HHS Public Access

Author manuscript

J Geriatr Oncol. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

J Geriatr Oncol. 2021 January ; 12(1): 96–101. doi:10.1016/j.jgo.2020.04.015.

Health-related and sociodemographic factors associated with physical frailty among older cancer survivors.

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Abstract

Objective: The purpose of this study was to examine factors associated with frailty in older cancer survivors.

Materials and methods: This is a cross-sectional study using data from the National Social Health and Aging Project (NSHAP) Wave 2, and includes an in-home, nationally representative sample of community-dwelling adults ≥50 years and older from the United States. Frailty score was computed for each individual using a modified 4-point scale based on the phenotypic frailty. Ordinal logistic regression was used to characterize the association between health-related, sociodemographic factors and frailty.

Results: Among the 3377 participants, 461 were cancer survivors (answered “yes” to “ever have cancer other than skin cancer”). A final sample of 394 cancer survivors were included: 59 participants (16.1%) were frail, 219 participants were pre-frail (59.8%), and 88 participants were non-frail (24.0%). The univariate analyses showed increasing age (OR 1.48; CI 1.29–1.72; *p*-value <.001), comorbidities (OR 1.43; CI 1.25–1.64; p-value <.001), depression (OR 1.27; CI 1.19–1.35; p-value <.001) and low mobility (OR 1.55; CI 1.37–1.78; p-value <.001) were associated with frailty. Participants with high self-rated (good/very good/ excellent) physical health (OR 0.18; CI 0.11–0.30; $p < .001$) and mental health (OR 0.27; CI 0.15–0.50; $p < .001$) were less likely to be

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Author Contributions

Conceived and designed the study: Koll, Beadle, and Semin.
Analyzed data: High.
Interpreted the data: All authors.
Wrote the manuscript: Koll, Beadle, Semin, Keehn, Brodsky, and High.
Edited the manuscript: All authors.
All authors revised for intellectual content and approved the final version of the manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

frail. In a multivariate model, frailty was associated with age, self-rated physical health, depression, ability to perform activities of daily living, and mobility ($p < .05$).

Conclusion: The findings highlight the importance of incorporating geriatric assessment into cancer survivorship to prevent and delay the progression of frailty.

Keywords

Frailty; Geriatric oncology; Survivorship; Older adults, cancer survivors

1. Introduction

By 2040, there will be 26.1 million cancer survivors and 73% will be patients 65 years and older [1]. Frailty is a geriatric syndrome that represents dysregulations across multiple physiologic systems and a diminished capacity to recover from even minimal stressors [2]. The clinical consequences of frailty include falls, worsening mobility, disability, hospitalizations, and death [3]. Physical frailty is an important, “medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death” [4]. Frailty is distinct from disability and comorbidity [5].

Comorbidities such as cancer contribute to the development of frailty and disability [5]. Frailty is an important predictor of treatment tolerance and mortality during treatment in solid [6–9] and hematological cancers [10,11]. Frail older cancer survivors have a lower perceived quality of life [12]. Clinical management of frailty should focus on the prevention, delay, and reduction in the severity of frailty. Experts in the frailty field have advised that physical frailty is distinct from the, “broader definition of frailty, which is a general state or condition,” and that physical frailty can be prevented and is a manageable condition [4]. Identifying physical frailty and potential contributing factors in cancer survivorship is important to improve survival and quality of life for older cancer survivors.

The National Social Health and Aging Project (NSHAP) Wave 2 is an in-home, nationally representative probability sample of older adults from households across the United States. This data set provides a unique opportunity to explore the impact of health and sociodemographic factors on frailty in older cancer survivors. Based on clinical observations as well as previous literature, we assessed comorbidity [13], cognition [14], depression [15], ability to perform activities of daily living and instrumental activities of daily living [13], social function [16], and self-rated health [16]. We hypothesized that age-related factors would contribute to frailty status, particularly those that are associated with functional limitations and comorbidity.

