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Physical functioning, frailty and risks of locally-advanced breast cancer among older women

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A B S T R A C T

Objective: Women with multiple comorbidities have competing health needs that may delay screening for early detection of breast cancer. Our objective was to determine associations between physical functioning and frailty with risk of locally-advanced breast cancer (BC).
Methods: We conducted a retrospective cohort study of women 65 years and older diagnosed with first primary stage I-III BC using the Surveillance, Epidemiology and End Results Medicare Health Outcome Survey Data Resource. Physical health-related quality of life was measured using Veterans RAND 12 Item Health Survey scales within two years before diagnosis; frailty was determined by calculating deficit-accumulation frailty index (DAFI) scores. Multivariable modified Poisson regression models were used to estimate rate ratios (RR) and 95% confidence intervals (CI) for risk of locally-advanced (stage III) versus early-stage (I-II) BC.
Results: Among 2411 women with a median age of 75 years at BC diagnosis, 2189 (91%) were diagnosed with incident stage I-II BC and 222 (9%) were diagnosed at stage III. Compared to women with early-stage disease, women with locally-advanced BC had lower physical component scores (37.8 vs. 41.4) and more classified as pre-frail or frail (55% vs. 50%). In multivariable models, frailty was not associated with increased risk of locally-advanced disease. However, worse physical function subscale scores (lowest vs. upper quartile; RR = 1.56, 95% CI 1.04–2.34) were associated with risk of locally-advanced BC.
Conclusions: Breast cancer screening among non-frail older women should be personalized to include women with limited physical functioning if the benefits of screening and early detection outweigh the potential harms.

1. Introduction

Higher physical activity decreases the risk of postmenopausal breast cancer [1]. In the aging U.S. population, the co-prevalence of frailty [2] and breast cancer diagnoses is expected to rise [3]. Women with multiple comorbidities and impaired physical functioning, the ability to perform activities of daily living, have competing health needs with respect to preventive care, including screening for early detection of breast cancer.

Frailty is a progressive accumulation of age-related biological deficits and physiological system declines which impair homeostatic balance [4]. Frail older adults are at increased risk of adverse health outcomes including falls, institutionalization, cardiovascular events, fractures, disability and mortality [5–7]. The mean prevalence of frailty increases with age, with ~10% of those aged 65 years and older and 25%–50% among those over age 85 meeting diagnostic criteria [8]. The deficit-accumulation frailty index (DAFI) is a measure that may be derived retrospectively and identifies a wide range of health deficits [9, 10]. The DAFI has been evaluated among older women with breast cancer in relation to risks of all-cause and breast cancer-specific mortality [11] but evidence on associations between the DAFI and breast cancer stage is limited.

In this study, our objective was to investigate whether frailty was associated with higher risk of locally advanced breast cancer in a population-based cohort of women enrolled in Medicare. We also investigated whether physical functioning, health related quality of life, was associated with higher breast cancer staging. We hypothesized that women with higher levels of frailty have competing health care needs and face physical challenges to obtaining health care services including routine screening which in turn may result in higher rates of locally-advanced stage III breast cancers.

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2. Methods

We conducted a retrospective cohort study of women 65 years and older diagnosed with first primary stage I-III breast cancer from 1998 to 2013 using the Surveillance, Epidemiology and End Results Medicare Health Outcome Survey Data Resource (SEER-MHOS). Patient characteristics and incident breast cancers were identified through the SEER population based cancer registries which were linked to responses to the longitudinal MHOS surveys [12]. The SEER Program of the National Cancer Institute includes cancer incidence and survival for approximately 35% of the U.S. population [13]. Patient and clinical characteristics obtained from SEER include demographics, incident cancer diagnoses, American Joint Committee on Cancer (AJCC) stage [14], extent of disease, tumor markers, surgery and receipt of radiation for first-course treatment [15]. MHOS surveys contain patient reported outcomes from a randomly selected group of Medicare Advantage managed care plan beneficiaries [12]. Baseline surveys contain self-reported demographics, socioeconomic status, comorbid conditions, functional status, and health related quality of life (HRQOL) measures. Follow up surveys are obtained every two years for all patients that are still Medicare Advantage enrollees, with an average response rate of 60% [16].

A cross-sectional analysis of longitudinal surveys was conducted in a retrospective cohort of women who met the following inclusion criteria: (i) aged 65 years and older; (ii) were diagnosed with a microscopically confirmed first primary stage I-III breast cancer between 1998 and 2013; and (iii) have completed at least one MHOS survey within two years prior to primary breast cancer diagnosis. The following surveys were excluded from the analysis: woman with a primary diagnosis of stage IV breast cancer or those with a missing diagnosis, and all surveys completed after a woman's diagnosis of breast cancer. Additionally, if multiple surveys were completed prior to diagnosis, the survey nearest the date of diagnosis was selected and all other surveys were excluded. A total of 2411 women met this outlined study inclusion criteria, presented in Fig. 1. This retrospective study of de-identified patients was reviewed and approved by the institutional review board of the University of Illinois Chicago.

2.1. Exposures

Frailty was defined by calculating the deficits accumulation frailty index (DAFI) [17] that was developed for patients responding to the MHOS based on a 25 item score using the Rockwood Accumulation of Deficits approach [18]. The sum of each item, valued from 0 to 1, was totaled across all 25 items and then divided by the sum of all scored valued at 1 with non-missing data. Each DAFI score calculated ranged from 0 to 1, with 0 indicating no frailty and 1 indicating the greatest frailty. Scores were categorized as robust (0 to <0.2), pre-frail (0.2 to <0.35), and frail (0.35–1) following an approach similar to other studies of older cancer patients [11,19].

