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Aging Perceptions and Non-Adherence to Aromatase Inhibitors among Breast Cancer Survivors

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Abstract

Purpose—Aromatase inhibitors (AIs) are a potentially life saving treatment for breast cancer survivors, yet poor adherence to treatment is a prevalent problem. A common adverse effect of AI treatment is arthralgia, which is identified by survivors as a major reason for treatment discontinuation. Women who experience arthralgia on AIs often report feeling they have aged rapidly while on the treatment. In the present study, we examined whether arthralgia-associated aging perceptions predicted non-adherence.

Patients and Methods—We conducted a prospective cohort study among women with stage I–III breast cancer who were on an aromatase inhibitor and completed the Penn Arthralgia Aging Scale within two years of AI initiation. Adherence data were abstracted from medical charts by trained raters. Cox-proportional hazard analysis was used to determine the relationship between aging perceptions and time to non-adherence. All analyses included adjustments for joint pain severity.

Results—Among 509 participants, 144 (28.3%) were non-adherent. As hypothesized, women with high levels of aging perceptions were at greater risk of non-adherence than women with low levels of aging perceptions (adjusted HR, 1.71; 95% CI, 1.10 – 2.67; $p = .02$). High levels of depressive symptoms were also uniquely associated with increased risk of non-adherence (adjusted HR, 1.63; 95% CI, 1.03 – 2.59; $p = .04$).

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Conflict of Interest Statement

Author Moriah Brier, author Dianne Chambless, author Jinbo Chen, and author Jun Mao declare that they have no conflict of interest.

Conclusion—Perceptions of aging related to arthralgia and depressive symptoms predicted non-adherence to AIs. These findings suggest that interventions that address negative beliefs about aging due to AI-related arthralgia and depressive mood can potentially improve rates of adherence to aromatase inhibitors.

Aging Perceptions and Risk of Medication Non-Adherence among Breast Cancer Survivors

Breast cancer is the second deadliest cancer among women.¹ Though treatments for early-stage breast cancer are effective, cancer recurrence remains a looming concern for many patients. Aromatase inhibitors (AIs), a form of adjuvant hormonal therapy for post-menopausal patients with hormone receptor-positive tumors, help to decrease the risk of cancer recurrence and thereby decrease mortality rates.^{2,3} Unfortunately, non-adherence to AIs is a prevalent problem⁴⁻⁸ and leads to poor disease outcomes.⁹ Many women identify joint pain, a common side effect of AIs,¹⁰ as the reason they prematurely discontinue their treatment.^{6,11} In a cohort study, joint pain severity was found to be a significant predictor of non-adherence risk such that women who scored above a predefined threshold of pain severity were more than twice as likely to prematurely discontinue their AI.^{12,13}

Despite the strong relationship between joint pain and adherence, not all women with high levels of arthralgia stop taking their AI. Understanding psychological responses to arthralgia may shed light on who is most at risk of non-adherence. Pain often triggers complex cognitive responses that independently contribute to physical and psychological impairment. For example, anticipation of pain and pain catastrophizing explain variance in individuals' activity levels, even after pain severity is accounted for.¹⁴⁻¹⁶

For women on AIs, joint pain has been found to trigger negative thoughts about aging. Qualitative investigations and case studies have shown that women on AIs who experience joint pain tend to feel they are aging faster than they should be and that time is passing them by.¹⁷⁻¹⁹ In prior cross-sectional work we have found that among AI patients, arthralgia-associated aging perceptions explain variance in depression, anxiety, and the degree to which pain interferes with daily functioning, over and above pain severity.²⁰ In longitudinal analyses of non-cancer populations, negative aging perceptions have been associated with lower life satisfaction, worse objective physical functioning, and higher mortality risk, even after adjustments are made for health status.²¹⁻²⁶ Aging perceptions have also been linked to self-reported preventative health behaviors, such as diet and exercise.²³ In sum, negative aging perceptions have been shown to have considerable impact on a person's psychological and physical wellbeing, as well as on self-care behaviors.

We hypothesized that breast cancer survivors who had heightened perceptions of arthralgia-associated aging would be at greater risk of non-adherence to their AIs. Identifying a psychological process that leads to non-adherence can inform the development of more targeted interventions to improve AI adherence.