2. Materials and Methods

2.1. Study Design

This is a cross-sectional study design. We used data from the National Social Health and Aging Project (NSHAP) Wave 2 collected between August 2010 and May 2011.

2.2. Participants

Among 3377 older adults, age ≥ 50 years in NSHAP Wave 2,461 individuals indicated “yes” to “ever have cancer other than skin cancer”. Individuals missing key covariates were excluded ($n = 67$), yielding a final sample of 394 individuals.

2.3. Ethical Considerations

All individuals participating in NSHAP Wave 2 provided written informed consent and the protocol was approved by the institutional review boards at the University of Chicago and the National Opinion Research Center (NORC). Secondary data analysis was approved by the Institutional Review Board at the University of Nebraska Medical Center.

2.4. Data Collection

Frailty was calculated with four components originally described by Fried et al. 2001 using a modified 4-point physical frailty scale [17,18]. Participants received one point for each of the four criteria: self-rated exhaustion, weakness, slow gait, and low physical activity. A total frailty score (0–4) was calculated and each person was categorized as non-frail (0), pre-frail (1–2), or frail (3–4).

Self-rated exhaustion was defined based on two questions from the modified Center for Epidemiologic Studies Depression (CES-D) scale [19] regarding participants feeling that everything was an effort and could not get going. A frailty point was assigned if they answered “occasionally” or “most of the time” to either question.

Weakness was measured using 5 timed serial chair stands (TCS) [20]. A frailty point was assigned if they completed the task in ≥17 s or could not complete the task.

Gait Speed was calculated using the best time of two trials of a three-meter Timed Up and Go (TUG) test [20]. A frailty point was assigned if the faster of the two walks were greater than 6 s or if they could not complete the task.

Physical Activity was measured using a survey question regarding the frequency of participation in rigorous physical activity. A frailty point was assigned if they indicated they participated 1 to 3 times per month or less.

Independent Variables.—Total scores for the following independent variables were calculated. Scoring criteria can be found in Appendix A.

Comorbidity.: A summed NSHAP comorbidity score (0–12) was calculated consisting of 15 categories using a method described by Vasilopoulos, et al. [21] Since all subjects are cancer survivors, the component for cancer was not included in the comorbidity score used in the statistical models.

Cognition.: Cognition was measured using a modified Montreal Cognitive Assessment (MoCA-SA) consisting of 18 items [22,23]. The raw scores were converted to a global MoCA score (0–30) that is highly correlated with the original MoCA [24]. A score of22 or

less is indicative of a positive screen for cognitive impairment based on cut-off identified in community-dwelling older adults [25].

Depression.: Depression was measured with a shortened version of the Center for Epidemiologic Studies Depression Scale (CES-D) [19] consisting of 11 items. A global score ranging from 0 to 22 was created using criteria used in previous publications [26]. A score of 9 or greater is indicative of frequent depressive symptoms [26].

Physical function.: Activities of daily living (ADLs) and instrumental activities of daily living (IADLs) global scores were calculated based on self-rated difficulty questions for each subcomponent using previously published scoring criteria [18]. Mobility was calculated using the best time of two trials of a three-meter Timed Up and Go (TUG) test.

Social function.: Socialization was measured using two survey questions focused on frequency (within the past year) of socializing with friends or relatives and attendance at meetings or organized activities. They were stratified into 2 groups (< 1 time/month or > 1 time/month).

Self-reported physical and mental health.: Self-rated health was assessed using two survey questions asking individuals to rate their physical and mental health as (1) poor, (2) fair, (3) good, (4) very good, or (5) excellent.

Covariates—The following covariates were included: age, gender, ethnicity/race, marital status, education, and time since diagnosis (years).

