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Self-reported cognitive function in older breast cancer survivors after chemotherapy treatment

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ABSTRACT

Purpose: This study evaluated self-reported cognitive function in older breast cancer survivors and its association with prior chemotherapy.

Materials and methods: Breast cancer survivors aged 65-years and older, diagnosed 2012–2013, with local and regional stage disease, were identified through the linked Texas Cancer Registry-Medicare dataset. Survivors completed the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-CogV3) instrument and provided demographic and clinical data. A PCI–sub-score of less than 54 was used to identify cognitive impairment. Linear regression models were used to examine the FACT-CogV3 primary score, and logistic regression models evaluated the PCI–sub-score.

Results: Of 4448 eligible survivors, 1594 (35.8 %) completed the FACT-Cog and 1065 completed all questions. The median time from diagnosis to survey completion was 68 months The median age at survey completion was 76 years. 26 % of patients had received adjuvant chemotherapy. In adjusted models, decreased FACT-Cog primary scores were associated with age 80-years and older ($p<0.01$ vs. age 65–69) and with depression ($p < 0.01$), and increased scores were associated with an education of 4-year college and above ($p = 0.01$).

For the PCI-subscale, 243 patients (27.9 %) reported PCI-score <54. In the adjusted models, patients who were older than 80-years were more likely to report perceived cognitive impairment (OR 3.03, vs age 65–69), as well as those with depression (OR 6.19, $p < 0.01$). Prior chemotherapy was not a significant predictor of PCI (OR 1.49, $p = 0.06$).

Conclusion: Adjuvant chemotherapy was not significantly associated with self-reported cognitive impairment in older breast cancer survivors 5–6 years after diagnosis.

1. Lay summary

In this study, we examined the cognitive function and perceived cognitive impairments reported by older breast cancer patients, years after treatment with chemotherapy. At 5–6 years after diagnosis, we found that there is no significant difference in self-reported cognitive function and perceived cognitive impairments for patients who received chemotherapy. These results could provide more information to patients and providers when making treatment decisions.

2. Background

With advances in cancer screening and treatment, the population of cancer survivors has been growing. In the United States, there are approximately 18 million cancer survivors, with the numbers projected to increase to 26 million survivors by the year 2040 [1]. Over 4 million women are breast cancer survivors, with 60 % of this population being 65 years and older. Cancer survivors are at risk for many late effects related to their prior cancer treatment, including cognitive impairment.

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However, little is known about patient-reported symptoms including cognitive impairment related to cancer treatments years after their primary treatment and diagnosis [2–4]. Older patients are likely more vulnerable to treatment-related toxicities such as the potential decline of cognitive function related to receipt of chemotherapy [5,6].

Cancer-related cognitive impairment can impact many domains of cognition, including memory, attention, processing speed, and executive function. [7]. Cancer and its treatments, particularly radiation therapy and cytotoxic chemotherapy, are hypothesized to accelerate the process of aging, causing cellular and molecular changes that are similar to those seen with normal aging among patients without cancer [8]. Many studies have reported short-term changes in cognition related to chemotherapy [5,9–14], but the data on whether these changes persist years into survivorship are conflicting. [15–17]. Therefore, the purpose of this study was to evaluate perceived cognitive function and perceived cognitive impairment (PCI) in older breast cancer survivors, 5 years after diagnosis, and to determine whether prior chemotherapy was associated with perceived cognitive outcomes.

3. Methods

3.1. Study population

The Texas Cancer Registry (TCR) and Medicare-linked claims data were used to identify patients with breast cancer who were ages 65 years and older at diagnosis, had local/regional stage disease, and were diagnosed from January 2012 to December 2013. Medicare is the US federal health insurance program that provides coverage to people age 65 years and older. Part A provides coverage for inpatient hospitalizations, home or skilled nursing, and hospice care. Part B provides coverage for doctors' services, preventative services, medical equipment, and home health care. To ensure availability of medical claims, patients were required to be Medicare beneficiaries with Part A and B coverage and without Health Maintenance Organization enrollment for 12 months continuously after their diagnosis. Texas Cancer Registry provided names and mailing addresses for 4726 residents and the physician of record. Of those, 278 were identified as deceased or as having undeliverable addresses; therefore, the survey was mailed to 4448 patients who met eligibility criteria. The survey included several sections, including the FACT-Cog V3 survey, selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), questions from the Medicare Health Outcomes Survey (MHOS), self-reported performance status, a decision regret scale regarding receipt of chemotherapy, and self-reported demographics, treatment, and disease status. The PRO-CTCAE items have been previously reported in Adesoye et al., 2023 [18], and the methods and procedures of survey administration are the same as previously described. This manuscript reports on the results of the FACT-Cog V3 survey.