Method

We conducted a prospective cohort study among postmenopausal breast cancer survivors as part of the Wellness After Breast Cancer (WABC) study. Inclusion criteria were the following: (1) female sex, (2) age 18 or older, (3) postmenopausal status, (4) diagnosed with stage I-III hormone receptor positive breast cancer, (5) prescribed a third-generation AI, (6) completed all primary cancer treatments (radiotherapy, chemotherapy, and/or surgery) at least one month prior to the survey date, and (7) fluent in English. Research assistants recruited cancer survivors at various stages in their AI treatment. Participants completed a survey in the breast cancer clinic after providing informed consent. The study was approved by the Institutional Review Board of the University of Pennsylvania.

We specifically focused our analysis on participants who had completed the baseline survey not more than 2 years after AI initiation. Given that arthralgia symptoms tend to emerge early in AI treatment,²⁷ cognitive appraisals of aging due to arthralgia would also likely develop near the beginning of the treatment course. A total of 862 breast cancer survivors were enrolled in the cohort study. Of these, one withdrew from the study, 11 did not complete the survey, and seven did not have enough information in their charts to discern any adherence behaviors. To create a more homogenous sample, we excluded another 10 participants from the analysis because they were prescribed less than five years of AI treatment (five years is the treatment length recommended by the American Society of Clinical Oncology²⁸). Of the remaining 833 participants, 509 were currently on an AI at the time of the survey, and had initiated their AI treatment less than two years prior, thus meeting inclusion criteria.

Measures

Non-Adherence—Adherence outcome data were abstracted from participants' medical charts with the most recent abstractions occurring in January of 2016. Non-adherence was defined as a treatment interruption (any time off an AI during the prescribed treatment period) and/or premature discontinuation (stopping the AI entirely before the prescribed treatment end-date). These two types of non-adherence were combined to achieve greater statistical power and because both have been found to predict risk of recurrence.⁹

Trained coders abstracted adherence information from appointment and telephone-call notes in participants' medical charts. On average, participants were observed for 18 months post-survey. Prior to abstracting data for the current study, five research assistants were trained to interrater reliability using a different data set ($\kappa = 0.88$ for the occurrence of a treatment interruption; $\kappa = 1.00$ for the occurrence of premature discontinuation; ICC [1,1] = 0.92 for time to first treatment interruption; ICC [1,1] = .86 for time to premature discontinuation). After data were abstracted from participants' charts, the first author re-abstracted a portion of cases (12.5%) to determine interrater reliability for the data used in the current analyses. The inter-rater reliability coefficients for the occurrence of treatment interruptions and for premature discontinuations were good to very good (treatment interruption: $\kappa = .75$; premature discontinuation: $\kappa = 0.87$). Inter-rater reliability was excellent for months to first treatment interruption (ICC [1,1]: .91) and for months to drug discontinuation or last known

date of usage (ICC [1,1]: .94). (The former ICC was only calculated for participants for whom both raters agreed that a treatment interruption had occurred).

Aging Perceptions—As part of the baseline survey, all participants completed the Penn Arthralgia Aging Scale (PAAS), a measure that we previously developed and validated in a subset of the current sample.²⁰ The scale consists of eight items with a Likert-type scale ranging from 0 (*not at all*) to 4 (*completely*). Instructions ask participants to reflect on how their joint pain over the preceding week has impacted how they currently feel about their “bodies and states of mind.” Items are summed, with a maximum possible total score of 32. In the current sample, the internal consistency of the scale was $\alpha = .94$. Because the distribution of scores in this sample was positively skewed, we binned the variable into five categories for these analyses. The first category consisted of all participants whose score on the PAAS was 0 (33.6% of the sample). The remaining participants were binned into 4 categories of roughly equal proportions (around 15% of the sample per bin; exactly equal proportions were not possible given the ordinal nature of the scale). We combined the lowest four bins (participants with scores of 17 or below) into a “low aging perceptions” category, and the remaining bin (scores between 18 and 31) was categorized as “high aging perceptions.”

Covariates—Race, age, education, partner status, joint pain, and depression symptoms were collected via self-report. The length of time a participant was on an AI at baseline, the type of AI she was prescribed at AI initiation (anastrozole, letrozole, or exemestane), cancer stage, and the total number of medications the participant had been prescribed at baseline were abstracted from medical charts.