2.5. Data Analysis

The statistical model evaluated frailty as the outcome with three levels (frail, pre-frail, non-frail) with a proportional odds logistic regression model. Odds ratios based on a cumulative logit with 95% confidence intervals were evaluated for each variable to determine if it influenced the likelihood of a person being frail (odds ratio greater than 1) or if it decreased the likelihood of frailty (odds ratio less than 1).

Because many of these explanatory factors are not independent of each other, yet not so strongly related as to cause collinearity problems, a multivariate logistic regression model was also evaluated with frailty as the outcome variable. The few combinations of variables that were highly correlated with others (e.g., ADL and IADL) were not included together in the model development. A backward selection technique was employed to drop insignificant variables one-at-a-time. In the final model, the effect of each variable is adjusted by other variables retained in the model with 95% confidence intervals for the odds ratios computed based on the profile likelihood method. All statistical significance tests for odds ratios are two-sided. Statistical analyses were generated with PROC LOGISTIC from SAS/STAT software, Version 9.4 (© 2002–2012) of the SAS System for Windows (Cary, NC).

3. Results

3.1. Sample Description

The sample sociodemographic and health characteristics are displayed in Table 1. The sample includes cancer survivors with a mean age of 74 years with 73% of the sample age 70 and older. There were fewer females (42%) than males. The participants were predominantly Caucasian (80%) and married or living with a partner (75%). Fifty percent of the sample received education beyond high school. The most common site of cancer was prostate (28.2%) followed by breast (18.3%) and colon (10.2%). For the majority of the participants (62.5%), it had been greater than 5 years since they had cancer in any site. Frailty status was assessed in 366 participants, 59 participants (16.1%) were frail, 219 participants were pre-frail (59.8%), and 88 participants were non-frail (24.0%) (28 subjects had missing frailty data). For self-rated health, most participants rated themselves as either good, very good, or excellent on both mental (87.3%) and physical health (71.8%). Most participants (66.5%) had 2 to 5 comorbidities. More than half of the sample had MoCA scores greater than 22 (54.6%). Fifteen percent of the sample reported probable depression as measured by the CES-D. In the domain of physical function, 33.5% reported impairment in ADLs and approximately half of the sample reported impairment in IADLs (57.4%). A large portion of the sample had mobility limitations (72.3%). The majority of participants were able to spend time with friends and relatives at least once a month or more (76.1%), but over half the sample attended organized group meetings less than once a month (53.1%).

3.2. Health-Related and Sociodemographic Factors Associated with Physical Frailty

In the univariate models, we examined the odds ratios for independent variables to assess whether each one increased the likelihood of a person being frail (odds ratio greater than 1) or if it decreased the likelihood of being frail (odds ratio less than 1) in older cancer survivors (Table 2). The variables that were significantly associated with a lesser likelihood of being frail included higher education, marital status or living with significant others, better self-rated health, higher cognitive and physical function, and more frequent attendance at social events. The following variables were associated with increased frailty: increasing age, comorbidity, depression and low mobility (longer timed walk). For example, with each five-year increase in age, the odds ratio for frail versus non-frail is 1.48. The following covariates were not significantly associated with frailty in the univariate analysis: gender, ethnicity and time since diagnosis.

In the multivariate logistic regression model, the variables that were associated with frailty include age, self-rated health, depression, ability to perform activities of daily living and mobility (Table 3). Individuals were less likely to be frail if they had higher reported ADL functioning and better self-reported physical health. In contrast, older age, a higher depression score, and increased timed walk (lower mobility) were associated with frailty.

4. Discussion

In a nationally representative sample of older cancer survivors, the NSHAP-W2, we found that age, self-rated physical health, depression, disability, and mobility limitations were

associated with frailty, but cognition and comorbidity were not. Previous studies have examined the prevalence and prognostic importance of frailty in older patients diagnosed with cancer at the time of treatment initiation or in patients receiving active treatment [6,7,9,27–32]. In the current study, most of the sample are survivors beyond one year after diagnosis. The prevalence of frailty in this study is 16.1%, which is higher compared to 13% (p-value: 0.02) in participants without a history of cancer matched by age, gender, ethnicity and marital status in NSHAP Wave 2 (data not shown).The results of this study highlight the value of incorporating the principles of geriatrics into survivorship care plans. Identifying factors associated with frailty after completion of treatment is crucial to improve not only the rates of survivorship but also their quality of life.

