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Frailty and risk of mortality in older cancer survivors and adults without a cancer history: Evidence from the National Health and Nutrition Examination Survey, 1999–2014

Dongyu Zhang, MD, PhD[1,2], **Erin M. Mobley, PhD, MPH**[2,3], **Todd M. Manini, PhD**[4], **Christiaan Leeuwenburgh, PhD**[4], **Stephen D. Anton, PhD**[4], **Caretia J. Washington, BS**[5], **Daohong Zhou, MD**[6], **Alexander S. Parker, PhD**[2,7], **Paul G. Okunieff, MD**[2,8], **Jiang Bian, PhD**[2,9], **Yi Guo, PhD**[2,9], **Marco Pahor, MD**[4], **Robert A. Hiatt, MD, PhD**[10], **Dejana Braithwaite, PhD**[1,2,11]

[1]Department of Epidemiology, University of Florida College of Public Health and Health Professions, Gainesville, Florida

[2]University of Florida Health Cancer Center, Gainesville, Florida

[3]Department of Surgery, University of Florida College of Medicine, Jacksonville, Florida

[4]Department of Aging and Geriatric Research, University of Florida College of Medicine, Gainesville, Florida

[5]University of Florida College of Medicine, Gainesville, Florida

[6]Department of Biochemistry and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, Texas

[7]University of Florida College of Medicine, Jacksonville, Florida

[8]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida

[9]Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, Florida

[10]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California

[11]Department of Surgery, University of Florida College of Medicine, Gainesville, Florida

Corresponding Author: Dongyu Zhang, MD, PhD, Department of Epidemiology, University of Florida College of Public Health and Health Professions, 2004 Mowry Rd, Gainesville, FL 32611-7011 (dzhang2@ufl.edu).

AUTHOR CONTRIBUTIONS

Dongyu Zhang: Conceptualization, methodology, data curation, statistical analysis, interpretation of results, drafting of the manuscript, editing, revision, and submission. **Erin M. Mobley:** Interpretation of results, editing, and revision. **Todd M. Manini:** Methodology, interpretation of results, editing, and revision. **Christiaan Leeuwenburgh:** Methodology, interpretation of results, editing, and revision. **Stephen D. Anton:** Methodology, interpretation of results, editing, and revision. **Caretia J. Washington:** Editing and revision. **Daohong Zhou:** Editing and revision. **Alexander S. Parker:** Editing and revision. **Paul G. Okunieff:** Editing and revision. **Jiang Bian:** Methodology, interpretation of results, editing, and revision. **Yi Guo:** Methodology, interpretation of results, editing, and revision. **Marco Pahor:** Methodology, interpretation of results, editing, and revision. **Robert A. Hiatt:** Methodology, interpretation of results, editing, and revision. **Dejana Braithwaite:** Conceptualization, methodology, interpretation of results, editing, revision, and funding support.

CONFLICT OF INTEREST DISCLOSURES

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Additional supporting information may be found in the online version of this article.

Abstract

BACKGROUND: Epidemiologic evidence reporting the role of frailty in survival among older adults with a prior cancer diagnosis is limited.

METHODS: A total of 2050 older adults (≥60 years old) surviving for at least 1 year after a cancer diagnosis and 9474 older adults without a cancer history from the National Health and Nutrition Examination Survey (1999–2014) were included for analysis. The exposure variable, a 45-item frailty index (FI), was categorized on the basis of validated cutoffs (FI ≤ 0.10 [fit], 0.10 < FI ≤ 0.21 [prefrail], and FI > 0.21 [frail]). All-cause mortality was ascertained via the National Death Index. Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence interval (CIs) for the FI, and this was followed by restricted cubic splines depicting dose-response curves.

RESULTS: For older cancer survivors, the mean age at the baseline was 72.6 years (SD, 7.1 years); 5.9% were fit, 38.2% were prefrail, and 55.9% were frail. Older adults without a cancer history were slightly younger (mean age, 70.0 years) and less frail (47.9% were frail). At each level of the FI, cancer survivors (1.9 per 100 person-years for FI ≤ 0.10, 3.4 per 100 person-years for 0.10 < FI ≤ 0.21, and 7.5 per 100 person-years for FI > 0.21) had higher mortality than their cancer-free counterparts (1.4 per 100 person-years for FI ≤ 0.10, 2.4 per 100 person-years for 0.10 < FI ≤ 0.21, and 5.4 per 100 person-years for FI > 0.21). The multivariable model suggested a positive association between the FI and all-cause mortality for survivors (aHR for FI > 0.21 vs FI ≤ 0.10, 2.80; 95% CI, 1.73–4.53) and participants without a cancer history (aHR for FI > 0.21 vs FI ≤ 0.10, 2.75; 95% CI, 2.29–3.32). Restricted cubic splines indicated that all-cause mortality risk increased with the FI in a monotonic pattern.