3.2. Primary outcome

The primary outcome measure was derived from the FACT-Cog V3, a survey instrument designed to evaluate the perceived cognitive function in patients with cancer [19]. The FACT-Cog V3 [9,19–21] was designed to test cognitive difficulties in cancer survivors and has been modified to be used in observational and treatment studies [12,22]. Importantly, patient-reported measures in the FACT-Cog provide insight regarding a patient's perspective of treatment effects and capture the perceived impact of cognitive impairment on quality-of-life [23–25]. The FACT-Cog V3 has been validated for use in patients with cancer and in other populations with some modifications to scoring [26]. The survey assesses both cognitive concerns (impairments or deficiency) and cognitive abilities with a primary score, derived from four subsections focusing on: 1) perceived cognitive impairment (PCI), 2) perceived impairments in quality of life, 3) perception and comments from others, and 4) perceived cognitive abilities [9,27]. Each subsection is scored following the FACT-Cog scoring guideline (version 3) [28].The sum of all the subsections results in a total score (primary score) to assess a patients' cognitive function. For this analysis, the total score and the perceived cognitive impairment (PCI) were used as primary outcomes, with results from the other subsections presented in the supplemental data. A PCI sub-score of less than 54 was used to identify cognitive impairment, as this cutoff has shown good ability to discriminate patients with cognitive impairment and was validated with data from breast cancer survivors in the Mind Body Study [12].

3.3. Study measures

Demographic and clinical variables were collected using a self-administered questionnaire and from TCR and Medicare claims. Age at diagnosis, marital status, disease stage and hormone receptor status were obtained from TCR data. Race/ethnicity, education, household income, height and weight were self-reported. Charlson co-morbidity score was constructed with Klabunde's algorithm [29], using inpatient and outpatient claims within a 12-month window preceding the 30-day timeframe of diagnosis. Individual comorbidities including hypertension, osteoporosis, and depression were also ascertained by diagnosis codes during the same time window. Receipt of radiation therapy and type of surgery were determined based on treatment billing codes abstracted from Medicare claims files in the 9-month treatment window post-diagnosis (Supplemental Table 1). Receipt of endocrine therapy was determined using national drug codes (NDC) from Medicare Part-D (prescription drug coverage benefit file) claims in a 12-month window after the diagnosis date and/or self-reported use. Receipt of chemotherapy was identified using billing codes (Healthcare Common Procedure Coding System J codes) within the first 6 months after the date of cancer diagnosis (Supplemental Table 1). The time windows were used to distinguish adjuvant therapy versus treatment for metastatic disease.

3.4. Data collection

Three weeks prior to contacting eligible patients, the physician of record received mailed notification of the study, per TCR requirements. Eligible patients received a mailed study invitation letter in English and Spanish with a study questionnaire in English and a US $10 incentive [30]. Reminder letters were sent to non-respondents at 2 weeks, 4–6 weeks, and 8–10 weeks after the initial mailing. Data were collected between April 2018 and October 2019.

3.5. Statistical analysis

The weighted percentage of receiving chemotherapy was compared by patient characteristics using the Rao-Scott Chi-Square test adjusted for response weight. Weighted means of FACT-Cog V3 primary score and sub-scale scores (Perceived Cognitive Impairments, Comments from Others, Perceived Cognitive Abilities, and Impact of Perceived Cognitive Impairments on QoL) were compared between groups using F-test adjusted for response weights. A linear regression model was conducted to examine the association of receiving chemotherapy with the FACT-Cog V3 primary score while controlling for respondent sociodemographic and clinical variables, including age at diagnosis, gender, education, income, marital status, Charlson comorbidity, and receipt of chemotherapy. We included covariate coefficient estimates, standard error (SE), and 95 % confidence intervals (CIs). Robust estimates of variance were obtained using the Jackknife resampling method. A logistic regression model was conducted to examine the likelihood of PCI score <54 while controlling for respondent sociodemographic and clinical variables. Candidate independent variables were included based on both clinical and statistical significance, and variables with $p < 0.01$ stayed in the final model. We included odds ratios (OR) and 95 % confidence intervals (CI) to present the likelihood of low PCI score (<54).

Response weight, normalized inversed probability weighting (IPW), was applied to all the analysis to address potential non-response bias due to the non-probability respondent sample [31]. IPW was obtained through a logistic regression model estimating response probability while adjusting for sociodemographic and clinical variables. Data analyses were performed using SAS (version 9.4 SAS Institute Inc., Cary, NC, USA). For each case, we computed the probability of being selected from a pool of 4099 eligible cases. The inversed value of the probability was used as a weight of each observation to balance out the bias due to non-response. Finally, the normalized inversed probability was generated by dividing the inverse probability by the mean and used as the final weight in the analysis. The study was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board and the Texas Cancer Registry Institutional Review Board.

