

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DISCLOSURES AND CONFLICT OF INTEREST STATEMENTS

The authors declare they have no conflicts of interest to disclose in relation to this work.

AUTHOR CONTRIBUTIONS

Study Concepts: JC Brown, MO Harhay, MN Harhay

Study Design: JC Brown, MO Harhay, MN Harhay

Data Acquisition: JC Brown, MO Harhay, MN Harhay

Quality Control of Data and Algorithms: JC Brown, MO Harhay, MN Harhay

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Manuscript Preparation: JC Brown (initial draft)

Manuscript Editing: JC Brown, MO Harhay, MN Harhay

Manuscript Review: JC Brown, MO Harhay, MN Harhay

Discussion—Patient-reported functional limitations are prevalent among cancer survivors, and associate with slower gait speeds and shorter survival. These data may provide increased insight on long-term prognosis and inform clinical decision-making by identifying subgroups of cancer survivors who may benefit from rehabilitative intervention.

Keywords

physical function; aging; oncology; disability; physical activity; exercise

INTRODUCTION

The assessment of functional limitations is an important component for evaluating the overall health and physiologic reserve of cancer survivors (1-3). After a diagnosis of cancer, patient-reported physical function deteriorates at an accelerated rate compared to that of age-matched cancer-free persons (4, 5). This may be a result of cancer treatment, which impairs multiple physiologic systems such as the cardiopulmonary (6, 7), neurologic (8), and musculoskeletal systems (9, 10), that are necessary to enable physical function. Treatment-related physiologic impairments may explain why cancer survivors are up to nine-fold more likely to report a functional limitation compared to similar-aged persons without a history of cancer (11, 12).

Clinicians that appropriately characterize functional limitations may have unique insight into their patients' risk of progression in the disablement pathway (13). Options to measure functional limitations include validated objective metrics of physical function such as gait speed, also known as walking speed, which predicts survival among older adults and cancer survivors (14, 15). Gait speed is also associated with cognitive impairment, cardiopulmonary disease, hospitalization, and nursing home placement (16). Alternatively, implementing patient-reported outcomes of physical function may be more feasible in clinical practice, but studies to date have not confirmed that patient-reported functional limitations correlate with objectively-measured physical function, such as gait speed, among cancer survivors.

Identifying clinical assessments that accurately risk-stratify patients who have survived cancer will benefit care providers and scientists in targeting therapies to the most vulnerable cancer survivors. Therefore, the goal of this study was to characterize the association between patient-reported functional limitations and objectively-measured physical function (i.e., gait speed), and describe the relationship between patient-reported functional limitations and mortality risk among a population-based sample of cancer survivors.

METHODS

Study Design

The Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) was a stratified multistage study designed to provide health information on a nationally-representative sample of U.S. civilians (17). A stratified multistage sampling design was used to select participants that were representative of the U.S. population. The four sampling stages included: 1) counties within states; 2) city blocks within each county; 3) households

within each city block and; 4) individuals within each household. The study protocol for NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. All participants provided written informed consent prior to participating in any study-related activities.

Study Participants

Participants aged ≥ 60 years were invited to complete an evaluation that included patient-reported measures of functional limitations and objective measures of physical function (18). We identified 4,881 participants who completed the requisite study measures, 428 (9%) of whom reported a prior diagnosis of non-skin-related cancer.

Patient-Reported Functional Limitations

Functional limitations were assessed by asking participants to report the level of difficulty for five common tasks that included: (1) walking for a ¼ quarter of a mile, (2) walking up 10-steps, (3) stooping, crouching, or kneeling, (4) carrying something as heavy as 10 pounds, and (5) standing up from an armless chair. For each question, participants were provided answers of: (1) no difficulty, (2) some difficulty, (3) much difficulty, and (4) unable to do. Participants who reported at least some difficulty were considered to have functional limitation in that task (19-21). Participants who reported limitations in three or more tasks were classified as disabled (19).

