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Impact of age, comorbidity and symptoms on physical function in long-term breast cancer survivors (CALGB 70803)

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Abstract

Purpose—The purpose of this study was to assess the impact of aging, comorbidities and symptoms on physical function in patients surviving 20 years since adjuvant treatment for breast cancer.

Patients & Methods—Patients were originally treated on CALGB 7581 (from 1975–1980), a randomized trial of three adjuvant therapies and reassessed (153 of 193 eligible survivors) 20 years from the onset of therapy for physical function and symptoms by the EORTC QLQ-C30 and comorbidities by the OARS questionnaire.

Results—The average age at reassessment was 64.5 years. 66% of patients had at least two comorbidities and 22% had four or more, but relatively little interference with activities. Older patients had greater multimorbidity. Physical function was generally high and comparable to matched population norms. Older patients had greater difficulty with strenuous activities. For every increase in number of comorbidities, physical function score decreased by 5.1 ($p<.001$). Symptoms were also frequent (80%) and correlated strongly with decreases in function (0–100u scale) ($p <.001$), to an even greater degree than comorbidities.

Conclusion—Very long-term cancer survivors have changes in physical function and symptoms largely consistent with their aging suggesting that the impact of cancer and its treatment is attenuated over time and largely replaced by the impact of age-related comorbidities and functional decline.

Keywords

Cancer survivors; physical function; comorbidity; symptoms; elderly

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Improvements in cancer treatment over the past two decades have resulted in an increasing number of long term cancer survivors.[1,2] While this is an issue previously seen predominantly in survivors of pediatric malignancies, we are now seeing similar improvements in the treatment of a number of adult malignancies resulting in increased numbers of long term survivors of adult cancers.[3,4] Moreover, at the current time over 60% of cancer survivors are over the age of 65.[5] With the increasing aging of the population it is likely that we will see a continuing increase in the number of older cancer survivors. However, there is relatively little known about the combined impact of the results of aging and the results of cancer and its treatment in such older cancer survivors. Older people differ in a number of ways from younger ones, but two factors in particular have relevance to older patients with cancer.[6] Aging is characterized by decreases in functional status which are contributed to by multiple factors including physiologic changes, environmental interactions and individual diseases as well as the increased prevalence of comorbidity. Thus the long term impacts of cancer and its treatment which have been demonstrated in adult survivors of cancer, when combined with the increasing number of diseases occurring with aging in the older cancer survivor, could produce a “double whammy” resulting in substantial declines in overall physical function. [7]

To assess the impact of age, comorbidities, and symptoms on the functional status of long term cancer survivors, we utilized the data from a follow-up study of patients surviving an average of twenty years after entry on a phase III randomized trial of adjuvant treatment for breast cancer (CALGB 7581)[8]. These subjects had been studied for long term psychological adjustment and constitute the longest prospectively followed adult cancer survivor cohort in which to assess these relationships [5,9].

Methods

Sample

Patients reported in this study had initially been treated on CALGB 7581[8] – a randomized phase III study comparing three adjuvant regimens (1. cyclophosphamide, methotrexate, 5-fluorouracil (5FU), vincristine and prednisone; 2. cyclophosphamide, methotrexate and 5FU; or 3. cyclophosphamide, methotrexate, 5FU and Bacillus Calmette-Guérin) for women with early stage breast cancer and followed for over twenty years following entry onto the trial (between May 1975 and June 1980). Subjects had completed all cancer treatment one or more years before the follow-up telephone interview and had no evidence of breast cancer at the time of interview, nor any other major psychiatric or cognitive disorder. As previously reported, in an analysis assessing the long term psychological adjustment of the patients, of the 401 evaluable patients originally entered on study there were 194 survivors, of whom 153 (79%) agreed to participate in this study [8,9]. Those who were not interviewed were more likely to be older by 6.3 years, to be older at diagnosis by 7.7 years and to be African American [9]. The general research procedures, informed consent, and methods of telephone interview and IRB approvals have been previously reported. [9]

