Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2021 April ; 30(4): 690–698. doi:10.1158/1055-9965.EPI-20-1473.

Ambulatory Function and Mortality among Cancer Survivors in the NIH-AARP Diet and Health Study

Elizabeth A. Salerno^{1,2,3}, Pedro F. Saint-Maurice³, Erik A. Willis⁴, Steven C. Moore³, Loretta DiPietro⁵, Charles E. Matthews³

¹Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St. Louis

²Cancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute

³Metabolic Epidemiology Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute

⁴Children's Healthy Weight Research Group, Center for Health Promotion and Disease Prevention, University of North Carolina

⁵Department of Exercise and Nutrition Sciences, Milken Institute School of Public Health, George Washington University

Abstract

Background: There is limited evidence describing associations between cancer and function in diverse cancer types and its relationship with mortality. We investigated the relationship between cancer and poor ambulatory function and associations between ambulatory function and subsequent mortality.

Methods: Participants included 233,135 adults (n=30,403 cancer; n=202,732 cancer-free) in the NIH-AARP Diet and Health Study (1994–1996) who self-reported ambulatory function (e.g., walking pace and mobility disability: being unable to walk or walking at the slowest pace) in 2004–2006. Participants were followed for mortality from the assessment of ambulatory function through 2011. Multinomial logistic regression quantified the association between cancer and ambulatory function. We then explored the independent effects of walking pace and mobility disability in cancer survivors, and the joint effects of both a cancer diagnosis and poor ambulatory function, on mortality using Cox proportional hazards models. Models explored type-specific associations across fifteen cancer types.

Results: Survivors had 42% greater odds of walking at the slowest pace [OR=1.42(CI=1.30–1.54)] and 24% greater odds of mobility disability [OR=1.24(CI=1.17–1.31)], compared to cancer-free participants, adjusting for baseline demographics, health indicators, and cancer type. Survivors reporting the slowest pace were at increased hazards than those who walked the fastest: all-cause [HR=2.22(CI=2.06–2.39)]; cancer mortality [HR=2.12(CI=1.83–2.45)]. Similar trends

emerged for mobility disability (HRs>1.64). All-cause mortality associations were significant for over nine cancer types.

Conclusions: A diagnosis of cancer is associated with poorer ambulatory function which is subsequently associated with increased mortality.

Impact: Widespread efforts should target ambulatory function during cancer survivorship for survival benefits.

Keywords

ambulatory function; survival; cancer survivorship; epidemiology

Introduction

Most individuals diagnosed with cancer are over the age of 50 years¹ and face a unique burden of both aging- and cancer-related symptoms, such as impaired physical function, worsened quality of life, and premature mortality². Ambulatory function, as indicated by walking pace and major mobility disability, is critical for independence into old age³ and often modifiable through behavior change such as increased physical activity.⁴ Functional impairments after diagnosis and treatment for cancer have been documented,^{5–9} but much of this work has focused on a limited number of cancer types^{10–13}, less than two years of follow-up since diagnosis^{5,6,11–13}, and used objective measures of function.⁹ More recently, Bluethmann and colleagues⁹ noted that survivors of cancer are more likely to walk at slower paces and show signs of disability. However, critical gaps remain surrounding the cancer-function association, specifically the reliance on objective measures of function. Such assessments are robust and important for their contribution to our understanding of the cancer-function relationship; however, they are often costly and limiting to many. There is a need to develop broad surveillance tools during cancer survivorship to identify those most in need of functional intervention. Further, it is no longer only the ‘big four’ cancer survivors who are living longer,¹⁴ yet there remains a paucity of evidence for differences in ambulatory function between the general population and survivors of rarer cancer types, as well as how long these differences may persist beyond the acute phase of diagnosis and treatment.

Poor ambulatory function has been consistently associated with worsened survival in healthy older adults.^{15–17} A pooled analysis from 9 large cohorts identified increased mortality with slower walking pace in adults over 65 years of age.¹⁶ Ambulatory function has often been referred to as the “sixth vital sign” given its validated and prognostic value for its functional perspective on health status.¹⁸ Such function-survival associations appear to extend to cancer survivors, as some work has identified increased risk of mortality with slower walking speeds.^{19–23} However, little has been done to investigate mortality risk by ambulatory function for a variety of cancer types, an important consideration in directing more precise interventions to promote functional health and longevity during survivorship.²⁴

To address these evidence gaps across fifteen different cancer types, we examined: (1) if a diagnosis of cancer is associated with lower ambulatory function and; (2) the independent

effects of these functional domains on mortality in cancer survivors specifically, as well as the joint effects of both a cancer diagnosis and poor ambulatory function on mortality. We hypothesized that cancer survivors would be at increased risk of lower ambulatory function than cancer-free controls and that poor ambulatory function would be associated with increased risk of all-cause and cancer-specific mortality in cancer survivors.

Materials and Methods

Participants and Study Design.

The National Institutes of Health (NIH) – American Association of Retired Persons (AARP) Diet and Health Study is a large prospective study of over 500,000 AARP members between the ages of 50 and 71 who responded to a baseline questionnaire assessing diet, medical history, and demographics in 1995–1996.²⁵ In 2004–2006, a follow-up questionnaire was sent to all surviving members of the cohort which assessed health status, lifestyle behaviors, body size and many other factors, including ambulatory function (response rate, 44%). Figure 1 describes the basic study design, including key data collection points and the mortality follow-up period. The NIH-AARP Diet and Healthy Study was approved by the U.S. National Cancer Institute Special Studies Institutional Review Board.