CONCLUSIONS: Frailty is associated with a higher risk of death in older cancer survivors and the elderly without a cancer history.

Keywords

cancer survivorship; epidemiology; frailty; geriatric oncology; gerontology; tertiary cancer prevention

INTRODUCTION

The proportion of the older adult population in the United States is growing at a rapid pace. Specifically, the US Census Bureau has estimated that approximately 25% of residents will be 65 years old or older by 2060,[1] and they will include a large number of older adults living with comorbidities.[2,3] Similar to many other chronic illnesses, cancer is an age-related disease.[4] According to data from the Surveillance, Epidemiology, and End Results program, the median age of cancer diagnosis in the United States is 66 years.[5] Moreover, with the development of antitumor treatment modalities, the prognosis of older patients with cancer has substantially improved. For example, the proportion of older adults among all cancer survivors is steadily rising in the United States: It increased from 50% in 1975 to 60% in 2010 and will reach more than 70% by 2040.[6] In addition to treatment, other health-related factors should also be considered in health care management for older adults with prior cancer diagnoses, and frailty is an extremely fundamental one.

Frailty describes the status of physiological decline, vulnerability to diseases, and age-related disturbed homeostasis.[7,8] It develops as a result of cumulative age-related decline across multiple organs and increases the risk of many adverse health outcomes, including death.[9] A meta-analysis synthesizing data from 46 observational studies reported that the incidence rate of frailty is 43.4 per 1000 person-years among community-dwelling adults 60 years old or older.[10] These data underscore the likelihood that many older adults are facing the consequences of frailty, such as slow recovery from chronic diseases, including cancer, and a reduction in life expectancy.

Studying the association between frailty and the risk of death in older adults with a prior cancer diagnosis can help cancer survivors and health care providers to better predict outcomes after treatment and improve survivorship. However, the existing studies reporting an association between frailty and death among older cancer survivors are limited and have some methodologic limitations. For example, these studies did not consider nutritional or lifestyle factors in their analyses or were performed solely in female cancer survivors.[11–13] In addition, these studies did not compare effect measures of frailty between cancer survivors and counterparts without a cancer history, and this makes us unable to judge whether the impact of frailty is more substantial in cancer survivors. To remedy these gaps, we used data from the National Health and Nutrition Examination Survey (NHANES) to more thoroughly study the impact of frailty on the mortality of older cancer survivors and compare the estimates with those for older adults without a cancer history.

MATERIALS AND METHODS

Data Source and Study Population

The NHANES is a program led by the Centers for Disease Control and Prevention that assesses nutritional status, health-related behaviors, medical service utilization, and burdens of illnesses among adults and children in the United States. It uses interviews with physical examinations and laboratory testing to measure the aforementioned items.[14] The National Center for Health Statistics has linked the 1999–2014 NHANES data with death certificate records from the National Death Index.[15] To generate the cohort for analysis, we linked exposures and relevant covariates in the 1999–2014 NHANES to the vital status measured during the same period. We used 60 years as the cutoff to define the elderly as suggested by the World Health Organization.[16] We referred to the definition used in the National Coalition for Cancer Survivorship[17] and treated people who survived for a period of time after their cancer diagnosis as cancer survivors. People with the following characteristics were included in our study:

1. They were ≥60 years old at the interview.
2. They had less than 20% missing data[18–21] for individual items incorporated into the frailty index (FI).
3. They had no missing data for covariates.
4. Cancer survivors should have survived for at least 1 year since their cancer diagnosis (because most patients with cancer will receive antitumor therapies

during the first year of survivorship,[22] which can substantially affect function and blood test results).

5. Older adults without cancer should have met criteria 1 to 3.

This yielded a total of 2050 older cancer survivors and 9474 older adults without a cancer history for analysis (Supporting Fig. 1).

Exposure and Outcome of Interest

To measure frailty, we used a cumulative index that was developed and validated in prior studies.[18–21] Specifically, our study used a 45-item FI that incorporated comorbidities, functional status, clinical measures, and laboratory testing results in accordance with the published literature.[18–21] At the baseline, health conditions (comorbidities [n = 15], functional impairments [n = 15], health services use [n = 3], and general health [n = 2]) were collected by self-report; clinical measures (n = 2) were obtained by trained examiners at a mobile examination center (MEC) at the baseline; and biomarkers (n = 8) were measured with the blood samples collected at the baseline.[23] The FI was calculated as a proportion whose denominator was 45 and whose numerator was the sum of scores associated with each individual item (individual item scores ranged from 0 to 1); thus, the FI ranged from 0 to 1, with a larger value suggesting a higher burden of frailty. Scores for each individual item are presented in Supporting Table 1. On the basis of published literature using the same algorithm,[18–21] participants with 20% or more missing data for individual items in the FI were excluded. The FI was categorized as an ordinal variable on the basis of cutoffs used in prior literature[18–21] to reflect fitness (FI ≤ 0.10), prefrailty (0.10 < FI ≤ 0.21), and frailty (FI > 0.21).

