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Fear of recurrence among older breast, ovarian, endometrial, and colorectal cancer survivors: Findings from the WHI LILAC study

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Abstract

Objective: To examine the prevalence of and factors associated with fear of recurrence (FCR) following treatment for breast, ovarian, endometrial, and colorectal cancer among older women.

Methods: Participants were enrolled in the Women's Health Initiative Life and Longevity After Cancer study. Descriptive statistics and multivariate logistic regression models were used to assess the association of demographic, clinical, and quality of life variables with survivors' FCR, dichotomized as <14 (low) or ≥14 (high) using the Cancer Worry Scale.

Results: Out of the 4259 participants, 3124 (73.3%) were diagnosed with breast cancer, 559 (13.1%) with colorectal cancer, 493 (11.6%) with endometrial cancer, and 83 (2%) with ovarian cancer. There were no significant differences in FCR by cancer type ($P = .75$), with a mean scale score of 10.8 ± 2.87 for all participants combined. Approximately 16% (n = 679) were in the high FCR group. Multivariable analyses indicated that being younger at diagnosis, reporting a symptom score of ≥8, receipt of chemotherapy, and lower self-rated health were significantly associated with high FCR. Women who were widowed or never married were less likely to report high FCR.

Conclusions: Fear of recurrence was experienced by a small but important proportion of older, long-term cancer survivors and is associated with multiple demographic and clinical variables.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

These results will better inform researchers and clinicians regarding the individuals who are at risk of FCR.

Keywords

cancer; cancer survivors; fear of cancer recurrence; older women; WHI LILAC

1 | BACKGROUND

There are currently approximately 15 million cancer survivors in the United States, with expectations that this number will increase to over 20 million in the next 10 years.[1] One of the most commonly reported problems of cancer survivors is fear of cancer recurrence (FCR).[2] FCR is defined as the fear, worry, or concern relating to the possibility that cancer will come back or progress in the same place or in another part of the body.[3] It also includes the perception that recurrence is unmanageable, and constitutes a threat to life.[4] FCR has been recognized as an issue of significant burden among patients with cancer and has been associated with morbidity and reduced quality of life.[2] Previous research, predominantly on short-term survivors (<5 years postdiagnosis), has shown that the percentage of cancer survivors experiencing FCR ranges from 39% to 97%, with up to 15% reporting a high level of FCR.[5] In studies with long-term (≥5 years postdiagnosis) survivors, there is still a substantial percentage ranging who report high levels of FCR (17%−35%).[2,6] There are several theories about the mechanisms of FCR; however, more research is needed,[7] because of the complexity and heterogeneity of the factors associated with recurrence fears. According to a model by Lee-Jones,[8] the patient's emotional reaction (fear) can be the result of interpretations and cognitions of cancer threat prompted by internal cues (eg, physical symptoms) and/or external cues (eg, follow-up appointments).

Previous research has indicated that FCR is associated with numerous factors including sociodemographic variables, clinical characteristics, social resources, physical and psychological factors, and coping resources. Factors consistently shown to be associated with greater FCR include younger age,[6,9,10] the presence and severity of physical symptoms,[5,6,10] psychological distress,[2,5,10] and lower reported quality of life.[5,9] Only a few studies have examined predictors among long-term cancer survivors, but these studies have found similar results, including sociodemographic factors, clinical characteristics, and psychological predictors.[2,9,11] However, cancer type as a predictor of FCR among both short-term and long-term survivors has found inconsistent results.[9,12]

Although there has been more research on the prevalence and predictors of FCR in recent years, these studies have mostly been limited to short-term breast cancer survivors. Currently, there is a paucity of research in the area of older, long-term cancer survivors of multiple cancer types. Despite being the majority of patients with cancer and survivors,[13] older adults are greatly understudied, particularly in long-term survivorship.[2,6] Knowledge about FCR and other possible psychosocial burdens in long-term survivors is crucial to ensure adequate and continued surveillance and support for this growing group.

The purpose of this study was to identify the prevalence of FCR and factors associated with FCR among older, long-term cancer survivors within the Women's Health Initiative (WHI)

Life and Longevity After Cancer Study (LILAC). Results can be used to develop more effective interventions among older women with various cancer types to reduce psychological distress related to FCR.

