

Relationships Between Self-Reported Physical and Cognitive Function During Anastrozole Therapy

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Abstract

Background: Adjuvant hormonal therapy has been shown to have negative cognitive effects in some women with breast cancer. Physical activity improves cognitive function in healthy older adults and may also benefit cognitive function in patients with cancer, however, this relationship has not been well-documented. Patients' perceptions of physical and cognitive functioning may impact their daily lives during a crucial period of cancer survivorship. Therefore, the purpose of this study was to examine the relationship between perceived cognitive function and perceived physical function in postmenopausal women with early-stage breast cancer. **Methods:** Perceived cognitive and physical function was measured in 145 women before aromatase inhibitor therapy and at 6 months post-initiation of therapy. Perceived cognitive function was assessed using the Patient Assessment of Own Functioning Inventory (PAOFI). The PAOFI measures patients' perceptions of overall cognitive function, memory, language and communication, sensorimotor, and higher level cognitive and intellectual functioning (HLCIF). Perceived physical functioning was measured using the physical and role functioning subscales of the Medical Outcomes Study Short Form 36 (version 2; SF-36) Health Survey. Descriptive statistics of the sample were run. PAOFI and SF-36 change scores were calculated by subtracting baseline scores from six month follow-up scores, and Spearman's rho was used to calculate correlations among the change scores. **Results:** The average age was 62 years with some college completed. The sample was predominantly white (97%) women who were currently married or partnered (64%). Mean change scores for overall cognitive function ($M=.64, SD=9.6$), as well as memory ($M=.29, SD=3.7$) and HLCIF ($M=.35, SD=3.6$), worsened from pre-anastrozole therapy to six months after the initiation of therapy. Although physical function worsened ($M=-.11, SD=16$), role-physical function improved ($M=8.2, SD=23$). We found a small but significant change in the role physical subscale of the PAOFI and total change ($r=-.21, p=.014$) and change in higher level cognitive and intellectual functioning ($r=-.19, p=.02$). As role-physical function improved, overall cognitive function and HLCIF also improved. We also found small but significant correlations between change in physical function and change in the PAOFI total score ($r=-.25, p=.002$), memory ($r=-.25, p=.003$), and HLCIF ($r=-.17, p=.04$). As physical function worsened, overall cognitive function, memory, and HLCIF worsened. **Conclusions:** These findings suggest that, for women whose functional ability declines during the first six months of anastrozole therapy, there may be a greater difficulty with memory, higher-level cognitive function, and overall cognitive function. Interventions targeted to improve physical function during this crucial period of cancer survivorship may also improve perceived cognitive function.

Keywords: Breast Cancer, Perceived Cognitive Function, Physical Function

1. Introduction

Currently one in eight women will develop invasive breast cancer in her lifetime¹. In 2014 there were over 230,000 new cases of invasive breast cancer diagnosed in the US¹. Due to a combination of factors including early detection, better treatments and improved supportive care, survival rates for women with breast cancer have greatly improved over the last 35 years, and the majority of women diagnosed with breast cancer today are living many years beyond their diagnosis. There are now over 3 million breast cancer survivors living in the US².

Treatment for breast cancer can include surgery to remove the cancer from the breast, radiation therapy to destroy any cancer cells remaining locally with high-energy beams, chemotherapy to destroy remaining rapidly dividing cells systemically, hormone (or endocrine) therapy to block or prevent the action of estradiol and other hormones, and targeted therapy to attack specific parts of cancer cells¹. Decisions about appropriate treatment combinations are based on the stage and progression of the cancer itself. Almost 80% of postmenopausal women with breast cancer have hormone-receptor positive disease. Hormone- receptor positive cancers are dependent on estrogen or progesterone as one mechanism to develop and thrive. Endocrine therapy works by preventing the production or blocking the action of hormones such as estrogen and progesterone. Aromatase inhibitors such as anastrozole and letrozole are the standard endocrine therapy for postmenopausal women with hormone-receptor positive breast cancer. Aromatase inhibitors work by blocking the enzyme aromatase from turning androgens to estrogen. This process is the primary means by which the body produces estrogen after menopause⁵.

Although cancer treatments have improved survival rates for women, negative side effects of therapy are increasingly well-documented. Cognitive complaints are common among breast cancer survivors. The most common complaints include: memory problems, comprehension issues, trouble concentrating³ and fatigue⁴. Additional side effects include bone joint pain and generalized weakness⁵. These side effects pose threats to survivors' quality of life, impede their social and occupational functioning⁶, and may also lead to non-adherence to treatment⁴. Elucidating the side effects of cancer treatment and improving survivors' quality of life during and after treatment is an important goal of research.

Little is known about women's perceptions of physical and cognitive function during therapy and how these perceptions may be related to each other. Therefore, the purpose of this study was to examine the relationship between perceived cognitive function and perceived physical function in postmenopausal women with early-stage breast cancer.