Objectively-Measured Physical Function

Gait speed is an objective measure that quantifies overall health and functional ability (15, 22), and has been shown to predict survival among cancer survivors (14). Gait speed was assessed using a 2.4-meter walk on a straight and level surface (18). Time required to complete the 2.4-meter course was recorded to the nearest tenth of a second using a stopwatch. Gait speed was quantified in units of meters per second (m/s), by dividing 2.4-meters into the number of seconds required to complete the walk.

Mortality Outcome

The primary outcome of this study was death from any cause. Vital status was identified using the National Death Index (NDI) database through December 31, 2006. Participants were linked to the NDI database using a probabilistic matching algorithm that included 12 identifiers including Social Security Number, sex, date of birth, race, state of residence, and marital status (23). The United States National Center for Health Statistics found that 96.1% of deceased participants and 99.4% of living participants were correctly classified using the probabilistic matching algorithm (24).

Covariates

Demographic information including date of birth and sex were patient-reported using a standardized questionnaire. Clinical information including type of cancer, date of cancer diagnosis, smoking history, alcohol consumption, hospitalizations in the prior year, patient-reported health status, and frequency of physical activity were assessed using standardized questionnaires. Bouts of walking in the past week were patient-reported and included any

bout of walking that was estimated to be 1 mile in duration, and of moderate or vigorous intensity. The presence of comorbid health conditions were determined by asking participants if a doctor had ever told them that they had any of the following: hypertension, diabetes, hyperlipidemia, asthma, arthritis, myocardial infarction, stroke, or congestive heart failure.

Height in meters and weight in kilograms were measured by study technicians. Body mass index was calculated as weight divided by the square of height (kg/m^2). The healthy eating index (HEI) was calculated from 24-hour food recalls to form a score than ranges from 0 to 100 to quantify aspects of a healthy diet (25). Hemoglobin was quantified using a Coulter S-Plus Jr electronic counter (Coulter Electronics, Hialeah, FL) with a coefficient of variation $<3.0\%$. Albumin was quantified using a Hitachi 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA) with a coefficient of variation $<2.8\%$. C-reactive protein was quantified using latex-enhanced nephelometry immunoassay (Behring Diagnostics, Somerville, NJ) with a coefficient of variation $<6.3\%$. Detailed blood collection procedures and laboratory assay methods used in NHANES III are described elsewhere (26).

Statistical Analysis

Descriptive variables are presented as means and 95% confidence intervals (95% CI) for continuous variables and percentages for categorical variables. We used unadjusted linear regression models to estimate the mean difference in gait speed by varying levels of patient-reported functional limitation. We used Cox proportional hazards regression models to estimate the hazard ratio (HR), and 95% CI for all-cause mortality by varying levels of patient-reported functional limitation. Models were estimated adjusted for sex and age (model 1) and fully-adjusted for demographic, behavioral, and clinical characteristics (model 2). We confirmed the assumption of proportional hazards for all analyses using log-log plots. To determine if the observed relationships varied between younger (<75 years) and older (≥ 75 years) cancer survivors we incorporated a statistical interaction between functional limitation and age category when modeling gait speed and survival. No statistically significant interactions were identified; consequently all analyses are presented for the overall cohort. We incorporated sample weights into all statistical analyses to account for nonresponse bias, multistage sampling probabilities, and the subpopulation of participants that were included in this analysis (27). Stata/SE v.13.1 statistical software was used for all analyses.

RESULTS

Participant Characteristics

Among 428 cancer survivors, the average age was 72.1 (95% CI: 71.3-73.0). Participant characteristics stratified by age category (**Table 1**) demonstrate that those who were older were less likely to be smokers, consumed fewer alcoholic drinks, less likely to report hyperlipidemia, and less likely to participate in regular physical activity, but were more likely to report a history of myocardial infarction and stroke, and had a slower gait speed.

