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## Self-Reported Major Mobility Disability and Mortality among Cancer Survivors

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### Abstract

**Objective**—To quantify the prevalence of self-reported major mobility disability (SR-MMD) and its association with mortality in a nationally-representative sample of cancer survivors.

**Materials and Methods**—This study included patients with a history of cancer who participated in the National Health and Nutrition Examination Survey 1999–2010. SR-MMD was defined as self-reported difficulty or inability to walk a quarter of a mile. Vital status through December 15, 2011 was ascertained from the United States National Center for Health Statistics. Multivariable-adjusted Cox regression models were used to quantify the hazard ratio (HR) and 95% confidence interval (CI) between SR-MMD and mortality.

**Results**—The study included 1,458 cancer survivors who averaged 67.1 years of age. At baseline, 201 (13.7%) participants had SR-MMD. During a median follow-up of 4.7 years, 434 (29.8%) participants died. SR-MMD was independently associated with a higher risk of all-cause mortality [Hazard Ratio (HR): 2.15 (95% Confidence Interval (CI): 1.56 2.97);  $P < 0.001$ ] and cancer-specific mortality [HR: 2.49 (95% CI: 1.53 4.07);  $P < 0.001$ ]. The association between SR-MMD and all-cause mortality was not modified by age, sex, time since cancer diagnosis, body mass index, or comorbid health conditions.

**Conclusion**—SR-MMD is an easily ascertainable metric of physical function that is associated with a higher risk of mortality among cancer survivors. Integrating measures of physical function

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#### Conflicts of interest

The authors declare no conflicts of interest.

#### Author Contributions

Study concepts (JCB, MOH, MNH), study design (JCB, MOH, MNH), data acquisition (JCB, MOH), quality control of data and algorithms (JCB, MOH, MNH), data analysis and interpretation (JCB, MOH, MNH), statistical analysis (JCB, MOH), manuscript preparation (JCB), manuscript editing (MOH, MNH), manuscript review (JCB, MOH, MNH).

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may help to guide clinical decision-making and improve long-term prognostication in this population. Interventions that prevent the development of SR-MDD, such as physical activity, should be evaluated in this population.

### Keywords

Physical function; Ambulation; Patient reported outcome; Survival; Physical activity

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## INTRODUCTION

Physical function is an important determinant of health-related quality-of-life among cancer survivors.<sup>1</sup> After a diagnosis of cancer, physical function deteriorates at an accelerated rate compared to that of age-matched cancer-free individuals.<sup>2</sup> It is hypothesized that cancer and its treatments impair the cardiovascular, pulmonary, neurologic, and musculoskeletal systems that are required to sustain adequate physical function.<sup>3,4</sup> Consequently, 57–66% of cancer survivors report at least one functional limitation, and many of these limitations persist for years after completing cancer treatment.<sup>5–7</sup>

The ability to walk 400 meters (m, approximately a quarter of a mile) is an objective measure of functional independence,<sup>8</sup> and predicts the ability to safely ambulate in the community.<sup>9</sup> Major mobility disability (MMD) is defined as the inability to walk 400 m without the use of a walker (use of a cane is acceptable).<sup>10</sup> MMD is prognostic of several important outcomes in older adults, including all-cause mortality and incident cardiovascular disease.<sup>11</sup> Despite the importance of objectively defined MMD, implementing the 400 m walk in practice may not be feasible given the need for a walking course of considerable length and dedicated staff time for in-person supervision.<sup>12</sup> To circumvent this issue, self-reported difficulty or inability to walk a quarter of a mile was validated as a proxy for objectively defined MDD.<sup>13,14</sup>

Given the unique functional consequences of cancer and its treatments, and the validation of self-reported MDD (SR-MMD), this study aimed to achieve four objectives using a nationally-representative sample of cancer survivors. The first goal was to estimate the prevalence of SR-MMD among community-dwelling cancer survivors in the United States (US). Second, we sought to quantify the association between SR-MMD and all-cause and cancer-specific mortality. Third, we aimed to quantify the association between SR-MMD and all-cause mortality within specific subgroups. Our fourth and final goal was to assess whether there is evidence of a dose-response between self-reported degree of difficulty walking one quarter of a mile and all-cause and cancer-specific mortality.

