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Role Function in Postmenopausal Women During Aromatase Inhibitor Therapy for Breast Cancer

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Abstract

Objective: Few studies have examined aromatase inhibitor therapy relating to role function in breast cancer survivors of working age. Our study sought to identify how pre-therapy sociodemographic and health/treatment-related characteristics, as well as patient-reported symptoms measured every six-months, influence role function during 18 months of AI therapy for early-stage breast cancer.

Methods: We performed a secondary analysis of longitudinal study data using linear mixed-effects modeling to examine role physical (RP) and role emotional (RE) functioning measured with the Medical Outcome Study Short Form 36 v2. The sample of postmenopausal women (N=351) consisted of three cohorts: chemotherapy followed by anastrozole (CAFI), anastrozole only (AI only), and non-cancer controls. Our choice of variables and interpretation of findings

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Author Contributions:

The study data for this secondary analysis was collected by Catherine Bender. All authors contributed to the design of the secondary analysis. Data preparation and analysis were performed by Halia Melnyk (first author) under the guidance of John Merriman (senior author) and Gary Yu. The manuscript was drafted by Halia Melnyk with guidance from Victoria Vaughan Dickson and John Merriman. All co-authors read, commented on, and approved the final manuscript.

Competing Interests:

The authors have no competing financial or non-financial interests to disclose.

Ethics Approval:

Approval for the parent study was granted by the University of Pittsburgh Institutional Review Board (IRB). Written informed consent was obtained. Expedited approval for this secondary analysis was received from the New York University IRB.

Consent to Participate:

Informed consent was obtained from all individual participants included in the study.

was theoretically based on the Cancer Survivorship and Work Model. Stepwise backward deletion determined which predictors to include in the final model, accounting for treatment group.

Results: Both treatment groups were associated with greater limitations in RP functioning than controls. CFAI had twice the impact on RP compared to AI only. While the RP model displayed significant predictors across sociodemographic, health/treatment, and symptom characteristics, only symptoms were associated with greater limitations in RE functioning. Findings were significant at $p < .05$.

Conclusion: Transitioning from acute to extended survivorship is a critical juncture in which multiple factors place breast cancer survivors at risk of diminished role function.

Implications for Cancer Survivors: Early interventions to address role function limitations during systemic treatment may lead to better work outcomes and improve the quality of long-term survivorship.

Keywords

Breast cancer survivorship; aromatase inhibitor therapy; health-related quality of life (HRQoL); role function; everyday and work life participation

Introduction

Women receiving a breast cancer (BC) diagnosis have witnessed a dramatic improvement in their survival rates during the past 50 years [1]. Breast cancer survivors (BCS) now represent the plurality (22% or 4.1 million) of the total U.S. cancer population [2]. Being able to participate as fully as possible in life's roles is an important survivorship concern that contributes to overall health-related quality of life (HRQoL) [3]. Role function may be understood as the lived experience in performing everyday and work roles given one's intrinsic health status, which will fluctuate over the life course [4,5]. The impact of cancer and its treatment on BCS perceptions of role function will vary according to the treatment adverse effect profile over the survivorship time frame. Most BC diagnoses occur in postmenopausal women [6]. The primary treatment prescribed to prolong survival in postmenopausal women is aromatase inhibitor (AI) therapy [6–9]. Women taking AIs report adverse effects that can be physically and psychologically debilitating. These adverse effects include arthralgias [8], cognitive impairment [10,11], and the return of menopausal symptoms [8]. Treatment effects may be short-term, long-term [12,13], or appear late [13] in the course of the recommended 5-10 year AI regimen (e.g., as with AI-related osteoporosis/bone fracture [8]). Studies of BCS taking endocrine therapy (ET), which includes all AIs and the selective estrogen receptor modulator Tamoxifen, have shown that women connect treatment-related effects with diminished HRQoL [9,14–17]. Moreover, HRQoL may predict long-term survival in older women with early stage BC independently of other prognostic factors [18]. Therefore, understanding the critical time points at which BCS are vulnerable to diminished HRQoL during AI therapy could improve patient outcomes. Insight into the timing of support would enhance the delivery of value-based coordinated care.

Relative to survivors of other commonly occurring cancers, BCS are younger at time of diagnosis [19]. The majority of BC diagnoses will occur in that segment of the population

considered to be of working age [20–24]. It is therefore highly likely that BCS will undergo treatment while still in their prime labor force participation years. Dealing with adverse treatment effects and other challenges may impair role function, which in turn may negatively impact cancer survivor work outcomes [25] and perceptions of employability [26]. For BCS in particular, the gendered biases attached to women's societal roles may represent formidable obstacles to overcoming the challenges that cancer presents [27,28]. Compared to men, women work fewer hours and have jobs that lack benefits (e.g., paid leave, health insurance, pensions) [28], work in occupations that are women-dominated and attached to lower wages [28–30], disproportionately do unpaid domestic/family caregiving work [31,32], and constitute more of the informal labor economy [33]. Women's long-term employment patterns (i.e., lower employment levels and unsteady work trajectories) are associated with lower wages later in their life [30]. Financial toxicity, the depletion of financial resources resulting from a combination of decreased earnings and increased spending on cancer treatment [34], may exacerbate pre-existing inequities resulting from women's unpaid-paid-informal-formal sectoral work patterns. Moreover, the modern economy is increasingly characterized by inconsistent, temporary work often linked to delayed retirement [35]. A chief consideration in ongoing cancer care, given that the intersection of gender, broad socio-economic labor conditions, and treatment factors may compromise the financial status of BCS and their families, should be monitoring role function against the backdrop of survivorship and work.

