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Fear of Cancer Recurrence Associated with Perceived Cognitive Impairment among Women with Cancers: Findings from the Women's Health Initiative Life and Longevity After Cancer Study

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Abstract

Background: Perceived cognitive impairments(PCI) are the most common complications that Non-Central Nervous System (Non-CNS) cancers survivors experience. Studies have suggested that those who expreience fear of cancer recurrence (FCR) tend to report cognitive problems; however, this association has not been examined.

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Disclosure statement

The author declares that (s)he has no relevant or material financial interests that relate to the research described in this paper.

Methods: Participants (n = 6,714) were enrolled in the Women's Health Initiative Life and Longevity After Cancer study. FCR was assessed using the Cancer Worry Scale and PCI was assessed using the PCI subscale of FACT-Cog. The association between FCR and PCI was analyzed using univariable and multivariable logistic regression models. A cut off score of ≥ 14 is indicative of high FCR and below 14 indicating low FCR. Scores lower than 60 indicated PCI.

Result: The multivariable model showed that higher FCR corresponded to an increase in odds of PCI (OR = 1.15, $p < 0.001$). We also found that older age at diagnosis ($p < 0.001$), less social support ($p = 0.01$), over ten pounds of weight gain after cancer treatment ($p = 0.02$), and mild or worse anxiety ($p < 0.001$) were also associated with increased odds of PCI from the multivariable analysis.

Discussion: Our findings indicate that survivors with higher FCR demonstrated poorer cognitive performance than those with lower FCR. These results suggest that those with higher FCR are more likely to report PCI.

Keywords

Cognition; Fear of cancer recurrence; Cancer survivors; Cognition; Older women

1. Background

The number of older cancer survivors continues to increase due to an increasing population of older adults, enhanced detection, and the development of cancer treatments [1]. In the United States, approximately 64% of cancer survivors are 65 years and older, which is expected to grow to 73% by 2040 [2,3]. Cancer is most prevalent among those older than 65, and it is no longer viewed as acute but as a chronic illness that needs to be managed for the remainder of their lives [4]. Thus, optimization of the health of older cancer survivors should include appropriate management of their cancer-related complications.

Studies have reported that older cancer survivors experience more side effects from cancer treatments and a more complicated recovery due to advanced age and comorbidities, relative to younger cancer survivors [4-6]. Cognitive impairments (CI) are the most common complications older survivors perceive after treatment [7], which include problems in memory, processing speeds, concentration, multitasking and word retrieval [8]. Such perceived cognitive impairments (PCI) significantly impact older survivors' functional status, level of independence, decision-making capacity, treatment adherence, quality of life, and ultimately their survival [9]. Therefore, investigating factors associated with PCI in older cancer survivors is crucial to identify targets for treatment.

Fear of cancer recurrence (FCR) may be associated with PCI. FCR is defined as the 'fear, worry, or concern relating to the possibility that cancer will come back or progress in the original cancer site or in another part of body' [10]. FCR is a broad concept that describes the emotion and attention to potential cancer recurrence, which is uncertain and unmanageable [11]. A recent systematic review has found that 59% of survivors reported moderate FCR and a further 19% reported severe FCR [12]. However, these findings have mostly been limited to short-term and young cancer survivors. Given that the number

of older cancer survivors is growing, it is important to examine FCR in this age group, particularly its association with perceived cognitive function across multiple cancer types.

Although the exact underlying mechanism of the association between FCR and perceived cognitive function remains unknown, several studies offer some potential cues. According to a model by Lee-Jones, FCR can result in negative consequences in psychological aspects, including anxiety [13]. Similarly, one recent study showed that higher FCR is associated with higher symptom distress, which is a known risk factor for PCI [14]. Other studies have further reported that FCR is associated with higher levels of emotional symptoms (e.g. anxiety), physical symptoms (e.g. fatigue), and dysfunctional behavior (e.g. hypervigilance) [15-17], which contribute to PCI [18].

However, despite the potential link between FCR and perceived cognitive functioning, this association has not been examined in older cancer survivors. To address this gap, we will investigate the associations between FCR and perceived cognitive function among older females with Non-Central Nervous System (Non-CNS) cancers (e.g. melanoma, colorectal, endometrial, lung, breast, non-Hodgkin lymphoma, leukemia, ovarian, fallopian tube, and peritoneal cancers) in the Women's Health Initiative (WHI) Life and Longevity After Cancer (LILAC) cohort. In this study, we hypothesized that higher FCR would be associated with greater reports of PCI among older females with Non-CNS cancers.