Association between Patient-Reported Functional Limitations and Objective Physical Function

The prevalence of patient-reported functional limitations ranged from 27.3% for standing up from an armless chair to 53.3% for stooping, crouching, and kneeling (**Table 2**). The average number of functional limitations was 1.8 (95% CI: 1.6-2.0) and 66% of participants reported 1 functional limitation. The average gait speed was 0.67 m/s (95% CI: 0.64-0.71). A cane and walker were used by 25 (5.8%) and 10 (2.3%) cancer survivors during the 2.4-meter walk, respectively. Participants with functional limitation in any of the five tasks had slower gait speed compared to those without functional limitation (all $P<0.001$). As the total number of functional limitations increased, gait speed decreased linearly, such that each additional functional limitation associated with a -0.08 m/s [(95% CI: -0.10 to -0.06); $P<0.001$] decrease in gait speed. The prevalence of disability was 31.1%, and disabled participants had slower gait speeds compared to participants who were non-disabled [-0.28 m/s (95% CI: -0.35 to -0.21); $P<0.001$].

Patient-Reported Functional Limitations and Survival

Limitations reported in walking ¼ mile, walking up 10-steps, lifting or carrying an object of 10 pounds, and standing up from an armless chair were associated with survival in multivariable-adjusted regression models (**Table 3**). Limitations in stooping, crouching, and kneeling were not associated with survival in the multivariable-adjusted regression model.

When the five functional limitations were simultaneously entered into a multivariable-adjusted regression model, patient-reported difficulty walking up 10 steps was associated with survival [HR=1.49 (95 % CI: 1.03-2.15); $P=0.035$]. Patient-reported difficulty walking ¼ mile [HR: 1.05 (95% CI: 0.62-1.78); $P=0.853$], stooping, crouching, kneeling [HR: 0.97 (95% CI: 0.68-1.36); $P=0.844$], lifting or carrying an object of 10 pounds [HR: 1.30 (95% CI: 0.85-2.01); $P=0.228$], and standing up from an armless chair [HR: 1.22 (95% CI: 0.76-1.95); $P=0.415$] were not independently associated with survival.

Figure 1 shows that as the total number of functional limitations increased, the risk of death increased [HR: 1.19 per additional limitation (95% CI: 1.09-1.29); $P<0.001$]. Disabled cancer survivors had a 76% greater risk of death than non-disabled cancer survivors [HR: 1.76 (95% CI: 1.26-2.44); $P=0.001$; (**Figure 2**)].

Given that more functional limitations could reflect impending death, in exploratory analyses we excluded participants who died within one to five years of completing the functional limitations questionnaire and our results remained unchanged (data not shown).

DISCUSSION

Cancer survivors are a heterogeneous population representing an array of functional capacities and physiologic reserves (28). In this nationally-representative cohort of cancer survivors, patient-reported functional limitations were highly prevalent, 66% of participants patient-reported one or more functional limitation and 31% of participants reported three or more functional limitations (i.e., functionally disabled). Cancer survivors with functional limitations were more likely to die than those without functional limitations, and patient-

reported limitations strongly correlated with the degree of objective limitations as measured by gait speed, a known predictor of mortality among cancer survivors (14). These data suggest that integrating queries of patient-reported physical function may provide increased insight on long-term prognosis of cancer survivors and aid in clinical decision making.

Our findings support prior reports that functional limitations are prevalent among cancer survivors (11, 12), and provide new evidence that patient-reported functional limitations are associated with slower measured gait speed. Cancer survivors are significantly more likely to report poor physical function compared to non-cancer controls (11, 12). However, interpretation of these prior reports has been challenging because certain subgroups of adults may be unable to accurately estimate their physical capacity (29). Gait speed is considered a gold-standard measure of physical function (30), and is associated with overall health, survival, cognitive impairment, cardiopulmonary disease, hospitalization, and nursing home placement among older adults (16). However, in settings in which implementing objective metrics of physical function are not as feasible as administering patient-reported metrics, our data demonstrate that patient-reported functional limitations are consistently associated with slower gait speeds among cancer survivors, as well as with mortality risk. For example, as an ordinal measure, each patient-reported functional limitation was associated with a -0.08 m/s slower gait speed ($P<0.001$). This is clinically meaningful because declines in gait speed are a predictor of disability (31) and conversely, improvements in gait speed are a predictor of improved survival (32). The observed relationship between patient-reported functional limitations and objectively-measured gait speed suggests that using patient-reported functional limitations to inform patient prognosis is a potentially valid strategy in cancer survivors. Our findings also highlight the gravity of prior studies that have documented that patient-reported functional limitations are highly prevalent among cancer survivors.