Role function is an aspect of HRQoL that may bear greatly upon the nature and quality of everyday and work participation in BCS. Few studies, however, have examined AI treatment specifically as it relates to role function. The purpose of this study was to identify characteristics associated with physical and emotional role function in women of working age belonging to one of two systemic therapy treatment groups for early stage BC: chemotherapy followed by AI (CFAI) or AI therapy only, and to compare them to a control group without cancer. Our objectives were to identify how sociodemographic and health/treatment-related characteristics at pre-AI therapy baseline, as well as symptom characteristics at 6-month intervals, related to role function over the initial 18-month treatment period. The 18-month timeframe represented the transition from acute BC treatment to extended survivorship.

Methods

Conceptual model

We chose the Cancer Survivorship and Work Model [25] to guide our selection of study variables. This model illustrates how cancer and its treatment may affect role function (an aspect of HRQoL) and, in turn, how role function may affect work participation [Online Resource Figure 1a]. Role function, our study outcome variable, is found in the “Short-term, Long-term, and Late Effects of Cancer and Treatments” model domain. Our study predictor variables are found in both the “Individual and Interpersonal Factors” and the “Short-term, Long-term, and Late Effects of Cancer and Treatments” model domains [Online Resource Figure 1b]. The model aligns with recent calls for greater integration of research across disciplines including occupational health, public health, life and social sciences [36].

Study design, setting, and population

We performed a secondary analysis of longitudinal study data from a prospective observational study that examined cognitive impairment in postmenopausal women with early-stage BC. Details of the parent study (R01CA107408, PI: Bender) were described in previous publications [10,37]. Briefly, women were eligible if they were newly diagnosed with stage I-IIIa BC, postmenopausal and ≤ 75 years old, and able to speak and read English with ≥ 8 years of education. Exclusion criteria included a history of neurological illness or cancer, hospitalization for psychiatric illness within two years, or evidence of metastases. The study was comprised of patients receiving CFAI or AI only and non-cancer controls who were frequency matched on age and years of education.

Informed consent

Approval for the parent study was granted by the University of Pittsburgh Institutional Review Board (IRB). Written informed consent was obtained. Expedited approval for this secondary analysis was received from the New York University IRB.

Sociodemographic and health/treatment-related predictors

Sociodemographic and health/treatment-related characteristics were collected via self-report, then confirmed by medical record review. The number of comorbid conditions was summed to achieve a total comorbidity count for each participant. BC was included in the comorbidity count for the treatment groups, consistent with analyses previously conducted and published on this data [11].

Symptom predictors

Symptom data were collected using patient-reported outcome measures administered after surgery but before beginning chemotherapy or AI therapy, and at 6-month intervals up to 18 months. In the CFAI group, the 6-month assessment occurred after chemotherapy, but before anastrozole initiation. The following validated instruments were used: Beck Depression Inventory-II [38], Brief Pain Inventory [39,40], Patient Assessment of Own Functioning Inventory [41], and Profile of Mood States Tension/Anxiety and Fatigue/Inertia subscales [42]. HRQoL was measured with the Medical Outcome Study Short Form 36 (SF-36v2) [43,44]. SF-36 scales were scored using population norm-based T-scores [5], with higher scores indicating better HRQoL. SF-36 role physical (RP) and role emotional (RE) scales measure perceived limitations in everyday and work role functioning due to physical and emotional problems [5]. The RP and RE scales are the primary outcome variables of our modeling.

Statistical analysis

Measures of central tendency and variability were calculated for continuous variables using Stata v17. Cases with unbalanced data were kept in the dataset because linear mixed-effects modeling (LMM) accounts for all available data. We assumed data were missing at random, given the nature of our missing data, to justify use of maximum likelihood estimation. There was no evidence in our dataset to suggest that missingness was related to unobserved values themselves, which would instead indicate missing not at random. Maximum likelihood

estimation is robust when data are missing at random. This approach is widely accepted in the field of mixed effects modeling and has been used by our team in other reports [45].

Power analysis: The joint cross-sectional and time series characteristics of the data set could reasonably be expected to violate assumptions for the use of OLS regression, which necessitated the use of linear mixed-effects modeling [46]. With four repeated measures per subject and an a priori intraclass correlation coefficient (ICC) of 0.05, a sample size of 345 was calculated as sufficiently powered to detect an effect size of f^2 of 0.060, alpha level of 0.05, power of at least 0.80, and a maximum of 40 predictors. The data set, which was comprised of $n=351$ participants with measurements taken at four observation points ($t=0, 6, 12$ and 18 months) and limited to a set of 14 predictors drawn from our conceptual model, was sufficiently powered to support the use of LMM.

