# Physical function as a prognostic biomarker among cancer survivors

J C Brown*,[1], M O Harhay[1] and M N Harhay[1,2]

[1]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 423 Guardian Drive, 8th Floor, Blockley Hall, Philadelphia, PA 19104, USA and [2]Renal-Electrolyte and Hypertension Division, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

**Background:** We tested the hypothesis that objectively measured physical function predicts mortality among cancer survivors.

**Methods:** We assessed objectively measured physical function including the short physical performance battery (SPPB) and fast walk speed in older adult cancer survivors.

**Results:** Among 413 cancer survivors, 315 (76%) died during a median follow-up of 11.0 years. In multivariable-adjusted analyses, each 1-unit increase in the SPPB score and $0.1\,\mathrm{m\,s^{-1}}$ increase in fast walk speed predicted a 12% reduction in mortality (hazard ratio (HR): 0.88 (95% confidence interval (CI): 0.82–0.94); $P<0.001$, and HR: 0.88 (95% CI: 0.82–0.96); $P=0.003$, respectively).

**Conclusions:** Objectively measured physical function may predict mortality among cancer survivors.

Despite improvements in cancer survival rates (DeSantis et al, 2014), cancer survivors frequently experience deleterious sequela resulting from treatment including impairments in the cardiovascular, pulmonary, neurologic, and musculoskeletal systems (Jones et al, 2009). Normally, these physiologic systems work in concert to enable physical function, and when one system is compromised, other systems may compensate (Dickinson et al, 2000, Ferrucci et al, 2000). However, when multiple physiologic systems are simultaneously compromised, patients are more likely to manifest impairments in physical function (Ferrucci et al, 2000), resulting in increased susceptibility to adverse health outcomes, such as premature mortality (Guralnik et al, 1994; Studenski et al, 2011). In this context, quantifying physical function status after cancer treatment may provide important insights to clinicians on the health, vitality, and prognosis of cancer survivors.

We tested the hypothesis that objectively measured physical function metrics, including the short physical performance battery (SPPB; Guralnik et al, 1994) and fast walk speed (Studenski et al, 2011), are capable of quantifying health and vitality by prognosticating premature mortality among a population-based sample of cancer survivors.

## MATERIALS AND 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 civilians living within the United States (Center for Disease Control, 1994). All participants provided written informed consent before participating in any study-related activities.

**Study participants.** Participants aged ≥60 years were invited to complete an evaluation that included objective measures of physical function (Ostchega et al, 2000). We identified 4809 participants who completed the requisite physical function measures, 413 (9%) of whom reported a prior diagnosis of non-skin-related cancer.

**Objective measures of physical function.** The physical function exam used in NHANES III was a modified version of the SPPB (Ostchega et al, 2000). The SPPB is a series of three objective measures that quantify balance, lower-extremity strength, and gait among older adults (Guralnik et al, 1994). Each of the three SPPB