Health related quality of life characteristics were derived from the Veterans RAND 12-item Health Survey (VR-12). The VR-12 is a valid patient-reported health survey comprised of 12 questions relating to physical and mental health [20]. The 12 items are summed into two scores, Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS is a summary measure of four subscales: general health, physical functioning, role-physical, and bodily pain. The MCS is a summary measure of four subscales: role-emotional, vitality, mental health, and social functioning. The physical functioning scale is measured through questions regarding an individual's ability to perform moderate activities and climb several flights of stairs. The VR-12 replaced the Short Form Health Survey for measuring health-related quality of life starting in 2006 in the SEER-MHOS data resource. Results from SF-36 and VR-12 were bridged using an algorithm to make

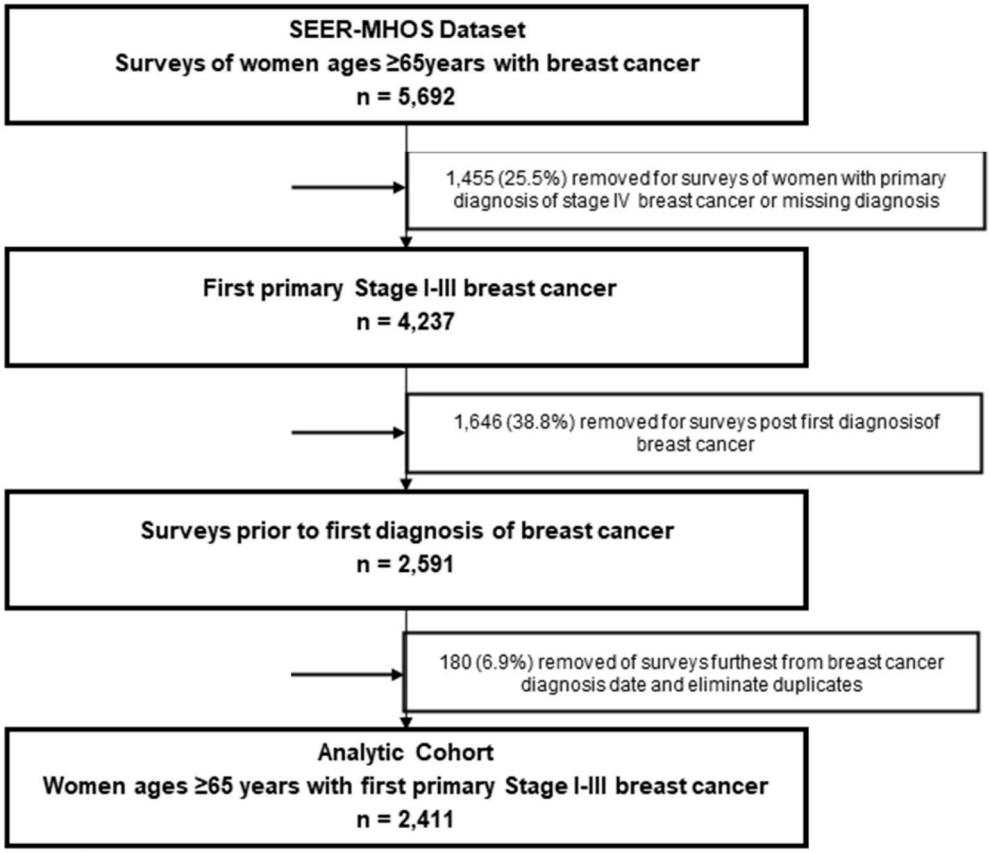

Fig. 1. CONSORT diagram illustrating inclusion and exclusion criteria.

scores comparable across all SEER-MHOS cohorts and account for missing data [21].

Data on variables including age (65–74, 75–84, 85+ years), year of diagnosis (1998–2003, 2004–2008, 2009–2013), race (white, Black, other), radiation (yes/no), surgery (breast conserving, mastectomy, no surgery) and estrogen and progesterone receptor status (positive or borderline, negative, unknown) were collected from SEER records; marital status (married, not married), education (less than high school, high school graduate or the Tests of General Educational Development [GED]), college graduate or above), smoking status (current, never) and body mass index (BMI) at diagnosis (<25, 25–29, 30–34, ≥35 kg/m2) were collected from survey responses prior to breast cancer diagnosis. Additionally, information on prevalence of comorbid conditions including heart conditions, stroke, cardiovascular conditions, diabetes, arthritis, asthma, chronic obstructive pulmonary disease (COPD) and emphysema at time of diagnosis were obtained. Our primary outcome of interest was later-stage breast cancer at diagnosis defined as AJCC stage III (versus stages I or II).

2.2. Statistical analyses

To examine differences in baseline covariates, descriptive statistics were used. For continuous variables, median and interquartile ranges (IQR) were utilized while frequencies display categorical variables. The Mann-Whitney *U* test was used for continuous variables and chi-square tests for categorical variables. The associations between frailty and physical functioning and the risk of locally-advanced breast cancer were determined using multivariable modified Poisson models with robust standard errors to estimate rate ratios (RR) and 95% confidence intervals (CI) [22]. Crude and multivariable models with adjustment for age at diagnosis, race, marital status, education, number of comorbid conditions, who completed the survey and survey type were selected a priori. P-values of ≤0.005 were considered statistically significant and to maintain a family wise type 1 error rate of 0.05 when up to 10 comparisons of subscales are made.