This study also found that patient-reported functional limitations were associated with survival, complementing the known relationship between objectively-measured physical function and survival among cancer survivors (14). The ability to perform functional activities without difficulty is critical to maintaining a high quality-of-life and avoiding premature morbidity and mortality. In a prior study of 7,417 patients representing 11 different types of cancer, higher patient-reported global physical functioning was associated with a reduced likelihood of death (33). Our study complements these findings by adding knowledge of the relationship of specific functional limitations and survival. For example, difficulty stooping, crouching or kneeling was not associated with survival (HR: 1.27, $P=0.117$). Conversely, difficulty walking up 10-steps emerged as the most important prognostic factor for mortality in a fully adjusted model (HR: 1.49, $P=0.035$). These data deepen our understanding between specific patient-reported functional limitations and survival among cancer survivors, and may inform prognosis of cancer survivorship beyond that of traditional demographic, behavioral, and clinical variables.

As a majority of participants in this study were older and long-term survivors of cancer, the results of this study may inform geriatric oncology practice. The National Comprehensive Cancer Network (NCCN) and International Society of Geriatric Oncology (SIOG) recommend that a geriatric assessment be performed to guide healthcare providers with selecting the best cancer treatments for older adults (2, 34). The geriatric assessment has

been emphasized at time points prior to the initiation of cancer treatment (3). While less focus has been made to the potential importance of the geriatric assessment after the completion of cancer treatment, this focus is necessary to promptly identify and intervene on functional impairments, before they contribute to a trajectory of worsening health (35). Therefore the geriatric assessment may be a clinically important tool at multiple points along the cancer care continuum, from pretreatment decision making to the monitoring of health and wellness in long-term survivorship.

Identifying cancer survivors who report functional limitations may help to demarcate a population that may benefit from rehabilitative intervention (36). Physical activity is a promising intervention that may provide numerous benefits for cancer survivors (37). For example, among 1,600 adults with lower-extremity functional limitations, a structured physical activity program focused on walking resulted in an 18% reduction in the development of major mobility disability, defined as the inability to walk 400-meters, over 2.6 years (38). A program of home-based diet and exercise significantly attenuated the loss of physical function among 641 older, overweight survivors of breast, colorectal, and prostate cancer over one year (39). Among breast cancer survivors, slowly progressive weight lifting slowed the rate of deterioration of physical function over one year (40). For certain cancer sites, observational studies suggest physical activity may be associated with a reduction in cancer-specific mortality (41, 42), though this relationship has not yet been confirmed in a randomized controlled trial setting. Collectively, these data demonstrate the potential utility for physical activity, and provide evidence for the continued investigation of physical activity as an adjuvant intervention in oncology practice.

The results of this study must be considered alongside its strengths and limitations. First, this analysis was not able to identify incident cases of patient-reported functional limitation. We cannot completely exclude the possibility that patient-reported functional limitation may be reflective of occult disease (i.e., reverse causality). In our exploratory analyses, excluding participants who died within one to five years of completing the functional limitations questionnaire did not alter our results. This study used a non-standardized measure of functional limitation that was designed to briefly cover a wide range of functional activities as derived from the work of Nagi, Rosow, Breslau, and Lawton (43). We did not have information regarding stage of cancer or specific cancer treatments received. Comorbid health conditions were self-reported, which may underestimate the burden of comorbidity in our sample. It is likely that these aforementioned variables may have attenuated the association between patient-reported functional limitation and survival by accounting for variation associated with cancer stage, specific cancer treatments received, and comorbid health conditions. However, this limitation is unlikely to impact the clinical importance of our findings to identify and rehabilitate cancer survivors with patient-reported functional limitations. Our analysis did not include cancer survivors who were unable to safely complete the 2.4-meter walk used to quantify gait speed (n=17). Therefore our analyses are applicable to cancer survivors who are able to safely walk without assistance from another person. We relied solely on gait speed as an objective measure of physical function. Gait speed does not quantify upper-extremity function such as that of the arm or hand.