| Table 1. Demographic and clinical characteristics, stratified by survival status[a] | | | | |
|---|---|---|---|---|
| | | **Died during follow-up** | | |
| **Characteristics** | **Overall (n = 413) (mean (s.e.) or n (%))** | **Yes (n = 315)** | **No (n = 98)** | **P-value** |
| Age (years) | 72.2 (0.47) | 74.4 (0.56) | 66.9 (0.61) | <0.001 |
| Sex | | | | <0.001 |
|     Male | 40.0% | 48.4% | 19.5% | |
|     Female | 60.0% | 51.6% | 80.5% | |
| Type of cancer | | | | 0.012 |
|     Breast | 26.6% | 24.4% | 31.8% | |
|     Genitourinary | 20.7% | 24.0% | 12.4% | |
|     Gastrointestinal | 18.4% | 19.6% | 15.4% | |
|     Gynaecologic | 13.7% | 10.3% | 21.9% | |
|     Lung | 3.4% | 4.8% | 0.0% | |
|     Haematologic | 2.5% | 1.5% | 5.0% | |
|     Other, missing, or cannot remember | 14.7% | 15.3% | 13.4% | |
| Time since cancer diagnosis (years) | | | | |
|     Mean (continuous) | 10.7 (0.64) | 10.1 (0.70) | 12.3 (1.39) | 0.151 |
|     <5 | 35.5% | 37.1% | 31.5% | 0.361 |
|     5–10 | 21.9% | 23.2% | 18.7% | |
|     ≥10 | 42.6% | 39.7% | 49.8% | |
| Body mass index (kg m$^{-2}$) | | | | |
|     Mean (continuous) | 25.8 (0.30) | 25.7 (0.35) | 26.1 (0.59) | 0.554 |
|     <18.5 | 3.1% | 4.4% | 0.0% | 0.380 |
|     18.5–24.9 | 43.8% | 42.6% | 46.6% | |
|     25.0–29.9 | 35.1% | 35.0% | 35.4% | |
|     ≥30.0 | 18.0% | 18.0% | 18.0% | |
| Smoking status, n (%) | | | | |
|     Never | 43.4% | 43.0% | 44.5% | 0.703 |
|     Former | 45.4% | 46.8% | 42.0% | |
|     Current | 11.2% | 10.2% | 13.5% | |
| Healthy eating index | 69.6 (0.86) | 68.2 (0.96) | 72.5 (1.73) | 0.035 |
| No. of alcoholic drinks consumed in past week | 1.1 (0.15) | 0.9 (0.16) | 1.6 (0.31) | 0.046 |
| Comorbid health conditions | | | | |
|     Hypertension | 46.4% | 46.0% | 47.2% | 0.872 |
|     Diabetes | 10.3% | 12.4% | 5.3% | 0.110 |
|     Hyperlipidaemia | 33.8% | 28.9% | 45.9% | 0.014 |
|     Asthma | 6.3% | 8.0% | 2.2% | 0.108 |
|     Arthritis | 44.8% | 45.1% | 44.0% | 0.878 |
|     Myocardial infarction | 15.3% | 20.0% | 4.0% | <0.001 |
|     Stroke | 6.7% | 8.6% | 2.1% | 0.023 |
|     Congestive heart failure | 6.2% | 7.1% | 4.1% | 0.367 |
| Hospitalisation(s) in past year, n (%) | 29.1% | 31.5% | 23.2% | 0.211 |
| Haemoglobin (g dl$^{-1}$) | 13.5 (0.08) | 13.6 (0.10) | 13.5 (0.13) | 0.702 |
| Albumin (g dl$^{-1}$) | 4.0 (0.02) | 4.0 (0.02) | 4.1 (0.04) | 0.271 |
| C-reactive protein (mg l$^{-1}$) | 0.6 (0.05) | 0.6 (0.06) | 0.4 (0.08) | 0.031 |
| Self-reported health | 50.1 (1.78) | 45.9 (1.97) | 60.5 (3.42) | <0.001 |
| No. of bouts of walking in past week | | | | |
|     0 | 74.3% | 80.5% | 59.2% | 0.004 |
|     1–3 | 7.6% | 5.7% | 12.2% | |
|     ≥3 | 18.1% | 13.8% | 28.6% | |
| Short physical performance battery | | | | |
|     Mean (continuous) | 9.1 (0.14) | 8.6 (0.18) | 10.2 (0.20) | <0.001 |
|     ≤6 | 13.9% | 18.5% | 2.6% | <0.001 |
|     7–9 | 33.6% | 35.8% | 28.1% | |
|     ≥10 | 52.5% | 45.7% | 69.3% | |
| Fast walk speed (m s$^{-1}$) | | | | |
|     Mean (continuous) | 0.72 (0.01) | 0.67 (0.02) | 0.82 (0.02) | <0.001 |
|     <0.6 | 26.7% | 34.1% | 8.5% | <0.001 |
|     ≥0.6 | 73.3% | 65.9% | 91.5% | |
| [a]Continuous variables are mean (s.e.) and categorical variables are column percentages. | | | | |