2. Methods

2.1 Research Design

Data were collected during in-person interviews at two time points: 1) pre-anastrozole therapy and 2) six months after initiation of anastrozole therapy. At both time points participants completed measures of perceived cognitive ability (Patient Assessment of Own Functioning Inventory (PAOFI) and functional ability (Medical Outcomes Study Short Form 36 (Version 2; SF-36) Health Survey).

2.2 Sample Population And Descriptive Statistics

The sample (n = 145) is a subset of women who participate in the Long-term Trajectory of Cognitive Function Related to Anastrozole Use in Women (i.e., AIM Study), a National Cancer Institute-funded study. The study investigates cognitive function in postmenopausal women with breast cancer who are receiving anastrozole therapy. To be eligible for the AIM Study women must be postmenopausal and diagnosed with early stage, invasive breast cancer (i.e., I, II, IIIa). They must also be able to read and speak English and have greater than eight years of education. They cannot have any distant metastasis or any current or previously diagnosed cancers, neurological problems, or psychiatric hospitalizations.

2.3 SF-36

Participants were asked to complete the SF-36 to measure their self-reported physical function. The SF-36 is a 36-item health survey that rates perception of physical function on a Likert scale ranging from 1 = "limited a lot" to 3 =

“not limited at all”. The SF-36 is composed of two domains, physical and mental health⁷. Two subscales of the physical health domain were included in this study: Physical Functioning (PF) and Role-Physical (RP). Items in these subscales include questions about subjects’ ability to complete daily activities including walking, climbing stairs, and carrying groceries. These activities are based on the amount of time needed to complete them and level of difficulty. Higher scores indicate less difficulty with physical activities of daily life.

2.4 PAOFI

Participants were asked to complete the PAOFI to measure their self-reported cognitive function. The PAOFI is a 33-item self-reported measure of perceived cognitive function. Participants rated each item on a 6-point scale from almost never to almost always. The PAOFI has five subscales including: memory, language and communication, use of hands, sensory-perceptual, and higher level cognitive and intellectual functions (HLCIF)⁸. The memory subscales measures how often participants forget something they have been told, people, and events. The language and communication subscale measures how often participants understand what is said to them and general verbal and auditory information. The use of hands subscale measures participants’ ability to complete tasks with both of their hands. Sensory-perceptual subscale measures difficulties with the senses of touch and vision. HLCIF measures whether participants believe they are confused at times or are easily distracted or have difficulty solving problems⁸.

2.5 Analysis

The statistical software package SPSS was used to compute descriptive statistics, change scores, and correlations. Change scores from six months minus baseline were computed for both the PAOFI and SF-36. Change scores were used for the correlational analyses. Spearman’s rho was used to measure the strength and direction of the relationship between the PAOFI and SF-36 change scores. A significance level of .05 was used to identify statistically significant relationships.

3. Results

Table 1. sample characteristics (n = 145)

Characteristics	Statistic
Age in years, M (SD)	62.4 (6.2)
Years of education, M (SD)	14.8 (2.9)
White, n (%)	141 (97.2)
Married or Partnered, n (%)	93 (64.1)
Stage1, n (%)	119 (82.1)

Table 1 summarizes the characteristics of the sample. Women were predominantly white, married or partnered. Participants were approximately 62 years of age, with 15 years of education (i.e., some college).

Table 2. PAOFI change scores

PAOFI Score	Mean (Standard Deviation)
Memory	.29 (3.7)
Language & Communication	-.20 (3.2)
Sensory Motor	.20 (2.3)
Higher Level Cognitive and Intellectual Function	.35 (3.6)
Total	.64 (9.6)

Tables 2 and 3 summarize the scores for the PAOFI and SF-36. The results indicate that women report worsening in memory, sensory-motor function, HLCIF, and total perceived cognitive functioning score, but an improvement in language and communication, after 6 months of anastrozole therapy.

Table 3. SF-36 change scores

SF-36 Score	Mean (Standard Deviation)
Physical Function	-.11 (16.3)
Role Physical Function	8.2 (23.1)

Women also reported improved role physical functioning from pre-anastrozole therapy to 6 months after the initiation of therapy.

Table 4. physical function and PAOFI score correlations

PAOFI Score	Physical Function r(p)	Role Physical r(p)
Memory	-.25 (.003)**	-.12 (.16)
Language & Communication	-.16 (.06)	-.13 (.11)
Sensory Motor	-.34 (.68)	-.09 (.26)
HLCIF	-.17 (.04)*	-.19 (.02)*
Total	-.25 (.002)**	-.21 (.01)*

* p<.05; ** p<.01

A small but significant correlation between the change scores for the role physical subscale of the SF36 and PAOFI total score and HLCIF was found. As role physical function improved, overall cognitive function and HLCIF also improved. A small but significant correlation between changes in physical function and change in PAOFI total scores, memory, and HLCIF was also discovered. As physical function worsened, overall cognitive function, memory, and HLCIF also worsened.