2. Methods

2.1. Study design and participants

Details of the WHI and the WHI LILAC cohort have been described previously [19,20]. Briefly, between 1993 and 1998, the WHI recruited postmenopausal women between the ages of 50 and 79 years from 40 clinical centers throughout the USA. Participants were randomized into one or more clinical trials (n = 68,132) or an observational study (n = 93,676). Participants were followed for up to 10 years within the WHI, and many continued follow-up in the WHI extension studies (including the LILAC study) that began in 2005. In 2013, the WHI LILAC study enrolled WHI participants who had been diagnosed with select cancers (breast, endometrial, ovarian, lung, and colorectal cancers, melanoma, lymphoma, and leukemia) after their enrollment in WHI. The goal of the WHI LILAC was to expand the existing WHI data to support studies of cancer outcomes, survivorship, and molecular epidemiology [19].

For the current analyses, WHI LILAC participants were included if they were diagnosed with Non-CNS cancers (e.g. melanoma, colorectal, endometrial, lung, breast, non-Hodgkin lymphoma, leukemia, ovarian, fallopian tube, and peritoneal cancers) and had non-missing data on FCR and cognitive functioning on the year-1 follow-up LILAC questionnaire. All materials used in the collection of records have been approved by the Fred Hutchinson Cancer Research Center's Institutional Review Board, which is the Institutional Review Board of record for the WHI (3647) and the WHI LILAC (8239, 2006C0007) study. All participants in the WHI and the WHI LILAC provided written informed consent.

2.2. FCR measure

FCR was measured on the year-1 LILAC follow-up questionnaire with the eight survey questions from the Cancer Worry Scale [21]. The scale includes such items as 'How often do you think about your chances of getting cancer again?' and 'Do these thoughts affect your mood?' Item response categories are on a 4-point Likert scale ranging from 1 (rarely or never) to 4 (all the time). Scale scores range from 8 to 32, with higher scores indicating more frequent worries about cancer recurrence. A cut off score of ≥ 14 is indicative of high FCR; below 14 indicating low FCR. Internal consistency for the score was high (Cronbach α = .87) [21] and has been validated among cancer survivors [22].

2.3. Perceived cognitive functioning measure

Cognitive functioning was measured on the year-1 LILAC follow-up questionnaire with the 20-item PCI subscale of the FACT-Cog [23]. Participants were asked to rate the frequency of cognitive problems that they had perceived in the past 7 days using a 5-point Likert type scale. Possible responses for each item ranged from 0 (never) to 4 (several times a day). Answers were reverse coded, and a total score ranged from 0 to 80, where lower scores indicate worse cognitive function (i.e. PCI). Scores lower than 60 indicated impairments in perceived cognitive functioning [24]. Cronbach's alpha for this subscale ranged from 0.77 to 0.86 [23].

2.4. Covariates

Factors that affect cognitive functioning were derived from published literature and included age, race, ethnicity, education, cancer stage, self-reported cancer treatment, comorbidities, and social support [25,26]. Participants self-reported comorbidities that include obesity, diabetes, high blood pressure, and heart disease on the WHI and LILAC baseline questionnaire (Form 340, Form 33, Form 80). Social support was measured on the LILAC baseline questionnaire using five survey questions from the Medical Outcome Study Social Support Survey [27]. Scores were transformed to 0-100, with higher scores indicating greater support.

2.5. Statistical analysis

Demographics and clinical information of the cohort were summarized descriptively, with continuous variables reported as median [first-third quartile] due to non-normal distributions of the data. The association between FCR and perceived cognitive functioning was analyzed using univariable and multivariable logistic regression models, with the odds ratios and 95% confidence intervals reported. Backward variable selection was used to create the multivariable model, including FCR and all other variables significant at the $p < 0.05$ level during the univariable analysis. From the initial model, variables were removed one at a time until all variables remaining in the final model had $p < 0.10$ (removed variables: diabetes, $p = 0.82$; marital status, $p = 0.21$; heart disease, $p = 0.12$). Interaction effects between each variable and FCR were tested in the final model; however, none were significant. Complete case analysis was used for modeling due to low levels of missing data. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Sample characteristics