Model building: Test statistics (i.e., ICC, Akaike Information Criterion/Bayesian Information Criteria [AIC/BIC]) on the null model determined that a random intercept, random slope LMM model provided the best general fit across the SF-36 RP and RE outcome measures. Based on sample characteristics and test statistics we conducted our LMM modeling using maximum likelihood estimation and an unstructured covariance structure following procedures described in Rabe-Hesketh & Skrondal (2022) and Hoffman (2015) [47,48].

We determined the significance of a treatment group by time (and quadratic time) interaction term on our outcome variables in unadjusted LMM models. The unadjusted models were then used to construct trend line graphs of predicted values exhibiting the effect of treatment group on the RP and RE outcomes over the course of the 18-month study timeframe. We repeated this process for the aggregated SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) outcome measures to provide a contextual background for our primary outcomes.

Our goal was to focus on the most predictive variables for our specific population that would facilitate clinical application, rather than all factors theoretically relevant in the Cancer Survivorship and Work Model. Therefore, we employed a stepwise backward deletion approach [49] to generate parsimonious final models, retaining predictors significant at $p \leq .05$ while accounting for treatment group.

The baseline LMM construction was a random linear time model. We evaluated linear and quadratic time as both fixed and random effects [47]. Treatment group membership (i.e., CFAI, AI, controls) served as a time-invariant proxy for treatment characteristics, with the control group used as the reference category in model construction. Treatment group was retained across all models regardless of significance due to its centrality in comparing differences in role function among study participants. Pre-therapy time-invariant sociodemographic and health/treatment-related predictors [Online Resource Figure 1b] were added to the models during the first iteration of backward stepwise deletion. Accounting for significant time-invariant predictors, we added time-varying predictors related to symptom burden [Online Resource Figure 1b], again using stepwise backward deletion.

Results

Participant summary

Sociodemographic, health/treatment-related, and patient-reported symptom characteristics for the final sample (n=351) are presented in Table 1. Participants in the AI only group were comparatively older than the CFAI and control groups ($p<.001$). Fewer participants in the treatment groups were employed ($p<.001$), and they had more comorbidities ($p<.001$) than controls. The CFAI group had higher stage of disease ($p<.001$). There were differences between the treatment and control groups across most patient-reported symptoms. Both treatment groups perceived greater pain severity and pain interference than the controls ($p<.001$). The CFAI group had comparatively higher perceptions of tension/anxiety ($p<.001$) than the AI only and control groups. Of note, the treatment groups had lower HRQoL scores (RP, $p<.001$; RE, $p=.002$) in comparison to the controls.

Model results

Overview: The treatment group unadjusted trend lines for RP, RE, PCS and MCS are presented in Figures 1 a–d. The trend line graphs depict the relationship between treatment protocol across time and each outcome variable. A significant positive treatment group by time interaction was found only in the RP ($p<.001$) and MCS ($p=.002$) models. The MCS trend lines displayed a partial downward sloping curvature. We include the unadjusted models for the summary scores of PCS and MCS solely as background context for RP and RE.

Turning to our primary outcomes of RP and RE, the final model results are presented in Table 2 (RP) and Table 3 (RE). A summary of the hypothesized and estimated coefficient direction and significance for the predictors for the final RP and RE models is presented in Online Resource 2. RP displayed significance with elements of both (a) sociodemographic and health/treatment-related time-invariant predictors in addition to the (b) symptom-related time-varying predictors. RE, in contrast, captured significant associations solely with respect to the symptom-related time-varying predictors. The treatment group by time interaction term in the final models was significant solely with respect to RP. RE showed no similar association.

Role Physical model: The final RP model, which accounts for both fixed and random effects, showed a significant improvement over the OLS model without random effects ($p<.001$). The ICC in this final model was 0.45, indicating that 45% of the total variance in RP scores was attributable to differences between participants. This ICC was lower than the ICC of 0.61 observed in the null model, suggesting that the final set of predictors explained a portion of the between-participant variance. Most of the variance in the model was due to differences in participants' mean baseline levels of RP functioning (random intercepts) rather than differences in how their functioning changed over time (random slopes).

The final model indicated several factors associated with RP limitations. Women with breast cancer receiving treatment, either CFAI or AI only, reported greater limitations compared to controls (both $p<.001$). The group by time interaction for both CFAI ($p<.001$) and AI

only ($p=.001$) indicated that RP limitations decreased over the first 18 months of systemic therapy relative to the control group. Employed women reported fewer limitations ($p=.004$), while women with more comorbidities reported greater limitations ($p=.003$). Controlling for these baseline factors, we found that greater self-reported depressive symptoms ($p=.006$), pain interference with function ($p<.001$), cognitive problems ($p<.001$), and fatigue/inertia ($p<.001$) were associated with greater limitations in RP functioning. Conversely, greater self-reported tension/anxiety was associated with fewer limitations ($p=.016$).

Role Emotional model: The final RE model showed a significant improvement over the OLS model without random effects ($p<.001$). Most of the variance in the model was also due to differences in participant intercepts as opposed to variance due to their slopes. As with RP, clustering by participant as measured by the ICC (0.42) remained strong, although somewhat reduced, in relation to the ICC (0.54) of the null model.