3. Results

Among the 2411 women with a first primary breast cancer diagnosis identified from the SEER-MHOS dataset from 1998 to 2013, the median age was 75 (interquartile range 71–80) and 73.3% were white (Table 1). The majority of women were diagnosed with earlier stage breast cancer (stage I-II, 90.8%) compared to late stage breast cancer (stage III, 9.2%). Women diagnosed with early stages I-II breast cancers were similar to women diagnosed with stage III breast cancer with respect to age at diagnosis and race. Compared to women with stage III breast cancer, a higher proportion of women with stages I-II breast cancer had hormone receptor positive breast disease (80% vs. 63.1%, $p < 0.001$). Compared to women diagnosed with stage III breast cancer, a higher proportion of women with stage I-II breast cancer were married (44% vs. 29%, $p < 0.001$) and reported good or better health status (73% vs. 65%, $p = 0.021$). Stage at diagnosis was similar in respect to comorbid conditions and the prevalence of each individual comorbidity. The median time between survey and diagnosis was 11 months (IQR 6–17), which did not differ by stage. The majority of surveys were administered by mail (59.7%) and completed by the patient themselves (61.5%). A slightly higher proportion of women diagnosed at stage III were frail (23.9% vs. 20.8%, $p = 0.344$) compared to stage I-II.

Descriptive characteristics of women by frailty status is represented in Table 2. On average, women who were younger were more robust (median age 74, IQR 70–79), compared to pre-frail (75, IQR 71–80) and frail (76, IQR 71–81). A higher proportion of robust patients are white (78% vs. 72% vs. 65%) diagnosed at stage I (62% vs. 59% vs. 52%), have a college education or more (46% vs. 36% vs. 26%), are more likely to be married (48% vs. 42% vs. 34%) and report they are in good or above good health (93% vs. 68% vs. 31%) compared to pre-frail and frail. Compared to robust women, a higher proportion of frail women reported depressive symptoms (58% vs. 15%). The median number of comorbid conditions was highest among women who were frail (5, IQR 3–6), compared to those who were pre-frail (3, IQR 2–4) or robust (2, IQR 1–2). Time in months from survey completion to diagnosis did not differ by frailty status (12 vs. 11 vs. 11). There was a higher proportion of frail women who had surveys completed by a person other than themselves, compared to those who were pre-frail or robust (16.1% vs. 7.2% vs. 4.4%).

The health-related quality of life measures derived from the VR-12 are reported in Table 3 by breast cancer stage at diagnosis. Women at early breast cancer stages had on average a higher PCS score (41.4% vs. 37.8%, $p = 0.152$), RF score (42.5% vs. 40.9%, $p = 0.233$) compared to those diagnosed at stage III. Stages I-II, and III were similar in regard to MCS (55.3 vs. 55.0, $p = 0.586$) and the BP score (41.8 vs. 41.8, $p = 0.674$). All other subscale measures were similar between stages, except for physical functioning (39.3 vs. 38.5), which was statistically different ($p < 0.01$).

Composite and subscale levels for health-related quality of life are reported in Table 4 by frailty categories. Compared to robust women, women that were frail and pre-frail had lower PCS scores (48.9 vs. 34.8 vs. 25.2, $p < 0.001$), physical functioning (PF) scores (49 vs. 37.1 vs. 19.6, $p < 0.001$), role limitations due to physical problems (RP) scores (55.6 vs. 33.4 vs. 26.1, $p < 0.001$), and bodily pain (BP) scores (49.4 vs. 39.6 vs. 31.3, $p < 0.001$).

Results from the multivariable Poisson regression models to assess the association between frailty and physical functioning subscales and the risk of locally advanced breast cancer diagnosis are reported in Table 5. In unadjusted analyses, frail health status was associated with 25% higher risk of being diagnosed with locally advanced breast cancer (RR 1.25, 95% CI 0.91–1.71, $p = 0.17$), and pre-frail status was associated with a 16% higher risk (RR 1.16, 95% CI 0.87–1.56, $p = 0.31$) compared to robust. After adjustment for age at diagnosis, race, marital status, education, number of comorbid conditions, who completed the survey, and survey type, the risk estimate associated with frail health status was attenuated (RR 1.16, 95% CI 0.80–1.69, $p = 0.45$) and not statistically significant. Compared to the highest quartile of PCS, those in the lowest quartile of PCS had a 11% increased risk of locally advanced breast cancer (RR 1.11, 95% CI 0.74–1.65, $p = 0.62$) that was not statistically significant. In comparison to the highest quartile of physical functioning, there was a 67% increased risk of locally advanced breast cancer (RR 1.67, 95% CI 1.13–2.48, $p = 0.01$) in quartile 3, a 28% increased risk in quartile 2 (RR 1.28, 95% CI 0.85–1.93, $p = 0.24$), and a 56% increased risk (RR 1.56, 95% CI 1.04–2.34, $p = 0.03$) in the lowest quartile 1. Lastly, in the RP highest quartile in comparison to the lowest was not statistically significant (RR 1.32, 95% CI 0.83–2.10, $p = 0.24$), nor was BP (RR 0.80, 95% CI 0.54–1.17, $p = 0.25$).