Among 6,714 women included in the study cohort, the median (Q1-Q3) age was 71 (66-77) years. The average time between cancer diagnosis and FACT-COG completion was 8.8 (SD = 5.0) years. The majority of women were Non-Hispanic White (92.6%), presently married (46.4%), and had at least a 4-year college degree (52.7%). A little more than half had breast cancer (58.4%) followed by colorectal (10.3%), endometrial (8.9%), melanoma (6.6%), lymphoma (5.9%), lung (5%), ovarian (2.7%), and leukemia (2.2%). In addition, 71% had localized Non-CNS cancers. Approximately 70% did not receive chemotherapy but received radiation, hormone, and other therapy (stem cell transplantation). The majority of women had high blood pressure (68.8%) followed by anxiety (41%), obesity (23.4%), diabetes (17.7%), and heart disease (16.9%). The median score of social support was 80 [range: 60-95], and that of FCR was 10 [range: 9-13]. Among study participants, approximately 20% reported higher FCR (FCR score > 14). In addition, approximately 79% scored above 60 on FACT-Cog PCI, meaning they likely did not have CI. Table 1 displays characteristics of the study participants. Table 2 displays univariable logistic regression comparing odds of PCI (FACT-Cog score < 60) by sample characteristics. The odds of PCI were related with age at diagnosis ($p < .001$), marital status ($p < .001$), education ($p < 0.001$), heart disease ($p < .001$), diabetes ($p = .01$), weight gain ($p = .002$), anxiety ($p < .001$), social support ($p < .001$), and FCR ($p < .001$).

3.2. Primary analysis: association between FCR and perceived cognitive functioning.

Results for the multivariable regression model are presented in Table 3. The univariable regression model (Table 2) showed the unadjusted associations between PCI (FACT-Cog score < 60) and potential risk factors. The multivariable model showed that a 2-point higher FCR corresponded to an increase in odds of reporting PCI (OR = 1.15, $p < .001$), after adjusting for covariates (social support, age at diagnosis, years since diagnosis, marital status, education, weight gain, and anxiety). In addition, odds of reporting PCI tended to increase with increasing age at diagnosis (OR = 1.66, $p < .001$), years since diagnosis (OR = 1.34, $p < 0.001$), anxiety (OR = 3.54, $p < 0.001$), and weight gain (OR = 1.27, $p = .02$). In contrast, PCI tended to decrease with increasing social support (OR = 0.96, $p = .01$) and level of education (some college, OR = 0.95; college degree, OR = 0.81; graduate degree, OR = 0.77). When interaction effects between FCR and other covariates were tested, none were statistically significant.

4. Discussion

To our knowledge, this is one of the few studies to examine the association of FCR with self-perceived cognitive functioning among a sample of US older female Non-CNS cancer survivors. Consistent with our hypothesis, our findings indicate that survivors with higher FCR report PCI more often than those with lower FCR.

Our findings on the association between FCR and perceived cognitive functioning are in line with previous studies. Past research has found that cancer survivors face uncertainty

such as FCR that has the potential to elicit anxiety about the future [28,29]. Experiencing uncertainty is common in cancer survivors throughout their illness trajectory, but each individual's reactions toward uncertainty differ. Some survivors may be intolerant to FCR and exhibit increased levels of anxiety, a known contributor to PCI [28,29]. This suggests that among cancer survivors, those most sensitive to FCR may experience anxiety resulting in increased vulnerability to PCI. Therefore, future studies that investigate the characteristics of survivors who demonstrate high FCR are needed. This understanding will help identify those at higher risk for PCI.

Our results also revealed that PCI is linked to increased age, heart disease, and weight gain. One possible explanation for this relationship is that cancer treatment regimens, including chemotherapy and radiation, are associated with incidences of hypertension and cardiovascular diseases [30,31]. Researchers have further noted that cancer survivors with cardiovascular diseases commonly incur cognitive problems, specifically in memory and attention [32,33]. Given that cardiovascular diseases are correlated with older age and weight gain, the current study findings are consistent with previous literature [34,35]. In contrast, we found that perceived cognitive function is positively associated with social support. It is possible that social support can alleviate psychological distress, thus leading to improved cognitive function [26,36]. Alternatively, having social interactions may have a direct effect on maintaining cognitive abilities and improve one's perceived cognitive function. Future studies should include repeated measures of cognitive functioning among cancer survivors to further explore the dynamics of the relationships with age, weight gain, heart disease, and social support, along with mechanisms that might explain each relationship.

4.1. Limitations

The strengths of this study include the large total number of study participants with extensive demographic and clinical data. However, this study has several limitations. First, this study was cross-sectional so we could not investigate a causal relationship between FCR and cognitive functioning. Second, the measure of cognitive function was specific to the subjective perception of overall CI. Future studies need to include objective assessments of cognitive performance across several cognitive domain (e.g. memory or verbal fluency; executive function) to better understand how each specific cognitive domain is associated with FCR. Additionally, the study participants were predominantly Non-Hispanic White (92.6%). This could limit the generalizability of these findings. Future studies are needed that include participants with diverse/ethnic backgrounds.