This study also possesses several strengths. As a result of the sampling framework of NHANES, our study cohort is a nationally-representative sample of community-dwelling cancer survivors in the United States (17). Our study had an extensive median length of follow up of 11.0-years, which allowed us to observe a high proportion of deaths. We accounted for a variety of covariates that may influence the association of patient-reported functional limitation and survival such as demographic, behavioral, and clinical characteristics, including blood chemistry measures.

In conclusion, patient-reported functional limitations are highly prevalent, are associated with slower gait speeds, and are associated with survival among cancer survivors. These data inform clinicians seeking to improve their insight on long-term prognosis and identify subgroups of cancer survivors in need of rehabilitative intervention. The findings demonstrate the need for additional research in the area of geriatric oncology, to find efficacious interventions to prevent or treat functional limitations among cancer survivors. Physical activity is a promising intervention with many possible benefits for cancer survivors. Randomized studies are necessary to determine if physical activity can prevent, delay, or rehabilitate functional limitations in this population, and improve cancer survivorship.

ACKNOWLEDGEMENT

Justin C. Brown had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Research reported in this publication was supported by the National Cancer Institute (F31-CA192560, R21-CA182726), National Heart, Lung, and Blood Institute (F31-HL127947) and the National Institute of Diabetes and Digestive and Kidney Diseases (F32-DK096758) of the National Institutes of Health.

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Figure 1.
Kaplan-Meier Plot of Survival, Stratified by Number of Patient-Reported Functional Limitations

Figure 2.
Kaplan-Meier Plot of Survival, Stratified by Composite Disability Outcome

Table 1Demographic and Clinical Characteristics, Stratified by Age Category^a

Characteristic	Overall (n=428) [mean or (%)]	Age		P-Value
		<75 years (n=204)	75 years (n=224)	
Age — yr.	72.1 (71.3-73.0)	67.2 (66.5-68.0)	80.4 (79.8-81.1)	<0.001
Sex				
Male	38.9%	37.4%	41.5%	0.483
Female	61.1%	62.6%	58.5%	
Type of Cancer				
Breast	26.8%	28.7%	23.5%	0.201
Genitourinary	21.0%	15.5%	24.1%	
Gastrointestinal	18.7%	19.6%	23.5%	
Gynecologic	14.2%	17.3%	9.0%	
Lung	2.9%	3.5%	1.8%	
Hematologic	2.3%	2.4%	2.4%	
Other, missing, or can't remember	14.1%	13.1%	15.7%	
Time Since Cancer Diagnosis — yr.				
Mean (continuous)	10.9 (9.7-12.1)	10.8 (9.1-12.5)	11.1 (9.5-12.7)	0.792
<5	33.9%	33.8%	34.0%	
5-10	21.4%	23.1%	18.6%	
10	44.7%	43.1%	47.4%	
Body Mass Index — kg/m ²				
Mean (continuous)	26.0 (25.3-26.7)	26.5 (25.5-27.4)	25.2 (24.5-26.0)	0.060
<18.5	3.4%	1.8%	6.1%	
18.5-24.9	43.4%	42.1%	45.5%	
25.0-29.9	34.5%	34.6%	34.4%	
30.0	18.7%	21.5%	14.0%	
Smoking Status — n (%)				
Never	41.7%	36.6%	50.3%	0.025
Former	45.3%	47.2%	42.1%	
Current	13.0%	16.2%	7.6%	
Healthy Eating Index	69.1 (67.4-70.8)	69.3 (67.1-71.6)	68.6 (66.2-71.1)	0.675
No. of alcoholic drinks consumed in past wk.	1.1 (0.8-1.4)	1.3 (0.9-1.7)	0.8 (0.5-1.1)	0.052
Comorbid health conditions				
Hypertension	48.1%	51.1%	43.1%	0.189
Diabetes	11.3%	9.9%	13.7%	
Hyperlipidemia	32.4%	38.2%	22.7%	0.008
Asthma	7.1%	7.7%	6.1%	0.596
Arthritis	46.9%	46.0%	48.5%	0.683
Myocardial infarction	14.5%	10.8%	20.8%	0.014
Stroke	8.2%	4.7%	14.1%	0.004