4. Discussion

In this retrospective cohort study of older women diagnosed with stage I-III breast cancer, we evaluated associations between frailty and physical health-related quality of life with risk of locally-advanced breast cancer. Overall, most health related quality of life measures for women diagnosed with locally advanced vs early staged breast cancer were lower but not significantly different, with the exception of the PF subscale. Breast cancer patients classified as frail according to the DAFI had significantly lower health related quality of life measures compared to women that were classified as robust or pre-frail. Poorer physical functioning was associated with an approximately 60–70% higher rate of diagnosis with locally-advanced breast cancer. This has potential implications for tailored screening recommendations in older females with physical functioning limitations that may still benefit from earlier detection of breast cancer.

Frailty, measured using the DAFI was first identified as a predictor for all-cause and breast cancer-specific mortality among older women in

Table 1
Descriptive characteristics at breast cancer diagnosis by stage.

	All Women *n* = *2411*		Stage I-II *n* = *2189*		Stage III *n* = *222*		*P*[a]
	n	%	n	%	n	%	
Characteristics at breast cancer diagnosis							
Age at diagnosis,							
Median (interquartile range)	75	(71–80)	75	(70–80)	75.5	(71–81)	0.178
65-74	1165	48.3%	1067	48.7%	98	44.1%	0.230
75-84	1028	42.6%	930	42.5%	98	44.1%	
85+	218	9.0%	192	8.8%	26	11.7%	
Year at diagnosis							
1998–2003	823	34.1%	739	33.8%	84	37.8%	0.348
2004–2008	515	21.4%	466	21.3%	49	22.1%	
2009–2013	1073	44.5%	984	45.0%	89	40.1%	
Race							
White	1776	73.7%	1606	73.4%	170	76.6%	0.183
Black	228	9.5%	204	9.3%	24	10.8%	
Other	407	16.9%	379	17.3%	28	12.6%	
Radiation							
Yes	1117	46.3%	1079	49.3%	107	48.2%	0.055
No	1186	49.2%	1019	46.6%	98	44.1%	
Unknown	108	4.5%	91	4.2%	17	7.7%	
Surgery							
Breast Conserving	1412	58.6%	1376	62.9%	36	16.2%	<0.001
Mastectomy	930	38.6%	765	34.9%	165	74.3%	
No Surgery	69	2.9%	48	2.2%	21	9.5%	
Estrogen/Progestin Receptor[b]							
Positive or Borderline	1911	79.3%	1767	80.7%	144	64.9%	<0.001
Negative	330	13.7%	271	12.4%	59	26.6%	
Missing	170	7.1%	151	6.9%	19	8.6%	
Marital status							
Married	1037	43.0%	971	44.4%	65	29.3%	<0.001
Not Married	1273	52.8%	1173	53.6%	153	68.9%	
Unknown	101	4.2%	45	2.1%	3	1.4%	
Education						0.0%	
Less than high school	565	23.4%	503	23.0%	62	27.9%	0.218
High School graduate or GED	860	35.7%	785	35.9%	75	33.8%	
College graduate or above	935	38.8%	857	39.2%	78	35.1%	
Missing	51	2.1%	44	2.0%	7	3.2%	
Smoking status							
Current	190	7.9%	170	7.8%	20	9.0%	0.782
Never	1796	74.5%	1634	74.6%	162	73.0%	
Unknown	425	17.6%	385	17.6%	40	18.0%	
Body mass index (kg/m^2)							
<25	449	18.6%	411	18.8%	38	17.1%	0.182
25-29	443	18.4%	403	18.4%	40	18.0%	
30-34	223	9.2%	210	9.6%	13	5.9%	
35+	151	6.3%	140	6.4%	11	5.0%	
Unknown	1145	47.5%	1025	46.8%	120	54.1%	
General Health Status, n (%)							
Good or Above	1748	72.5%	1603	73.2%	145	65.3%	0.021
Fair or Poor	621	25.8%	551	25.2%	70	31.5%	
Depression Symptoms, n (%)							
Yes	684	28.4%	616	28.1%	68	30.6%	0.260
No	1654	68.6%	1510	69.0%	144	64.9%	
DAFI Scores, n (%)							
Robust	1194	49.5%	1094	50.0%	100	45.0%	0.344
Pre-frail	709	29.4%	640	29.2%	69	31.1%	
Frail	508	21.1%	455	20.8%	53	23.9%	
Clinical Characteristics							
Number of comorbid conditions							
Median	2	(1–4)	2	(1–4)	2	(1–4)	0.974
0-2	1236	51.3%	1122	51.3%	114	51.4%	0.632
3 or more	1166	48.4%	1058	48.3%	108	48.6%	
Missing	9	0.4%	9	0.4%	0	0.0%	
Heart Conditions							
At least 1	1768	73.3%	1613	73.7%	155	69.8%	0.224
None	632	26.2%	565	25.8%	67	30.2%	
Missing	11	0.5%	11	0.5%	0	0.0%	
Stroke							
Yes	169	7.0%	151	6.9%	18	8.1%	0.230
No	2198	91.2%	2001	91.4%	197	88.7%	
Missing	44	1.8%	37	1.7%	7	3.2%	
Cardiovascular conditions							
At least 1	1787	74.1%	1631	74.5%	156	70.3%	0.197
None	614	25.5%	548	25.0%	66	29.7%	
Missing	10	0.4%	10	0.5%	0	0.0%	

(*continued on next page*)

Table 1 (*continued*)