There were no significant demographic and health/treatment-related characteristics in the final RE model. With the addition of symptom burden predictors in the second iteration, we found that greater self-reported depressive symptoms ($p<.001$), pain interference with functioning ($p=.007$), cognitive problems ($p<.001$), and tension anxiety ($p<.001$) were associated with greater limitations in RE functioning.

Discussion

Our study aimed to identify characteristics that are associated with physical and emotional role function in postmenopausal women over an initial 18-month course of systemic therapy. We examined both time-invariant predictors (i.e., sociodemographic and health/treatment-related characteristics) and time-varying predictors (i.e., symptom-related characteristics). Our findings revealed a notable difference: RP functioning was associated with both time-invariant and time-varying predictors, while RE functioning was associated only with time-varying predictors. We will interpret our findings on role function within the context of cancer survivorship and work, as highlighted in our introduction. This perspective aligns with the Cancer Survivorship and Work Model and is particularly relevant to this population of postmenopausal women undergoing aromatase inhibitor therapy.

RP and RE: Sociodemographic and health/treatment-related predictors

Sociodemographic: The time-invariant sociodemographic predictors used in our analysis were age, education, employment status, and married/partnered status. Only having employment was associated with better RP functioning. No significant sociodemographic predictors were found for RE functioning. Our finding is consistent with Mahar et al. (2008), who reported a significant positive association between BCS' full-time working status and overall physical health using the SF-12 in a cross-sectional study [50]. Multiple studies have supported a positive association between work and HRQoL, of which role function is a component, in both general cancer survivor populations [51,52] and BCS specifically [50,53,54].

BCS' employability hinges on understanding how AI treatment intersects with a woman's life stage, a factor included in the Cancer Survivorship and Work Model. Notably, Mahar

et al. (2008) reported a mean age of 48.8 [7.6] at diagnosis, while our study's mean ages were 59.7 [5.17] in the CFAI group and 62.3 [SD 6.23] for the AI only group. Most of the women in our study were still within working age, albeit at an age more likely to encompass retirement planning. The psychosocial experiences of older versus younger BCS are not fully understood [55], including possible differences in perceived employment vulnerabilities [56]. Our findings suggest perceptions of diminished role function that may introduce added employment vulnerability. Understanding the unique circumstances of retirement-age BCS is key to preventing unplanned early departure from work [57] or promoting work reentry later in life [26]. Early in systemic therapy, when RP functioning is lowest (see Figure 1a), may be an opportune time for interventions to improve role function.

Health/Treatment-related: Health/treatment-related predictors examined in our study included the number of comorbidities and treatment group. Having more comorbidities was associated with lower RP functioning. Previous studies have found similar associations across different age ranges: Fu et al. (2015) reported that having more comorbidities was associated with lower SF-36 scores in four of eight domain scales at 12 months post-diagnosis in a relatively younger population with a mean age of 58.8 [11.8] [58], while Ganz et al. (2003) reported that having more comorbidities was associated with lower SF-36 Physical Functioning scale scores at 15-months post-diagnosis in older women age 65- ≥80 years [59]. Ganz, however, did not assess the SF-36 RP scale. Fu's assessment included the entire set of eight SF-36 scales. Similar to Ganz, Fu found that greater number of comorbidities was associated with greater limitations in the Physical Functioning scale, which represents levels and kinds of limitations in physical activities ranging from easy to difficult [5], but did not report significance for the SF-36 RP scale that was the focus of our study. Overall, our studies suggest that comorbidities affect different aspects of HRQoL across a broad age spectrum of BCS during systemic therapy. In fact, a recent meta-review highlighted the need for further investigation of comorbidities' impact on BCS' psychosocial experience during systemic therapy [60]. Given our findings, perceived role function may be a key consideration in older BCS with greater comorbidities during the initial phase of systemic therapy.

Regarding treatment, we found that both CFAI and AI only groups were associated with worse RP functioning relative to controls, with CFAI having twice the impact on RP functioning compared to AI only. In contrast, a systematic review of thirteen randomized clinical trials (RCTs) conducted by Xiao et al. (2018) found that long-term use of ET (≥5years) was unlikely to adversely affect HRQoL in postmenopausal women [61]. Multiple differences may explain this discrepancy, including different ET agents, timeframes, and HRQoL instruments across studies. Furthermore, HRQoL outcomes were secondary and may have been underpowered. Only two RCTs in the Xiao review had similar treatment groups to our study, but these were extensions of earlier studies in women who had completed chemotherapy well before the extension [62,63] and one was in women who were older (≥70 years) [62] relative to the participants in our study. Future examination of survival relative to HRQoL outcomes such as role function is warranted to guide treatment decisions in working age postmenopausal BCS.