4.2. Clinical implications

This study not only advances the knowledge of perceived cognitive functioning but is also the foundation of more effective interventions that will improve cognitive outcomes for Non-CNS cancer survivors. For example, psychological interventions that help cancer survivors relieve FCR and become more tolerant of such uncertainty to facilitate cognitive recovery. In the clinical setting, health professionals may provide therapy that helps cancer survivors reevaluate uncertainty as a normal part of their lives, alter their maladaptive responses to uncertainty, and empower them to participate in everyday activities despite this uncertainty

[37]. In addition to this therapy, health professional may encourage cancer survivors with higher FCR to get involved them in social activities to offset FCR, which will ultimately promote their cognitive functioning [26].

5. Conclusion

Among older women with non-CNS cancer, those with higher FCR had poorer cognitive performance than those with lower FCR. This study contributes to the existing literature that suggests the importance of FCR as a factor associated with cognitive health. Future studies should focus on testing strategies to reduce FCR and their impacts on PCI in cancer survivors.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1.

Description of sample characteristics (n = 6714).

Age at diagnosis (years)	**Median [Q1-Q3]**
N = 6714	71 [66-77]
Years from diagnosis to FACT-Cog survey	**Median [Q1-Q3]**
N = 6714	8.1 [4.4-13.0]
Race	**n (%)**
American Indian/Alaskan Native	10 (0.1%)
Asian	114 (1.7%)
Native Hawaiian/Pacific Islander	4 (0.1%)
Black	247 (3.7%)
White	6220 (92.6%)
More than 1 race	72 (1.1%)
Unknown/Not reported	47 (0.7%)
Ethnicity	**n (%)**
Not Hispanic/Latino	6575 (97.9%)
Hispanic/Latino	123 (1.8%)
Unknown/Not reported	16 (0.2%)
Marital status	**n (%)**
Married or living as married	3118 (46.4%)
Widowed	2170 (32.3%)
Divorced/separated	839 (12.5%)
Never married	288 (4.3%)
Unknown/missing	299 (4.5%)
Education	**n (%)**
≤ High school	958 (14.3%)
Some college, AD, Vocational school	2214 (33.0%)
College grad	1935 (28.8%)
Post grad	1567 (23.3%)
Unknown/missing	40 (0.6%)
Cancer Types	**n (%)**

Breast	3922 (58.4%)
Colorectal	692 (10.3%)
Endometrial	595 (8.9%)
Lung	337 (5.0%)
Ovarian	181 (2.7%)
Leukemia	146 (2.2%)
Lymphoma	397 (5.9%)
Melanoma (invasive)	444 (6.6%)
Cancer Stage	**n (%)**
Local	4765 (71.0%)
Regional	1371 (20.4%)
Distant	494 (7.4%)
Unknown	84 (1.2%)
Cancer Treatment (Self-reported or from medical records abstraction)	**n (%)**
Chemotherapy (n = 38 missing data)	1980 (29.7%)
Radiation (n = 39 unknown)	3103 (46.5%)
Hormone/Endocrine (n = 108 missing data)	2821 (42.7%)
Other (Stem cell transplantation, tumorvaccine) (n = 137 missing data)	288 (4.4%)
Comorbidities	**n (%)**
High blood pressure	4486 (66.8%)
Heart disease	1133 (16.9%)
Diabetes	1188 (17.7%)
Obesity (BMI > 30) (n = 4 missing data)	1569 (23.4%)
Weight gain > 10 lb (n = 913 unknown)	942 (16.2%)
Anxiety in past4weeks (mild/moderate/severe; n = 156 missing)	2691 (41%)
Social Support	**Median [Q1-Q3]**
N = 6158	80 [60-95]
Fear of cancer recurrence (FCR)	**n (%)**
Low (< 14)	5512 (82.1%)
High (≥ 14)	1202 (17.9%)
Cognitive impairment	**n (%)**
Yes (FACT-Cog score < 60)	1444 (21.5%)

No (Score 60-80)	5270 (78.5%)

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Table 2.

Univariable logistic regression comparing odds of perceived cognitive impairment (FACT-Cog score < 60).