The unique contributions of our study include the examination of frailty in older cancer survivors using a nationally representative sample and comprehensive characterization of health and function using geriatric assessment. Geriatric assessment is an important tool to evaluate and manage frail older adults. Understanding the prevalence of geriatric syndromes and their contribution to frailty can lay the groundwork for the design of interventions to prevent or delay the progression of frailty.

In this study, older age, depression, disability (impaired ability to perform activities of daily living), and mobility limitations are associated with frailty in older cancer survivors. Consistent with previous research in older adults without a history of cancer [15], we found an association between frailty and depression in older cancer survivors. Depression is consistently found to occur in more older adults suffering from chronic illnesses [33,34]. Other factors may be involved in the onset of depression or have indirect effects on frailty through depression. For example, older adults who were depressed during first-line chemotherapy treatment had a higher incidence of functional decline during treatment, hence influencing the development of frailty [35,36]. Our study expands on prior knowledge of frailty in older cancer survivors by demonstrating frailty increases with poor/fair self-rated physical health, increasing dependency in activities of daily living (ADLs), and mobility limitations. This finding suggests that frailty and self-rated health are associated with both objective and subjective measures of physical functioning. This is clinically relevant because self-rated health is an independent predictor of adverse health outcomes in the older adult population [37,38] as well as older cancer survivors [39]. Functional impairment is also associated with older cancer survivors' perceptions of disability and self-rated health, suggesting there may be bidirectional relationships between perceived health and resulting functional measures, including frailty [40]. Future research is needed using longitudinal methods to examine whether self-rated physical health is a predictor of long term frailty and poorer functional outcomes in older cancer survivors.

An unexpected finding is that comorbidity was not associated with frailty in this study. Comorbidity is hypothesized to be associated with frailty because both are highly prevalent with aging and chronic diseases may contribute to the development of frailty and worsen physiological reserve, if not managed. Our sample includes a significant number of older adults with a higher comorbidity burden (>50%). A possible explanation for this finding is that comorbidity may have an indirect effect on frailty status through functional impairment and low physical activity. In older cancer survivors, comorbidity, regardless of time since

diagnosis, correlates with impaired functional status [41], low physical activity [42], and participation restrictions [43].

We also found that cognition was not associated with frailty. A previous study reported an 'accelerated' decline in self-reported cognition was associated with frailty and comorbidity in older cancer survivors [44]. However, this study only included individuals who were not impaired based on a negative cognitive screening test, whereas our study included a significant number of older adults with possible cognitive impairment as defined by a MoCA score of <22 (45%). Another study in older patients with hematological malignancies found a correlation of small effect size between probable cognitive impairment (assessed by cognitive tasks, e.g., delay recall task), and frailty status using the Fried criteria [45]. The inconsistent findings may be explained by differences in patient population (patients at diagnosis versus cancer survivors >1 year after diagnosis) and different cognitive measures (executive functioning and delayed recall versus global cognitive function). More research is needed to further elucidate the relationships between frailty and cognition in cancer survivors that include patients with and without cognitive impairments and using more sensitive and comprehensive tasks.