4. Results

Of 4448 eligible patients who were mailed a study invitation and questionnaire, 1594 survivors (35.8 %) responded to the FACT-Cog V3, and of those, 1065 respondents completed all 4 sections of the survey. Eighty of those 1065 respondents self-reported disease recurrence which excluded them from the analyses to avoid biases, leaving a total of 985 eligible respondents for this study (Fig. 1). Compared to non-respondents, respondents were younger, more likely be married, White, with no comorbidities, and had received chemotherapy (Supplemental Table 1). Median survey return time was 32 days (IQR 20–60 days).

The median time from cancer diagnosis to survey completion was 68 months (IQR 62–73). Demographic and clinical characteristics of respondents are summarized in Table 1. Overall, 98.3 % (n = 973) of participants were female. The median age at diagnosis was 70 years (IQR 67–74), and the median age at survey completion was 76 years (IQR 73–80). Most respondents were white and 58.2 % had Charlson Comorbidity Score of 0. Hormone receptor positive disease was the breast cancer subtype diagnosed in 78.8 % (n = 765) of patients and 76.0 % (n = 768) of patients had localized disease. A lumpectomy was performed in 55.5 % (n = 557) of patients and 44.5 % (n = 371) received a mastectomy.

Chemotherapy was administered to 287 of respondents (26.2 %) and of these, 159 had localized disease. A total of 46.3 % (n = 464) received endocrine therapy. Compared to respondents who did not receive chemotherapy, those who received chemotherapy were younger, white, and were less likely to have been diagnosed with localized stage and hormone receptor positive disease (Supplemental Table 2).

The primary FACT-Cog scores, overall and by patient demographics, cancer characteristics, and treatment are shown in Table 2. The primary FACT-Cog possible score range is 0–132. The weighted mean for the primary FACT-Cog score was 104.1 (95 % CI 102.0–106.2). Among respondents who received chemotherapy, there was no significant difference in primary FACT-Cog score compared to those who had not (105.0 vs. 103.8, p = 0.55).

Significant differences in primary FACT-Cog score were seen in respondents age 80+ with a lower weighted mean of 90.3 (95 % CI 82.0–98.6, vs age 65–69). Respondents with a high school education or less had decreased weighted mean scores of 99.6 (95 % CI 96.1–103.1 vs. some college and above). Having an income of less than $19,999 was associated with a significantly lower weighted mean score of 96.9 (95 % CI 89.1–104.8) compared to a score of 107.1 (95 % CI 104.1–110.0) for respondents with an income between $50,000-$99,999. The presence of comorbidities was associated with a lower weighted mean primary score, as respondents with low comorbidity score had a mean of 101.2 (95 % CI 96.6–105.9 vs. 0), and respondents with two or more comorbidities had a mean of 98.7 (95 % CI 93.1–104.4 vs. 0). Patients with depression had significantly lower weighted mean scores 88.6 (95 % CI 83.9–93.3) with depression vs. 109.1 (95 % CI 106.8–114.6) without depression.

4.1. Linear model

We conducted a linear regression model to examine the significance of receiving chemotherapy on FACT-Cog V3 primary score while controlling for respondent sociodemographic and clinical variables. Results are shown in Table 3. The model showed no significant difference between those who did and did not receive chemotherapy (p = 0.14). Decreased FACT-Cog primary scores were associated with patients older than age 80 years (β = −17.29, 95 % CI = −25.5 to −9.1, p < 0.01 vs. age 65–69) and with depression (β = −19.22, 95 % CI = −24.1 to −14.1, p < 0.01. Increased scores were associated with an education of 4-year college and above (β = 6.59, 95 % CI = 1.9 to 11.3, p < 0.01).

4.2. FACT-Cog subscale

We evaluated patient scores on the PCI subscale of the FACT-Cog. Results from the PCI subscale are shown in Table 4, and the subscale regression model is shown in Table 5. For the PCI subscale (range 0–72