Our finding of a significant treatment group by time interaction indicates that the negative effect of treatment on RP diminished over time. While RP functioning for the CFAI group was lower than that of the AI only group at baseline, the trend lines converged by 18 months. Previous research in postmenopausal BCS found that HRQoL trend lines were significantly lower for chemotherapy recipients relative to an ET only group at 3 months [64]. While the treatment groups in that study are not directly comparable to ours, consistent with our study the treatment group HRQoL trends improved over time with no significant differences at 18 months [64]. Although we found no meaningful difference between CFAI and AI only groups at 18 months (Cohen's $d=0.04$), we observed moderate effect sizes for differences between each treatment group and the control group (CFAI: Cohen's $d=0.54$; AI only: Cohen's $d=0.43$) that are potentially clinically meaningful [65–67].

While not the focus of our analysis on role functioning, it is worth noting that physical health component summary (PCS) scores remained below the threshold for impaired functioning [5] throughout the study (Figure 1c). The improvement in RP functioning over time, contrasted with consistently impaired PCS scores, suggests that BCS may compensate using coping strategies and problem-solving skills. We posit this consideration based upon the Cancer Survivorship and Work Model's portrayal of a bidirectional influence between an array of factors in two of its domains; the Individual and Interpersonal domain in which coping and problem-solving are included and Effects of Cancer and Treatment domain in which role functioning is contained. More research is needed to understand whether BCS deploy coping mechanisms in order to maintain physical role function despite early adverse treatment effects and if such performance is sustainable especially if poor perceptions of overall physical health persist.

RP and RE: Symptom-related predictors

We found that a constellation of time-varying symptoms was related to both RP and RE functioning. Notably, only symptoms were associated with RE functioning, whereas time-invariant predictors and symptoms were associated with RP functioning. Our findings align with Martino et al. (2020), who reported that only anxiety levels, not demographic or clinical characteristics, predicted SF-36 MCS scores in a sample of postmenopausal BCS [68]. While Martino did not report RE outcomes, the MCS is a measure of mental well-being that is highly correlated with the RE scale in part because the RE scale contributes to the MCS score [5].

BCS undergoing ET often report persistent symptoms that adversely affect HRQoL [9,69]. We evaluated three of the 15 most prevalent AI-related symptoms identified by Zhu et al. (2019) [70], namely fatigue, pain, and anxiety. We found that increased depressive symptoms, pain interference, cognitive problems, and fatigue were associated with worse RP functioning. Unexpectedly, higher levels of anxiety were associated with better RP functioning. For context, mean anxiety scores across study groups remained close to the normative mean for adult women throughout the study [10,71]. It has been postulated that expectation of future treatment may impact BCS HRQoL [64,72]. In one study BC patients who knew their systemic treatment would be short experienced better HRQoL than those who anticipated longer regimens [64]. Anticipatory anxiety regarding future treatment may

offer a plausible explanation for our finding. For example, patients in our study may have perceived improvements in their RP functioning post-chemotherapy while simultaneously experiencing increased anxiety about a lengthy follow-up course of AI therapy.

While our unadjusted model showed no change in RE functioning over time (Figure 1b), there was a concave downward trajectory for MCS (Figure 1d). Our MCS trend line finding suggests that patient perceptions of overall mental health decline as they approach the 18-month mark. To better understand the distinct RE and MCS trajectories, we examined symptom expression patterns in this population. Li et al. (2020) analyzed a similar sample from the same study and identified two symptom clusters (i.e., a neurocognitive cluster, a psychological cluster) [73]. These two clusters merged into a larger aggregation at 18 months comprised of perceived cognitive problems, fatigue, depression, anxiety, difficulty concentrating, being easily distracted, forgetfulness, and excitability [73]. This finding of a late-emerging cluster by Li et al. (2020) may partially explain the distinct MCS trajectory found in our study. In an LMM for MCS (see Online Resource 3), we found significant associations of MCS scores with the AI only treatment group by time interaction and a negative quadratic time term. This suggests that late-emerging AI symptoms may affect overall perceptions of mental HRQoL in this population. Monitoring the effect of symptoms over a longer course of survivorship following AI therapy initiation is needed to better understand the potential impact of late-emerging treatment effects on MCS, which is correlated with RE functioning.

Strengths and limitations

Our study included limitations. First, while generic HRQoL instruments may not detect some ET effects in healthier BCS [66], a HRQoL instrument tailored to ET would not be suitable for a non-cancer control group. However, the SF-36, a generic measure that has been extensively used and validated [74], did detect changes in RP functioning related to treatment in our study. Second, to maintain consistency with the extensive BCS HRQoL literature and calls to harmonize the analysis and reporting of HRQoL findings [13,63], we focused on research that employed the SF-36 or SF-12 and, when possible, included BCS undergoing ET. This approach led us to consider older studies to maximize comparisons with our findings. Third, we examined role function in a heterogeneous population of employed and unemployed BCS. The use of the SF-36 to measure daily and work role function may blur boundaries between these similar, yet distinct, role constructs [75]. However, BCS report that the fluid nature of boundaries between their work and home roles and the quality of support in both spheres often governs how well they function in each environment [56], so the blurring of role boundaries is a phenomenon we must address in the study of BCS.