A strength of this study is that it included a large, nationally representative sample of older cancer survivors to assess the relationship between frailty and sociodemographic and health factors. Geriatric assessment was available to robustly characterize geriatric syndrome in a cohort of older cancer survivors. The sample consists of over 60% of participants greater than 5 years since the last cancer diagnosis who are an understudied population. However, this study is not without limitations. Because the present study includes a cross-sectional design, we cannot make conclusions about cause and effect relationships between self-rated health, functional status, ability to perform activities of daily living, depression, mobility, and frailty. In addition, this study did not compare older adults without cancer to older cancer survivors, thus, it is unknown if older cancer survivors have worse self-rated health, depression, disability, and mobility limitations. Furthermore, data regarding treatment and incidence of disease/tumors are not available and would provide valuable insight into how different types of cancer treatment as well as aggressiveness of the cancer can modify frailty status. Finally, this sample was predominantly Caucasian and a majority were high school educated and married.

These findings have clinical implications for health care providers who work with older cancer survivors, and for future planning for current patients with cancer. First, frailty screening should be incorporated throughout survivorship. Second, self-rated health, depression screening, and perceived disability are subjective measures that can be used to identify factors that can be addressed in interventions. Third, the management of depression and interventions, such as exercise, to improve functioning and mobility may be important targets for preventing or delaying the progression of frailty in older cancer survivors.

5. Conclusions

Frailty is an important marker of poor outcomes, including falls, worsening mobility, disability, hospitalizations, and death [3]. In this population-based sample, self-rated

physical health, depression, ability to perform activities of daily living, and mobility were associated with frailty. However, comorbidity and cognition were not associated with frailty. These observations can help identify patients who may be at high risk for poor outcomes and serves as a basis for designing interventions to improve the quality of life in older cancer survivors.

Acknowledgements

The project described is supported by the National Institute of General Medical Sciences, U54 GM115458, which funds the Great Plains IDeA-CTR Network. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Funding was also provided by the Division of Geriatrics, Gerontology, and Palliative Medicine at the University of Nebraska Medical Center. JNB received funding from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20 GM130447.JNB also received funding from Program of Excellence funds from the University of Nebraska.

Appendix A. Appendix

Domain	Tool	Scale
Comorbidities	Modified NSHAP Comorbidity Scale [1]	0 (no comorbidities) – 12 (many comorbidities)
Cognition	Montreal Cognitive Assessment (MoCA) Global Score [2]	Range 0–30; <22 indicates possible cognitive impairment
Depression	Center for Epidemiologic Studies Depression Scale (CES-D) [3]	Range 0–22; ≥9 indicative of frequent depressive symptoms
Functional status	Activities ofDaily Living (ADLs) Difficulty Score [4]	0 (fully dependent)–7 (fully independent)
	Instrumental Activities ofDaily Living (IADLs) Difficulty Score [5]	0 (fully dependent)–8 (fully independent)

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Table 1

Sample demographic and health characteristics ($N = 394$).

Variables		N (%)
Age (years)	<60	5 (1.3%)
Mean (standard deviation): 74 (7.4)	60–64	39 (9.9%)
Median: 74	65–69	61 (15.5%)
Range: 54–93	70–74	104 (26.4%)
	75–80	84 (21.3%)
	>80	100 (25.4%)
Gender	Male	227 (57.6%)
	Female	167 (42.4%)
Race	Caucasian	315 (79.9%)
	African American	44(11.2%)
	Hispanic	22 (5.6%)
	Other	10 (2.5%)
Marital status	Married or living with partner	296 (75.1%)
	Divorced or separated	29 (7.4%)
	Widowed	62 (15.7%)
	Single, never married	7 (1.8%)
Education	<High School	49 (12.4%)
	High School/GED	153 (38.8%)
	Associate's degree	81 (20.6%)
	Bachelor's degree	67 (17.0%)
	Graduate degree	43 (10.9%)
Most recent cancer site	Breast	72 (18.3%)
	Colon	40 (10.2%)
	Prostate	111 (28.2%)
	Lung	20 (5.1%)
	Lymphoma/Leukemia	16 (4.1%)
Time since most recent cancer site Mean (in years): 10.21 (11.28)	1 year or less	43 (11.2%)
	From 1 to 5 years	101 (26.3%)
	greater than 5 years	240 (62.5%)
Frailty score	Non-frail (Score = 0)	88 (24.0%)
	Pre-frail (Score = 1–2)	219 (59.8%)
	Frail (Score = 3–4)	59 (16.1%)
Self-rated health		
Mental	(Good / very good / excellent)	344 (87.3%)
Physical	(Good / very good / excellent)	282 (71.8%)
Comorbidity *	0–1	111 (28.2%)
	2–5	262 (66.5%)
	6–9	21 (5.3%)
Cognitive function		