## MATERIALS and METHODS

### Study Design

The National Health and Nutrition Examination Surveys (NHANES) are a series of consecutive cross-sectional studies designed to provide health information on a nationally-representative sample of non-institutionalized United States civilians. Participants reside in counties across the country, fifteen of which are visited annually. The current analysis used

six consecutive cycles of NHANES data from 1999 to 2010. The study protocol 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

NHANES participants included were males and females, aged  $\geq 21$  years, with a self-reported history of cancer (excluding non-melanoma skin cancer). Participants were also required to have the requisite measure necessary to define SR-MMD (described below).

### Self-Reported Major Mobility Disability

SR-MMD was defined using a single question that asked participants to report “By yourself and without any special equipment, how much difficulty do you have walking for a quarter of a mile (that is about 2 or 3 blocks)?” Participants were not explicitly advised what modalities are included in the term “special equipment.” Possible responses included: “no difficulty”, “some difficulty”, “much difficulty”, or “unable to do”. The two responses of “much difficulty” and “unable to do” is validated to define the presence of SR-MMD.<sup>13</sup>

### Mortality Outcome

The primary outcome of this study was all-cause mortality, defined as the time from assessment of SR-MMD to death from any cause. The secondary study outcome was cancer-specific mortality, defined as the time from assessment of SR-MMD to death attributable to cancer. Vital status was identified using the National Death Index database on December 31, 2011. Participants were linked to the National Death Index database using a probabilistic matching algorithm that included 12 identifiers, such as Social Security Number, sex, date of birth, race, state of residence, and marital status.<sup>15</sup>

### Covariates

Demographic information including date of birth and sex, race, annual household income, and clinical information, including type of cancer, date of cancer diagnosis, and smoking history were ascertained from standardized participant questionnaires. Body mass index (BMI; kilograms (kg) per meter (m) squared;  $\text{kg}/\text{m}^2$ ) was calculated using participant height (m) and weight (kg), as measured by a study technician, and then categorized as underweight, normal weight, overweight, and obese using the World Health Organization definitions.<sup>16</sup> Participation in any physical activity was defined as self-reported engagement in at least one bout of moderate- or vigorous-intensity physical activity of  $\geq 10$  minutes in duration within the past month. Self-rated health status was assessed using the first question of the SF-36 questionnaire.<sup>17</sup> The presence of comorbid health conditions was ascertained from participant responses to the question of whether a doctor had ever told them that they had any of the following: type 2 diabetes mellitus, myocardial infarction, stroke, and/or congestive heart failure.

## Statistical Analysis

Descriptive variables are presented as means and standard errors for continuous variables and percentages for categorical variables. We fit multivariable logistic regression models to estimate the Odds Ratio (OR) and 95% Confidence Interval (CI) to determine demographics and clinical characteristics that were associated with cohort inclusion. We fit Cox proportional hazards regression models to estimate the Hazard Ratio (HR), and 95% CI for SR-MMD and the time-to-death outcomes. Models were first adjusted for sex and age (model 1) and then fully adjusted for demographic, behavioral, and clinical characteristics (model 2). The assumption of proportional hazards was confirmed using log-log plots. We incorporated a statistical interaction term into the regression models to determine if the observed associations were modified by certain a priori designated patient and clinical characteristics, with these results presented as subgroup analyses to facilitate interpretation. Sample weights were integrated into all statistical analyses to account for nonresponse bias, multistage sampling probabilities, and the subpopulation of participants that were included in this analysis. Sensitivity analyses were conducted to quantify the strength that an unmeasured confounder would have to exert to explain the observed associations.<sup>18</sup>  $P < 0.05$  (two-sided) was considered to indicate statistical significance. Stata/SE v.15.1 statistical software was used for all analyses.