Measures

For the analyses reported here, the following measures were utilized. Social and demographic characteristics were derived from the CALGB database. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 1.0) physical function scale, role function scale, and symptom scale were administered.[10] Comorbid conditions and the degree to which they interfered with daily activities (not at all, a little, or a great deal) were assessed using the modified Older Americans Resources and Services Questionnaire (OARS).[11,12]

Statistical Methods

Data analyses were performed on 153 survivors. There were two primary aims of this study. The first was to describe disease and functional relation impairments in older cancer survivors. Basic descriptive statistics were used to summarize patient baseline demographics, comorbidities, EORTC physical functional impairment and EORTC symptom scores dichotomized as a score of zero or more than zero. The chi-square test was conducted to examine differences of demographic endpoints between the two age groups (<65 years old and ≥65 years old). The second was to examine the relationship between comorbidities, symptoms and functional status and to compare them with published population norms. Fisher's exact test was used to determine the association between comorbidities/symptom related variables and age (< 65 years old and ≥65 years old). A one-sample t-test was used to compare the mean scores of physical function in the patients of this study to the published population norms. Univariate linear regression was conducted to assess the relationship of comorbidities to physical function and role function scores. Two sample t-tests were applied to compare physical function scores of the patients with low symptom scores versus those of patients with higher scores. Multivariate linear regression was conducted to determine if the comorbidity scores or symptom scores were predictive of the physical function scores by adjusting for age, education and marital status. A significance level of 0.01 was prespecified to reduce problems associated with multiple testing.

Results

As previously reported, patients were assessed from 17–25 years (mean=20 years) since diagnosis.[9] At the time of follow-up, patients' age ranged from 40 to 86 years, with a mean of 64.5 years. Comparing patients younger than age 65 with those ≥ 65, the older and younger patients were generally similar with a greater proportion of the older group widowed and retired (both p<.001). (Table 1) Twenty-five patients had a recurrence and were retreated from two to nineteen years (mean of 10.2 years) prior to assessment. There was no age difference between those with or without recurrence.

The distribution of comorbidities by age group (Table 2) was quite similar with only high blood pressure occurring significantly more often in the older group (p<.001). When analyzed with age as a continuous variable, results were the same. Most subjects noted no or only some interference of these comorbidities with daily activities. Among the more common comorbidities, approximately 20% of patients with osteoporosis, circulation difficulties, arthritis, and urinary tract infections noted a great deal of interference with activities and 55% of those with broken bones or fractures noted a great deal of interference. There was a significant difference by age for these interference scores. Two-thirds of all patients had at least two comorbidities, and 22% reported four or more. Older survivors had a higher prevalence of multiple morbidities (Table 1).

The majority of patients were quite functional (Table 3). However, a substantial number of subjects showed difficulty with strenuous strength related activities such as carrying a heavy shopping bag or suitcase, and with endurance activities such as taking a long walk. Among these various physical activities, older patients were significantly more likely to have difficulty only with respect to taking a long walk (p<.001). Overall physical condition and quality of life were generally rated in the very good to excellent range by patients in both age groups.

To gain an appreciation of the function of the cancer survivors reported here, relative to a reasonably similar general population, we compared our patients physical function scores on

the EORTC QLQ-C30 to published population norms using this instrument [13,14] (Table 4). When compared to all subjects, and all female subjects (means age 47.7), our cancer survivors' physical function was significantly worse. However, when compared to a more similar age group (older women), our older cancer survivors' function did not differ significantly from those in the general population survey. Our patients also had function equivalent to those with other active chronic diseases and physical conditions in the population survey [13, 14]. The same pattern was seen in assessing role function scores from the EORTC QLQ-C30.