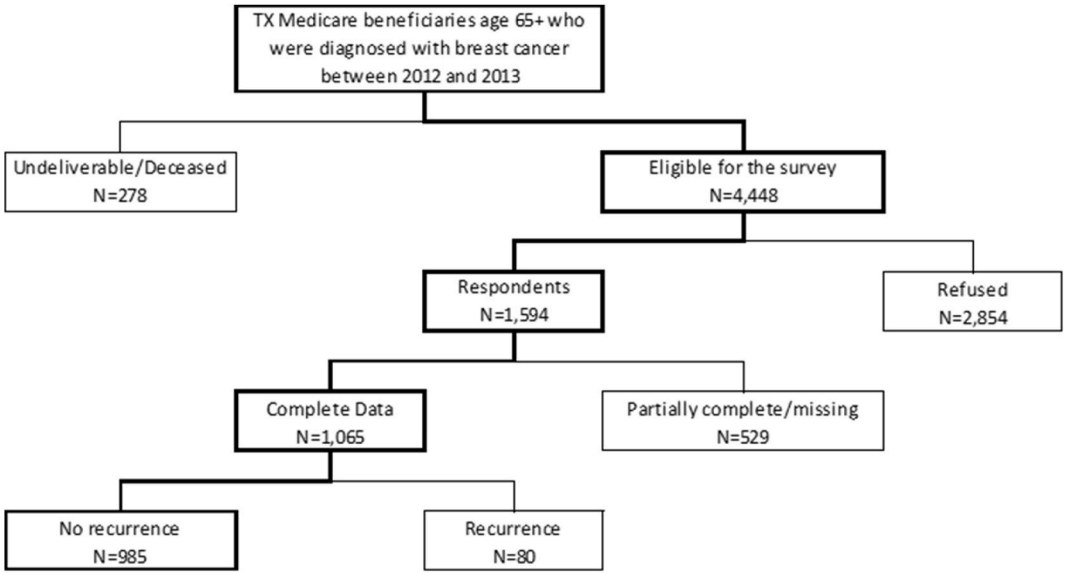

Fig. 1. Selection of study participants.

Table 1
Demographic, clinical and treatment characteristics of survey respondents by receipt of chemotherapy.

	Total		Chemo		No Chemo		P[a]
	N	Weighted Col%	N	Weighted Row %	N	Weighted Row %	
All	985	100.0	287	26.2	698	73.8	–
Age at dx							<0.01
65–69	433	35.1	156	36.7	277	63.3	
70–74	308	26.4	90	28.7	218	71.3	
75+	244	38.5	41	15.0	203	85.0	
Marital status							0.95
Married	406	36.9	116	26.9	290	73.1	
Not married	214	28.8	66	25.7	148	74.3	
UNK	365	34.3	105	26.0	260	74.0	
Race/Ethnicity							0.11
White non-Hispanic	817	82.5	231	25.1	586	74.9	
Black	54	6.4	22	37.6	32	62.4	
Hispanic	91	11.0	29	31.0	62	69.0	
Education							0.81
High school or under	335	36.3	94	25.8	241	74.2	
Some college	305	31.6	98	28.3	207	71.7	
College graduate	165	16.9	46	24.5	119	75.5	
Graduate degree	167	15.2	46	24.8	121	75.2	
Income							0.11
Less than $19,999	104	12.2	30	25.3	74	74.7	
$20,000-$49,999	287	30.1	83	24.1	204	75.9	
$50,000-$99,999	250	23.0	81	32.9	169	67.1	
$100,000 or more	147	13.4	46	28.2	101	71.8	
UNK/Mis	197	21.3	47	21.3	150	78.7	
Charlson Comorbidity							0.28
0	631	58.2	193	28.4	438	71.6	
1	201	23.4	56	23.1	145	76.9	
2+	124	18.4	29	23.0	95	77.0	
Diagnosis year							0.70
2012	485	47.6	133	25.6	352	74.4	
2013	500	52.4	154	26.8	346	73.2	
Stage at Diagnosis							<0.01
Localized	768	76.0	159	18.5	609	81.5	
Regional	217	24.0	128	50.7	89	49.3	
Hormone receptor (ER+/PR+)							<0.01
Yes	765	78.8	178	21.1	587	78.9	
No	220	21.2	109	45.3	111	54.7	
Radiation therapy							0.40
Yes	593	51.2	160	25.0	433	75.0	
No	392	48.8	127	27.5	265	72.5	
Surgery							<0.01
Lumpectomy	557	55.5	121	19.7	436	80.3	
Mastectomy	371	44.5	158	36.5	213	63.5	
Endocrine							<0.01
Yes	464	46.3	107	20.7	357	79.3	
No	521	53.7	180	31.0	341	69.0	
Hypertension							0.43
Yes	711	73.9	208	26.4	503	73.6	
No	#	#	#	26.1	#	73.9	
UNK	#	#	#	12.3	#	87.7	
Osteoporosis							0.25
Yes	386	40.9	123	29.2	263	70.8	
No	#	#	#	24.1	#	75.9	
UNK	#	#	#	26.2	#	73.8	
Depression							0.69
Yes	231	24.2	65	22.9	166	77.1	
No	#	#	#	27.2	#	72.8	
UNK	#	#	#	33.0	#	67.0	

suppressed due to cell size <11.
Abbreviations: UNK Unknown, ER Estrogen Receptor, PR Progesterone Receptor.
[a] Rao-Scott p-value.

with a cut-off of 54), 243 respondents (27.9 %) reported cognitive impairment. A significantly greater proportion of scores were below the cut-off for respondents age 80+ (44.0 %, $p < 0.01$), those with depression (56 % vs 18.3 %, $p < 0.01$), those with less education (33.5 % high school or less vs 19.8 % graduate degree, $p = 0.04$), and those with a high Charlson Comorbidity score (36.1 %, $p = 0.03$). Patients who had received chemotherapy had no significant difference in proportions for lower PCI scores (29.4 % with chemotherapy vs 27.4 % without, $p = 0.59$). The results of the other FACT-Cog subsections are shown in Supplemental Table 3 and Table 4.