Variables		N (%)
Cognitive impairment	MoCA score > 22	215 (54.6%)
	MoCA score ≤ 22	179 (45.4%)
Psychological function		
Depression	CES-D score < 9	334 (84.8%)
	CES-D score ≥ 9 (Possible depression)	60 (15.2%)
Physical function		
ADL * impairment (<7)	Yes	132 (33.5%)
	No	262 (66.5%)
IADL * impairment (<8)	Yes	226 (57.4%)
	No	168 (42.6%)
Mobility * impairment for 3 m walk in seconds (s) (best of 2 trials)	Yes (8+ s) Major	28 (7.4%)
	Yes (4–7 s) Minor	244 (64.9%)
	No (<3 s)	104 (27.7%)
Social function		
Socialization with friends and relatives in the past year	Less than once a month	82 (23.9%)
	Once a month or more often	261 (76.1%)
Attendance at meetings of organized groups in the past year	Less than once a month	179 (53.1%)
	Once a month or more often	158 (46.9%)

MoCA: Montreal Cognitive Assessment; CES-D: Center for Epidemiologic Studies Depression Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living.

* NSHAP comorbidity score: higher scores indicate more comorbidities; cancer diagnosis not included in the total score.

Table 2

Odd ratios for frailty status among older patients with cancer (N = 394).

Variables	Odds Ratio	CI (95%)	p-Value
Age	1.48	1.29–1.72	<0.001
Education	0.81	0.68–0.95	0.010
Marital status			
Married/significant others vs. single	0.52	0.32–0.83	0.007
Gender			
Male vs. female	0.77	0.51–1.17	0.22
Ethnicity			
Caucasian vs. Other	1.10	0.65–1.87	0.70
Time since diagnosis (years)	1.01	0.99–1.03	0.43
Self-rated health			
Physical health: good vs. fair/poor	0.18	0.11–0.0.30	<0.001
Mental health: good vs. fair/poor	0.27	0.15–0.50	<0.001
Comorbidity			
NSHAP comorbidity score	1.43	1.25–1.64	<0.001
Cognitive function			
MoCA	0.90	0.85–0.95	<0.001
Psychological function			
CESD	1.27	1.19–1.35	<0.001
Physical function			
Impairment in ADL	0.50	0.41 −0.59	<0.001
Impairment in IADL	0.50	0.42–0.60	<0.001
Impairment in mobility	1.55	1.37–1.78	<0.001
Social function			
Socialization with friends and relatives in the past year	0.81	0.67–0.98	0.032
Attendance at meetings of organized groups in the past year	0.84	0.75–0.93	0.001

NSHAP: National Social Health and Aging Project; MoCA: Montreal Cognitive Assessment; CES-D: Center for Epidemiologic Studies Depression Scale; ADL: Activities ofDaily Living; IADL: Instrumental Activities of Daily Living.

Table 3

Multivariate logistic regression model for frailty among older patients with cancer (N = 394).

Variables	Odds Ratio	CI	p-Value
Age (units = 5 years)	1.46	1.24–1.73	<0.0001
Self-rated physical health	0.62	0.48–0.81	0.0006
Depression (CES-D)	1.23	1.15–1.33	<0.0001
ADL	0.72	0.58–0.89	0.0033
Mobility	1.40	1.22–1.63	<0.0001

ADL: Activities of Daily Living; CES-D: Center for Epidemiologic Studies Depression Scale.