We next assessed the relationship of comorbidities to physical function and role function. For every increase in the number of comorbid conditions the physical function scores decreased by 5.1 (SE 0.9 T statistic (df)-5.8(1) ($p<.001$)) and the role function scores decreased by 6.6 (SE1.1 T statistic (df)-6.2(1) ($p<.001$)) (EORTC physical and role functioning scores range from 0 to 100).

Since to some extent symptoms may be considered a surrogate for the presence of active comorbidities, we evaluated the symptoms score from the EORTC QLQ-C30 (Table 5). Symptoms were frequent, occurring in 80% of the subjects, with fatigue, insomnia, pain and dyspnea being the most common. Other symptoms such as nausea, vomiting and diarrhea, perhaps more generally thought of as related to active cancer or cancer treatments, were much less prevalent. There were no differences by age.

The presence of symptoms overall was strongly associated with decreases in both physical function and role function ($p<0.001$). When assessing the relative strength of the association between symptom scores or comorbidity scores, with both physical function and role function scores, (Table 6) symptoms scores had a substantially stronger relationship with both role and physical function as suggested by the substantially higher F-test values for symptoms scores versus comorbidity scores in each case, when controlling for the same baseline variables. There was not a significant interaction between symptoms score and comorbidity score ($p=0.14$). Even after controlling for comorbidity score or symptom scores, age still had a significant relationship to decreased physical function ($p<0.01$), but not role function.

Since the degree of interference of comorbidities with activities (as assessed by the OARS comorbidity scale) is also a measure of physical function derived independently from the EORTC QLQ-C30 physical function scale, we assessed the relationship of the physical function score from the modified OARS to the EORTC physical and role function scales. Pearson correlation for interference scores with physical function was −0.417 and for role function was −0.359 (both $p < .001$). For each unit increase in interference score of the OARS, physical function score of the EORTC scales declined by 12.4 units and role function score by 13.2 units.

Discussion

In this report of a cohort of long term survivors of breast cancer, we characterized physical function, comorbidities and symptoms and their relationship to age of the patients. It had previously been demonstrated in this cohort that twenty years after initial diagnosis there was minimal impact on survivors' psychological adjustment.[9] Here we have demonstrated that twenty year breast cancer survivors are also generally high functioning with respect to physical function. There were a substantial array of morbidities experienced by these patients but they did not differ substantially with age. A substantial number experienced difficulties with physical function but only with respect to ability to walk a long distance, where older subjects were significantly worse. Both with respect to physical and role

function, these cancer survivors appear to have similar function as a comparable aged, population based sample.[13,14] This would suggest that late effects of cancer and/or treatment are contributing only minimally to the physical and role functional decline, relative to the contribution made by multiple morbidities and age related functional decline per se.

Symptoms such as fatigue, insomnia, pain and dyspnea were common in this cohort, but did not differ by age. However, these same symptoms were also quite common in a general population survey using the EORTC Symptom Scale.[14] We also found that comorbidities and symptoms were related to lower physical function and decline but that symptoms appeared to have a stronger relationship. A similar observation has been made in older subjects with mobility dysfunction [15] and in short term cancer patients [16]. As suggested by some models of impairment and disability, it is possible that symptoms may bear a more proximate relationship to the impairment or disability than a disease process per se.[17] In a sense, symptoms may be the manifestations of the disease at the impairment level which is related to the physical disability. It is conceivable that the symptoms themselves may actually be in the causal pathway towards decreased physical function, but in a cross-sectional study such as this causal links cannot be made.