4.3. PCI logistic regression model

A logistic regression model was used to examine the relationship between PCI scores and respondent sociodemographic and clinical variables (Table 5). Patients older than age 80 years were more likely to report cognitive impairment (OR 3.03, 95 % CI 1.70–5.42, vs age 65–69), as well as those with depression (OR 6.19, 95 % CI 4.28–8.94).

Table 2
Primary scores of cognitive functional assessment of cancer therapy by survey respondents characteristics.

	Mid	IQR	Weighted Mean(SE)	95 % CI	P
All	112	97–123	104.1(1.1)	(102.0–106.2)	–
Age at diagnosis					
65–69	113	100–124	108.3(1.0)	(106.3–110.2)	Ref.
70–74	112	98–123	107.0(1.3)	(104.5–109.5)	0.43
75–79	111	97–124	105.4(2.2)	(101.1–109.7)	0.23
80+	102	83–117	90.3(4.2)	(82.0–98.6)	<0.01
Gender					
Male	108	84–121	86.6(13.6)	(59.9–113.3)	Ref.
Female	112	97–123	104.4(1.1)	(102.3–106.5)	0.19
Marital status					
Married	112	97–123	103.9(1.5)	(100.9–106.9)	Ref.
Not married	109	97–121	101.9(2.6)	(96.9–107.0)	0.51
UNK	113	99–123	106.2(1.6)	(103.0–109.4)	0.31
Race/Ethnicity					
White non-Hispanic	112	98–123	104.8(1.1)	(102.7–106.9)	Ref.
Black	104.5	92–121	98.6(4.2)	(90.3–106.9)	0.15
Hispanic	113	93–123	106.5(2.9)	(100.8–112.1)	0.59
Others	112	98–126	91.5(13.8)	(64.5–118.5)	0.34
Education					
High school or under	104	90–121	99.6(1.8)	(96.1–103.1)	Ref.
Some college	111	98–123	105.5(2.1)	(101.3–109.6)	0.03
College graduate	113	102–123	107.5(2.6)	(102.3–112.7)	0.01
Graduate degree	119	101–125	110.4(2.2)	(106.1–114.8)	<0.01
Missing	102	77–111	86.7(12.4)	(62.3–111.0)	0.30
Income					
Less than $19,999	104	91–120	96.9(4.0)	(89.1–104.8)	Ref.
$20,000-$49,999	109	96–122	102.7(1.7)	(99.3–106.1)	0.19
$50,000-$99,999	113	95–122	107.1(1.5)	(104.1–110.0)	0.02
$100,000 or more	120	104–126	108.0(4.6)	(99.0–117.0)	0.07
UNK/Mis	110	99–121	104.6(2.1)	(100.5–108.7)	0.09
Charlson Comorbidity					
0	113	99–124	106.7(1.4)	(104.0–109.4)	Ref.
1	108	94–121	101.2(2.4)	(96.6–105.9)	0.05
2+	107.5	89–121	98.7(2.9)	(93.1–104.4)	0.01
UNK	120	104–124	109.8(4.7)	(100.6–119.0)	0.52
Diagnosis year					
2012	111	97–122	104.5(1.4)	(101.8–107.2)	Ref.
2013	112	98–123	103.8(1.7)	(100.5–107.1)	0.74
Stage at Diagnosis					
Localized	113	98–123	104.8(1.3)	(102.3–107.3)	Ref.
Regional	107	97–121	102.0(2.1)	(97.8–106.2)	0.27
Hormone receptor (ER+/PR+)					
Yes	111	97–123	103.3(1.3)	(100.8–105.9)	Ref.
No	113	99–123	107.1(1.6)	(104.0–110.2)	0.07
Chemotherapy					
Yes	111	96–122	105.0(1.4)	(102.2–107.7)	Ref.
No	112	98–123	103.8(1.4)	(101.1–106.5)	0.55
Radiation therapy					
Yes	112	98–123	106.3(1.0)	(104.3–108.3)	Ref.
No	111	97–123	101.8(1.9)	(98.0–105.6)	0.04
Surgery					
Lumpectomy	113	98–123	105.0(1.3)	(102.5–107.6)	Ref.
Mastectomy	111	97–122	103.2(1.9)	(99.5–107.0)	0.43
None/UNK	111	101–122	102.5(5.1)	(92.5–112.4)	0.62
Endocrine therapy					
Yes	112	98–123	104.2(1.5)	(101.2–107.2)	Ref.
No	111	97–122	104.0(1.5)	(101.0–107.1)	0.94
Hypertension					
Yes	110	97–123	103.4(1.3)	(100.9–106.0)	Ref.
No	114	100–124	106.1(2.0)	(102.2–110.0)	0.27
UNK	102.5	98–122.5	102.7(8)	(87.1–118.4)	0.93
Osteoporosis					
Yes	108.5	94–122	100.3(2.1)	(96.2–104.3)	Ref.
No	113	99–123	106.8(1.1)	(104.5–109.0)	<0.01
UNK	113	101–123	107.1(4.0)	(99.2–115.0)	0.13
Depression					
Yes	97	79–114	88.6(2.4)	(83.9–93.3)	Ref.
No	115	101–124	109.1(1.2)	(106.8–111.4)	<0.01
UNK	1113	98–123	106.8(4.0)	(98.9–114.6)	<0.01

Abbreviations: Ref. Reference, UNK Unknown, ER Estrogen Receptor, PR Progesterone Receptor, SE Standard Error, IQR Inter Quartile Range.