## RESULTS

### Participant Characteristics

A total of 2,992 adults aged  $\geq 21$  years self-reported a prior diagnosis of cancer, and sufficient information to define SR-MMD was available on 1,458 (48.7%). The 1,458 cancer survivors in this analysis were older [OR: 1.08 (95% CI: 1.06 1.09);  $P < 0.001$ ], less likely to have melanoma [OR: 0.54 (95% CI: 0.33 0.88);  $P = 0.013$ ], less likely to report a myocardial infarction [OR: 0.69 (95% CI: 0.48 0.99);  $P = 0.045$ ], and less likely to report congestive heart failure [OR: 0.50 (95% CI: 0.33 0.76);  $P = 0.002$ ] when compared to the 1,534 cancer survivors who were excluded from this analysis. No other reported variables were predictive of participant inclusion.

Among 1,458 cancer survivors, age ranged from 21 to 85 years (Table 1). Most participants reported a history of breast (23.7%), genitourinary (22.7%), gynecologic (15.7%) or gastrointestinal (10.9%) cancer. Time since cancer diagnosis ranged from zero to 78 years. Approximately one-third of participants were within five years of their cancer diagnosis (33.7%). Most participants were overweight (40.9%) or obese (28.4%). BMI ranged from 15.2 to 65.5 kg/m<sup>2</sup>.

### Association Between Self-Reported Major Mobility Disability and Mortality

At baseline, 201 (13.7%) participants had SR-MMD. During a median follow-up of 4.7 years [interquartile range 2.7 7.9], 434 (29.8%) participants died from all-causes, and 174 died from cancer (11.9%).

SR-MMD was independently associated with a higher risk of all-cause mortality [HR: 2.15 (95% CI: 1.56 2.97);  $P < 0.001$ ; Table 2; Figure 1]. In sensitivity analysis, the minimum

strength of association, on the HR scale, independent of all other variables, that an unmeasured confounder must have with SR-MMD and all-cause mortality to fully attenuate the observed association with SR-MMD would be 2.78. There was a dose-response association between the degree of difficulty reported in walking one quarter of a mile and all-cause and all-cause mortality ( $P_{\text{trend}} < 0.001$ ; Figure 2).

SR-MMD was independently associated with cancer-specific mortality [HR: 2.49 (95% CI: 1.53 4.07);  $P < 0.001$ ]. In sensitivity analysis, the minimum strength of association, on the HR scale, independent of all other variables, that an unmeasured confounder must have with SR-MMD and cancer-specific mortality to fully attenuate the observed association with SR-MMD would be 3.15. There was a dose-response association between degree of difficulty walking one quarter of a mile and cancer-specific mortality ( $P_{\text{trend}} < 0.001$ ).

### Subgroup Analyses

In pre-planned exploratory subgroup analyses, age, sex, time since cancer diagnosis, BMI, and comorbid health conditions did not modify the association between SR-MMD and all-cause mortality (Table 3).

## DISCUSSION

In this nationally-representative sample, more than one-in-seven cancer survivors had SR-MMD. SR-MMD was associated with a higher risk of all-cause and cancer-specific mortality. There was a dose-response association between difficulty walking a quarter of a mile and mortality, such that as reported difficulty increases, mortality risk increases proportionally. These data support the hypothesis that self-reported physical function represents vital information that may be useful in clinical decision-making and prognostication.<sup>19</sup>

These findings are consistent with prior studies that have demonstrated that self-reported physical function and frailty predict mortality in cancer survivors.<sup>5,20–22</sup> In a cohort of 428 cancer survivors, self-reported disability (defined as having 3 functional limitations in activities of daily living) was associated with a significantly slower measured gait speed (0.28 m/s) and independently associated with a 76% higher risk of death when compared to participants without self-reported disability.<sup>5</sup> Physical function is a central determinant of quality-of-life,<sup>1</sup> and predicts chemotherapy toxicity in older adults.<sup>23–26</sup> Prior studies of cancer survivors observe maximal cardiopulmonary capacities that are 27% below age-matched healthy sedentary controls,<sup>27</sup> and it is estimated that 10% have cardiopulmonary capacities that are insufficient for independent functioning.<sup>28</sup> Similar patterns have been observed for muscle strength and muscle mass.<sup>29</sup> The accumulation of these and other physiologic impairments among cancer survivors likely underlie many of the functional impairments observed in this population.