2 | METHODS

2.1 | Study design

This study used data collected as part of the WHI and the WHI LILAC studies, funded by the National Cancer Institute. The WHI main study design has been described elsewhere.[14,15] Briefly, between 1993 and 1998, postmenopausal women between the ages of 50 to 79 years were recruited from 40 clinical sites across the United States into 1 or more randomized clinical trials (WHI-CT n = 68 132) or an observational study (WHI-OS n = 93 676). The WHI-CT and WHI-OS were closed in 2004 to 2005, and participants were invited to continue survey-based follow-up in the WHI Extension Study 1 (2005–2010), Extension Study 2 (2010–2015), and Extension 3 (2015–2020). Beginning in 2013, the WHI LILAC Study[16] enrolled WHI participants who have been diagnosed with select cancers after WHI study enrollment into a cancer survivorship cohort (Figure S1 in the online supplemental materials). One of the specific goals of the WHI LILAC study was to obtain cancer treatment information and late and long-term cancer outcomes for women diagnosed with 1 of 8 selected cancers (breast, endometrial, ovarian, lung, and colorectal cancers, melanoma, lymphoma, and leukemia).[16] The ultimate goal was to expand the existing WHI data to support studies of cancer outcomes, participant survivorship, and molecular epidemiology. LILAC participants were asked to complete an initial survey about their initial cancer treatments and recurrences, as well as updated demographic information, medications, symptoms, social support, financial problems, mental and physical functioning, quality of life, and unmet needs.

For this paper, eligibility criteria were LILAC participants with a diagnosis of breast (n = 3124), ovarian (n = 83), endometrial (n = 493), or colorectal (n = 559) cancer; completion of the LILAC baseline and 1-year follow-up forms, and a WHI Form 151 (completed annually by all WHI participants still in follow-up); and completed within 1.5 years of the LILAC 1-year follow-up form. Breast, ovarian, endometrial, or colorectal cancer types were chosen because they were the more prevalent solid tumor cancers in the WHI, with the majority of survivors living with nonmetastatic disease, unlike lung cancer. The sample sizes of women with leukemia and lymphoma were also low within the LILAC database. In addition, the melanoma participants included a number of in situ cases, which were inappropriate for the aims of this manuscript. No women who had experienced a cancer recurrence or second malignancy were included in this study's sample.

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 (3467) and the WHI LILAC (8239, 2006C0007) study. All participants in the WHI and the WHI LILAC provided written informed consent.

2.2 | Measures

2.2.1 | Fear of recurrence—Participants' FCR was measured by the 8-item Cancer Worry Scale (CWS).[17] 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 cutoff score of ≥14 is indicative of those who may be experiencing greater FCR,[17] with those below 14 indicating low FCR.

Compared to other measures of FCR, the CWS does demonstrate some promise as it is a brief measure with strong psychometric properties (α = .87)[17] that has been validated in multiple cancer types and among survivors up to 88 years old.[18,19] In addition, the CWS's clinical cutoff scores are empirically based. In its development, the CWS assessed sensitivity, specificity, and positive and negative predictive values at each cutoff point against 2 items of the Cancer Acceptance Scale.[20] Despite the CWS's psychometric soundness among patients with breast cancer, it has not been validated against a clinical assessment of FCR and additional research is needed to establish clinical cutoffs of the CWS used in different cancer types.

2.2.2 | Symptom score—Participants were asked to indicate the occurrence and severity of 24 physical and psychological symptoms experienced within the past 4 weeks. Symptoms assessed were physical (ie, abdominal/pelvic pain, bloating or gas, constipation, coughing or wheezing, diarrhea, difficulty breathing, feeling tired, general aches and pains, headaches or migraines, heartburn, hot flashes, joint pain or stiffness, night sweats, pain or burning while urinating, shortness of breath, uncontrolled leaking of feces, uncontrolled leaking of urine, vaginal or genital discharge, vaginal or genital dryness, and vaginal or genital irritation or itching) and psychological (ie, difficulty sleeping, feeling anxious, feeling depressed, trouble concentrating). The presence of symptoms (yes/no) and their severity (mild, moderate, severe) were totaled to create a symptom score. Scores ranged from 0 to 72, with higher scores indicating higher symptom burden.[21]