Table 3
Regression model of Fact-Cog primary score.

	Full Model				Reduced Model			
	β	SE	95 % CI	P	β	SE	95 % CI	P
Intercept	88.10	4.1	(80.0–96.2)	<0.01	88.18	2.6	(83.0–93.3)	<0.01
Age at diagnosis								
65–69	Ref.				Ref.			
70–74	−1.22	1.6	(-4.3 to 1.8)	0.43	−1.48	1.5	(-4.5 to 1.5)	0.33
75–79	−2.80	2.1	(-6.9 to 1.4)	0.19	−2.96	2.1	(-7.1 to 1.2)	0.17
80+	−17.10	4.2	(-25.4 to −8.8)	<0.01	−17.29	4.2	(-25.5 to −9.1)	<0.01
Education								
High school or under	Ref.				Ref.			
Some college	3.10	2.4	(-1.7 to 7.9)	0.20	3.45	2.5	(-1.4 to 8.3)	0.16
College graduate	5.96	3.0	(0.1–11.8)	0.05	6.65	2.7	(1.4–11.9)	0.01
Graduate degree	6.23	2.5	(1.3–11.2)	0.01	6.59	2.4	(1.9–11.3)	<0.01
Missing	−11.35	12.2	(-35.3 to 12.6)	0.35	−12.52	12.1	(-36.3 to 11.2)	0.30
Osteoporosis								
Yes	Ref.				Ref.			
No	4.25	2.1	(0.1–8.4)	0.05	4.31	2.0	(0.3–8.3)	0.03
UNK	3.67	6.0	(-8.1 to 15.4)	0.54	4.21	5.4	(-6.4 to 14.9)	0.44
Depression								
No	Ref.				Ref.			
Yes	−18.57	2.3	(-23.1 to −14.0)	<0.01	−19.22	2.5	(-24.1 to −14.4)	<0.01
UNK	1.04	5.4	(-9.5 to 11.5)	0.85	0.19	4.9	(-9.5 to 9.8)	0.97
Hypertension								
Yes	Ref.							
No	−0.02	2.3	(-4.4 to 4.4)	0.99				
UNK	−2.97	10.0	(-22.6 to 16.6)	0.77				
Gender								
Female	Ref.							
Male	−13.97	8.9	(-31.4 to 3.4)	0.12				
Income								
Less than $19,999	Ref.							
$20,000-$49,999	1.52	3.8	(-5.9 to 8.9)	0.69				
$50,000-$99,999	4.22	3.9	(-3.5 to 11.9)	0.28				
$100,000 or more	2.97	5.5	(-7.8 to 13.7)	0.59				
UNK/Mis	4.12	4.1	(-3.9 to 12.1)	0.31				
Charlson Comorbidity								
0	Ref.							
1	−2.55	2.3	(-7.1 to 2.0)	0.27				
2+	−2.66	3.0	(-8.5 to 3.2)	0.37				
UNK	1.12	3.7	(-6.1 to 8.4)	0.76				
Chemotherapy								
No	Ref.							
Yes	−2.66	1.8	(-6.1 to 0.8)	0.14				

Abbreviations: Ref. Reference, UNK Unknown.

Prior chemotherapy was not a significant predictor of cognitive impairment (OR 1.49, 95 % CI 0.99–2.26).

5. Discussion

To our knowledge, this is the first study to evaluate the association of baseline demographics, clinical factors, and cancer treatments with self-reported cognitive function in a population-based sample of long-term older breast cancer survivors. We found that patients who had previously received chemotherapy within 6 months after diagnosis scored slightly lower on the FACT-Cog than those who did not, but the results were not significant. There was also no significant difference in the FACT-Cog subscale score for PCI in patients who had undergone chemotherapy. These results suggest that the receipt of chemotherapy does not have a major long-term impact on perceived cognitive function in older breast cancer survivors.