Identification of Cancer Survivors.

Cancer survivors were identified through linkage of the cohort to state cancer registries through December 31, 2006. Survivors were those with a registry-confirmed diagnosis (except non-melanoma skin cancer) prior to completion of the follow-up questionnaire. Registries provided information on cancer diagnosis date, histology, stage, grade, and first course of treatment reported within one year of diagnosis. Assessment of cancer cases through the state registries has been estimated to be over 90%.²⁶

Development of the Analytic Sample.

Of the 566,398 respondents to the baseline questionnaire, 294,870 returned the follow-up questionnaire. To maintain temporality, we excluded cancer survivors diagnosed after the follow-up questionnaire (n=35,721). To reduce the potential for confounding due to poor health status²⁷ or reporting inaccuracies, we further excluded survivors with metastatic disease (n=1,944), recurrent disease (n=138), non-registry confirmed diagnosis (n=59), and those with more than a year between diagnosis and treatment (n=1,476). All eligible participants who had missing ambulatory function information on the follow-up questionnaire were also excluded (n=22,397), leaving a final analytic sample of 30,403 cancer survivors and 202,732 individuals free of cancer (233,135 total participants). Cancer type-specific analyses included only those cancer types with at least 100 cases.

Covariate Assessment.

The baseline questionnaire assessed age, sex, race, body mass index, highest level of educational attainment, and health status. Leisure-time physical activity and morbid conditions were self-reported on the follow-up questionnaire. A frailty index was created using the deficit accumulation approach,²⁸ such that 26 morbid conditions reported at follow-up (see Supplementary Table 1) were summed, then divided by the total number of

conditions available. Individuals were then categorized as robust (<0.15), prefrail ($0.15-0.24$), mildly frail ($0.25-0.34$), or moderately-to-severely frail (>0.35).²⁹ Cancer type and treatment were assessed through state cancer registries and represent the first primary cancer type and first course of treatment (surgery, radiation, chemotherapy).

Ambulatory Function Assessment.

At follow-up, participants self-reported their normal walking pace: [*easy* (<2 mph); *normal, average* ($2-2.9$ mph); *brisk* ($3-3.9$ mph); *very brisk, striding* (>4 mph); *unable to walk*]. Ambulatory function was evaluated in terms of walking pace and mobility disability. *Brisk* and *very brisk, striding* categories were collapsed together to better represent previous studies of gait speed in older adults¹⁶. To prevent overestimation on analyses specific to walking pace, those who responded that they were *unable to walk* were removed ($n=6,501$): [*easy, normal, brisk*]. Mobility disability was classified as a report of being *unable to walk* or *easy* as has been done previously in the NIH-AARP Diet and Health Study.³⁰ For clarity, an *easy* pace will be referred to as *slow* throughout the rest of the manuscript, given it was the slowest pace reported by participants.

Mortality Assessment.

All-cause and cancer-specific mortality were assessed through linkage to the Social Security Administration Death Master File as well as the National Death Index through December 31, 2011. ICD-9 and ICD-10 codes were used to classify deaths due to all-causes and with a cancer as the underlying cause. Ascertainment of deaths in this cohort is estimated to be more than 93%.³¹

Statistical Analysis.

Because a large proportion of the original baseline cohort was not examined due to non-response on the follow-up questionnaire or participants moving out of areas covered by study-specific cancer registries, we used inverse probability weighting to account for the potential impact of differences between participants in the cohort at baseline and those who completed the follow-up questionnaire.³² Briefly, among all participants alive at the time of the follow-up questionnaire, we calculated a propensity score of completing the follow-up questionnaire using multiple logistic regression that included baseline age, sex, race, education, marital status, self-reported health status, smoking history, body mass index, cancer, diabetes, heart disease, end-stage renal disease, gallbladder stones or disease, emphysema, osteoporosis, bone fracture after age 45, and polyps of colon or rectum. We then categorized participants into deciles based on this propensity score and assigned individuals weights that were inversely proportional to the number of individuals in their category that completed the questionnaire.³³ These weights were then applied to all models.

To describe the association between a diagnosis of cancer and ambulatory function, multinomial logistic regression models estimated the odds of different walking paces for those with and without a cancer diagnosis. The odds of having mobility disability at follow-up by cancer status was assessed using logistic regression models. We further examined the associations between diagnosis for specific cancer types and ambulatory function. Models included those diagnosed with the cancer of interest and all controls in the cohort.

Sensitivity analyses quantified how time since diagnosis may have contributed to the overall association using indicator variables (e.g., <1, 1–4.9, ≥5 years). Models were adjusted for age, sex, race, body mass index, self-reported health status, time under observation, frailty index, and cancer type (except in cancer-specific analyses).