We used the first item of the Brief Pain Inventory²⁹ to assess joint pain severity. This item asks participants to “rate your joint pain by filling in the oval beside the number that best describes your pain at its worst in the past 7 days.” Anchors of the Likert-scale are 0 (*No pain*) and 10 (*Pain as bad as you can imagine*). This single item, when dichotomized at four or above, has predicted premature discontinuation in a sample of breast cancer survivors on AIs.¹² Depression, which has been found to be associated with non-adherence in meta-analyses looking at a variety of illness groups, including adjuvant endocrine therapy in women with breast cancer,^{30,31} was measured using the depression subscale of the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). We categorized scores into depressed or non-depressed using a validated cut-off score of eight (≥ 8 = depressed).³³ Age was split into three groups (less than or equal to 55, between 56 and 70, and greater than 70) given that prior research has shown that young and old age are associated with non-adherence.³⁴

Statistical Analyses

Survival analyses, using Cox proportional hazards regressions, were used to model the time from participants’ completion of the survey to non-adherence. We first conducted univariate analyses to determine which covariates should be included in the final model. All variables associated with time to non-adherence with $p < .10$ were selected. Participants were censored if they had not yet completed their AI treatment when their adherence data were

abstracted from their charts or if they had experienced any of the following events prior to their completion of five years of AI therapy: breast cancer recurrence, metastasis, death, or lost to follow-up. Since some women in the cohort study discontinued their AI before they completed the baseline survey, and were therefore not included in this study, the current sample was left truncated. To account for the bias thereby imposed, time from AI initiation to study entry was used as the left-truncation (delayed entry) point.^{35,36} All analyses were run in STATA version 14.1³⁷ and were two-sided, with p -values less than 0.05 indicating statistical significance.

We performed a power estimation in STATA prior to conducting the analysis. With a sample of 509 participants, we had 80% power to detect a hazard ratio of = 1.87, assuming 21% of the sample was not adherent, and that arthralgia-associated aging perceptions were moderately associated with covariates in the final model. The non-adherence rate of 21% was selected based on rates of non-adherence found in a similar cohort from the same cancer clinic.¹³

Results

Participants

The majority of participants were White (80.4%), living with a partner (61.1%), and had at least some college education (77.9%). Most of the women in the sample (57.8%) were diagnosed with stage I cancer. The high majority of women were prescribed anastrozole and fell in the 56–70 age range. Overall, depression levels were low in this group with only a small portion (12.0%) meeting the clinical cut-off. The average length of time a participant had been on AI when she completed the baseline survey was approximately 12 months. See Table 1.

Prevalence of non-adherence

Of the 509 participants, 144 (28.3%) did not adhere to their AI during the course of our observation. For 84 women (16.5%), their first non-adherence event was a treatment interruption (some of whom later prematurely discontinued), and for 60 participants (11.8%), their first (and only) non-adherence event was premature discontinuation.

Predictors of non-adherence

In univariate analysis, with the lowest category of aging perceptions as the referent group, only those in the highest of the five categories of aging perceptions (16.3% of the population) had increased risk of non-adherence (HR, 2.30; 95% CI, 1.47 – 3.60, $p < .001$). See Figure 1. Consequently, aging perceptions was transformed into a dichotomous variable with the lowest four categories collapsed into one category (a score of 17 or below on the PAAS; coded as 0; $n = 426$), and the highest category of aging perceptions remained its own category (a score of 18 or above on the PAAS; coded as 1; $n = 83$). In univariate analyses, joint pain, depression, and AI type also predicted time to non-adherence ($p < 0.10$) and were included in the final model. See Table 2.

In multivariable Cox proportional hazard regression, arthralgia-associated aging perceptions predicted risk of non-adherence (HR, 1.71; 95% CI, 1.10 – 2.67; $p = 0.02$). Participants with high levels of aging perceptions were at 70% increased risk of non-adherence compared to participants with low aging perceptions, even after we adjusted for depression, drug type, and joint pain severity. Depression remained a significant predictor of adherence risk (HR, 1.63; 95% CI, 1.03 – 2.59), whereas joint pain did not (HR, 1.21; 95% CI, 0.84 – 1.75, $p = .30$). As far as AI type, women on exemestane were at higher risk of non-adherence than women on anastrozole (HR, 2.53; 95% CI, 1.17 – 5.47).