All-cause death was identified by linkage to the National Death Index through December 31, 2015. The follow-up time was the interval from the baseline interview to the date of death or December 31, 2015, whichever occurred first. Participant were treated as censored if they were alive.

Other Covariates

Demographic factors (age, sex, and race) were self-reported at the baseline interview. Age was categorized as a 3-level variable (60–69, 70–79, or ≥80 years); sex was treated as female or male; and race was categorized as White, Black, or other. Education was classified as an ordinal variable (high school or less, attended college, or graduated from college). Participants who were never married, separated, divorced, or widowed were treated as not married in our study, and we pooled married individuals and individuals living with partners as 1 category. Smoking status was treated as a categorical variable (current, former, or never); in particular, participants who self-reported ever smoking at least 100 cigarettes in their life were treated as current smokers or former smokers if they had quit. The baseline body weight and height were measured by trained staff at the MEC. The body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2), and we categorized it as an ordinal variable (<25, 25–29.9, or ≥30 kg/m^2) by using cutoffs recommended by the World Health Organization.[24] At the baseline MEC, participants self-reported alcohol consumption during the past year; because some evidence suggested a

potential for low to moderate alcohol consumption to lower frailty risk,[25–28] we treated alcohol consumption as an ordinal variable that incorporated the following: nondrinker, low to moderate consumption (≤1 drink per day), and high consumption (>1 drink per day). We included the dietary intake of protein and energy measured by 24-hour food recall at the baseline MEC because population-based evidence suggested that they could affect frailty and mortality[29–31]; we used certain cutoffs to categorize them as ordinal variables to approximate quartiles in cancer survivors, and the same cutoffs were applied for participants without a cancer history. Self-reported cancer-related variables included the following: history of more than 1 cancer, age at cancer diagnosis (<60 vs ≥60 years), time elapsed since the cancer diagnosis (0–4, 5–9, or ≥10 years), and cancer type (breast cancer, prostate cancer, colorectal cancer, melanoma, or other). Because of the wide time span associated with the study population, we included the survey year in our analysis. Covariates were selected on the basis of a priori knowledge regarding their relationships with exposure and outcome.

Statistical Analysis

The overall analytical strategy was mainly based on an unweighted approach because the NHANES weight was generated to reflect the distribution of the general US population, whereas we focused on older adults who were heterogeneous in comparison with the general population.

First, we descriptively summarized distributions of the FI and other covariates in older cancer survivors and adults without a cancer history. Because prior studies[32,33] suggested that age, sex, and race were associated with burdens of illnesses and function, we used a generalized linear model adjusting for age, sex, and race to investigate whether the distributions of the FI differed between older cancer survivors and those without a cancer history. Kaplan-Meier curves were used to visualize the risk of all-cause mortality by FI categories in these 2 groups. We used the follow-up in NHANES as the time scale, and log-rank tests were performed to examine whether the risk differed by FI categories. We then estimated the death rate by FI categories based on the numbers of deaths and person-years contributed by participants.

Univariate and multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the FI, with FI ≤ 0.10 used as the reference. The multivariable model adjusted for age, sex, race, education, marital status, BMI, smoking, alcohol drinking, protein and energy consumption, and survey year; for cancer survivors, we additionally adjusted for the age at cancer diagnosis and a history of more than 1 cancer. The proportionality assumption of the Cox model was examined by visual inspections of log(−log[S]) plots, and there was no violation of the assumption.[34] In addition, we corrected for the NHANES sampling weight in multivariable models adjusting for the same covariates to explore whether effect measures of the FI changed substantially. We conducted tests for trend by treating the FI as a continuous variable in the model. To depict the potential nonlinear dose-response relationship between the FI and the risk of death, we applied a restricted cubic spline[35] in the multivariable Cox models, with FI = 0.21 used as the reference for the dose-response curve; we assessed the nonlinearity by

contrasting the model fit using restricted cubic splines with a model fit assuming linearity for the FI via a likelihood ratio test.[36]

Subgroup analyses were based on age, sex, race, and nutrition-related factors (BMI, alcohol consumption, and dietary intake of protein and energy). Because of sample size considerations, we treated frailty as a binary variable in subgroup analyses (FI > 0.21 vs FI ≤ 0.21). An interaction term between the factor used for stratification and frailty was added to the model, and we used Wald tests to examine whether there were significant interactions between them.

In sensitivity analyses, multiple imputations fit with 5 replicates of chained equations were applied to examine whether missing data substantially affected the association pattern of the FI. We further applied the primary multivariable model to participants with breast cancer, prostate cancer, colorectal cancer, and melanoma separately and explored whether associations identified in the primary analysis changed for these specific types of cancer; we treated frailty as a binary variable (FI > 0.21 vs FI ≤ 0.21) in analyses for specific cancer types for sample size consideration.