Our study is novel in that we studied patients 5–6 years after treatment to evaluate whether self-reported cognitive impairment persisted longer into cancer survivorship. Prior studies of cognitive function among patients with breast cancer have shown that chemotherapy is associated with cognitive impairments in the domain of executive functioning [13] as well as a decline in processing speed and a short-term impact on verbal ability [11,14] Receipt of chemotherapy may also accelerate the normal aging process, according to the accelerated aging hypothesis [5,9–14]. Patients with breast cancer report more cognitive difficulties up to 6 months after therapy when compared to their age-matched noncancer controls [10]. Previous studies have, for the most part, been limited to assessments during therapy and in the short-term post-treatment and have not focused on older cancer survivors [5,9–14]. We were able to assess PCI more than 5 years after the completion of chemotherapy; our findings showed no significant differences between patients treated with chemotherapy, which may be due to the longer time since treatment in our study. A longitudinal study showed a potential reversibility of cognitive changes induced by chemotherapy in early-stage breast cancer patients. Cognitive functions were assessed prior to adjuvant chemotherapy, 1 week after the last cycle of chemotherapy and subsequently after 6 months. Significant cognitive decreases immediately after completing the chemotherapy were followed by improvements 6 months after chemotherapy [32].

The results from our FACT-Cog study show that advanced age and depression are associated with lower cognitive function scores. Age has been shown to be a risk factor for cognitive impairment and neurodegenerative diseases in patients with cancer [33–35]. Studies have shown that older patients with breast cancer may be more susceptible to cognitive decline from chemotherapy and adjuvant endocrine therapies compared to their younger counterparts [11,36]. Furthermore, older age and receipt of chemotherapy have all been strongly associated with cognitive impairment [37,38]. Comorbidities such as cardiovascular disease and diabetes independently increase the risk of cognitive impairment [39], and comorbidities may be a marker of insulin

Table 4
FACT-Cog V3 subscale score – demographics by perceived cognitive impairments (cut-off 54).

	Perceived Cognitive Impairments (0–72)				P
	<54		≥ 54		
	N	Weighted Row %	N	Weighted Row %	
All	243	27.9	742	72.1	
Age at diagnosis					<0.01
65–69	98	23.6	335	76.4	
70–74	73	24.0	235	76.0	
75–79	38	26.1	113	73.9	
80+	34	44.0	59	56.0	
Marital status					0.19
Married	107	30.0	299	70.0	
Not married	57	30.6	157	69.4	
UNK	79	23.5	286	76.5	
Race/Ethnicity					0.43
White non-Hispanic	199	27.5	618	72.5	
Black	17	35.8	37	64.2	
Hispanic	23	25.5	68	74.5	
Education					0.04
High school or under	104	33.5	231	66.5	
Some college	72	27.5	233	72.5	
College graduate	30	22.9	135	77.1	
Graduate degree	32	19.8	135	80.2	
Income					0.33
Less than $19,999	35	33.2	69	66.8	
$20,000-$49,999	75	29.6	212	70.4	
$50,000-$99,999	69	30.4	181	69.6	
$100,000 or more	21	20.2	126	79.8	
UNK/Mis	43	24.7	154	75.3	
Charlson Comorbidity					0.03
0	141	24.4	490	75.6	
1	60	32.1	141	67.9	
2+	38	36.1	86	63.9	
Diagnosis year					0.19
2012	115	25.6	370	74.4	
2013	128	30.1	372	69.9	
Stage at Diagnosis					0.47
Localized	187	27.2	581	72.8	
Regional	56	30.2	161	69.8	
Hormone receptor (ER+/PR+)					0.32
Yes	192	28.8	573	71.2	
No	51	24.8	169	75.2	
Chemotherapy					0.59
Yes	77	29.4	210	70.6	
No	166	27.4	532	72.6	
Radiation therapy					0.15
Yes	142	25.5	451	74.5	
No	101	30.5	291	69.5	
Surgery					0.63
Lumpectomy	134	27.1	423	72.9	
Mastectomy	97	29.6	274	70.4	
None/UNK	12	23.3	45	76.7	
Endocrine therapy					0.71
Yes	111	27.2	353	72.8	
No	132	28.5	389	71.5	
Hypertension					0.13
Yes	188	29.5	523	70.5	
No	#	22.9	#	77.1	
UNK	#	45.3	#	54.7	
Osteoporosis					0.05
Yes	110	33.1	276	66.9	
No	#	24.0	#	76.0	
UNK	#	38.7	#	61.3	
Depression					<0.01
Yes	118	56.5	113	43.5	
No	#	18.3	#	81.7	
UNK	#	47.2	#	52.8	

suppressed due to cell size <11.
Abbreviations: UNK Unknown, ER Estrogen Receptor, PR Progesterone Receptor.

resistance [40], cancer development [41], and diseases that accelerate the aging process [42], but comorbidity score was not a significant predictor of perceive cognitive impairment in our study. Consistent with prior studies, we found that a history of depression was associated with perceived cognitive impairment [43].