To gain a better understanding of how aging perceptions may have impacted the relationship between the covariates and risk of non-adherence, we built a model without aging perceptions and subsequently added aging perceptions to see how the hazard ratios changed. Adding aging perceptions to the model reduced the hazard ratio for joint pain by 14% (from HR, 1.41; 95% CI, 1.01 – 1.98, $p = .047$ to HR, 1.21; 95% CI, 0.84 – 1.75, $p = .30$). Post-hoc examination of the relationship between joint pain and aging perceptions demonstrated that most participants with high aging perceptions also had high levels of joint pain, yet a substantial subset of women with high joint pain levels did not endorse high aging perceptions. See Figure 2.

With aging perceptions in the model, the hazard ratio of depression was reduced by 18% but remained a significant predictor of non-adherence (from HR, 1.94; 95% CI, 1.26 – 2.98, $p = .002$ to HR, 1.63; 95% CI, 1.03 – 2.59, $p = .04$). This suggests that although aging perceptions and depression have overlap in explaining non-adherence risk, each variable also has unique effects. We then examined the relationship between aging perceptions and depression, given the likelihood that one could lead to the other. See Figure 3. They were found to be associated such that high aging perceptions was more common among women with depression than among women with no depression; however, the overlap was not complete in that many women with depression did not endorse these perceptions.

Discussion

In this prospective cohort study, we found that breast cancer survivors on AIs who experience a heightened sense of aging in response to their joint pain are approximately 70% more likely to non-adhere to AI treatment. Examination of the relationship between joint pain and aging perceptions revealed that higher levels of joint pain are likely necessary for developing high arthralgia-associated aging perceptions, but not everyone is susceptible to these cognitions: A substantial portion of women with high levels of joint pain did not have heightened levels of aging perceptions. This underscores the importance of considering survivors' psychological reaction to pain, and not just pain severity, in understanding their decisions related to treatment continuation.¹³

Depression was also found to be a significant predictor of AI non-adherence. Prior literature on this topic has been mixed and has had many limitations^{34,38–41}; this is the first study to investigate this relationship with a validated measure of depression in a demographically diverse sample of AI patients across multiple years of treatment. Interestingly, depression and aging perceptions were found to be significantly associated and their relationship was

only partially explained by joint pain. Depression may be a risk factor for developing heightened aging perceptions. Alternatively, aging perceptions may, in part, lead to depression. Further research is needed to determine the nature of these relationships. Understanding their temporal order is important for knowing how and when to intervene.

Our findings can be used to inform the development of adherence interventions. To address heightened perceptions of aging, clinicians can employ both behavioral and cognitive approaches. Behavioral approaches can be used to increase physical activity (which some women mistakenly believe they need to avoid as a way to prevent further aggravation of their joints); physical activity can simultaneously reduce arthralgia pain⁴² and potentially weaken individuals' negative beliefs about their agility by demonstrating that they are in fact more physically able than they previously thought, as well as by reducing depression symptoms,⁴³ which may in part be driving high aging perceptions. Cognitive interventions can be used to explore alternative interpretations of joint pain. For example, evidence from retrospective analyses of two different clinical trials suggests that AI-associated arthralgia is a positive sign that the treatment is working: Those who developed joint pain had a significantly lower risk of breast cancer recurrence and higher chance of overall survival compared to those who did not develop joint pain.^{44,45} Sharing these research findings with patients and making patients aware of the positive associations of joint pain may help them re-conceptualize their side effects as a sign of increased longevity, as opposed to a sign of aging. Interventions including cognitive-behavioral techniques need to be developed and tested to determine its effect on arthralgia, arthralgia-related aging perceptions, and ultimately adherence behaviors.