Despite the importance of preserving physical function in cancer survivors, few therapeutic options exist and there is no standard of care for its management.<sup>30,31</sup> Participation in physical activity is one of the strongest predictors of physical function among older adults without a history of cancer.<sup>32,33</sup> In a phase II randomized clinical trial among 428 older

adults at risk for mobility disability, a structured moderate-intensity physical activity program significantly improved surrogate measures of MMD, including short physical performance battery score and gait speed.<sup>34</sup> The confirmatory phase III clinical trial among 1,635 older adults demonstrated that physical activity reduced the incidence of MMD by 18% over a median of 2.6-years.<sup>35</sup> Evidence from randomized clinical trials in cancer survivors demonstrates that slowly-progressive weight lifting exercise prevents the definitive deterioration of self-reported physical function by 51% over 12-months.<sup>36</sup> A combination of dietary modification, weight loss, and aerobic exercise was shown to attenuate the rate of decline in physical function in older overweight and obese survivors of colorectal, breast, and prostate cancer.<sup>37,38</sup>

The main strength of this study is the complex probability sample, which makes our inferences generalizable to the population of community-dwelling cancer survivors living within the United States. There are also several limitations to this study. We did not have data on stage of cancer at the time of diagnosis and the receipt of any cancer-directed treatments, such as surgery, chemotherapy, and radiation. It is possible that the inclusion of these variables would shift our effect size estimates towards the null. Our sensitivity analyses suggested that an unmeasured confounder would need to be large (HR of 2.9–3.3) to explain away the observed associations. Further, though it is possible that SR-MMD may differentially associate with mortality by cancer site, we did not have sufficient sample size to conduct meaningful subgroup analyses stratified by primary cancer site. Also, SR-MMD was a single cross-sectional measurement, therefore, we were unable to determine the onset of SR-MMD, and it is possible that some participants had SR-MMD prior to their cancer diagnosis. Nonetheless, these data suggest the SR-MMD is relatively common and prognostic of poor outcomes among cancer survivors.

In conclusion, our study supports SR-MMD as a predictor of mortality among cancer survivors. We observed a dose-response association between reported difficulty walking a quarter of a mile and mortality, such that as difficulty increases, mortality risk increases proportionally. This simple, easily ascertainable metric may be useful to guide clinical prognostication, and justifies the design of prospective randomized trials to prevent the development of MMD in this vulnerable and expanding population.