While measuring daily and work roles as a combined construct may lack some specificity, using one instrument to measure role function regardless of employment status changes offers consistency. The SF-36 role function scales can be used consistently across sectoral work patterns (i.e., unpaid, paid, informal, formal) typical of women's labor force participation. Their value during ongoing, long-term treatment with AIs may be in their potential to identify opportunities to support women's role function holistically given their

work patterns. However, we could not track the relationship between work changes and role function over time because employment status was a baseline measure, which is a limitation future research should address.

A strength of our study is the use of a conceptual model to support the set of predictors that were considered in building our models. While the RP and RE models exhibited a strong statistical fit, we found that different predictors contributed uniquely to the variation in our final models. Our findings are in line with previous research suggesting that the predictors influencing different scales within a single HRQoL instrument can vary substantially [76]. Characteristics presented in the Cancer Survivorship and Work Model that were not included in our models may lessen the conceptual gaps and residuals in future model results.

Implications for research and practice

Early interventions to address role function limitations during systemic treatment for BC may lead to better work outcomes and improve the quality of long-term survivorship. Further research is necessary before clinical guidelines are recommended. However, role function may be considered by practitioners as an umbrella assessment to capture the effects of multiple factors contributing to perceptions of diminished role function. For employed BCS, work-related role functioning could be more discretely measured as an adjunct to generic role function scales [75]. Work ability, recently proposed for consideration as a common measure of economic and global wellbeing in cancer survivors [28], could be measured with a single-item question from the Work Ability Index [77] to reduce survey fatigue. Future research on how best to measure both daily life and work role function in this population is warranted.

Patients, regardless of current work status, could be provided with a list of available resources and programs that could support their role function. Notably, some resources and programs might support both role function and employability. The Cancer Survivorship and Work Model suggests that behavioral interventions such as physical fitness programs could promote employment. Interestingly, an exercise intervention demonstrated improvements in both SF-36 RP and RE scale scores in older BCS during AI therapy [78]. Patient input should guide future research on the types of interventions that would improve their ability to participate in everyday and work roles.

Conclusion

We found that multiple sociodemographic, health/treatment-related, and symptom factors contribute to diminished perceptions of role function in postmenopausal BCS during the first 18 months of systemic therapy. As the locus of cancer care shifts from the acute phase of survivorship and active treatment to an extended survivorship phase, care is often overseen by primary care providers. This transition may lead to a lack of continuity of care [79,80]. Increasingly, care continuity and coordination is embedded in cancer care recommendations [81] and survivorship models [25]. Older BCS report the need for professional guidance and resources to navigate the adverse effects of AI treatment [14,15,59]. The exacerbation of pre-existing socioeconomic inequities between men and women are an additional concern, since women cancer survivors report poorer HRQoL

relative to men [82]. Clinician attentiveness to role function against the backdrop of survivorship and work could facilitate beneficial needs-based support during this critical juncture. Recent advocacy for greater attention to the ways women's lives intersect with cancer care [82] underscores the relevancy of our analysis toward achieving patient-centered care for postmenopausal BCS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The dataset used for this secondary analysis is available upon reasonable request from Catherine Bender, the principal investigator of the parent study, subject to data-sharing rules in place at the time of NIH funding for the parent study.

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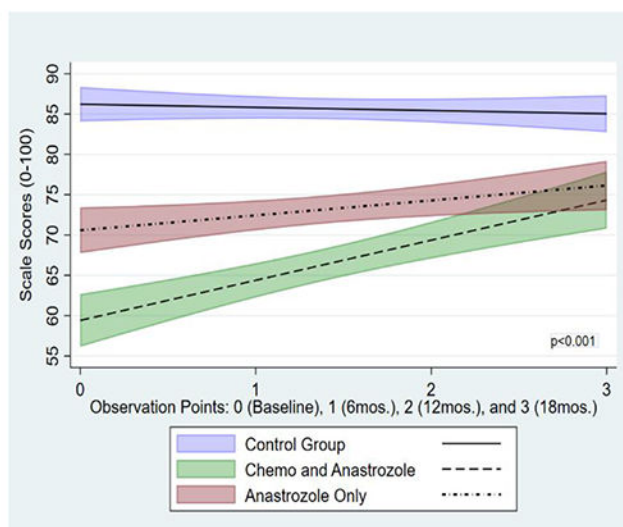
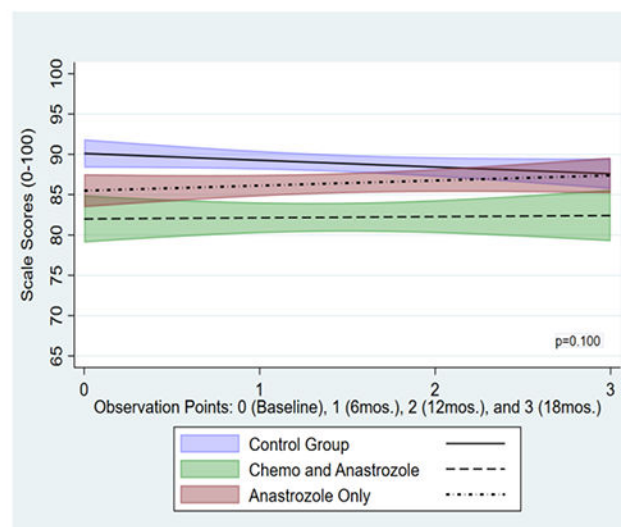
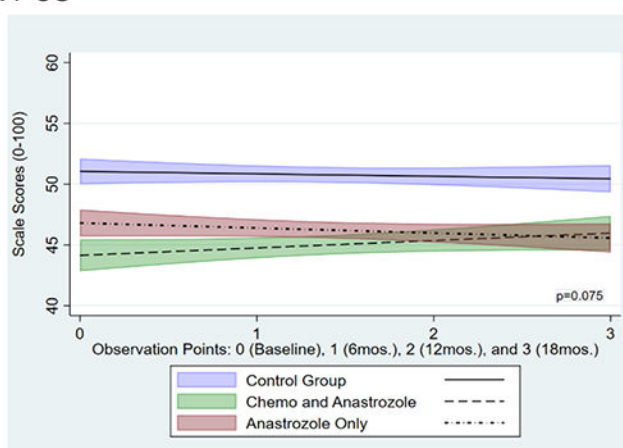
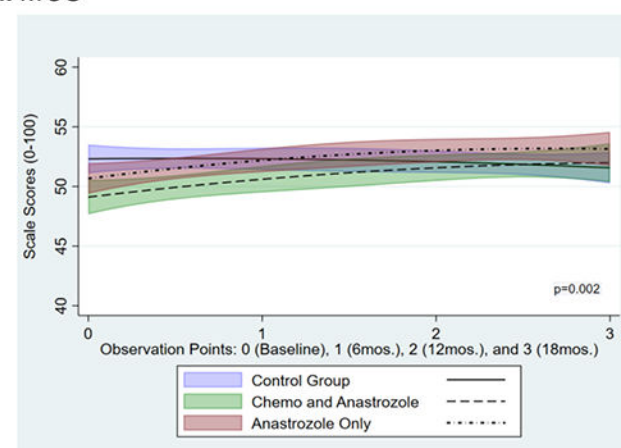
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a. RP**b. RE****c. PCS****d. MCS****Fig. 1.**