Two-sided values of $P < .05$ were considered to be statistically significant. Statistical analyses were conducted with Stata 15.0 (StataCorp LLC, College Station, Texas) and SAS v9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Table 1 presents distributions of study characteristics. Overall, for the 2050 older cancer survivors, the mean age at the baseline was 72.6 years (SD, 7.1 years); 5.9% were fit (FI ≤ 0.10), 38.2% were prefrail (0.10 < FI ≤ 0.21), and 55.9% were frail (FI > 0.21). Older adults without a cancer history were slightly younger than the cancer survivors, and their mean age was 70.0 years (SD, 7.3 years); the FI distribution in older adults without cancer (11.0% fit, 41.1% prefrail, and 47.9% frail) was different from that in cancer survivors, and the generalized linear model indicated that the difference was statistically significant ($P < .01$). Sex was almost evenly distributed regardless of prior cancer history. Compared with older adults without a cancer history, older cancer survivors had a higher proportion of White participants (cancer survivors, 74.9%; no cancer history, 50.8%). Detailed distributions of other covariates can be found in Table 1. In older cancer survivors and adults without a cancer history, the prevalence of frailty increased with age (Supporting Table 2); in each age category, cancer survivors (60–69 years, 45.4%; 70–79 years, 56.6%; and ≥80 years, 69.7%) had a higher prevalence of frailty than their cancer-free counterparts (60–69 years, 39.1%; 70–79 years, 51.8%; and ≥80 years, 67.7%), and this pattern was more substantial among participants younger than 80 years. More detailed distributions of frailty by study characteristics are present in Supporting Table 2.

A total of 738 older cancer survivors and 2521 participants without a cancer history died during the follow-up, and the former had a slightly shorter median follow-up (cancer survivors, 6.1 years; no cancer history, 6.9 years). The Kaplan-Meier curves suggested that the risk of death significantly increased with the FI in both populations (log-rank *P* values

< .01; Fig. 1A,B), although the survival curves declined more drastically for older cancer survivors. The overall death rate of cancer survivors was 5.4 per 100 person-years, which was 50% higher than the death rate of adults without a cancer history (3.6 deaths per 100 person-years); similarly, at each level of the FI (Table 2), the death rate of older cancer survivors (1.9 per 100 person-years for FI ≤ 0.10, 3.4 per 100 person-years for 0.10 < FI ≤ 0.21, and 7.5 per 100 person-years for FI > 0.21) was higher than that of participants without a cancer history (1.4 per 100 person-years for FI ≤ 0.10, 2.4 per 100 person-years for 0.10 < FI ≤ 0.21, and 5.4 per 100 person-years for FI > 0.21). The multivariable Cox model (Table 2) suggested a positive association between the FI and all-cause mortality (adjusted hazard ratio [aHR] for FI > 0.21 vs FI ≤ 0.10, 2.80; 95% CI, 1.73–4.53; *P* trend < .01) in older cancer survivors; similar patterns were also observed for older adults without a cancer history (aHR for FI > 0.21 vs FI ≤ 0.10, 2.75; 95% CI, 2.29–3.32; *P* trend < .01). For older cancer survivors, effect measures of the FI obtained in the model correcting for sampling weight increased to some extent (aHR for FI > 0.21 vs FI ≤ 0.10, 3.41; 95% CI, 1.96–5.94; *P* trend < .01), but the corresponding 95% CIs largely overlapped that of the primary model. Correcting for sampling weight did not change the effect measures in older adults without a cancer history. Results from restricted cubic splines were in line with primary Cox models and suggested that the risk of death increased with the FI in a monotonic dose-response pattern (Fig. 2A,B); the likelihood ratio tests did not support nonlinearity of the dose-response curves (*P* nonlinearity for cancer survivors = .24; *P* nonlinearity for no cancer history = .08).

In subgroup analyses (Table 3), frailty was associated with a higher risk of all-cause mortality in all subgroups. We did not observe any significant interaction in older adults without a cancer history (*P* interaction > .05). For older cancer survivors, a significant interaction was identified for age; specifically, in comparison with survivors 75 years old or older (aHR, 1.59; 95% CI, 1.27–1.97), the effect measure of frailty was much more substantial for survivors 60 to 74 years old (aHR, 2.62; 95% CI, 2.00–3.43; *P* interaction < .01). Although effect measures of frailty were largely different by BMI values in older cancer survivors (aHR for BMI < 30 kg/m^2, 1.92; 95% CI, 1.59–2.33; aHR for BMI ≥ 30 kg/m^2, 3.00; 95% CI, 2.04–4.40), the interaction was only marginally significant (*P* interaction = .06). No significant interactions were identified in other sets of subgroup analyses.