Characteristic	Overall (n=428) [mean or (%)]	Age		P-Value
		<75 years (n=204)	75 years (n=224)	
Congestive heart failure	7.8%	7.0%	9.3%	0.495
Hospitalization(s) in past yr. — n (%)	28.9%	30.6%	26.1%	0.382
Hemoglobin (g/dL)	13.5 (13.4-13.7)	13.6 (13.4-13.8)	13.5 (13.3-13.7)	0.648
Albumin (g/dL)	4.0 (3.9-4.1)	4.0 (4.0-4.1)	3.9 (3.9-4.0)	0.064
C-reactive protein (mg/L)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.7 (0.5-0.8)	0.153
No. of bouts of walking in past wk.				
0	76.0%	69.7%	86.6%	0.003
1-3	6.7%	8.3%	3.9%	
3	17.3%	22.0%	9.5%	
Gait Speed — meters/second				
Mean (continuous)	0.67 (0.64-0.71)	0.75 (0.71-0.79)	0.55 (0.51-0.59)	<0.001
<0.6	31.2%	16.9%	55.3%	<0.001
0.6	68.8%	83.1%	44.7%	

^aContinuous variables are mean (95% confidence interval) and categorical variables are column percentages

Table 2
Prevalence of Patient-Reported Functional Limitation and Association with Objectively Measured Physical Function

Patient-Reported Functional Limitation	Proportion (%)	Gait Speed, Mean (95% CI)	Mean Difference (95% CI)	P
Walking ¼ Mile				
Limited	33.4%	0.50 (0.44–0.56)		
Not Limited	66.6%	0.77 (0.74–0.80)	–0.27 (–0.33 to –0.20)	<0.001
Walking Up 10-Steps				
Limited	30.8%	0.49 (0.42–0.55)		
Not Limited	69.2%	0.76 (0.73–0.79)	–0.27 (–0.34 to –0.20)	<0.001
Stooping, Crouching, Kneeling				
Limited	53.3%	0.60 (0.55–0.66)		
Not Limited	46.7%	0.76 (0.73–0.79)	–0.15 (–0.22 to –0.09)	<0.001
Lifting or Carrying Object of 10 lb.				
Limited	32.0%	0.53 (0.46–0.60)		
Not Limited	68.0%	0.75 (0.72–0.78)	–0.22 (–0.29 to –0.14)	<0.001
Standing Up From Armless Chair				
Limited	27.3%	0.47 (0.40–0.54)		
Not Limited	72.7%	0.75 (0.72–0.78)	–0.28 (–0.36 to –0.21)	<0.001
Total Number of Limitations				
0	33.8%	0.78 (0.74–0.82)	0.00 — Referent ^b	
1	24.4%	0.75 (0.69–0.81)	–0.03 (–0.10 to 0.04)	0.346
2	10.7%	0.74 (0.68–0.80)	–0.05 (–0.12 to 0.02)	0.202
3	8.1%	0.67 (0.63–0.73)	–0.10 (–0.17 to –0.04)	0.001
4	8.0%	0.61 (0.51–0.72)	–0.17 (–0.28 to –0.06)	0.004
5	15.0%	0.32 (0.24–0.39)	–0.47 (–0.55 to –0.38)	<0.001
Composite Disability Outcome ^a				
Disabled	31.1%	0.49 (0.42–0.54)		
Non-Disabled	68.9%	0.76 (0.73–0.79)	–0.28 (–0.35 to –0.21)	<0.001

^aDefined as self-reporting limitations in 3 of 5 functional limitations.

H_q trend > 0.001; the mean difference and 95% CI for total number of functional difficulties as a continuous variable was -0.08 (-0.10 to -0.06).