Physical functional capacity appears to be an important overall barometer of the combined effects of other factors relating to the health of the older individual. Thus the ability of older individuals to perform activities of daily living such as housework, walking up and down stairs and bathing is predictive of future functional decline and progression to disability and mortality.[18] In studies to assess health-related quality of life of the general population, using the EORTC QLQ-C30, it was shown that overall quality of life and specific physical function varied by gender as well as by age and suggested that these parameters need to be considered when interpreting data from cancer patients.[13,14] While it has been suggested that adult cancer survivors and older survivors in particular have declines in physical functional status, it is not clear how much of this is due to the impact of cancer or cancer treatment and how much is due to the impact of comorbid diseases and other contributions of the aging process per se.[19,20]

Results of previous studies have been somewhat variable in the assessment of this relationship. In part this may relate to the heterogeneity and variations in the populations studied in particular with respect to duration of survival.[5] Thus older patients with cancer assessed in early survivorship (1–2 years)[21,22] demonstrate significantly decreased levels of physical function compared to those without cancer. Patients surviving for somewhat longer (>5 years) continue to show functional limitations but to a much lesser degree and with an increasing relationship to non-cancer morbidities.[23–30] [b]. In those surviving even longer (10–15 years) their function appears even more like similar aged populations without cancer.[30–31] Both Michael[32] and more recently Goodwin[33] have suggested that the risk of functional health status decline might attenuate over time since diagnosis. Our study extends this observation to even longer term survivors and add substance to this trend, with these older survivors physically functioning at a generally high level and comparable to that of population norms.

The relevance of this shifting relationship is indicated by the findings of Braithwaite, et al [24] that breast cancer survivors with functional limitations compared to those without limitations had equivalent cancer specific survival but significantly shorter competing cause (non-cancer related) survival. This again suggests that as cancer survivors age and move further from diagnosis, other morbidities begin to dominate their clinical picture. This is consistent with our findings that physical function scores decline as comorbidity increases and as symptoms increase, and previous reports indicating that functional status has a

substantial impact on the life expectancy of older people [18]. Though the physical limitations described here may be more related to comorbidities than cancer per se it is still important to identify them. Survivors with comorbid conditions are at increased risk for inactivity as well as poorer physical function.[34,35] Exercise, even of relatively low level and conducted at home, can improve both activity levels and physical function in older cancer survivors and improve quality of life.[36] Thus such interventions should be included as part of the "survivorship plan" for long term, as well as shorter term cancer survivors, especially the older ones.[37,38]

Our study has limitations. First, it is cross-sectional not longitudinal and thus causality cannot be determined. Moreover, as participants in a clinical trial, the subjects are likely a selected population, made somewhat more so by the age and race differences of the non-responders. Treatments for breast cancer have changed over the years since these patients were treated in the late 1970s and thus one cannot be certain how our findings would apply to a new generation of survivors treated with more recent regimens. Finally we did not have a direct non-cancer control group. However we utilized data collected from general populations with the same survey instrument used in our study. This is not ideal of course since these populations are European and thus not entirely comparable.

This study provides new information to add to our understanding of the relationships of comorbidity, age and functional alterations likely to be seen in older long term cancer survivors. Such information is of particular importance as the number of older cancer survivors increases and will present challenges for the healthcare system resulting from the multiple problems they experience as individuals. The generation of cancer survivorship plans has been a response to the overall issue of communication and guidance on planning for cancer survivors, while our patients are a clinical trials selected group and perhaps represent a best case scenario, our data, in context of other studies suggests that the longer cancer patients survive from their diagnoses and treatment, the more like their similar aged cohort they are and the more their physical, psychological function and quality of life became a reflection of their age related morbidities and symptoms. Thus, those caring for older long-term cancer survivors (while still remaining cognizant of cancer related limitations) will have to take into account the even more complex, non-cancer related, multifaceted array of threats to maintenance of high quality of life facing such individuals. [7,20,38]