After multiple imputation, the effect measures of the FI in both study populations slightly increased, but their 95% CIs largely overlapped those estimated from primary multivariable models (Supporting Table 3). Positive associations between frailty and the risk of all-cause mortality were observed for individuals with a history of breast cancer, prostate cancer, colorectal cancer, or melanoma, although the effect measure for colorectal cancer was not statistically significant (Supporting Table 4).

DISCUSSION

Our study suggests that older cancer survivors have a higher prevalence of frailty than older adults without cancer, and this phenomenon may be caused by the effect of cancer-related pathogenesis (eg, chronic inflammation) accelerating aging processes and toxicities

of antitumor treatment.[37,38] The multivariable analyses suggest that frailty is associated with a higher risk of all-cause mortality in older adults regardless of prior cancer history. The magnitude of association between the burden of frailty and mortality is similar between older cancer survivors and adults without a cancer history, and it exists in a monotonic dose-response pattern. However, within the same level of the FI, older cancer survivors have a higher risk of death than their cancer-free counterparts, which could be caused by the synergistic effects between frailty and cancer-related burden.

We observed that the HR of frailty was less substantial for cancer survivors 75 years old or older than for younger survivors. One speculation is that, among older cancer survivors, the life expectancy of those 75 years old or older is much shorter than that of younger counterparts; this predisposes survivors 75 years old or older to an inherently high risk of death that is less likely to be affected by the frailty burden. Obesity has the potential to affect multiple biological pathways (eg, insulin signaling, inflammation, and apoptosis) that are relevant to cancer recurrence, progression, and long-term treatment toxicities,[39–41] and this suggests that it can enhance the impact of frailty on the mortality of cancer survivors in a synergistic manner. Although we found that the point estimate of frailty was much larger in survivors with higher BMIs, the Wald test suggested only a marginally significant interaction, and this indicates that the potential modification effect of obesity should be further verified by larger studies in the future. On the other hand, we did not observe any interaction between frailty and age or BMI among older adults without a cancer history; one possibility is that negative effects of cancer treatment (eg, treatment toxicities) and preexisting factors relevant to carcinogenesis (eg, chronic inflammation) make cancer survivors heterogeneous from their cancer-free counterparts, and this leads to distinct outcomes when we are testing for interaction.

Our results are in line with previous studies investigating associations between frailty and the risk of death in older cancer survivors. A cohort study measured frailty by a 36-item index in 518 older adults with a cancer history (median age, 72 years) and followed them for 3.7 years on average; the multivariable analysis suggested that frailty was associated with a higher risk of all-cause mortality (HR, 2.36; 95% CI, 1.51–3 .68).[11] Another cohort study used 35 illnesses and functional items to reflect frailty at the baseline in 1280 older patients with breast cancer (mean age, 72.4 years) and followed them for a maximum of 7 years; the results found that frailty was associated with a 1.4-fold relative increase in the risk of all-cause mortality.[12] Moreover, a cohort study using a sample (median age, 63 years) from the Women's Health Initiative measured frailty by a score derived from the Fried phenotype and reported that frail women (vs nonfrail women) had a 40% relative increase in their mortality risk after a cancer diagnosis.[13] In contrast to the aforementioned studies, our analysis considered both sexes, used a more comprehensive frailty measure, considered nutritional and lifestyle factors, and compared the results between older adults with a cancer history and those without a cancer history; this makes the estimated association more robust and indicates a consistent prognostic role of frailty in older adults regardless of their prior cancer history.

Several mechanisms may partially explain the positive association between frailty and mortality identified in our analysis. First, previous studies indicated a link between frailty

and chronic inflammation.[42,43] A meta-analysis[43] synthesized 32 cross-sectional studies and reported that frailty was associated with higher blood levels of C-reactive protein and interleukin 6, which have been found to be related to a higher risk of all-cause mortality in prior population-based studies.[44–47] Second, frail adults have a higher rate of coexisting immunosenescence, although their causal relationship has not been fully uncovered[48,49]; this suggests that immune surveillance in older frail individuals with a cancer history can be compromised, and this increases the risk of cancer recurrence or an unfavorable prognosis.[50–52] For example, Mima et al[51] analyzed 729 patients with stage I to III colorectal cancer (46% were ≥75 years old; the median follow-up was 3.5 years); they reported that patients with frailty had a higher risk of recurrence than nonfrail patients (HR, 1.70; 95% CI, 1.25–2.31).

Our study has several notable strengths in its design and analysis. First, we used a 45-item FI that incorporated preexisting illnesses, functional status, clinical measures, and biomarkers; this made the exposure comprehensive.[18,19] Second, using death certificates to measure mortality ensured the robustness of our outcome and largely reduced the risk of misclassification. Third, a model correcting for the sampling weight, a dose-response analysis, and an application of multiple imputation further validated the results obtained in the primary multivariable model. Fourth, comparing results between older cancer survivors and counterparts without a cancer history can make the conclusions more generalizable to older populations regardless of their cancer status. Fifth, compared with geriatric assessment (GA), using an FI in NHANES samples can better reflect the frailty burden of older cancer survivors in real-world settings. In oncology practices, clinicians use GA to identify frailty, and it is usually initiated before cancer treatment to improve communications, decision-making, and disease management.[53–55] However, cancer survivors' frailty levels can change after treatment; this indicates that pretreatment GA-based frailty may not accurately reflect the frailty burden in the survivorship period, and the nature of clinical settings can make a GA estimate the frailty burden with bias in older adults diagnosed with cancer.