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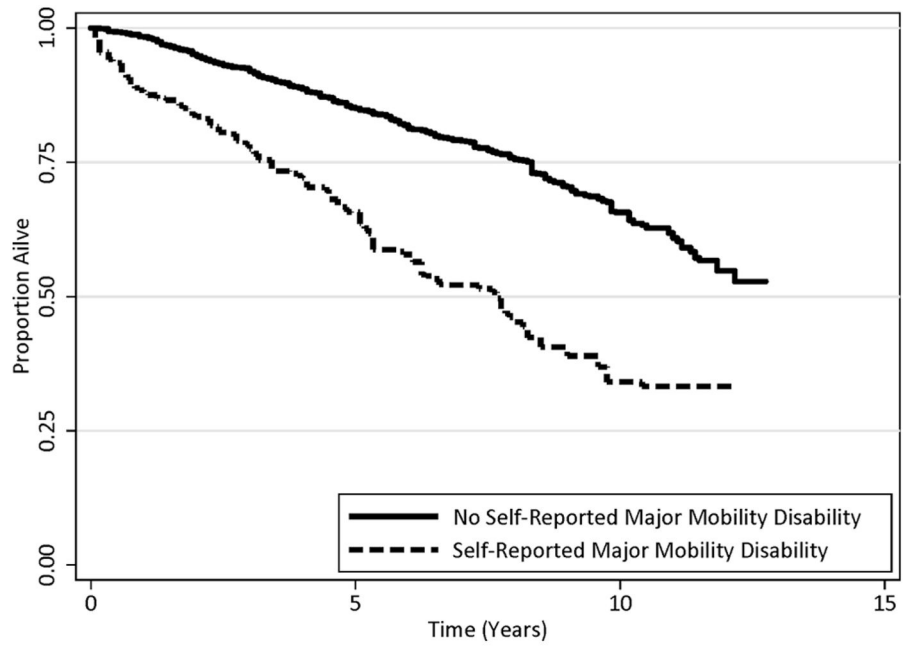
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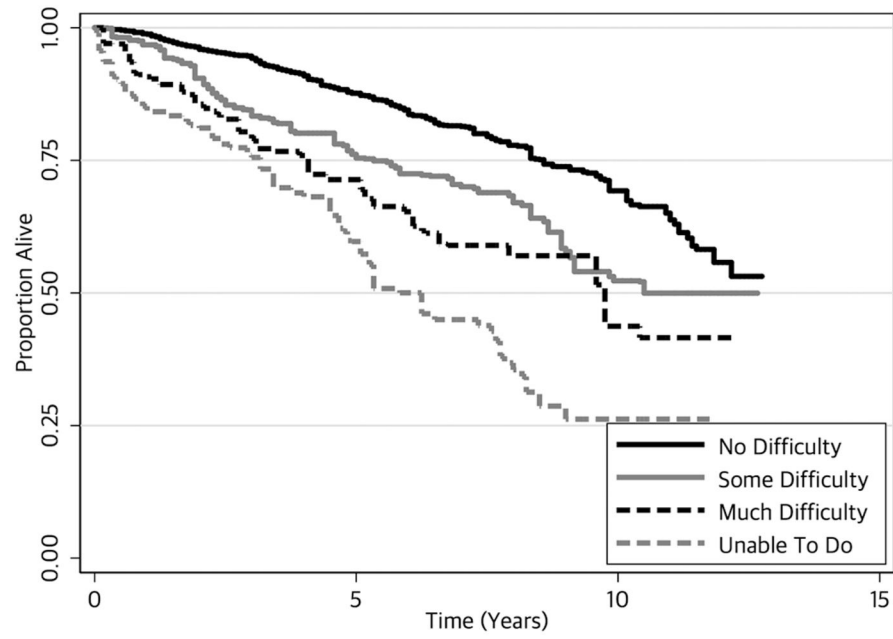
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**Figure 1.** Kaplan-Meier all-cause survival estimates, by self-reported major mobility disability



**Figure 2.** Kaplan-Meier all-survival estimates, by self-reported degree of difficulty walking one quarter of a mile.

**Table 1**

Demographic and clinical characteristics (N=1,458)

Characteristic	Mean ± Standard Error or N (%)
Age, years	67.1±0.5
Sex	
Male	41.7%
Female	58.3%
Race and ethnicity	
Non-Hispanic White	84.5%
Non-Hispanic Black	7.4%
Other	8.1%
Annual household income	
<\$25,000	31.2%
\$25,000 \$74,999	46.5%
\$75,000	11.3%
Refused, unknown, missing	11.0%
Type of cancer	
Breast	23.7%
Gastrointestinal	10.9%
Genitourinary	22.7%
Gynecologic	15.7%
Lung/Thoracic	5.6%
Hematologic	4.4%
Melanoma	7.8%
Other/Don't know	9.3%
Time since cancer diagnosis, years	
Mean (continuous)	10.8±0.4
<5	33.7%
5—10	25.3%
10	41.0%
Body mass index, kg/m <sup>2</sup>	
Mean (continuous)	28.1±0.2
<18.5	2.4%
18.5—24.9	28.3%
25.0—29.9	40.9%
30.0	28.4%
Smoking	
Never	41.6%
Former	43.5%
Current	14.8%