There are several limitations to this study. First, the overall response rate was 35.8 % despite the application of standard methods utilized in population-based surveys [44,45]. Given the differences between responders and non-responders, the low response rate may limit the generalizability of our findings and introduce bias. The FACT-Cog survey was included as part of a larger study questionnaire that conferred a potentially greater respondent burden, which also may have contributed to the response rate. It is possible or even likely that patients with severe decline in cognitive function may have been less likely to complete the survey, which could limit our ability to detect differences in cognitive function related to treatment. Additionally, we do not have information on different chemotherapy regimens and patients who received chemotherapy differed in patient characteristics from those who did not. We would expect these differences to minimize the measured difference in cognitive function between groups, as those patients with better cognitive function, younger age, and better health at baseline would be more likely to have received chemotherapy. This study did not include cognitive assessment before chemotherapy, and we did not administer the survey at multiple time points, both of which limit our ability to understand the temporal patterns of cognitive impairment. We also have no information on symptom management through the follow up period, utilization of healthcare services, and subsequent impact on severity. Finally, we note that subjective measures of cognitive function do not always correlate with findings on quantitative testing.

Previous studies have shown that breast cancer survivors can have an excellent quality of life, years after their diagnosis with proper care and social support. However, those same studies also note the potential adverse effects of systemic therapy on patients' physical health 5–10 years after treatment [46]. While our findings are reassuring that self-reported cognitive changes were not associated with chemotherapy use in breast cancer survivors, the non-significant findings do not provide definitive evidence that chemotherapy does not impact long-term cognitive function, given the study's design limitation. More studies are needed to determine the long-term impact of cancer treatment, particularly among older cancer patients, to optimize symptoms management and quality of life in cancer survivors.

6. Conclusion

In summary, our findings demonstrate that chemotherapy treatment was not significantly associated with more self-reported cognitive impairment in older breast cancer survivors, even 5–6 years after diagnosis. The difference between patients who received chemotherapy versus those who did not, was modest, suggesting limited impact of chemotherapy overtime on cancer survivors. Even so, the potential risk of decreased cognitive function highlights the importance of patient-centered discussions to make an informed decision on a patient's treatment plan to ensure the best quality of life for older patients with breast cancer.

CRediT authorship contribution statement

Rachel Kim: Writing – review & editing, Writing – original draft. **Julia Peña:** Writing – review & editing, Resources. **Kai-Ping Liao:** Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation. **Susan K. Peterson:** Writing – review & editing, Writing – original draft, Software, Investigation, Data curation, Conceptualization. **Liang Li:** Writing – review & editing, Methodology, Conceptualization. **Daria Zorzi:** Writing – review & editing, Writing – original draft. **Holly M. Holmes:** Writing – review & editing. **Mariana Chavez-MacGregor:** Writing – review & editing. **Sharon H. Giordano:**

Table 5
Logistic regression Model of Perceived Cognitive Impairments (cut-off 54).

	Full model			Reduced model		
	OR	95 % CI	P	OR	95 % CI	P
Age at diagnosis						
65–69	**1.00**			**1.00**		
70–74	1.10	(0.72–1.67)	0.66	1.12	(0.75–1.67)	0.59
75–79	1.26	(0.76–2.09)	0.36	1.23	(0.77–1.98)	0.39
80+	3.36	(1.83–6.17)	<0.01	3.03	(1.70–5.42)	<0.01
Depression						
No	**1.00**			**1.00**		
Yes	5.79	(3.98–8.41)	<0.01	6.19	(4.28–8.94)	<0.01
UNK	3.43	(0.72–16.28)	0.12	3.75	(1.03–13.70)	0.05
Gender						
Female	**1.00**					
Male	1.50	(0.55–4.06)	0.43			
Marital status						
Married	**1.00**					
Not married	0.70	(0.41–1.19)	0.18			
UNK	0.63	(0.41–0.97)	0.04			
Education						
High school or under	**1.00**					
Some college	0.91	(0.58–1.43)	0.69			
College graduate	0.65	(0.35–1.20)	0.17			
Graduate degree	0.65	(0.38–1.10)	0.11			
Missing	1.43	(0.36–5.63)	0.61			
Income						
Less than $19,999	**1.00**					
$20,000-$49,999	1.11	(0.60–2.05)	0.75			
$50,000-$99,999	1.28	(0.66–2.48)	0.46			
$100,000 or more	0.83	(0.32–2.18)	0.71			
UNK/Mis	0.80	(0.40–1.58)	0.52			
Charlson Comorbidity						
0	**1.00**					
1	1.25	(0.81–1.95)	0.32			
2+	1.28	(0.74–2.21)	0.38			
UNK	0.50	(0.20–1.28)	0.15			
Chemotherapy						
No	**1.00**					
Yes	1.49	(0.99–2.26)	0.06			
Hypertension						
Yes	**1.00**					
No	0.83	(0.53–1.32)	0.43			
UNK	2.80	(0.35–22.26)	0.33			
Osteoporosis						
Yes	**1.00**					
No	0.72	(0.48–1.06)	0.10			
UNK	0.94	(0.19–4.54)	0.94			

Abbreviations: UNK Unknown, OR Odds Ratio, CI Confidence Interval.

Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Disclosures

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Declaration of conflict interest

The authors do not have any conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104468.

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