The trend line graphs display the predicted values of outcome means within their 95% Confidence Intervals.

Table 1
Demographic, Health-related, and Patient-reported Symptom Characteristics Among the Groups at Enrollment

Characteristic	Chemotherapy followed by AI therapy (1) n=80(22.7%)	AI therapy only (2) n=134(38.1%)	Controls (3) n=137(39.2%)	Statistic	P-value and post hoc comparisons
Age (years)	59.7 (5.2)	62.3 (6.2)	59.1 (6.0)	F (2, 379.3)= 11.1	<.001; 2>1, 3
Education (years)	15.2 (2.7)	14.7 (2.8)	15.4 (3.0)	KW (2)= 4.2	.124
Employed (yes)	52 (65.0%)	84 (62.7%)	115 (83.9%)	χ^2 (2)= 17.2	<.001; 3>1, 2
White (yes)	76 (95.0%)	130 (97.0%)	126 (92.0%)	FE	.195
Hispanic ethnicity (yes)	0 (0.0%)	1 (0.8%)	3 (2.2%)	FE	.455
Married/partnered (yes)	57 (71.3%)	92 (68.7%)	80 (58.4%)	χ^2 (2)= 4.8	.091
Comorbidities (count 0-6) ^a	3.8 (1.5)	4.0 (1.6)	2.4 (1.6)	KW (2)= 66.4	<.001; 3<1, 2
Breast cancer stage				FE	<.001
1	32 (40.0%)	109 (82.0%)			
2a	24 (30.0%)	16 (12.0%)			
2b	12 (15.0%)	7 (5.3%)			
3a	12 (15.0%)	1 (0.8%)			
Breast Conserving Surgery ^b	61 (83.6%)	112 (86.8%)		χ^2 (1)= 0.40	.526
Radiation (yes)	69 (86.3%)	109 (87.2%)		χ^2 (1)= 0.04	.844
BDI-II ^c	5.7 (5.6)	4.9 (5.1)	5.0 (5.8)	F (2, 1.2)= 0.8	.450
BPI					
Mean severity	1.9 (2.1)	1.7 (2.1)	1.1 (2.1)	KW (2)= 15.4	<.001; 3<1, 2
Mean interference	1.7 (2.2)	1.2 (2.1)	0.74 (1.7)	KW (2)= 19.8	<.001; 3<1, 2
PAOFI	17.6 (12.9)	17.9 (13.7)	20.1 (13.3)	KW (2)= 3.5	.176
POMS_SF					
Tension/Anxiety ^c	9.3 (6.1)	6.9 (5.7)	6.1 (5.5)	F (2, 9.8)= 8.6	<.001; 1>2, 3
Fatigue/Inertia ^c	5.0 (4.8)	5.7 (6.3)	5.5 (5.4)	F (2, 0.5)= 0.3	.742
SF36					
Role physical	63.1 (26.1)	67.7 (26.7)	86.1 (21.1)	KW (2)= 64.6	<.001; 3>1, 2
Role emotional	82.2 (21.6)	84.5 (20.1)	89.9 (17.9)	KW (2)= 12.4	.002; 3>1, 2