In summary, during the first 6 months after the initiation of aromatase inhibitor therapy, participants had greater difficulty with memory, HLCIF, and overall cognitive function as physical function declined. When role physical function improved, overall cognitive function and HLCIF also improved.

4. Discussion

The purpose of this study was to examine the relationship between perceived cognitive function and perceived physical function in a cohort of postmenopausal women with early-stage, invasive breast cancer who were receiving anastrozole therapy alone. To our knowledge, this is the first study to report on the relationship between changes in perceived cognitive and physical function over time in this population. Findings add to a small but growing body of literature documenting the trajectory of these changes during therapy.

We found that women in this study reported a worsening in overall perceived cognitive function between pre-therapy and 6 months post-initiation of therapy, as well as in the specific domains of memory HLCIF. Women also reported poorer physical function from pre-therapy to 6 months post-initiation of therapy. However, role physical scores improved over time. We found a small but significant correlation in the change scores for the role physical subscale of the SF-36 and PAOFI total score and HLCIF. As role-physical function improved, overall cognitive function and HLCIF also improved. We found small but significant correlations between change in physical function and change in the PAOFI total score, memory, and HLCIF. As physical function worsened, overall cognitive function, memory, and HLCIF worsened. These findings suggest that, for women whose functional ability declines during the first six months of anastrozole therapy, there may be a greater difficulty with memory, higher-level cognitive function, and overall cognitive function.

Other studies have examined the relationships between endocrine therapy and objective cognitive function in relation to memory, and visual and verbal learning as well as physical function and joint pain. B. Collins et al. found poorer cognitive function, processing speed, and verbal memory compared to healthy participants and an increase in fatigue compared to healthy participants at each time point⁹. The ATAC Trial concluded that women with hormone-receptor-positive breast cancer developed significantly more joint symptoms than women with hormone-receptor-negative breast cancer¹⁰. While increased fatigue and joint pain could be symptoms that might lead to a decrease in physical function, we found an increase in function at 6 months after initiation.

These data are important because they indicate a relationship between perceived cognitive and physical function. Unexpectedly, the results showed an improvement in role physical function after the initiation of therapy. As aromatase inhibitor therapy begins to work, patients may complain of joint pain, weakness, and cognitive changes. These side effects may lead to a decrease in physical function. One potential explanation for the improvement of physical function from baseline to 6 months may be a result of a decrease in the stress and anxiety experienced by women initially after their diagnosis of breast cancer. As the stress of diagnosis and initiation of treatment subsides and women begin to return to their normal lives, perceived role function may improve. Also, patients may work less after diagnosis or while recovering from surgery. Future studies ought to look at predictors for a change in physical function prior to initiation and during therapy.

Currently, there is also a body of literature that supports the findings that as women undergo adjuvant therapy there is an increase in cognitive problems and fatigue⁴. Complaints one year after initiating therapy include slower processing speed^{3,6}, inability to remember names and appointments, as well as trouble recalling events³. Poppelreuter et al. noted an above average rate of depression and anxiety in cancer patients⁶, while Lynn found no difference in anxiety, depression, and fatigue in patients exposed to endocrine therapy and those not exposed⁴.

As therapy continues it is natural to believe that subjective complaints would change from the onset of therapy through the duration of therapy. We found an increase in perceived cognitive complaints after 6 months of therapy. Shilling et al. also found that over one time point (add 12 for chemo; 18 for non-chemo) there was a decrease in memory complaints for chemotherapy patients, but an increase of memory complaints in non-chemotherapy patients¹¹.

Previous studies evaluated cognitive function during chemotherapy and endocrine therapy at one year post-chemotherapy^{3,4}. These studies lacked a pre-treatment assessments and longitudinal evaluations to measure change from baseline throughout the duration of therapy. The present study included two time points including baseline (i.e., after surgery before the initiation of anastrozole) to six months after initiation of therapy to allow for assessment of change in cognitive and physical function. Strengths of this study include the longitudinal assessment and evaluation of perceived physical function. No other studies were found that examined the relationship between perceived physical function and perceived cognitive function.

The limitation for this study include the short follow-up time frame and that the sample was predominantly white and highly educated. As the AIM study continues there will be additional follow-up assessment to determine the long term relationships between perceived cognitive function and physical function. Future studies should also examine the relationship between objectively measured cognitive functioning and physical function.

This research is important because women are experiencing many negative side effects from endocrine therapy. As the number of breast cancer survivors continues to increase, it is also important to identify interventions to improve their quality of life and decrease the side effects of therapy. Findings of this study may begin to inform interventions targeted to improve physical function during this crucial period of cancer survivorship and also improve perceived cognitive function.

5. Acknowledgements

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