measures is scored from 0 to 4, with higher scores indicating greater physical function. Each of the three individual SPPB scores is aggregated to derive a summary SPPB score, ranging from 0 to 12, with higher scores indicating greater physical function. Modifications to the SPPB used in NHANES III did not include the side-by-side and semi-tandem balance tests (assessing only full-tandem balance), and measured gait speed at a pace twice that of the usual walking speed (*vs* usual speed), referred to herein as fast walk speed. Fast walk speed alone has been shown to predict outcomes similarly to the full SPPB battery (Guralnik *et al*, 2000). Therefore, in addition to examining the prognostic relationship between the SPPB and mortality, we also examined the prognostic relationship between fast walk speed alone and mortality. Fast walk speed was quantified in units of $m\,s^{-1}$. Additional information about the objective measures of physical function is provided in the online Supplementary Methods.

**Mortality outcome.** The primary outcome of this study was all-cause mortality. Vital status was identified using the National Death Index database through 31 December 2006 (National Center for Health Statistics, 2006). Additional information about the mortality outcome is provided in the online Supplementary Methods.

**Covariates.** Detailed information for all study covariates is provided in the online Supplementary Methods.

**Statistical analysis.** We fit Cox proportional hazards regression models to estimate the hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality by varying levels of physical function.

The SPPB score was examined as a categorical and continuous variable in separate regression models. The categorical SPPB score variable classified participants into one of three groups: $\leqslant 6$, 7–9, and $\geqslant 10$, to denote increasing levels of physical function, respectively. This categorisation schema predicts limitations in activities of daily living and mobility-related disability among older adults (Guralnik *et al*, 1995). The continuous SPPB score is presented for each 1-unit increase to reflect a clinically meaningful change in physical function (Perera *et al*, 2006).

Fast walk speed was examined as a categorical and continuous variable in separate regression models. The categorical fast walk speed variable classified participants into one of two groups: $<0.6\,m\,s^{-1}$ or $\geqslant 0.6\,m\,s^{-1}$ to denote slow and fast walk speed, respectively. This categorisation schema predicts dependency in activities of daily living, self-reported health status, and frequency of hospitalisation among older adults (Studenski *et al*, 2003). The continuous fast walk speed variable is presented for each $0.1\,m\,s^{-1}$ increase, which is acknowledged to reflect a clinically meaningful change in physical function (Perera *et al*, 2006). Additional information about the statistical analysis is provided in the online Supplementary Methods.

## RESULTS

**Characteristics associated with mortality.** Among 413 cancer survivors, we observed 315 deaths during a median of 11.0 years of follow-up. Participant characteristics are depicted overall and stratified by vital status (Table 1).