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Table 1

Demographic data

	<65 (40–64)		≥65 (65–86)	
	n	**%**	**n**	**%**
Gender				
Female	79	100	74	100
Ethnicity				
White	70	89	70	95
Other	9	11	4	5
Education				
Less than high school	7	8.9	9	12.2
High school graduate	23	29.1	22	29.7
Some college/junior college	26	32.9	21	28.4
Bachelor's degree or higher	22	27.9	22	29.7
Unknown	1	1.3	0	0
Marital Status – *				
Single, never married	4	5.1	3	4.0
Married	58	73.4	43	58.1
Separated/Divorced	12	15.2	5	6.8
Widowed	5	6.3	22	29.7
Unknown	0	0	1	1.4
Household composition				
Lives alone	12	15.2	20	27.0
Employment status – **				
Full/part-time	42	53.2	8	10.8
Retired	11	13.9	47	63.5
Homemaker/unemployed	19	24.1	19	25.7
Unknown	7	8.9	0	0.0
Type of Mastectomy				
Radical	31	39.2	23	31.1
Modified radical	47	59.5	51	68.9
Recurrent and Re-treated	12	15.2	13	17.6
Lymphedema	33	41.8	29	39.2
Numbness	28	35.4	22	29.7
# Comorbid Conditions				
0	13	16.5	5	6.8
1	21	26.6	13	17.6
2–3	33	41.8	35	47.3
4+	12	15.2	21	28.4

* chi-square test, chi-square=16.8, p<0.01.

** chi-square test, chi-square=52.4, p<0.001

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Table 2

Prevalence of Comorbidities

	<65(n=79)		≥65(n=74)		
	n	**(%)**	**n**	**(%)**	**p-value**
Arthritis, rheumatism, or other connective tissue disorders	39	(49.4)	44	(59.5)	0.252
Glaucoma	3	(3.8)	7	(9.5)	0.200
Asthma	3	(3.8)	2	(2.7)	1.000
Emphysema or chronic bronchitis	6	(7.6)	1	(1.4)	0.117
High blood pressure	14	(17.7)	35	(47.3)	<.001
Heart Trouble	10	(12.7)	18	(24.3)	0.092
Circulation trouble in arms or legs	12	(15.2)	18	(24.3)	0.221
Diabetes	7	(8.9)	5	(6.8)	0.765
Epilepsy	0	(0.0)	0	(0.0)	-
Ulcers (of the digestive system)	6	(7.6)	2	(2.7)	0.276
Other stomach or intestinal disorders or gall bladder problems	14	(17.7)	12	(16.2)	0.830
Osteoporosis	13	(16.5)	16	(21.6)	0.537
Liver disease	0	(0.0)	2	(2.7)	0.245
Kidney disease	0	(0.0)	4	(5.4)	0.053
Other urinary tract disorders	8	(10.1)	6	(8.1)	0.781
Stroke	2	(2.5)	3	(4.1)	0.675
Parkinson’s disease	1	(1.3)	2	(2.7)	0.613
Thyroid or other glandular disorders	9	(11.4)	12	(16.2)	0.484
Skin disorders, such as pressure sores, leg ulcers, or severe burns	2	(2.5)	3	(4.1)	0.675
Anemia	4	(5.1)	3	(4.1)	1.000
Broken bones, fractures	10	(12.7)	12	(16.2)	0.648
Other Cancer or leukemia	5	(6.3)	5	(6.8)	1.000

P-values are from fisher’s exact test.