To quantify independent effects of ambulatory function on mortality in cancer survivors, Cox proportional hazards regression models estimated adjusted hazards ratios (HRs) and 95% confidence intervals (CI). Time from the follow-up questionnaire was the underlying time metric. We further examined these associations in specific cancer types; thus, we included only those diagnosed with the cancer of interest. Models were adjusted for all previous covariates plus leisure-time physical activity, time since diagnosis, and cancer treatment. Sensitivity analyses explored these associations by cancer treatment receipt (yes/no). To determine the joint effects of a cancer diagnosis and poor ambulatory function on mortality risk, we created indicator variables to directly compare the coexistence of both conditions against controls who walked the fastest and did not have mobility disability (referent groups). All statistical tests were conducted in SAS 9.4 (SAS Institute), and significance level was set to 0.05.

Results

Participant characteristics are detailed in Table 1. Briefly, individuals were just over 60 years of age ($M_{\text{age}}=61.8\pm5.36$) at baseline, Caucasian (92.6%), male (57.7%), and generally healthy (57.4% reporting 'very good' health). Cancer survivors were mostly early stage (67.4% stage I disease) and previously had surgery for their disease (59.3%). Cancer types with ≥100 cases included breast, colon, endocrine, endometrial, melanoma, Non-Hodgkin's lymphoma, oral, ovarian, prostate, rectum, respiratory system, stomach, soft tissue, urinary, and vulva (Table 2; *International Classification of Disease for Oncology*, Third Edition (ICD-O-3)).³⁴ The average time between cancer diagnosis and assessment of ambulatory function in survivors was 4.6 ± 2.8 years. Follow-up time between ambulatory function assessment and death or censoring averaged 6.3 ± 1.7 years for survivors and 6.7 ± 1.1 years for controls.

Associations between Cancer and Ambulatory Function.

A diagnosis of cancer was associated with increased odds of poor ambulatory function (Table 2, sorted by walking pace strength of association). Relative to the fastest walking pace, individuals with a diagnosis of cancer had 42% higher odds of walking at the slowest pace compared to adults without a cancer diagnosis [OR=1.42 (1.30–1.54)]. Similarly, survivors had significantly higher odds of mobility disability at follow-up [OR=1.24 (1.17–1.31)], after adjustment for demographics, BMI, health status, and cancer type. Sensitivity analyses indicated that regardless of time since diagnosis, survivors had increased odds of poor ambulatory function compared to controls ($p<.001$; see Supplementary Table 2).

The association between cancer diagnosis and lower ambulatory function persisted in nine different cancer types compared to controls (Table 2). A diagnosis of breast, colon, oral, prostate, rectal, respiratory, soft tissue, stomach, and urinary cancer was significantly associated with higher odds of slow walking [ORs>1.05]. A similar pattern emerged for

mobility disability, such that a diagnosis of breast, colon, endometrial, oral, prostate, rectal, respiratory, soft tissue, and urinary cancer was associated with greater risk of being disabled than controls. Across both ambulatory function indicators, the strongest associations were evident for respiratory and oral cancers [ORs>1.60]. Survivors with melanoma had significantly lower odds of poor ambulatory function than controls [ORs<0.88].

Associations between Ambulatory Function and Mortality in Cancer Survivors.

We found significant independent effects of ambulatory function on mortality. Slower walking paces were significantly associated with higher risk of all-cause and cancer-specific mortality, adjusting for demographics and cancer characteristics (Figure 2). Compared to the fastest walking survivors, those reporting slower walking had over a doubling of risk for all-cause mortality [HR=2.22 (2.06–2.39)]. Mobility disability after cancer was also significantly associated with increased hazards of all-cause mortality [HR=1.80 (1.73–1.88)]. This pattern of association persisted for cancer-specific mortality. Sensitivity analyses indicated no significant differences by treatment receipt (interaction $p>0.106$; see Supplementary Table 3).

Of the fifteen cancer types examined, poor ambulatory function was associated with increased mortality risk across most cancers (Figure 3, Supplementary Tables 4&5). In nine cancer types, survivors who reported the slowest walking pace were at significantly increased risk of all-cause mortality, including breast, colon, melanoma, Non-Hodgkin's lymphoma, oral, prostate, rectal, respiratory, and urinary cancers (HRs>1.91). More robust associations were evidenced for mobility disability. Thirteen different cancers had significant associations between mobility disability and all-cause mortality, including breast, colon, endometrial, endocrine, melanoma, Non-Hodgkin's lymphoma, oral, ovarian, prostate, rectal, respiratory, stomach, and urinary cancers (HRs>1.34).

Joints Associations of Cancer and Ambulatory Function on Mortality.

Finally, we examined the joint effects of poor ambulatory function and cancer on mortality in both cancer survivors and controls and found a statistically significant interaction between ambulatory function and a previous cancer diagnosis ($p<.001$; Figure 4). Lower ambulatory function was associated with increased risk of all-cause mortality in both survivors and controls; however, the adverse risk association was much stronger in survivors. For example, compared to the fastest walking controls, cancer survivors who walked the slowest had a much higher hazard ratio than controls who walked the slowest (10.37 vs. 3.91). Similar patterns emerged for mobility disability.

Discussion

Our findings suggest that diagnosis and treatment for cancer is associated with poor ambulatory function up to 5 years later. These results were consistent across nine different types of cancer, suggesting that more cancer types may predispose individuals to poor ambulatory function than previously studied. Lower ambulatory function placed cancer survivors at increased risk of death, highlighting the importance of these functional domains during survivorship. Importantly, our results also suggest that risks associated with lower

ambulatory function may be two to three times stronger for early mortality in survivors compared to the general population.