Characteristic	Mean $\pm$ Standard Error or <i>N</i> (%)
Physical activity, past month	34.7%
Self-rated health status	
Excellent	7.6%
Very good	27.4%
Good	41.5%
Fair	18.4%
Poor	5.1%
Conditions	
Type 2 diabetes	13.3%
Myocardial infarction	8.7%
Stroke	7.2%
Congestive heart failure	6.0%

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**Table 2**  
Association of walking difficulty and self-reported major mobility disability with mortality

	No. of Events/No. at Risk	Death Rate per 100 Person-Years	Age & Sex Adjusted		Multivariable Adjusted <sup>a</sup>	
			HR (95% CI)	P	HR (95% CI)	P
<b>All-Cause Mortality</b>						
<b>Self-Reported Major Mobility Disability</b>						
No	329/1,257	3.7 (3.3—4.3)	1.00	—	1.00	—
Yes <sup>b</sup>	105/201	9.5 (7.4—12.1)	2.74 (2.08—3.61)	<0.001	2.15 (1.56—2.97)	<0.001
<b>Walking for a quarter mile difficulty</b>						
No difficulty	238/975	3.3 (2.8—3.9)	1.00	—	1.00	—
Some difficulty	91/282	5.5 (4.3—7.2)	1.80 (1.34—2.41)	<0.001	1.59 (1.16—2.17)	0.004
Much difficulty	47/106	7.5 (5.2—11.0)	2.72 (1.90—3.90)	<0.001	2.34 (1.52—3.60)	<0.001
Unable to do	58/95	11.8 (8.7—16.1)	3.64 (2.36—5.51)	<0.001	2.70 (1.68—4.34)	<0.001
<b>Cancer-Specific Mortality</b>						
<b>Self-Reported Major Mobility Disability</b>						
No	134/1,257	1.6 (1.3—2.0)	1.00	—	1.00	—
Yes <sup>b</sup>	40/201	4.0 (2.7—6.0)	2.76 (1.87—4.10)	<0.001	2.49 (1.53—4.07)	<0.001
<b>Walking for a quarter mile difficulty</b>						
No difficulty	100/975	1.3 (1.0—1.7)	1.00	—	1.00	—
Some difficulty	34/282	2.6 (1.7—4.1)	2.15 (1.39—3.32)	0.001	2.07 (1.30—3.28)	0.002
Much difficulty	24/106	4.1 (2.5—7.1)	3.52 (2.15—5.77)	<0.001	3.60 (1.97—6.56)	<0.001
Unable to do	16/95	3.9 (2.1—7.6)	3.24 (1.72—6.11)	<0.001	2.98 (1.50—5.94)	0.002

HR, hazard ratio; CI, confidence interval.

<sup>a</sup>Multivariable adjusted for age, sex, race, annual household income, type of cancer, time since cancer diagnosis, body mass index, physical activity, self-rated health status, type 2 diabetes, myocardial infarction, stroke, and congestive heart failure.

<sup>b</sup>Defined as walking for a quarter mile difficulty as “much difficulty” or “unable to do”

**Table 3**  
Association of self-reported major mobility disability with all-cause mortality, by subgroup

Subgroup	Age & Sex Adjusted HR (95% CI)	P	P interaction
Age, years			0.921
70	2.79 (1.51 5.15)	0.001	
>70	2.75 (1.97 3.82)	<0.001	
Sex			0.865
Male	2.69 (1.78 4.08)	<0.001	
Female	2.80 (1.92 4.08)	<0.001	
Time since cancer diagnosis, years			0.414
7	2.91 (2.56 3.32)	<0.001	
>7	2.54 (1.68 3.84)	<0.001	
Body mass index, kilograms per meter squared (kg/m <sup>2</sup> )			0.380
<30	2.87(2.17 3.80)	<0.001	
30	2.23 (1.02 4.89)	<0.001	
Conditions			0.060
0	2.81 (2.03 3.88)	<0.001	
1	4.02 (2.39 6.77)	<0.001	

HR, hazard ratio; CI, confidence interval.