Limitations of this study include the method used to measure and summarize adherence. We collapsed treatment interruptions and premature discontinuation into one non-adherence variable even though it is possible that each type of non-adherence may be explained by a different process. Secondly, adherence was abstracted from patients' charts, which are subject to reporting bias on the part of patients, and recall bias on the part of both patients and clinical staff. Third, participants were not recruited at AI initiation, and patients who discontinued their AI prior to enrolling into the WABC cohort study were not included in these analyses. Though we used statistical tools which reduce this bias,³⁵ it may not have been completely eliminated. Fourth, we did not examine ways in which women sought to manage their pain (such as through exercise, medications, psychotherapy, etc.) and how these efforts may have impacted adherence outcomes. Future studies need to elucidate how pain management strategies may contribute to patterns of non-adherence.

Conclusions

Despite its limitations, this study has numerous strengths including a prospective design, a large sample of participants, use of a validated instrument to measure arthralgia related aging perceptions developed specifically for this population, and statistical controls for joint pain, depression, and other clinical covariates. We found that heightened perceptions of aging related to joint pain increased risk of non-adherence by 70% among women receiving AI therapy. Clinicians can elicit and acknowledge these psychological experiences during women's follow-up visits to provide emotional support and help patients reframe their

experience of joint pain as well as educate and motivate patients to engage in activities that will address their pain.

Research is also needed to develop and test interventions that target arthralgia related-aging perceptions and depressive symptoms to help women improve symptom control, coping, and adherence to AI therapies.

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Highlights

- Many breast cancer survivors on aromatase inhibitors (AIs) who experience joint pain feel a sense of accelerated aging.
- We demonstrate that heightened perceptions of aging due to AI use predicts non-adherence to AIs, after controlling for both joint pain severity and depression.
- AI-related aging perceptions are potentially modifiable and can be targeted in interventions to improve adherence to AIs.

Figure 1. Survival curves of non-adherence by scores on the Penn Arthralgia Aging Scale (curves account for left truncation). PAAS = Penn Arthralgia Aging Scale.

Figure 2. Relationship between arthralgia-associated aging perceptions and joint pain. Bars represent 95% confidence intervals. $\chi^2 (1, N = 509) = 68.34, p < .001$.

Figure 3. Relationship between arthralgia-associated aging perceptions and depression. Bars represent 95% confidence intervals. $\chi^2 (1, N = 509) = 66.37, p < .001$.

Table 1

Participant Characteristics (N = 509)

	N	%
Age		
55	105	20.6%
56 – 70	299	58.7%
> 70	105	20.6%
Race		
White	409	80.4%
Non-White	100	19.7%
Partner Status		
Living with partner	311	61.1%
Living alone	198	38.9%
Education		
Some college or more	395	77.9%
HS or less	112	22.1%
Cancer stage *		
Stage I	289	56.8%
Stage II	145	28.5%
Stage III	66	13.0%
AI type		
anastrozole	448	88.0%
letrozole	15	9.0%
exemestane	46	3.0%
HADS – Depression Subscale		
Not Depressed (< 8)	448	88.0%
Depressed (≥ 8)	61	12.0%
	Mean	SD
Time since AI initiation (months)	11.9	5.1
Total Medications	9.0	4.8

Note. AI = aromatase inhibitor; HADS = Hospital Anxiety and Depression Scale; HS = high school.

* Percentages do not add to 100% due to missing data.

Table 2

Univariate and Adjusted Analyses of Predictors of Time to Non-Adherence (N = 509)

	% of Sample	Univariate Analysis			Multivariable Analysis		
		HR	95% CI	p	HR	95% CI	P
Perceptions of aging							
Low	83.7	1.00	–	–	1.00	–	–
High	16.3	2.20	1.50 – 3.21	<.001	1.71	1.10 – 2.67	.02
Joint pain							
Low	48.7	1.00	–	–	1.00	–	–
High	51.3	1.51	1.08 – 2.11	.02	1.21	0.84 – 1.75	.30
Depression							
No depression	88%	1.00			1.00		
Mild to severe	12%	2.05	1.34 – 3.12	.001	1.63	1.03 – 2.59	.04
AI type							
anastrozole	81.9%	1.00			1.00		
letrozole	3.0%	1.20	0.69 – 2.09	.52	1.18	.68 – 2.06	.56
exemestane	9.0%	2.36	1.10 – 5.07	.03	2.53	1.17 – 5.47	.02

Note. AI = aromatase inhibitor.