Age at diagnosis (years)		**Cognitive impairment n (%)**	**OR (95% CI)**	***P*-value**
10-year increase		n/a	1.27 (1.18-1.37)	< 0.001
Years from diagnosis to FACT-Cog survey				
5-year increase		n/a	1.05 (0.99-1.12)	0.08
Marital status				
Married or living as married		620/3118 (19.9)	Ref	< 0.001
Widowed		526/2170 (24.2)	1.29 (1.13-1.47)	
Divorced/separated		174/839 (20.7)	1.05 (0.87-1.27)	
Never married		43/288 (14.9)	0.71 (0.51-0.99)	
Education				
≤ High school		235/958 (24.5)	Ref	< 0.001
Some college, AD, Vocational school		523/2214 (23.6)	0.95 (0.80-1.14)	
College grad		372/1935 (19.2)	0.73 (0.61-0.88)	
Post grad		306/1567 (19.5)	0.75 (0.62-0.91)	
Cancer Types				
Breast		848/3922 (21.6)	Ref	0.92
Colorectal		155/692 (22.4)	1.05 (0.86-1.27)	
Endometrial		124/595 (20.8)	0.95 (0.77-1.18)	
Lung		73/337 (21.7)	1.00 (0.77-1.31)	
Ovarian		39/181 (21.6)	1.00 (0.69-1.43)	
Leukemia		26/146 (17.8)	0.79 (0.51-1.21)	
Lymphoma		90/397 (22.7)	1.06 (0.83-1.36)	
Melanoma (invasive)		89/444 (20.1)	0.91 (0.71-1.16)	
Cancer Stage				
Local		1022/4765 (21.5)	Ref	0.93
Regional		299/1371 (21.8)	1.02 (0.88-1.18)	
Distant		104/494 (21.1)	0.98 (0.78-1.23)	
Cancer Treatment (Self-reported or from medical records abstraction)				
Chemotherapy	Yes	417/1980 (21.1)	0.97 (0.85-1.10)	0.61

		Cognitive impairment n (%)	OR (95% CI)	*P*-value
Age at diagnosis (years)				
	No	1015/4696 (21.6)	Ref	
Radiation	Yes	664/3103 (21.4)	1.00 (0.89-1.12)	0.99
	No	765/3572 (21.4)	Ref	
Hormone/Endocrine	Yes	592/2821 (21.0)	0.98 (0.87-1.10)	0.74
	No	807/3785 (21.3)	Ref	
Other (Stem cell transplantation, tumor vaccine)	Yes	54/288 (18.8)	0.85 (0.63-1.15)	0.29
	No	1343/6289 (21.4)	Ref	
Comorbidities				
High blood pressure	Yes	991/4486 (22.1)	1.11 (0.98-1.26)	0.10
	No	453/2228 (20.3)	Ref	
Heart disease	Yes	299/1133 (26.4)	1.39 (1.20-1.61)	< 0.001
	No	1145/5581 (20.5)	Ref	
Diabetes	Yes	287/1188 (24.2)	1.20 (1.04-1.39)	0.01
	No	1157/5526 (20.9)	Ref	
Obesity (BMI > 30)	Yes	320/1569 (20.4)	0.92 (0.80-1.05)	0.22
	No	1123/5141 (21.8)	Ref	
Weight gain > 10 lb	Yes	232/942 (24.6)	1.30 (1.11-1.54)	0.002
	No	974/4859 (20.1)	Ref	
Anxiety in past 4 weeks (mild/moderate/severe)	Yes	936/2691 (34.8)	3.98 (3.51-4.51)	< 0.001
	No	457/3867 (11.8)	Ref	
Social Support				
10-point increase		n/a	0.91 (0.88-0.93)	< 0.001
Fear of cancer recurrence				
Low (< 14)		1044/5512 (18.9)	Ref	< 0.001
High (≥ 14)		400/1202 (33.3)	2.14 (1.86-2.45)	
2-point increase (modeled continuously)		n/a	1.24 (1.20-1.29)	< 0.001

Table 3.

Multivariable logistic regression estimating the association between FCR and odds of perceived cognitive functioning in women with any non-CNS cancers.

	Odds ratio	95% Confidence Interval	*P*-value
Fear of cancer recurrence (2-point increase)	1.15	1.10-1.20	< 0.001
Covariates			
Social support (10-point increase)	0.96	0.93-0.99	0.01
Age at diagnosis (10-point increase)	1.66	1.46-1.89	< 0.001
Years from diagnosis to FACT-Cog survey (5-year increase)	1.34	1.21-1.47	< 0.001
Education			0.06
HS or less	Ref	Ref	
Some college/ Assoc. deg.	0.95	0.76-1.19	
College degree	0.81	0.64-1.02	
Graduate degree	0.77	0.60-0.99	
Weight gain > 10 lbs	1.27	1.05-1.54	0.02
Mild or worse anxiety	3.54	3.04-4.12	< 0.001

*Multivariable model only contains variables included after model selection