Our finding that a diagnosis of cancer was associated with poor ambulatory function is consistent with the literature highlighting pervasive and detrimental effects of cancer on functional health.^{5–8,21,35,36} To date, most of this work has been confined to common cancer types, such as breast.^{8,37} The novel contributions of this study allowed us to examine longitudinal associations between cancer and ambulatory function across fifteen different cancer types. A wide variety of cancer types were associated with lower ambulatory function, including those of the gastrointestinal tract, hormonally related cancers, and even cancers with watch-and-wait treatment recommendations (prostate). Interestingly, melanoma was associated with lower odds of poor ambulatory function, which may be due to the known relationship between leisure-time physical activity and increased melanoma risk.³⁸ The biological and/or psychosocial mechanisms of the differential odds of ambulatory function in specific cancer types should be explored further. The present sample of cancer survivors are on average several years beyond treatment cessation, and a better understanding of both pre- and post-diagnosis behavioral, biological, and cancer-specific factors will be important to fully envision these complex relationships. Specifically, future research would do well to explore changes in ambulatory function across the cancer continuum, not just post-treatment, to better identify where functional changes occur for each cancer type and optimal time(s) for intervention.

Walking pace and mobility disability were also independently associated with increased mortality risk in cancer survivors, just as ambulatory function has emerged as a robust predictor of survival in healthy older adults.^{16,39} These findings corroborate a recent analysis of self-reported mobility disability and mortality among survivors.²¹ Brown and colleagues identified 215% and 249% increased risk of all-cause and cancer mortality with mobility disability (as assessed via one's perceived difficulty walking for a quarter of a mile), respectively, among 1,458 cancer survivors in the National Health and Nutrition Examination Survey (NHANES). Other studies have also noted increased mortality hazards in survivors with slower walking paces, albeit with binary definitions and limited cancer types.^{20,40} Importantly, we explored the function-mortality relationship among multiple walking pace categories and fifteen different cancer types, highlighting significant associations among nine cancers for walking pace and thirteen cancers for mobility disability. Previously unexplored, these findings provide a foundation for future research into potential cancer-specific mechanisms that may be increasing mortality risk. Despite chemotherapy's notorious reputation for deleterious late effects, sensitivity analyses suggested that these results cannot be explained by treatment regimen alone; future research would do well to investigate other cancer type- or aging-specific factors that may explain the function-survival relationship. That said, poor function was associated with mortality in most cancer types studied herein, suggesting that universal efforts towards improving ambulatory function during survivorship are worthwhile. Such efforts may include physical activity, which has been consistently associated with improved gait speed during survivorship.⁴¹

Indeed, our joint effects of cancer and function on all-cause mortality point to substantially increased risk of death in survivors with poor functioning compared to healthy controls. If replicated, these findings suggest that ambulatory function may be more important for survival in cancer survivors for reasons we do not yet fully understand. Potentially due to an accelerated aging trajectory², coupled with other cancer-specific characteristics unavailable in this sample (e.g., specific chemotherapies, multiple treatments, medications), clarifying the underlying biological mechanisms of these findings is warranted.

Of further interest is the self-reported nature of ambulatory function in the current analysis and its implications for widespread surveillance of cancer survivors. Historically, objective measures of walking pace^{20,40} and clinical indicators such as the ECOG performance status⁴² and Karnofsky performance status⁴³ have served as prognostic factors of survival in cancer survivors. Despite their importance, implementing these measures in practice may be unrealistic for many older cancer survivors due to burden, cost, and time,²¹ and they certainly are not applicable to broader population assessment. While ECOG and Karnofsky performance statuses or other objective functional batteries were unavailable in the current sample, our findings suggest that simple patient-reported outcomes, such as one question about walking pace, may be efficient alternatives for screening survivors on a large scale to identify those who may need follow-up with more rigorous assessments of ambulatory function. Future research should include multiple functional measures to determine the independent prognostic ability of self-reported walking pace and/or mobility disability for determining survival.

Our results should be interpreted in the context of the study's strengths and limitations. The primary strength of this analysis is its prospective nature, allowing us to test temporal associations between cancer and future ambulatory function, and ambulatory function and future mortality. Our large sample size also allowed us to explore these relationships in multiple cancer types that had previously been unexplored. We acknowledge that our analytic sample was comprised of less than the original NIH-AARP cohort, thus results may be more relevant to individuals who filled out the follow-up questionnaire. However, we conducted inverse probability weighting to statistically account for these differences. Further, most survivors were early stage and multiple years post-diagnosis. Limited treatment information from cancer registries also made it difficult to understand the specific regimens that may be detrimental to ambulatory function. It is nonetheless encouraging that such associations emerged in a relatively healthy sample, suggesting that the cancer-function relationship may be more pronounced, and potentially even more important, in more diverse samples. It is also worth noting that other unmeasured factors (e.g., mild cognitive impairment or dementia) may confound the relationships reported herein. However, we included a constellation of potential confounders to estimate the association to the best of our ability with the data available. Finally, despite research highlighting the robust association between self-reported and objective measures of ambulatory function,⁴⁴ we are unable to say with certainty that self-reported walking pace in the current study paralleled true gait speed; however, these subjective measures allowed for broad, cost-effective identification of at-risk survivors.