	All Women *n* = *2411*		Stage I-II *n* = *2189*		Stage III *n* = *222*		*P*[a]
	n	%	n	%	n	%	
Diabetes							
Yes	496	20.6%	439	20.1%	57	25.7%	0.142
No	1881	78.0%	1719	78.5%	162	73.0%	
Missing	34	1.4%	31	1.4%	3	1.4%	
Arthritis							
Yes	949	39.4%	1288	58.8%	132	59.5%	0.774
No	1420	58.9%	862	39.4%	87	39.2%	
Missing	42	1.7%	20	0.9%	1	0.5%	
Asthma/COPD/Emphysema							
Yes	329	13.6%	299	13.7%	30	13.5%	0.244
No	2032	84.3%	1848	84.4%	184	82.9%	
Missing	50	2.1%	42	1.9%	8	3.6%	
Survey Characteristics							
Months from survey to diagnosis							
Median (interquartile range)	11	(6-17)	11	(17-6)	12	(18-6)	0.676
MHOS survey administration							
Mail	2076	86.1%	1892	86.4%	184	82.9%	0.145
Telephone	335	13.9%	297	13.6%	38	17.1%	
Who completed survey							
Patient	2080	86.3%	1904	87.0%	176	79.3%	<0.001
Person other than patient	185	7.7%	158	7.2%	27	12.2%	
Unknown	146	6.1%	127	5.8%	19	8.6%	

cNumber of comorbid conditions was totaled from presence/absence of: angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, stroke, emphysema/asthma/COPD, Crohn's disease/ulcerative colitis/inflammatory bowel disease, arthritis of the hip/knee, arthritis of the hand/wrist, sciatica, diabetes/high blood sugar/sugar in urine, and hypertension. If patient is missing data on at least one comorbidity, then number of comorbid conditions is considered missing.

dPossible patient reported heart conditions include hypertension, angina or coronary artery disease, congestive heart failure, acute myocardial infarction, other heart conditions.

eIncludes heart conditions and stroke.

Note: Column percentages do not sum to 100% for some variables due to missing data.

[a] Statistical test used to compare groups include Chi-square tests.

[b] Estrogren/Progestin receptor positive or borderline status was defined as being positive in either estrogen or progestin receptor. Negative was defined as being negative for both estrogen and progestin receptors, and all others were defined as missing.

a retrospective cohort study by Mandelblatt et al. [11]. Their analysis showed an increase in all-cause mortality as frailty increases to pre-frail and frail compared to robust, HR 1.7 (95% CI 1.3–2.4) and 2.4 (95% CI 1.5–4.0) respectively. A similar relationship was observed among breast cancer-specific mortality, with HR 1.6 (95% CI 1.0–2.6) for pre-frail vs robust women and increasing to HR 3.1 (95% CI 1.6–5.8) for frail vs robust women. Greater evidence on associations between frailty and breast cancer outcomes is critical given the underrepresentation of older women, particularly those that are frail or with physical limitations, in cancer clinical trials. Utilizing frailty assessments as a tool for making informed clinical decisions, including treatment decisions, for patients with breast cancer are increasing recommended over of the use of 'chronological' age alone [23]. In turn, the multiple breast cancer treatment modalities that have improved survival, including radiotherapy and multi-agent chemotherapy regimens, have meaningful impacts on physical health, especially in patients with existing frailty. After breast cancer survival, lower levels of physical functioning are then associated with higher morbidity and mortality [24]. There is little evidence on how frailty screenings can be best utilized in the breast cancer treatment pathway.

Increasing frailty in older women with breast cancer is also associated with poorer health related quality of life outcomes, including physical functioning [25]. These measures are important, as both physical function and health related quality of life are predictors of breast cancer survival [26,27]. Furthermore, several studies have shown that a decrease in physical functioning is associated with an increase in all-cause and breast cancer-specific morbidity and mortality [24,27]. As physical activity has been shown to decrease cancer mortality among cancer survivors, interventions to improve physical functioning after breast cancer diagnosis may help improve quality of life measures and overall survival [28].

Beyond physical functioning, the effect of other health related quality of life measures on staging at breast cancer diagnosis were null. These findings could be explained by several factors. Individuals with severe mobility limitations have a decrease utilization of preventive services, reduced access to medical services, and are at greater risk of negative health outcomes [29–33]. Within the Medical Outcomes Study 36-item Short-Form health Survey (SF-36), the physical functioning scale includes ten questions which score a respondent's limitations performing various physical activities, with a higher reported score representing better physical functioning [34]. While this scale purely reflects mobility limitations, other health related quality of life measures reflect mental conditions, or both physical and mental conditions [35]. It is plausible that the health related quality of life measure of physical functioning effectively captured the limitations of a respondent with extreme mobility issues to obtain preventive services, including screening mammography.

A patient's frailty level often dictates the use of screening mammography in older women. The benefits of screening mammography are rightfully weighed against the potential burden of further work-up from a positive mammogram in frail adults. In a cohort study of 216 frail older women with a mean age of 81 years, only 4 were ultimately diagnosed with stage 1 cancer or ductal carcinoma in situ [36]. Our study, with a relatively larger sample size, suggests that older women with higher levels of frailty and lower levels of physical functioning are at the highest risk of being diagnosed with stage III breast cancer. We therefore suggest that the risk of locally-advanced breast cancer be weighed among potential benefits and harms when recommending screening for older women with physical functioning limitations.