2.2.3 | Self-rated health—Participants were asked to rate their current health status using the following questionnaire item: "In general, would you say your health is excellent, very good, good, fair or poor?" Scores ranged from 1 (excellent) to 5 (poor), with a higher score indicating worse health. Better self-rated health is highly associated with better quality of life and functioning.[22]

2.2.4 | Global quality of life—Participants were asked to rate their current quality of life using the following item: "Overall, how would you rate your quality of life?" Scores ranged from 0 to 10, with a higher score indicating higher overall quality of life.[23] Scores were transformed to a 0 to 100 scale for data analyses. This item has high internal reliability (α = 0.86–0.89) and has been validated among cancer survivors.[24]

2.2.5 | RAND-36 physical functioning subscale—Participants' physical functioning was measured using the 10-item RAND-36 physical functioning subscale.[25] Responses to

the single items were (1) no, not limited at all; (2) yes, limited a little; and (3) yes, limited a lot. Single items were summed together to create the subscale score and then were transformed to a 0 to 100 scale. Higher scores indicated better physical functioning. The RAND-36 has high reliability ($\alpha > .90$)[25] and has been validated among cancer survivors.[26]

2.2.6 | Social support construct—Participants were asked about their social support that was assessed using a 5-item scale derived from the Medical Outcomes Study Social Support Questionnaire,[27] previously used in earlier WHI-based studies.[22,28] Responses to each item was on a 5-point scale ranging from 1 = “none of the time” to 5 = “all of the time,” with higher scores indicating higher levels of social support. Raw scores were transformed to a scale of 0 to 100 for analyses. The Medical Outcomes Study Social Support Questionnaire has high reliability ($\alpha > .90$)[27] and has been validated among cancer survivors.[22,28]

2.2.7 | Financial toxicity—Participants were asked to indicate whether they had experienced any of the following experiences related to their financial status following their cancer diagnosis (yes/no): denied health insurance, denied life insurance, health insurance refusal to pay for a medical claim, large debts/bills to pay, trouble getting a mortgage or loans, needing to get legal assistance, declaration of bankruptcy, and not having enough money to pay for basic necessities.[29] The responses were summed with scores ranging from 0 to 8 with higher scores indicating higher financial toxicity (described as financial problems hereafter) after one’s cancer diagnosis.

2.2.8 | Analyses—Descriptive statistics and univariable and multivariable logistic regression models were used to assess the association of demographic, clinical, and quality of life variables with FCR, dichotomized as <14 (low FCR) or ≥14 (high FCR). Univariable logistic regression using complete data was used to examine variables associated with FCR. All variables significant at a 0.2 level were considered for inclusion in a multivariable model after imputing any missing data. Fifty multiple imputed datasets were created utilizing the fully conditional specification methods[30] in SAS PROC MI. The symptom score, social support construct, RAND-36 physical functioning subscale, and global quality of life were categorized because of pronounced skewing prior to the imputation process. Global quality of life was dichotomized based on its median value of 8, and the others were divided into roughly equal tertiles. Variables that were strongly correlated and represented similar theoretic constructs were carefully evaluated with the most predictive retained for consideration in the final model. Multivariable logistic models were fit to each of the datasets, and results were combined using SAS PROC MIANALYZE. In a backward selection process, the least significant predictor was eliminated and the models were refit until only those predictors significant at the 0.10 level remained. As cancer type was of primary interest, it was retained in all multivariable models. All analyses were performed in SAS v9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Fear of cancer recurrence

Out of the 4259 total participants, 679 (15.9%) long-term survivors were in the high FCR group. Specifically, 499 (16.0%) of 3124 participants with breast, 91 (16.3%) of 559 with colorectal, 73 (14.8%) of 493 with endometrial, and 16 (19.3%) of 83 with ovarian cancers were in the high FCR group (Table S1 in the online supplemental materials).

3.2 | Sample characteristics

The demographic characteristics of participants (n = 4259) by low and high FCR and univariate predictors of FCR are presented in Table S1. The average age of the sample was 77.6 years (range = 64–95), and the majority were white, married, and with some college education. The average number of years since their cancer diagnosis was 9.5 years (SD = 4.9). There were no significant differences in FCR by cancer type ($P = .75$). The mean FCR score was 10.84 (SD = 2.87) for all cancer types combined.