To our knowledge, this is the first prospective analysis to have considered both the role of a cancer diagnosis on ambulatory function and the implications of poor function on subsequent survival in fifteen different cancer types. Our findings confirm an increased risk of poor ambulatory function after cancer as well as survivors' increased risk of mortality with lower functional health. Notably, these associations persisted in at least nine different cancer types, highlighting the need for comprehensive surveillance and targeting of ambulatory function during survivorship, potentially through cancer rehabilitation and/or behavioral change (e.g., physical activity). Given cancer survivors with poor ambulatory function had two-three times greater mortality risk than their cancer-free peers, public health efforts should focus on identifying and targeting survivors who are at-risk for poor functional health to ultimately improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute. Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia. Cancer incidence data from California were collected by the California Cancer Registry, California Department of Public Health's Cancer Surveillance and Research Branch, Sacramento, California. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, Lansing, Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (Miami, Florida) under contract with the Florida Department of Health, Tallahassee, Florida. The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Health Sciences Center School of Public Health, New Orleans, Louisiana. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, The Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, Raleigh, North Carolina. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services, Phoenix, Arizona. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Division of Public and Behavioral Health, State of Nevada Department of Health and Human Services, Carson City, Nevada.

We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7–34. doi:10.3322/caac.21551 [PubMed: 30620402]
2. Henderson TO, Ness KK, Cohen HJ. Accelerated Aging among Cancer Survivors: From Pediatrics to Geriatrics. *Am Soc Clin Oncol Educ B*. 2014;(34):e423–e430. doi:10.14694/edbook_am.2014.34.e423

3. Lowry KA, Vallejo AN, Studenski SA. Successful aging as a continuum of functional independence: lessons from physical disability models of aging. *Aging Dis.* 2012;3(1):5–15. Accessed August 12, 2019. <http://www.ncbi.nlm.nih.gov/pubmed/22500268> [PubMed: 22500268]
4. Nelson W Rejeski Jack Steven N Blair ME, Duncan James O Judge PW. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116(9):1094–1105. doi:10.1161/CIRCULATIONAHA.107.185650 [PubMed: 17671236]
5. Avis NE, Deimling GT. Cancer survivorship and aging. *Cancer.* 2008;113(S12):3519–3529. doi:10.1002/cncr.23941 [PubMed: 19058151]
6. Bellizzi KM, Mustian KM, Palesh OG, Diefenbach M. Cancer survivorship and aging. *Cancer.* 2008;113(S12):3530–3539. doi:10.1002/cncr.23942 [PubMed: 19058147]
7. Demark-Wahnefried W, Pinto BM, Gritz ER. Promoting health and physical function among cancer survivors: potential for prevention and questions that remain. *J Clin Oncol.* 2006;24(32):5125–5131. doi:10.1200/JCO.2006.06.6175 [PubMed: 17093274]
8. Petrick JL, Reeve BB, Kucharska-Newton AM, et al. Functional status declines among cancer survivors: Trajectory and contributing factors. *J Geriatr Oncol.* 2014;5(4):359–367. doi:10.1016/J.JGO.2014.06.002 [PubMed: 24981125]
9. Bluethmann SM, Flores E, Campbell G, Klepin HD. Mobility Device Use and Mobility Disability in U.S. Medicare Beneficiaries With and Without Cancer History. *J Am Geriatr Soc.* Published online September 24, 2020:jgs.16789. doi:10.1111/jgs.16789
10. Given CW, Given B, Azzouz F, Stommel M, Kozachik S. Comparison of Changes in Physical Functioning of Elderly Patients with New Diagnoses of Cancer. *Med Care.* 38:482–493. doi:10.2307/3767029
11. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: Quality of life and psychosocial adjustment in the 15 months after diagnosis. *J Clin Oncol.* 2003;21(21):4027–4033. doi:10.1200/JCO.2003.08.097 [PubMed: 14581426]
12. Arndt V, Merx H, Stürmer T, Stegmaier C, Ziegler H, Brenner H. Age-specific detriments to quality of life among breast cancer patients one year after diagnosis. *Eur J Cancer.* 2004;40(5):673–680. doi:10.1016/j.ejca.2003.12.007 [PubMed: 15010067]
13. Kroenke CH, Rosner B, Chen WY, Kawachi I, Colditz GA, Holmes MD. Functional impact of breast cancer by age at diagnosis. *J Clin Oncol.* 2004;22(10):1849–1856. doi:10.1200/JCO.2004.04.173 [PubMed: 15143077]
14. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* 2019;69(5):363–385. doi:10.3322/caac.21565 [PubMed: 31184787]
15. Hirvensalo M, Rantanen T, Heikkinen E. Mobility Difficulties and Physical Activity as Predictors of Mortality and Loss of Independence in the Community-Living Older Population. *J Am Geriatr Soc.* 2000;48(5):493–498. doi:10.1111/j.1532-5415.2000.tb04994.x [PubMed: 10811541]
16. Studenski S, Perera S, Patel K, et al. Gait Speed and Survival in Older Adults. *JAMA.* 2011;305(1):50. doi:10.1001/jama.2010.1923 [PubMed: 21205966]
17. Stamatakis E, Kelly P, Strain T, Murtagh EM, Ding D, Murphy MH. Self-rated walking pace and all-cause, cardiovascular disease and cancer mortality: individual participant pooled analysis of 50 225 walkers from 11 population British cohorts. *Br J Sports Med.* 2018;52(12):761–768. doi:10.1136/bjsports-2017-098677 [PubMed: 29858463]
18. Fritz S, Lusardi MM. White Paper: Walking Speed: the Sixth Vital Sign. *J Geriatr Phys Ther.* 2009;32(2):2–5. doi:10.1519/00139143-200932020-00002 [PubMed: 19856629]
19. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. *Br J Cancer.* 2015;112(1):194–198. doi:10.1038/bjc.2014.568 [PubMed: 25393366]
20. Pamoukdjian F, Lévy V, Sebbane G, et al. Slow gait speed is an independent predictor of early death in older cancer outpatients: Results from a prospective cohort study. *J Nutr Health Aging.* 2017;21(2):202–206. doi:10.1007/s12603-016-0734-x [PubMed: 28112777]
21. Brown JC, Harhay MO, Harhay MN. Self-reported major mobility disability and mortality among cancer survivors. *J Geriatr Oncol.* 2018;9(5):459–463. doi:10.1016/J.JGO.2018.03.004 [PubMed: 29550343]