In our study, several limitations should still be noted. Participants self-reported their comorbidities, and this is less accurate than a medical record review or measures from claims data. The health status of participants can change during the follow-up, whereas the FI can be established only on the basis of baseline measures; this makes it hard to perform a time-varying analysis. Because of the study design used for NHANES, a large proportion of the participants are not incident cancer cases. In our study sample, 46.3% were diagnosed 10 or more years before the baseline assessment, and 71% survived for at least 5 years since their cancer diagnosis. This raises the possibility of a survivorship bias that should be considered when one is interpreting the results because those with shorter survival times may already be deceased before the baseline assessment. In addition, the cancer treatment and the stage at diagnosis are very important factors that can affect survival, but the NHANES did not measure these variables at the interview; this leads to some residual confounding in the analysis of cancer survivors.

In light of the positive association between frailty and the risk of death, health interventions, either behavioral or nutritional, should be considered to reduce the impact of frailty among older cancer survivors because improving lifestyle behaviors has been found to have

favorable effects on measures incorporated into the FI such as comorbidities, functional status, and other patient-reported outcomes, including quality of life.[17,56–59]

In conclusion, older cancer survivors will be at higher risk for mortality if they are living with substantial burdens of frailty. Understanding the frailty status is informative for developing long-term interventions for promoting the health of older cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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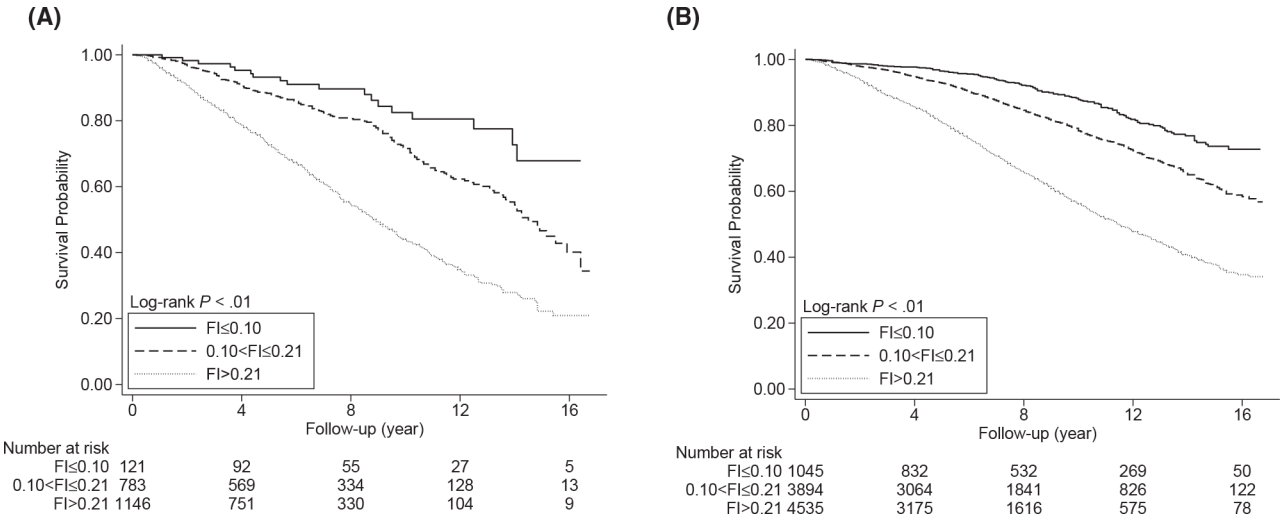

Figure 1.

Kaplan-Meier curves for (A) older cancer survivors and (B) older adults without a cancer history. FI indicates frailty index.