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Table 3

EORTC QLQ-C30 physical functional impairment

	<65		≥65		p-value
	n*	%*	n*	%*	
Do you have trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	34	(43.0)	37	(50.0)	0.420
Do you have any trouble taking a long walk?	13	(16.5)	33	(44.6)	<.001
Do you have any trouble taking a short walk outside of the house?	4	(5.1)	9	(12.2)	0.150
Do you have to stay in a bed or chair for most of the day?	3	(3.8)	6	(8.1)	0.316
Do you need help with eating, dressing, washing yourself or using the toilet?	1	(1.3)	2	(2.7)	0.611
Are you limited in any way in doing either your work or doing household jobs?	20	(25.3)	17	(23.0)	0.851
Are you completely unable to work at a job or to do household jobs?	3	(3.8)	5	(6.8)	0.484
How would you rate your overall physical condition in the past week?					
1 (Very poor)	1	(1.3)	1	(1.4)	0.974
2	1	(1.3)	3	(4.1)	
3	1	(1.3)	1	(1.4)	
4	12	(15.2)	12	(16.2)	
5	22	(27.8)	19	(25.7)	
6	22	(27.8)	21	(28.4)	
7 (Excellent)	19	(24.1)	17	(23.0)	
How would you rate your overall quality of life during the past week?					
1 (Very poor)	2	(2.5)	1	(1.4)	0.988
2	2	(2.5)	2	(2.7)	
3	2	(2.5)	3	(4.1)	
4	7	(8.9)	8	(10.8)	
5	20	(25.3)	16	(21.6)	
6	20	(25.3)	19	(25.6)	
7 (Excellent)	26	(32.9)	25	(33.8)	

P-value for binary endpoints are based on Fisher's exact test, p-value for overall physical condition and quality of life are based on chi-square test.

*For questions 1–7 n(%) = those answering yes.

Table 4

Study Patients' EORTC-QLQ-C30 Physical Function scores compared to population norms

Population grouping	Population Norms		Our Study Population			p-value *
	Mean Score	n	Mean Score	n	Standard Deviation	
All Patients **	89.9	1965	81.4	153	22.7	< .001
Female Patients	86.4	949	81.4	153	22.7	0.007
Female patients 70 and older	67.7	171	71.2	41	27.9	0.427
Physical Problems +	79.6	694	77.1	98	21.0	0.241
Chronic Disease ++	82.5	779	79.1	92	24.6	0.188

*P-value is based on a one sample t-test comparing the means from the study population to the overall population norms.

**Age range for population norm for all patients is 19 to 93 (mean = 47.7)

+For the population norms physical problems include arthritis, sciatica, and paralyzed/weak limb. For our population this includes patients with arthritis, osteoporosis, and broken bones.

++The Chronic group includes those suffering from diabetes, hypertension, chronic allergies, and chronic skin problems and those who answered 'yes' to unspecified chronic medical conditions. For our population this includes those with glaucoma, asthma, high blood pressure, diabetes, epilepsy, liver disease, kidney disease, UT disorder, Parkinson's disease, thyroid, skin disorders and anemia.

Table 5

Symptom Distribution from EORTC Symptom Scale

Symptom	<65 (n=79)		≥ 65 (n=74)	
	n*	%	n*	%
Dyspnea	24	(30.4)	27	(36.5)
Pain	29	(36.7)	35	(47.3)
Fatigue	52	(65.8)	48	(64.9)
Insomnia	36	(45.6)	30	(40.5)
Nausea & Vomiting	4	(5.1)	7	(9.5)
Constipation	10	(12.7)	16	(21.6)
Diarrhea	7	(8.9)	6	(8.1)
Appetite	7	(8.9)	11	(14.9)
Any Symptoms	62	(78.5)	59	(79.7)

n(%)=number (%) reporting symptom

* All p-values > .05 by age (< 65 vs. ≥ 65)

Table 6

Multivariate Analysis for Physical and Role Function, Relationship to Comorbidity and Symptom Scores

		Physical Function	
Model	**Factor**	**F-test (df)**	**P-value**
1	Comorbidity Scores	27.5 (1)	< .001
	Age	3.9 (1)	0.049
2	Symptom Scores	53.6 (1)	<.001
	Age	10.4 (1)	<.002
		Role Function	
1	Comorbidity Scores	36.9 (1)	<.001
	Age	0.4 (1)	0.0544
2	Symptom Score	56.3 (1)	<.001
	Age	3.5 (1)	0.063

Model 1. The independent variables are comorbidity score+age+education+marital status

Model 2. The independent variables are symptom score+age+education+marital status

Each factor reported is controlled for other variables in the model. Only those with significant relationships are shown in the table.