A major strength of this study was the availability of robust data through the linkage of MHOS and SEER databases. This population-based information with linkage to the MHOS surveys provided a range of comprehensive patient characteristics that enabled the construction

Table 2
Demographic, clinical and survey characteristics among women at breast cancer diagnosis by frailty status.

	Robust (0 to <0.2) *n = 1194*		Pre-Frail (0.2 to <0.35) *n = 709*		Frail (0.35–1) *n = 508*		*P*[a]
	n	%	N	%	N	%	
Characteristics at breast cancer diagnosis							
Age at diagnosis							
Median (interquartile range)	74	(70–79)	75	(71–80)	76	(71–81)	<0.001
65-74	626	52.4%	313	44.1%	226	44.5%	
75-84	499	41.8%	318	44.9%	211	41.5%	
85+	69	5.8%	78	11.0%	71	14.0%	
Year at diagnosis							
1998–2003	421	35.3%	235	33.1%	167	32.9%	0.495
2004–2008	260	21.8%	155	21.9%	100	19.7%	
2009–2013	513	43.0%	319	45.0%	241	47.4%	
Race							
White	936	78.4%	508	71.7%	332	65.4%	<0.001
Black	75	6.3%	66	9.3%	87	17.1%	
Other	183	15.3%	135	19.0%	89	17.5%	
Radiation							
Yes	618	51.8%	347	48.9%	221	43.5%	0.015
No	518	43.4%	332	46.8%	267	52.6%	
Unknown	58	4.9%	30	4.2%	20	3.9%	
Breast Cancer Stage							
Stage I	736	61.6%	417	58.8%	26	52.2%	<0.001
Stage II	358	30.0%	223	31.5%	19	37.4%	
Stage III	100	8.4%	69	9.7%	5	10.4%	
Surgery							
Breast Conserving	734	61.5%	410	57.8%	268	52.8%	<0.001
Mastectomy	439	36.8%	277	39.1%	214	42.1%	
No Surgery	21	1.8%	22	3.1%	26	5.1%	
Estrogen/Progestin Receptor[b]							
Positive or Borderline	963	80.7%	561	79.1%	387	76.2%	0.210
Negative	155	13.0%	92	13.0%	83	16.3%	
Missing	76	6.4%	56	7.9%	38	7.5%	
Marital status							
Married	570	47.7%	294	41.5%	172	33.9%	<0.001
Not Married	603	50.5%	397	56.0%	327	64.4%	
Unknown	21	1.8%	18	2.5%	9	1.8%	
Education							
Less than high school	189	15.8%	197	27.8%	179	35.2%	<0.001
High School graduate or GED	437	36.6%	235	33.1%	188	37.0%	
College graduate or above	550	46.1%	255	36.0%	130	25.6%	
Missing	18	1.5%	22	3.1%	11	2.2%	
Smoking status							
Current	94	7.9%	50	7.1%	46	9.1%	0.471
Never	882	73.9%	530	74.8%	384	75.6%	
Unknown	218	18.3%	129	18.2%	78	15.4%	
Body mass index (kg/m^2)							
<25	248	20.8%	130	18.3%	71	14.0%	<0.001
25-29	252	21.1%	110	15.5%	81	15.9%	
30-34	86	7.2%	82	11.6%	55	10.8%	
35+	39	3.3%	54	7.6%	58	11.4%	
Unknown	569	47.7%	333	47.0%	243	47.8%	
General Health Status, n (%)							
Good or Above	1108	92.8%	484	68.3%	156	30.7%	<0.001
Fair or Poor	63	5.3%	218	30.7%	340	66.9%	
Depression Symptoms, n (%)							
Yes	175	14.7%	217	30.6%	292	57.5%	<0.001
No	985	82.5%	468	66.0%	201	39.6%	
Clinical Characteristics							
Number of comorbid conditions							
Median	2	(1–2)	3	(2–4)	5	(3–6)	<0.001
0-2	927	77.6%	249	35.1%	60	11.8%	
3 or more	262	21.9%	456	64.3%	448	88.2%	
Missing	5	0.4%	4	0.6%	0	0.0%	
Heart Conditions							
At least 1	724	60.6%	579	81.7%	465	91.5%	<0.001
None	465	38.9%	125	17.6%	42	8.3%	
Missing	5	0.4%	5	0.7%	1	0.2%	
Stroke							
Yes	24	2.0%	51	7.2%	94	18.5%	<0.001
No	1158	97.0%	644	90.8%	396	78.0%	
Missing	12	1.0%	14	2.0%	18	3.5%	
Cardiovascular conditions							
At least 1	731	61.2%	585	82.5%	471	92.7%	<0.001
None	458	38.4%	120	16.9%	36	7.1%	
Missing	5	0.4%	4	0.6%	1	0.2%	

(*continued on next page*)

Table 2 (*continued*)