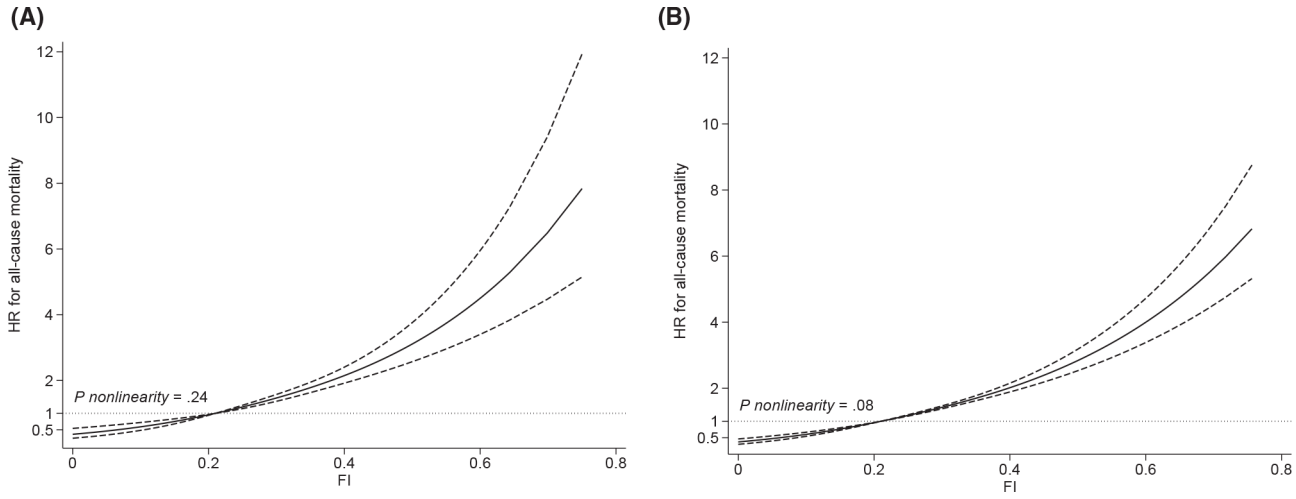

Figure 2.

Restricted cubic splines depicting dose-response relationships between the FI and the risk of all-cause mortality in (A) older cancer survivors and (B) older adults without a cancer history. The model adjusted for the following: age, sex, race, education, marital status, body mass index, smoking, alcohol drinking, protein and energy consumption, age at cancer diagnosis (for cancer survivors), history of more than 1 cancer (for cancer survivors), and survey year. The solid lines are fitted lines, the dashed lines are the 95% confidence intervals, and the dotted lines are the reference lines. FI = 0.21 is the reference in the curve. FI indicates frailty index; HR, hazard ratio

TABLE 1.

Study Characteristics of Older Cancer Survivors and Adults Without a Cancer History

Study Characteristic	Cancer Survivors (n = 2050), No. (%)	No Cancer History (n = 9474), No. (%)
FI		
≤0.10	121 (5.9)	1045 (11.0)
>0.10 to 0.21	783 (38.2)	3894 (41.1)
>0.21	1146 (55.9)	4535 (47.9)
Age at interview		
60–69 y	712 (34.7)	4949 (52.2)
70–79 y	837 (40.8)	2911 (30.7)
≥80 y	501 (24.4)	1614 (17.1)
Sex		
Female	978 (47.7)	4842 (51.1)
Male	1072 (52.3)	4632 (48.9)
Race		
White	1536 (74.9)	4817 (50.8)
Black	277 (13.5)	1910 (20.2)
Other	237 (11.6)	2747 (29.0)
Education		
High school or less	995 (48.5)	5795 (61.2)
Attended college	546 (26.6)	2100 (22.2)
Graduated from college	509 (24.8)	1579 (16.6)
Marital status		
Not married	764 (37.3)	3897 (41.1)
Married or living with partner	1286 (62.7)	5577 (58.9)
BMI		
<25.0 kg/m^2	607 (29.6)	2486 (26.2)
25.0–29.9 kg/m^2	768 (37.5)	3555 (37.5)
≥30.0 kg/m^2	675 (32.9)	3433 (36.3)
Smoking status		
Never	877 (42.8)	4590 (48.4)
Current	198 (9.7)	1228 (13.0)
Former	975 (47.5)	3656 (38.6)
Alcohol consumption		
No consumption	689 (33.6)	3460 (36.5)
≤1 drink per day	565 (27.6)	2110 (22.3)
>1 drink per day	796 (38.8)	3904 (41.2)
Protein intake		
<51.4 g/d	505 (24.6)	2732 (28.8)
51.4–68.0 g/d	511 (24.9)	2415 (25.5)
68.1–86.2 g/d	521 (25.4)	2103 (22.2)
≥86.3 g/d	513 (25.1)	2224 (23.5)

Study Characteristic	Cancer Survivors (n = 2050), No. (%)	No Cancer History (n = 9474), No. (%)
Energy intake		
<1351.0 kcal/d	505 (24.6)	2866 (30.2)
1351.0–1735.4 kcal/d	519 (25.3)	2342 (24.7)
1735.5–2180.9 kcal/d	510 (24.9)	2137 (22.6)
≥2181.0 kcal/d	516 (25.2)	2129 (22.5)
History of more than 1 cancer		
No	1816 (88.6)	—
Yes	234 (11.4)	—
Age at cancer diagnosis		
<60 y	808 (39.4)	—
≥60 y	1242 (60.6)	—
Time elapsed since cancer diagnosis		
1–4 y	595 (29.0)	—
5–9 y	506 (24.7)	—
≥10 y	949 (46.3)	—
Cancer type		
Breast cancer	353 (17.2)	—
Prostate cancer	414 (20.2)	—
Colorectal cancer	170 (8.3)	—
Melanoma	115 (5.6)	—
Other	998 (48.7)	—
Survey year		
1999–2002	434 (21.1)	2147 (22.7)
2003–2006	475 (23.2)	2272 (24.0)
2007–2010	643 (31.4)	2752 (29.0)
2011–2014	498 (24.3)	2303 (24.3)

Abbreviations: BMI, body mass index; FI, frailty index.