Note. n=351. Data are provided as mean(SD) or n(%). AI=Aromatase Inhibitor; BDI=Beck Depression Inventory-II; BPI=Brief Pain Inventory; FE=Fisher's Exact; KW= Kruskal-Wallis test; PAOFI= Patient's Assessment Own Functioning; POMS_SF= Profile of Mood States Short Form; SF36= Medical Outcome Study Short Form 36 (v2). Post hoc pair-wise comparisons: Bonferroni (Age, POMS_SF Tension/Anxiety); Chi-squared (Employed); Wilcoxon Rank Sum (Comorbidities, BPI: Mean Severity, Mean Interference, SF36: Role Physical, Role Emotional)

^aComorbidities were self-reported (no. 0- 5). Breast cancer was included as a comorbidity in Chemotherapy AI and AI only groups (no. 1-6).

^bAs opposed to Mastectomy

^cAlthough the actual means and SDs are reported for each subgroup, analysis of variance was performed on the transformed variable due to its nonnormal distribution.

Bold=p<.05

Table 2
Role Physical Parameter Estimates and Model Tests

Fixed Effects	Est.	SE	P-value	CI
Intercept (CONSTANT)	89.98	5.26	<0.001	(79.67, 100.29)
Time (Observations at Baseline, 6, 12, & 18 mos.)	-0.66	0.69	0.345	(-2.08, 0.71)
Treatment Group				
Control	Base			
Chemotherapy followed by Anastrozole (CFAI)	-20.49	2.65	<0.001	(-25.68, -15.29)
Anastrozole (AI) Only	-10.75	2.35	<0.001	(-15.35, -6.16)
Group * Time Interaction				
Chemotherapy followed by AI	6.24	1.17	<0.001	(3.95, 8.53)
AI Only	3.41	1.00	0.001	(1.45, 5.36)
Education	0.44	0.27	0.099	(-0.08, 0.97)
Employed (Yes)	5.04	1.74	0.004	(1.63, 8.44)
Married/Partnered (Yes)	2.73	1.61	0.090	(-0.42, 5.89)
Comorbidities	-1.54	0.51	0.003	(-2.54, -0.54)
Beck Depression Inventory (BDI-II) Total Score	-0.36	0.13	0.006	(-0.62, -0.10)
BPI Mean Interference Score	-3.01	0.32	<0.001	(-3.64, -2.38)
Patient Assessment Own Functioning Inventory (PAOFI) Total Score	-0.26	-0.05	<0.001	(-0.35, -0.16)
Profile of Mood States Short Form (POMS SF) Tension/Anxiety Score	0.32	0.13	0.016	(0.06, 0.59)
POMS-SF Fatigue/Inertia Score	-0.99	0.13	<0.001	(-1.24, -0.73)
Random Effects	Variance	SE	CI	
By Participant ID (Variance Unstructured)				
Var(Time)	16.04	5.55	(8.14, 31.61)	
Var(CONSTANT)	163.63	26.13	(119.66, 223.75)	
Cov(Time-CONSTANT)	-21.08	10.07	(-40.82, -1.33)	
Var(RESIDUAL)	202.10	11.95	(179.99, 226.93)	
Model Tests	ICC	LR Test	AIC	BIC
	0.45	169.96 (p<.001)	10701.40	10798.81

Note. The LR test is in comparison to the linear model

Bold=p<.05

Table 3
Role Emotional Parameter Estimates and Model Tests

Fixed Effects	Est.	SE	P-value	CI
Intercept (CONSTANT)	98.51	8.46	<0.001	(81.93, 115.08)
Treatment Group				
Control	Base			
CFAI	-2.19	1.72	0.202	(-5.55, 1.18)
AI Only	-0.33	1.57	0.832	(-3.40, 2.74)
Age	-0.01	0.12	0.959	(-0.23, 0.22)
Education	0.23	0.22	0.296	(-0.20, 0.65)
Employed (Yes)	2.47	1.48	0.095	(-0.43, 5.37)
Married/Partnered (Yes)	1.87	1.31	0.152	(-0.69, 4.43)
Comorbidities	-0.43	0.42	0.305	(-1.25, 0.39)
BDI-II Total Score	-1.04	0.11	<0.001	(-1.25, -0.83)
BPI Mean Interference Score	-0.73	0.27	0.007	(-1.26, -0.20)
PAOFI Total Score	-0.36	0.04	<0.001	(-0.44, -0.28)
POMS SF Anxiety Subscale Score	-0.37	0.11	<0.001	(-0.60, -0.16)
Random Effects	Variance	SE	CI	
By Participant ID (Variance Unstructured)				
Var(Time)	13.54	4.41	(7.16, 25.62)	
Var(CONSTANT)	109.02	18.50	(78.17, 152.04)	
Cov(Time-CONSTANT)	-18.60	7.67	(-33.82, -3.39)	
Var(RESIDUAL)	152.08	9.02	(135.40, 170.83)	
Model Tests	ICC	LR Test	AIC	BIC
	0.42	128.70 (p<.001)	10328.12	10410.18

Note. The LR test is in comparison to the linear model

Bold=p<.05