Significant differences were observed between the low and high FCR groups regarding age, race, marital status, financial problems, years since diagnosis, receipt of chemotherapy, BMI, symptom score, physical functioning, self-rated health, global quality of life, and social support. Survivors who were older at diagnosis, White, widowed/single, had fewer financial problems, were greater years from diagnosis, did not receive chemotherapy, had lower BMI and symptom scores, and had better physical functioning, self-rated health, global quality of life and social support, and had lower FCR.

3.3 | Multivariate predictors of high FCR

Multiple imputation was used to create 50 imputed datasets. Using a backward selection process on the combined model estimates, a final multivariable model was created. Cancer type was retained in all models. The final model (Table S2 in the online supplemental materials) found that women who were older at diagnosis (OR = 0.98, 95% CI = 0.97–1.00 for 1-year increase) and were widowed (OR = 0.73, 95% CI = 0.60–0.90) and never married (OR = 0.62, 95% CI = 0.39–0.96) were less likely to report high FCR. Women who received chemotherapy (OR = 1.35, 95% CI = 1.11–1.63) were more likely to report high FCR. Women who rated their health as good (OR = 1.60, 95% CI = 1.25–2.06) and fair/poor (OR = 3.59, 95% CI = 2.82–4.56) were more likely than those who reported their health as excellent/very good to have high FCR. Lastly, women who reported a symptom score of 8 to 13 (OR = 1.60, 95% CI = 1.25–2.06) and 14 to 72 (OR = 3.59, 95% CI = 2.82–4.56) were more likely to report high FCR than those who reported 0 to 7 symptoms. Cancer site was not associated with high FCR among these older, long-term survivors ($P = .93$).

4 | DISCUSSION

This study examined the prevalence of FCR and factors associated with FCR among older, long-term cancer survivors from the WHI LILAC study. Results indicated that high levels of FCR were experienced by a small proportion (15.9%) of the sample, falling slightly lower than rates reported from previous studies among older, long-term cancer survivors.[2,6] In

addition, the proportion of participants in this study who reported a high FCR was also lower compared to other studies that used the CWS.[17–19] However, it is important to note that the current study's prevalence of high FCR is, on average, 9 years past diagnosis, which demonstrates the importance of continuing to monitor and address these long-term symptoms over time.

In this study, FCR did not differ by cancer type. Previous research examining FCR by cancer type has been inconsistent. For example, Koch-Gallenkamp[31] and Deimling[11] report that cancer type was not a significant predictor of FCR in long-term cancer survivors, yet Kornblith[12] has found that long-term breast cancer survivors scored significantly higher FCR than those with endometrial cancer. However, high FCR was associated with multiple demographic and clinical variables. This finding adds to the growing evidence[5,9,11,31,32] on the multifaceted predictors of FCR including age, presence or severity of symptoms (physical and mental), psychological distress, social support, and quality of life.

Similar to previous studies among long-term cancer survivors,[2,11,32] younger age was associated with high FCR. Studies of high FCR in studies of middle-aged or younger women are often cited greater fears to be associated with the unexpected, "off-time" event of cancer, interference on life's goals (children, career), the lack of peers with serious illness, and fewer coping resources than their older counterparts.[33] What was remarkable in the LILAC study of women diagnosed with cancer in their 60s and 70s is that even among this cohort of older women, we still found differences by age. This study not only corresponds to previous literature regarding age as a factor for FCR[13] but also adds to the literature on FCR among an older age cohort. Given that the mean age in our study was 77.6 years, these results point to the necessity of further breaking down age categories among those age 65 and older (eg, 65–74 vs. 75–84 years).

Women who were widowed or never married were less likely to report high FCR compared to married women. Spousal support has been found to be as a major source of social support among women with cancer.[34] Yet, in the context of FCR, the association between marital status and FCR is unclear. For example, Koch et al[2] found a positive association while others[33,35] have found no association between marital status and FCR among long-term cancer survivors. A potential reason for this finding is that never married women likely also do not have children. Previous research has found that women tend to care more about how their health affects those in their close social networks (ie, kids, spouses/partners) than perhaps they do about what happens to them individually.[36] Therefore, not being married (and/or having children) may generate less fear than if they were married or had children. Taken together, further identification of the sources and frequency of social support would be helpful in understanding if spousal or friend relationships differ in their association with FCR.