22. Cesari M, Cerullo F, Zamboni V, et al. Functional status and mortality in older women with gynecological cancer. *J Gerontol A Biol Sci Med Sci*. 2013;68(9):1129–1133. doi:10.1093/gerona/glt073 [PubMed: 23733856]
23. Klepin HD, Geiger AM, Tooze JA, et al. Physical performance and subsequent disability and survival in older adults with malignancy: results from the health, aging and body composition study. *J Am Geriatr Soc*. 2010;58(1):76–82. doi:10.1111/j.1532-5415.2009.02620.x [PubMed: 20122042]
24. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590 [PubMed: 31912902]
25. Schatzkin A, Subar AF, Thompson FE, et al. Design and Serendipity in Establishing a Large Cohort with Wide Dietary Intake Distributions. *Am J Epidemiol*. 2001;154(12):1119–1125. doi:10.1093/aje/154.12.1119 [PubMed: 11744517]
26. Michaud D, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. Published online January 1, 2005. Accessed July 25, 2019. <https://www.scienceopen.com/document?vid=c78c5756-2cad-431d-b965-fd2ee06106c2>
27. Matthews CE, Troiano RP, Salerno EA, et al. Exploration of Confounding Due to Poor Health in an Accelerometer–Mortality Study. *Vol Publish Ah.*; 2020. doi:10.1249/mss.0000000000002405
28. Theou O, Walston J, Rockwood K. Operationalizing Frailty Using the Frailty Phenotype and Deficit Accumulation Approaches. In: *Interdisciplinary Topics in Gerontology and Geriatrics*. Vol 41. Karger Publishers; 2015:66–73. doi:10.1159/000381164 [PubMed: 26301980]
29. Kim DH, Glynn RJ, Avorn J, et al. Validation of a Claims-Based Frailty Index Against Physical Performance and Adverse Health Outcomes in the Health and Retirement Study. *Journals Gerontol Ser A*. 2019;74(8):1271–1276. doi:10.1093/gerona/gly197
30. DiPietro L, Jin Y, Talegawkar S, Matthews CE, Newman A. The Joint Associations of Sedentary Time and Physical Activity With Mobility Disability in Older People: The NIH-AARP Diet and Health Study. Newman A, ed. *Journals Gerontol Ser A*. 2018;73(4):532–538. doi:10.1093/gerona/glx122
31. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994;140(11):1016–1019. doi:10.1093/oxfordjournals.aje.a117191 [PubMed: 7985649]
32. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22(3):278–295. doi:10.1177/0962280210395740 [PubMed: 21220355]
33. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007;45(10 SUPPL. 2). doi:10.1097/mlr.0b013e31806518ac
34. Fritz AG, ed. *International Classification of Disease for Oncology: ICD-O.*; 2013.
35. Keating NL, Nārrredam M, Landrum MB, Huskamp HA, Meara E. Physical and Mental Health Status of Older Long-Term Cancer Survivors. *J Am Geriatr Soc*. 2005;53(12):2145–2152. doi:10.1111/j.1532-5415.2005.00507.x [PubMed: 16398900]
36. Deimling GT, Sterns S, Bowman KF, Kahana B. Functioning and Activity Participation Restrictions among Older Adult, Long-Term Cancer Survivors. *Cancer Invest*. 2007;25(2):106–116. doi:10.1080/07357900701224813 [PubMed: 17453822]
37. Sweeney C, Schmitz KH, Lazovich D, Virnig BA, Wallace RB, Folsom AR. Functional Limitations in Elderly Female Cancer Survivors. *JNCI J Natl Cancer Inst*. 2006;98(8):521–529. doi:10.1093/jnci/djj130 [PubMed: 16622121]
38. Moore SC, Lee I-M, Weiderpass E, et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA Intern Med*. 2016;176(6):816. doi:10.1001/jamainternmed.2016.1548 [PubMed: 27183032]
39. Hardy SE, Perera S, Roumani YF, Chandler JM, Studenski SA. Improvement in Usual Gait Speed Predicts Better Survival in Older Adults. *J Am Geriatr Soc*. 2007;55(11):1727–1734. doi:10.1111/j.1532-5415.2007.01413.x [PubMed: 17916121]