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Table 3
Association of Patient-Reported Functional Limitation and Association with All-Cause Mortality

Patient-Reported Functional Limitation	Death Rate, Per 100 Person-Years (95% CI)	Median Survival, Years [Interquartile Range]	Hazard Ratio (95% CI)		
			Model 1 ^a	P	Model 2 ^b
Walking ¼ Mile					
Limited	12.3 (9.9–15.2)	6.3 [2.5–11.2]	1.88 (1.40–2.52)	<0.001	1.57 (1.12–2.21)
Not Limited	6.1 (5.2–7.2)	13.1 [6.5–NR] ^f	1.00 — Referent	—	1.00 — Referent
Walking Up 10-Steps					
Limited	12.5 (10.1–15.4)	6.3 [2.6–11.8]	2.01 (1.52–2.66)	<0.001	1.78 (1.33–2.39)
Not Limited	6.1 (5.2–7.3)	12.1 [6.3–NR] ^f	1.00 — Referent	—	1.00 — Referent
Stooping, Crouching, Kneeling					
Limited	8.9 (7.5–10.7)	8.7 [3.2–15.0]	1.31 (1.01–1.70)	0.046	1.27 (0.94–1.71)
Not Limited	6.3 (5.1–7.8)	12.1 [6.5–NR] ^f	1.00 — Referent	—	1.00 — Referent
Lifting or Carrying Object of 10 lb.					
Limited	10.2 (8.1–12.8)	7.8 [2.6–13.1]	1.57 (1.16–2.11)	0.003	1.64 (1.16–2.32)
Not Limited	6.7 (5.6–7.9)	12.1 [5.5–16.7]	1.00 — Referent	—	1.00 — Referent
Standing Up From Armless Chair					
Limited	11.9 (9.0–15.4)	6.7 [2.5–11.2]	1.66 (1.21–2.29)	0.002	1.73 (1.25–2.41)
Not Limited	6.5 (5.6–7.6)	12.0 [5.7–NR] ^f	1.00 — Referent	—	1.00 — Referent
Total Number of Limitations					
0	5.2 (4.0–6.7)	13.7 [7.1–NR] ^f	1.00 — Referent ^d	—	1.00 — Referent ^e
1	7.5 (5.7–9.8)	11.3 [4.2–16.7]	1.32 (0.92–1.90)	0.129	1.39 (0.87–2.23)
2	8.0 (5.5–11.5)	11.2 [4.1–15.6]	1.37 (0.87–2.16)	0.171	1.35 (0.80–2.26)
3	8.7 (5.9–12.8)	8.6 [5.5–13.9]	1.70 (1.06–2.72)	0.027	1.86 (1.03–3.37)
4	10.3 (7.3–14.4)	8.0 [4.7–11.7]	1.71 (1.12–2.61)	0.013	1.71 (1.04–2.79)
5	15.2 (9.9–22.6)	4.9 [1.6–8.8]	2.84 (1.77–4.56)	<0.001	2.71 (1.67–4.41)
Composite Disability Outcome ^c					
Disabled	11.7 (9.3–15.6)	6.7 [2.6–11.3]	1.80 (1.34–2.42)	<0.001	1.76 (1.26–2.44)
Non-Disabled	6.3 (5.4–7.5)	12.5 [6.2–NR] ^f	1.00 — Referent	—	1.00 — Referent

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^aAdjusted for age and sex.

^bMultivariable-adjusted for age, sex, type of cancer, time since cancer diagnosis (continuous), body mass index (continuous), smoking status, healthy eating index, weekly drinking, hypertension, diabetes, asthma, arthritis, myocardial infarction, stroke, congestive heart failure, hospitalization in the prior year, hemoglobin, albumin, and C-reactive protein, and weekly walking (ordinal).

^cDefined as self-reporting limitations in 3 of 5 functional limitations.

^d $h_{trend}=0.001$; the age and sex-adjusted hazard ratio and 95% CI for total number of functional difficulties as a continuous variable was 1.20 (1.10-1.30).

^e $P_{trend}<0.001$; the multivariable-adjusted hazard ratio and 95% CI for total number of functional difficulties as a continuous variable was 1.19 (1.09-1.29).

^fNR: not reached