**Objective physical function and all-cause mortality.** Median survival was 10.5 and 13.4 years in the groups with an SPPB score of 7–9 and $\geqslant 10$, respectively, as compared with 5.0 years in the group with an SPPB score of $\leqslant 6$ (Figure 1A). In multivariable-adjusted analyses, an SPPB score of 7–9 and $\geqslant 10$ predicted a 43% (HR: 0.57 (95% CI: 0.37–0.89); $P = 0.014$) and a 50% (HR: 0.50 (95% CI: 0.32–0.77); $P = 0.001$) reduction in the risk of premature mortality, relative to an SPPB score of $\leqslant 6$ (Table 2). As a
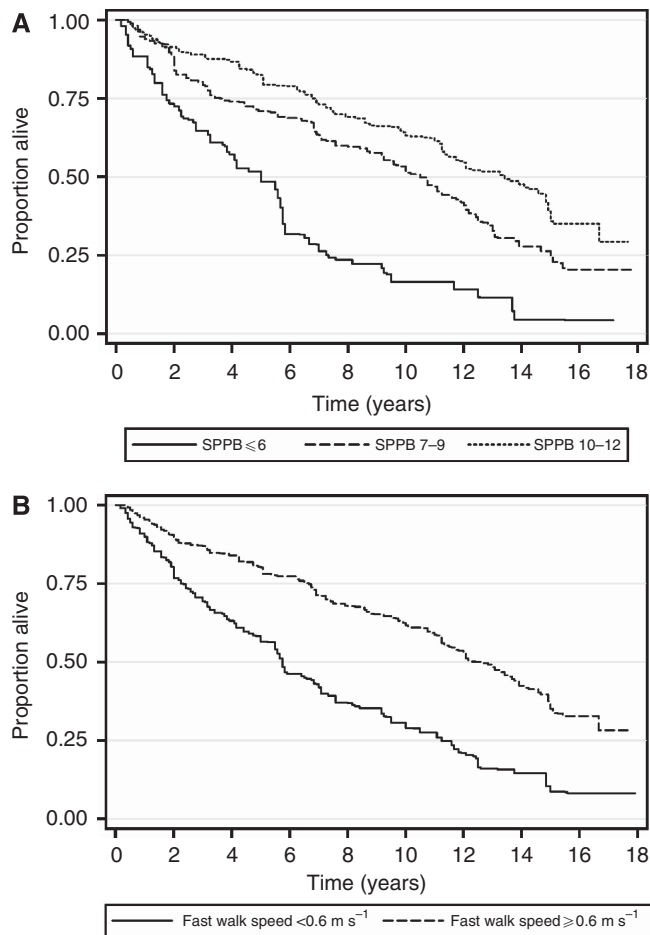


Figure 1. Kaplan–Meier survival plot, stratified by Category of Physical Function for (**A**) short physical performance battery (SPPB) and (**B**) fast walk speed.

continuous variable, each 1-unit increase in the SPPB score predicted a 12% reduction in the risk of premature mortality (HR: 0.88 (95% CI: 0.82–0.94); $P < 0.001$).

Median survival was 12.6 years in the group with a fast walk speed $\geqslant 0.6\,m\,s^{-1}$, as compared with 5.8 years in the group with a fast walk speed $<0.6\,m\,s^{-1}$ (Figure 1B). In multivariable-adjusted analyses, a fast walk speed $\geqslant 0.6\,m\,s^{-1}$ predicted a 34% reduction in the risk of premature mortality, relative to a fast walk speed $<0.6\,m\,s^{-1}$ (HR: 0.66 (95% CI: 0.47–0.93); $P = 0.019$). As a continuous variable, each $0.1\,m\,s^{-1}$ increase in fast walk speed predicted a 12% reduction in the risk of premature mortality (HR: 0.88 (95% CI: 0.82–0.96); $P = 0.003$).

The tests of interaction between objective physical function and mortality by cancer type are provided in the online Supplementary Results. The discriminative capacity of objective physical function to predict 5- and 10-year mortality is provided in the online Supplementary Results.

## DISCUSSION

The principal finding of this study is that cancer survivors with higher levels of physical function are less likely to die prematurely, relative to cancer survivors with lower levels of physical function. Our findings provide evidence that objectively measured physical function may be a useful biomarker to quantify the health and vitality of cancer survivors by prognosticating premature mortality.