40. Cesari M, Cerullo F, Zamboni V, et al. Functional Status and Mortality in Older Women With Gynecological Cancer. *Journals Gerontol Ser A Biol Sci Med Sci*. 2013;68(9):1129–1133. doi:10.1093/gerona/glt073
41. Kirkham AA, Bland KA, Sayyari S, Campbell KL, Davis MK. Clinically Relevant Physical Benefits of Exercise Interventions in Breast Cancer Survivors. *Curr Oncol Rep*. 2016;18(2):12. doi:10.1007/s11912-015-0496-3 [PubMed: 26769117]
42. Zubrod CG, Schneiderman M, Frei E, et al. Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chronic Dis*. 1960;11(1):7–33. doi:10.1016/0021-9681(60)90137-5
43. Karnofsky DA BJH. The clinical evaluation of chemotherapeutic agents in cancer. *Evaluation of Chemotherapeutic Agents*. Columbia Univ Press. Published online 1949:191–205. Accessed September 22, 2020. <https://ci.nii.ac.jp/naid/10005058071>
44. Brown JC, Harhay MO, Harhay MN. Patient-reported versus objectively-measured physical function and mortality risk among cancer survivors. *J Geriatr Oncol*. 2016;7(2):108–115. doi:10.1016/J.JGO.2016.01.009 [PubMed: 26907563]

Figure 1.

Timeline

Timeline of data collection in the NIH-AARP Diet and Health Study

Figure 2.

Walking pace, mobility disability & hazards of all-cause and cancer mortality in cancer survivors

Covariates: age, sex, race, highest level of education, years of follow-up, body mass index, self-reported health status, leisure time physical activity, cancer treatment, frailty index, and time between cancer diagnosis and follow-up questionnaire

3A. Walking Pace

Cancer	Cases, No.	Deaths, No.	HR (95% CI)	P value
All Cancers	29,468	5,784	2.22 (2.06, 2.39)	<0.001
Soft Tissue	107	25	4.60 (0.70, 30.19)	0.261
Non-Hodgkin's Lymph	635	167	3.04 (1.89, 4.90)	<0.001
Breast	5,045	686	2.37 (1.84, 3.05)	<0.001
Melanoma	2,428	382	2.31 (1.74, 3.07)	<0.001
Ovarian	127	41	2.24 (0.68, 7.32)	0.183
Urinary	2,483	653	2.23 (1.77, 2.79)	<0.001
Rectum	795	187	2.10 (1.40, 3.16)	<0.001
Endocrine	275	42	2.07 (0.83, 5.16)	0.120
Prostate	11,801	1,942	2.00 (1.78, 2.25)	<0.001
Oral	451	132	1.98 (1.18, 3.35)	0.010
Colon	2,026	425	1.93 (1.45, 2.57)	<0.001
Respiratory	1,257	551	1.91 (1.45, 2.52)	<0.001
Endometrial	784	101	1.42 (0.70, 2.85)	0.330
Vulva	109	20	1.03 (0.16, 6.76)	0.977
Stomach	124	56	0.55 (0.24, 1.28)	0.166

3B. Mobility Disability

Cancer	Cases, No.	Deaths, No.	HR (95% CI)	P value
All Cancers	30,403	6,194	1.80 (1.73, 1.88)	<0.001
Non-Hodgkin's Lymph	659	177	2.08 (1.59, 2.72)	<0.001
Rectum	827	199	2.03 (1.58, 2.61)	<0.001
Ovarian	135	46	1.99 (1.04, 3.82)	0.038
Stomach	128	58	1.99 (1.21, 3.27)	0.006
Urinary	2,574	701	1.82 (1.60, 2.07)	<0.001
Endometrial	844	129	1.82 (1.27, 2.62)	0.001
Colon	2,098	461	1.81 (1.54, 2.13)	<0.001
Breast	5,298	768	1.78 (1.55, 2.03)	<0.001
Melanoma	2,474	400	1.77 (1.49, 2.11)	<0.001
Endocrine	284	45	1.77 (1.00, 3.14)	0.052
Prostate	11,997	2,028	1.73 (1.60, 1.86)	<0.001
Soft Tissue	116	27	1.67 (0.67, 4.19)	0.276
Respiratory	1,317	593	1.61 (1.40, 1.86)	<0.001
Oral	469	141	1.34 (1.01, 1.78)	0.040
Vulva	116	21	0.63 (0.25, 1.58)	0.321

Figure 3.

Hazards of all-cause mortality in cancer survivors: A) reporting a slow pace compared to those reporting a brisk walking pace and; B) reporting mobility disability compared to those without mobility disability

Covariates: age, sex, race, highest level of education, years of follow-up, body mass index, self-reported health status, leisure time physical activity, cancer treatment, frailty index, and time between cancer diagnosis and follow-up questionnaire

Figure 4.
 Hazards of all-cause mortality by coexistence of poor ambulatory function & cancer: A)
 walking pace and; B) mobility disability
 HR=hazard ratio

Table 1.