Column percentages are reported.

TABLE 2.

Association Between the FI and Mortality in Older Cancer Survivors and Those Without a Cancer History

FI	No. of Deaths/Total	Person-Years	Deaths per 100 Person-Years (95% CI)	cHR (95% CI)	aHR (95% CI)[a]	aHR (95% CI)[b]
Cancer survivors (n = 2050)						
≤0.10	18/121	963.8	1.9 (1.2–3.0)	REF	REF	REF
>0.10 to 0.21	198/783	5742.3	3.4 (3.0–4.0)	1.92 (1.19–3.11)	1.39 (0.86–2.27)	1.58 (0.89–2.80)
>0.21	522/1146	6940.7	7.5 (6.9–8.2)	4.49 (2.80–7.18) *P* trend < .01	2.80 (1.73–4.53) *P* trend < .01	3.41 (1.96–5.94) *P* trend < .01
No cancer history (n = 9474)						
≤0.10	128/1045	8843.2	1.4 (1.2–1.7)	REF	REF	REF
>0.10 to 0.21	757/3894	31,088.5	2.4 (2.3–2.6)	1.73 (1.43–2.09)	1.38 (1.14–1.66)	1.28 (1.05–1.56)
>0.21	1636/4535	30,577.3	5.4 (5.1–5.6)	4.03 (3.37–4.83) *P* trend < .01	2.75 (2.29–3.32) *P* trend < .01	2.71 (2.23–3.29) *P* trend < .01

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; FI, frailty index; REF, reference.

[a]The multivariable Cox model adjusted for the following: age, sex, race, education, marital status, body mass index, smoking, alcohol drinking, protein and energy consumption, age at cancer diagnosis (only for participants with a cancer history), history of more than 1 cancer (only for participants with a cancer history), and survey year.

[b]The multivariable model corrected for the sampling weight and adjusted for the same set of covariates as the main model.

TABLE 3.

Association Between Frailty (FI > 0.21) and All-Cause Mortality in Subgroups Defined by Study Covariates

	Cancer Survivors (n = 2050)		No Cancer History (n = 9474)	
	No. of Deaths/Total	**aHR (95% CI)**	**No. of Deaths/Total**	**aHR (95% CI)**
Age				
<75 y	274/1160	2.62 (2.00–3.43)	1141/6707	2.25 (1.99–2.54)
≥75 y	464/890	1.59 (1.27–1.97) *P* interaction < .01	1380/2767	2.05 (1.82–2.31) *P* interaction = .13
Sex				
Female	305/978	2.46 (1.85–3.28)	1120/4842	2.18 (1.91–2.49)
Male	433/1072	1.89 (1.53–2.33) *P* interaction = .19	1401/4632	2.03 (1.82–2.27) *P* interaction = .46
Race				
White	581/1536	2.06 (1.70–2.50)	1510/4817	2.12 (1.89–2.37)
Non-White	157/514	2.00 (1.38–2.90) *P* interaction = .89	1011/4657	2.05 (1.79–2.34) *P* interaction = .67
BMI				
<30 kg/m^2	541/1375	1.92 (1.59–2.33)	1773/6041	2.07 (1.88–2.29)
≥30 kg/m^2	197/675	3.00 (2.04–4.40) *P* interaction = .06	748/3433	2.16(1.83–2.55) *P* interaction = .85
Alcohol drinking				
No	256/689	2.08 (1.54–2.80)	955/3460	2.30 (1.99–2.65)
Yes	482/1361	2.15 (1.75–2.64) *P* interaction = .88	1566/6014	2.00 (1.80–2.23) *P* interaction = .10
Protein intake				
<68.1 g/d	413/1016	2.18 (1.73–2.76)	1530/5147	2.10 (1.88–2.35)
≥68.1 g/d	325/1034	1.97 (1.54–2.51) *P* interaction = .68	991/4327	2.09 (1.83–2.38) *P* interaction = .93
Energy intake				
<1735.5 kcal/d	404/1024	2.08 (1.65–2.63)	1508/5208	2.11 (1.88–2.36)
≥1735.5 kcal/d	334/1026	2.04 (1.60–2.60) *P* interaction = .96	1013/4266	2.09 (1.83–2.39) *P* interaction = .80

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; FI, frailty index.

The models adjusted for the same sets of covariates as those in Table 2 except for the ones used for stratification.