**Table 2. Association between physical function and all-cause mortality**

| Performance measures | No. of participants | HR and 95% CI | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model 1[a] | P-value | Model 2[b] | P-value | Model 3[c] | P-value |
| **Short physical performance battery** | | | | | | | |
| Categorical | | | | | | | |
| ≤6 | 84 | 1.00 | | 1.00 | | 1.00 | |
| 7–9 | 159 | 0.43 (0.29–0.65) | <0.001 | 0.55 (0.40–0.76) | <0.001 | 0.57 (0.37–0.89) | 0.014 |
| 10–12 | 170 | 0.29 (0.19–0.43)[d] | <0.001 | 0.43 (0.30–0.61)[d] | <0.001 | 0.50 (0.32–0.77)[d] | 0.001 |
| Continuous, per 1-unit increase | 413 | 0.81 (0.77–0.86) | <0.001 | 0.87 (0.83–0.92) | <0.001 | 0.88 (0.82–0.94) | <0.001 |
| **Fast walk speed** | | | | | | | |
| Categorical | | | | | | | |
| <0.6 m s$^{-1}$ | 153 | 1.00 | | 1.00 | | 1.00 | |
| ≥0.6 m s$^{-1}$ | 260 | 0.42 (0.31–0.59) | <0.001 | 0.58 (0.44–0.76) | <0.001 | 0.66 (0.47–0.93) | 0.019 |
| Continuous, per 0.1 m s$^{-1}$ increase | 413 | 0.82 (0.77–0.88) | <0.001 | 0.87 (0.82–0.93) | <0.001 | 0.88 (0.82–0.96) | 0.003 |

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Model 1 is unadjusted.
[b]Model 2 is adjusted for age and sex.
[c]Model 3 is adjusted for age, sex, body mass index (continuous), type of cancer, time since cancer diagnosis (continuous), smoking status, healthy eating index, weekly drinking, hypertension, diabetes, asthma, arthritis, myocardial infarction, stroke, congestive heart failure, hospitalisation in the prior year, self-reported health status, weekly walking (ordinal), haemoglobin, albumin, and C-reactive protein.
[d]Test for linear trend of ordered categories: $P_{trend} < 0.002$.

Lifestyle behaviour modification such as physical activity, weight loss, and eating a healthful diet may preserve or improve the physiologic systems necessary to sustain physical function. Participation in physical activity preserves fast walk speed, improves SPPB, and delays the onset of major mobility disability among older adults (LIFE Study Investigators et al, 2006, Pahor et al, 2014). Coupled with physical activity, weight loss and eating a healthful diet are efficacious to improve physical function among older breast, prostate, and colon cancer survivors (Demark-Wahnefried et al, 2006; Morey et al, 2009). The promotion of lifestyle behaviours that include physical activity, weight management, and healthful eating are important among cancer survivors, as they may translate to improvements in patient-reported and clinical outcomes (Demark-Wahnefried et al, 2012; Rock et al, 2012).

One weakness of this study is the absence of information in this cohort relating to the stage of cancer and type of treatment received. A second weakness is the use of self-reported clinical and comorbidity information. Inaccurate clinical information or undiagnosed comorbidity may bias our results. For example, it has been reported that for each known case of diabetes, there exists one undiagnosed case (Dunstan et al, 2002). A third weakness is the limited sample size of cancer-specific subgroups. Future studies will require larger samples to examine the prognostic impact of physical function among cancer-specific subgroups. Although it is unlikely that stage of cancer or type of treatment interact with the prognostic importance of physical function (Klepin et al, 2010; Cesari et al, 2013), we had insufficient data to corroborate this finding in our data set. A fourth weakness is that physical function was a cross-sectional measurement in this cohort. Declines in longitudinally measured self-reported physical function associate with mortality among breast cancer survivors (Sehl et al, 2013). Conversely, a major strength of this study was the population-based sampling framework of NHANES, which permitted our analyses to represent community-dwelling older adult cancer survivors in the United States.

In conclusion, physical function, quantified using the SPPB or fast walk speed, is a prognostic biomarker among older adult cancer survivors. This finding is consistent with the hypothesis that physical function possesses the capacity to synchronously describe the performance and coordination of various physiologic systems that may be impaired as a result of cancer treatment. Additional work is necessary to confirm the prognostic importance of this biomarker among cancer survivors and to establish an evidence base to support integrating physical function measures in the oncologic standard of care.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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