	Robust (0 to <0.2) *n* = *1194*		Pre-Frail (0.2 to <0.35) *n* = *709*		Frail (0.35–1) *n* = *508*		*P*[a]
	n	%	N	%	N	%	
Diabetes							
Yes	119	10.0%	172	24.3%	205	40.4%	<0.001
No	1062	88.9%	525	74.0%	294	57.9%	
Missing	13	1.1%	12	1.7%	9	1.8%	
Arthritis							
Yes	488	40.9%	495	69.8%	437	86.0%	<0.001
No	687	57.5%	197	27.8%	65	12.8%	
Missing	10	0.8%	10	1.4%	1	0.2%	
Asthma/COPD/Emphysema							
Yes	75	6.3%	111	15.7%	143	28.1%	<0.001
No	1105	92.5%	581	81.9%	346	68.1%	
Missing	14	1.2%	17	2.4%	19	3.7%	
Survey Characteristics							
Months from survey to diagnosis							
Median (interquartile range)	12	(6-17)	11	(5-17)	11	(6-18)	0.284
MHOS survey administration							
Mail	1031	86.3%	616	86.9%	429	84.4%	
Telephone	163	13.7%	93	13.1%	79	15.6%	
Who completed survey							
Patient	1087	91.0%	611	86.2%	382	75.2%	<0.001
Person other than patient	52	4.4%	51	7.2%	82	16.1%	
Unknown	55	4.6%	47	6.6%	44	8.7%	

Note: Column percentages do not sum to 100% for some variables due to missing data.

[c]Number of comorbid conditions was totaled from presence/absence of: angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, stroke, emphysema/asthma/COPD, Crohn's disease/ulcerative colitis/inflammatory bowel disease, arthritis of the hip/knee, arthritis of the hand/wrist, sciatica, diabetes/high blood sugar/sugar in urine, and hypertension. If patient is missing data on at least one comorbidity, then number of comorbid conditions is considered missing.

[d]Possible patient reported heart conditions include hypertension, angina or coronary artery disease, congestive heart failure, acute myocardial infarction, other heart conditions.

[e]Includes heart conditions and stroke.

[a] Statistical test used to compare groups include Chi-square tests.

[b] Estrogren/Progestin receptor positive or borderline status was defined as being positive in either estrogen or progestin receptor. Negative was defined as being negative for both estrogen and progestin receptors, and all others were defined as missing.

Table 3
Health-related quality of life (HRQOL) characteristics derived from the Veterans RAND 12-Item Health Survey (VR-12) among women at breast cancer diagnosis by breast cancer stage at diagnosis.

	Overall		Stage I-II		Stage III		P-Value[a]
	n = 2411		n = 2189		n = 222		
Characteristics, Median (IQR)							
PCS	41.0	29.8–49.5	41.4	30.0–49.5	37.8	29.0–48.7	0.152
MCS	55.2	45.1–60.2	55.3	45.2–60.2	55.0	43.1–60.4	0.586
PF	39.3	28.4–50.2	39.3	28.4–50.2	38.5	25.9–48.2	0.006
RP	42.2	27.9–55.6	42.5	28.9–55.6	40.9	27.5–55.6	0.233
BP	41.8	35.4–53.6	41.8	35.4–53.6	41.8	35.4–53.6	0.674
GH	44.7	39.0–55.7	44.7	39.0–55.7	44.7	38.2–55.3	0.218
MH	54.9	42.1–59.5	54.9	42.1–59.5	54.9	42.1–59.5	0.841
RE	55.7	37.9–56.9	55.7	37.9–56.9	55.7	37.9–55.7	0.234
SF	51.7	35.0–57.0	57.0	35.0–57.0	46.2	35.0–57.0	0.112
VT	46.9	42.3–58.7	46.9	42.7–58.7	46.9	39.9–56.7	0.103

IQR: Interquartile range, SRH: Self-reported health, PCS: Physical component summary score, MCS: Mental component summary score, PF: Physical Functioning, RP: Role limitations due to physical problems, BP: Bodily pain, GH: General health perceptions, MH: General mental health, RE: Role limitations due to emotional problems, SF: Social functioning, VT: Vitality.

[a] Mann-Whitney *U* test.

of a DAFI score retrospectively. In addition, survey responses to health related quality of life measures were recorded prior to any cancer diagnoses, providing this study the ability to assess the potential impact of frailty and quality of life on staging at breast cancer diagnosis.

This study also has several limitations including generalizability, lack of information on individual provider screening recommendations and potential healthy user bias. The SEER Program contains cancer incidence data from 35% of the US population, but lacks representation during this study period from other diverse states, including Texas and Florida. There is additional concern that Medicare Advantage enrollees randomly selected to answer surveys within the MHOS database are systematically different from other beneficiaries, including those in Medicare Fee-For-Service [37]. As the patients in this study were majority white, other racial/ethnic groups were underrepresented. Therefore, our findings may not be entirely representative of the experience of younger women with breast cancer, those lacking health coverage and racial/ethnic minority women. Another limitation is that variables associated with differences in breast cancer risk were unmeasured or had a high degree of missingness, such as variables related to body weight, BMI, and adiposity. Furthermore, variables related to individual provider screening recommendations and the use of palliative care were unmeasured within the SEER-MHOS linked data resource.

Table 4
Health-related quality of life (HRQOL) characteristics derived from the Veterans RAND 12-Item Health Survey (VR-12) among women at breast cancer diagnosis by DAFI scores.