Participant demographics and cancer-specific characteristics at baseline

	Full Sample (N=233,135)	No Cancer (n=202,732)	Cancer (n=30,403)
	M (SD) or %	M (SD) or %	M (SD) or %
Age (years)	61.82 (5.36)	61.61 (5.39)	63.22 (5.00)
Body mass index	26.93 (4.91)	26.91 (4.94)	27.02 (4.74)
Caucasian	92.41%	92.23%	93.60%
Male	56.69%	55.13%	67.08%
Self-reported health status			
Excellent	18.98%	19.29%	16.96%
Very Good	37.46%	37.52%	37.10%
Good	33.20%	32.93%	35.00%
Fair	8.19%	8.11%	8.69%
Poor	0.87%	0.87%	0.87%
Frailty index			
Robust	58.31%	58.83%	54.85%
Pre-Frail	32.35%	32.00%	34.65%
Mildly Frail	7.74%	7.60%	8.71%
Moderately-to-Severely Frail	1.19%	1.17%	1.27%
Cancer stage	-	-	
0	-	-	11.06%
I	-	-	67.43%
II	-	-	7.51%
III	-	-	5.14%
Unknown	-	-	8.86%
Cancer treatment	-	-	
Chemotherapy	-	-	10.41%
Radiation	-	-	27.20%
Surgery	-	-	59.29%
Time between diagnosis and ambulatory function assessment (years)	-	-	4.55 (2.83)

Table 2.

Multinomial and logistic regression odds of poor ambulatory function of cancer survivors compared to cancer-free controls

Cancer	Cases, No.	Walk Pace	OR (95% CI)	Cases, No.	Mobility Disability OR (95% CI)
All Cancers [‡]	29,468	Slow	1.42 ** (1.30, 1.54)	30,403	1.24 * (1.17, 1.31)
		Normal	1.20 ** (1.11, 1.29)		
		Brisk (ref)	1.00		
Respiratory [§]	1,257	Slow	2.62 ** (2.24, 3.05)	1,317	1.95 ** (1.77, 2.14)
		Normal	1.49 ** (1.29, 1.73)		
		Brisk (ref)	1.00		
Oral	451	Slow	1.97 ** (1.56, 2.48)	469	1.60 ** (1.37, 1.88)
		Normal	1.33 * (1.08, 1.64)		
		Brisk (ref)	1.00		
Soft Tissue	107	Slow	1.92 * (1.13, 3.24)	116	1.46 * (1.04, 2.05)
		Normal	1.68 * (1.05, 2.67)		
		Brisk (ref)	1.00		
Stomach	124	Slow	1.72 * (1.06, 2.78)	128	1.18 (0.87, 1.60)
		Normal	1.49 (0.95, 2.33)		
		Brisk (ref)	1.00		
Ovarian	127	Slow	1.44 (0.90, 2.31)	135	1.23 (0.91, 1.66)
		Normal	1.37 (0.88, 2.12)		
		Brisk (ref)	1.00		
Urinary	2,483	Slow	1.42 ** (1.28, 1.57)	2,574	1.27 ** (1.18, 1.36)
		Normal	1.18 * (1.08, 1.29)		
		Brisk (ref)	1.00		
Colon	2,026	Slow	1.37 ** (1.22, 1.53)	2,098	1.21 ** (1.12, 1.30)
		Normal	1.17 * (1.05, 1.30)		
		Brisk (ref)	1.00		
Rectum	795	Slow	1.32 * (1.11, 1.57)	827	1.15 * (1.02, 1.30)
		Normal	1.22 * (1.04, 1.42)		
		Brisk (ref)	1.00		
Endocrine	275	Slow	1.24 (0.92, 1.66)	284	1.20 (0.97, 1.48)
		Normal	1.05 (0.81, 1.38)		
		Brisk (ref)	1.00		

Cancer	Cases, No.	Walk Pace	OR (95% CI)	Cases, No.	Mobility Disability OR (95% CI)
Endometrial	784	Slow	1.18 (0.96, 1.43)	844	1.15 [*] (1.02, 1.31)
		Normal	1.04 (0.86, 1.25)		
		Brisk (ref)	1.00		
Non-Hodgkin's Lymph	635	Slow	1.12 (0.92, 1.37)	659	1.11 (0.96, 1.28)
		Normal	1.04 (0.87, 1.24)		
		Brisk (ref)	1.00		
Breast	5,045	Slow	1.11 [*] (1.03, 1.20)	5,298	1.07 [*] (1.02, 1.12)
		Normal	1.06 (0.99, 1.14)		
		Brisk (ref)	1.00		
Prostate	11,801	Slow	1.05 [*] (1.01, 1.10)	11,997	1.05 [*] (1.01, 1.08)
		Normal	1.00 (0.97, 1.04)		
		Brisk (ref)	1.00		
Vulva	109	Slow	0.95 (0.59, 1.53)	116	0.91 (0.67, 1.25)
		Normal	1.06 (0.68, 1.63)		
		Brisk (ref)	1.00		
Melanoma	2,428	Slow	0.86 [*] (0.77, 0.95)	2,474	0.88 [*] (0.81, 0.95)
		Normal	0.95 (0.88, 1.04)		
		Brisk (ref)	1.00		

Covariates: age, sex, race, highest level of education, years of follow-up, body mass index, self-reported health status, and frailty index

Sorted by walking pace strength of association

[‡] also adjusted for cancer type

[§] Respiratory system includes cancers of the nose, nasal cavity, middle ear, larynx, lung & bronchus, pleura, trachea, mediastinum, and other respiratory.

^{*} $p=0.05$

^{**} $p<0.001$