Higher presence of physical and mental symptoms and lower self-rated health were found to be associated with FCR in this study corresponding with previous studies on long-term cancer survivors.[6,9] In research among cancer survivors, knowledge of these physical and psychosocial burdens as they relate to FCR must be taken into account. In the current study, symptom score of ≥14 was the greatest predictor of high FCR, representing more than a

threefold risk. Helping survivors identify and address their cancer-related symptoms can greatly influence their FCR.[37] For older women, it may be difficult discerning between a cancer-related symptom and what is assumed as an age-related condition or change. Older individuals may not report their symptoms because of the assumption that the symptom is age-related not cancer-related, which may result in underreported or untreated symptoms. Clinicians and researchers need to be aware of this potential age effect and work to foster effective patient-provider communication to treat and manage bothersome symptoms.

Receipt of chemotherapy was also associated with high FCR in this study. Previous studies,[38] but not all,[6] have found receipt of chemotherapy to be associated with FCR. The result may reflect a perception of having a more serious disease.[38] Previous studies have posited that receipt of chemotherapy can increase the perceived disruptiveness of the cancer experience and feelings of vulnerability.[4,35] Lastly, chemotherapy is often used to reduce the risk of cancer recurrence[39]; thus, the choice of undergoing chemotherapy might be motivated by a woman's FCR.

4.1 | Clinical implications

Despite frequent studies on FCR and its determinants, some interventions[37,40] have been developed specifically to address and reduce FCR. For example, in a randomized controlled trial, Dieng and colleagues[40] found that a telephone-based psychoeducational intervention was effective in reducing FCR and stress and increasing disease knowledge. Another study by Lichtenthal et al[40] found that their home-delivered, computer-based cognitive bias modification intervention reduced health worries among breast cancer survivors. Recently, van de Wal and colleagues[19] found that blended cognitive behavior therapy significantly reduced the severity of FCR among breast, prostate, or colorectal cancer survivors. These studies and the growing number of others demonstrate that the multidimensional nature of FCR can be addressed through different approaches and ultimately reduced by these interventions. Future research is warranted to determine their efficacy in the long term and among diverse survivor populations.

It is important to note that there are various ways of measuring FCR and there are no clearly defined, clinically significant levels of FCR, which hinders comparisons across studies using different measures of FCR.[6,36,37] Researchers and clinicians are beginning to address this problem by developing research groups specifically focused on FCR and publishing calls for action.[10,38] Future efforts need to consider the many measures of FCR including the CWS, determine the optimal cutoffs for clinically significant FCR, develop a gold-standard measure of FCR, and implement such a measure into clinical practice as a routine screening.[10,38]

4.2 | Limitations

Several study limitations must be noted. First, the study clinical measures were self-reported and may be subject to recall and survivor bias. Second, the majority of the participants were breast cancer survivors who were white, non-Hispanic, and educated. Thus, this study lacked diversity by race ethnicity and education. In methodology, this study used a backward selection multiple regression model, which may result in statistically significant but spurious

predictors of FCR. Further, the CWS is not validated against a clinical assessment of FCR. However, the CWS is a brief measure with strong psychometric properties that has been validated in multiple cancer types. Lastly, the LILAC cohort suffers from survivorship bias in that only those women who survived long enough following their diagnosis (an average of 9 years) to take the survey are included in the sample. The sample size of certain cancer types (eg, ovarian) limits the study generalizability and longer interval between diagnosis, and the FCR assessment may bias the results as certain cancer types do have higher likelihood of recurrence and possible higher mortality rates.

A major strength of this study is the sample size and the abundant measures of demographic, clinical, psychosocial, and quality of life variables. This study adds to the existing literature, because it is the largest to examine the prevalence and predictors of high levels of FCR among older, long-term survivors of several cancer types, a growing population that is understudied.

4.3 | Conclusion

This study aimed to identify the prevalence of and factors associated with FCR among a large sample of older, long-term cancer survivors. This information can be used to develop more effective interventions to reduce FCR among older women with various cancer types. Results indicated that FCR was experienced by a small (15%) but significant proportion of cancer survivors, and is associated with multiple demographic (age, marital status) and clinical (chemotherapy, symptom score, general health) variables. These results may better inform researchers and clinicians regarding the individuals who are at risk of FCR and the continuation of these fears nearly a decade after diagnosis. As the number of older, long-term cancer survivors increases, additional research regarding clinical and psychosocial care is needed to guarantee the highest possible well-being and quality of life for this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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