	Overall		Robust		Pre-Frail		Frail		P-Value
	n = 2411		n = 1194		n = 709		n = 508		
Characteristics, Median (IQR)									
PCS	41.0	29.8–49.5	48.9	42.8–53.7	34.8	28.7–42.0	25.2	21.1–30.8	<0.001
MCS	55.2	45.1–60.2	58.5	53.4–61.0	52.7	43.7–59.7	42.9	35.1–52.5	<0.001
PF	39.3	28.4–50.2	49.0	43.7–53.9	37.1	26.2–41.5	19.6	16.5–29.1	<0.001
RP	42.2	27.9–55.6	55.6	48.2–55.8	33.4	27.5–49.5	26.1	26.0–28.9	<0.001
BP	41.8	35.4–53.6	49.4	41.8–58.4	39.6	35.4–43.8	31.3	27.3–36.6	<0.001
GH	44.7	39.0–55.7	54.9	44.7–55.7	44.7	36.5–47.4	32.8	30.7–43.9	<0.001
MH	54.9	42.1–59.5	57.3	52.9–59.9	50.0	41.8–57.3	41.8	32.9–50.0	<0.001
RE	55.7	37.9–56.9	55.7	55.7–56.9	50.2	35.5–55.7	35.5	25.4–55.7	<0.001
SF	51.7	35.0–57.0	57.0	57.0–57.3	43.3	34.5–57.0	34.5	23.8–42.5	<0.001
VT	46.9	42.3–58.7	56.7	46.9–58.7	43.9	42.3–47.1	36.0	32.7–42.7	<0.001

IQR: Interquartile range, SRH: Self-reported health, PCS: Physical component summary score, MCS: Mental component summary score, PF: Physical Functioning, RP: Role limitations due to physical problems, BP: Bodily pain, GH: General health perceptions, MH: General mental health, RE: Role limitations due to emotional problems, SF: Social functioning, VT: Vitality.
[a]Mann-Whitney *U* test.

Table 5
Multivariable Poisson regression models to assess the association between frailty and physical functioning subscales and the risk of locally advanced breast cancer diagnosis.

	Crude Model			Adjusted Model[a]		
	RR	95%CI	P-value	RR	95%CI	P-value
DAFI Categories						
Robust	1.00	–	–	1.00	–	–
Pre-frail	1.16	0.87–1.56	0.31	1.15	0.83–1.59	0.41
Frail	1.25	0.91–1.71	0.17	1.16	0.80–1.69	0.45
PCS Quartiles						
1	1.19	0.82–1.73	0.35	1.11	0.74–1.65	0.62
2	1.28	0.89–1.84	0.19	1.22	0.84–1.78	0.29
3	0.91	0.62–1.36	0.66	0.91	0.61–1.36	0.65
4	1.00	–	–	1.00	–	–
PF Quartiles						
1	1.67	1.14–2.45	0.01	1.56	1.04–2.34	0.03
2	1.35	0.90–2.02	0.15	1.28	0.85–1.93	0.24
3	1.67	1.13–2.46	0.01	1.67	1.13–2.48	0.01
4	1.00	–	–	1.00	–	–
RP Quartiles						
1	1.41	0.91–2.20	0.13	1.32	0.83–2.10	0.24
2	1.24	0.79–1.94	0.35	1.25	0.79–1.97	0.34
3	1.31	0.86–2.01	0.21	1.33	0.86–2.05	0.20
4	1.00	–	–	1.00	–	–
BP Quartiles						
1	0.87	0.61–1.25	0.45	0.80	0.54–1.17	0.25
2	0.96	0.69–1.34	0.81	0.94	0.66–1.33	0.71
3	0.74	0.49–1.11	0.15	0.73	0.49–1.11	0.14
4	1.00	–	–	1.00	–	–

RR: Rate Ratio, CI: confidence intervals, IQR: Interquartile range, DAFI: deficit-accumulation frailty index, PCS: Physical component summary score, PF: Physical Functioning, RP: Role limitations due to physical problems, BP: Bodily pain, GH: General health perceptions.
[a] Adjusted for age at diagnosis, race, marital status, education, number of comorbid conditions, who completed the survey question, and survey disposition.

Finally, the healthy user effect is a likely source of bias in observational studies, characterized as the tendency of patients receiving preventive therapy to seek other preventive services. Within our study, almost half of the participants were classified as robust, reflecting a better health status than those pre-frail or frail. Healthier, robust patients with a propensity for positive health seeking behaviors may have been more likely to receive routine breast cancer screening. This could explain why the majority of robust patients were diagnosed in early stages of breast cancer while pre-frail and frail patients were more often diagnosed in advanced stages of breast cancer.

5. Conclusions

We found that older breast cancer patients with increased frailty report lower measures of quality of life, including physical functioning. Our findings suggest that poor physical functioning may be associated with diagnosis of later-stage, locally-advanced breast cancer. This presents the need for clinicians and providers to carefully consider frailty and physical functioning when individualizing a patient's need for breast cancer screening.

Author Contributions

Chandler Coleman: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing. **Connie H. Yan**: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing. **Naomi Y. Ko**: Conceptualization; Writing – review & editing. **Nadia A. Nabulsi**: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing. **Kent F. Hoskins**: Conceptualization; Writing – review & editing. **Brian C.-H. Chiu**: Conceptualization; Writing – review & editing. **Gregory S. Calip**: Conceptualization; Data Curation; Formal Analysis; Funding Acquisition; Investigation; Methodology; Project Administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Data availability

The authors have full control of all primary data. The data that support the findings of this study are available from the SEER-MHOS data resource. Restrictions apply to the availability of these data, which were used under license of this study.

Ethical approval

The data used in the study were de-identified and compliant with the

Health Insurance Portability and Accountability Act (HIPAA). This study was determined to be exempt by the Institutional Review Board of the University of Illinois Chicago.

Informed consent

The Institutional Review Board of the University of Illinois Chicago determined this study to be exempt from obtaining informed consent from individual participants.

Declaration of competing interest

Please confirm your COI and any other disclosures

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