Quality of life and psychological functioning in postmenopausal women undergoing aromatase inhibitor treatment for early breast cancer

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Abstract

Introduction

Aromatase inhibitors (AIs) dramatically increased breast cancer (BC) survival, leading to enhanced attention to their long-term consequences on psychological functioning. Conflicting data has been examined regarding the association between AIs administration and the clinical psychological features in BC survivors (BCSs).

Purpose

As psychological symptoms often occur in such chronic diseases, our study aimed at exploring anxious and depressive symptoms and the perceived quality of life (QoL) in BCSs assessed for osteoporosis.

Methods

The total sample consisted of a clinical sample of 51 outpatient postmenopausal women, diagnosed with BC, and a control group composed of 51 healthy postmenopausal women. All recruited participants were evaluated through the clinical gold standard interview and completed the following self-rating scales: the Hamilton Anxiety Rating Scale, Beck Depression Inventory II edition, and 36-Item Short Form Health Survey, which were administered at baseline and after 6 months in BCSs in AIs treatment, compared with controls. Moreover, all participants were assessed for vitamin D status, bone mineral density (BMD) and subclinical vertebral fractures. Data regarding age, age at menopause, body mass index (BMI), smoking habits and alcohol consumption was collected.
Results
BCSs (n = 51) showed higher anxious and depressive symptoms, and lower perceived QoL vs. controls (n = 51) (p<0.05 for all). After 6 months of treatment with AIs, BCSs showed significant reduction of anxious and depressive symptoms and a significantly higher perceived QoL for both physical and mental components, vs. controls.

Conclusions
The improvement of clinical psychological features and perceived QoL was associated with AIs treatment in women being treated with, for early breast cancer. Further studies are needed to obtain a deeper comprehension of the correlation between clinical psychological and physical features in BCSs.

Introduction
One of the major health diseases affecting women worldwide is breast cancer (BC), which is the most prevalent cancer and the first cause of cancer mortality among women, although in these last decades, a significant reduction in BC mortality due to improved screening programs and treatments has been observed [1]. Recently, there has been an increased interest in the impact of BC and its treatments on psychological functioning and the perceived quality of life (QoL) [2–4].

Most BC survivors (BCs) are estrogen receptor positive inducing advantageous outcomes by adjuvant endocrine therapy (ET) [5]. It is known that the aromatase enzyme converts androgens into estrogens and represents the main source of peripheral estrogen production in postmenopausal women. Aromatase inhibitors (AIs), blocking endogenous estrogen synthesis through the inhibition of peripheral aromatase, represent the gold standard adjuvant hormone therapy for postmenopausal women with hormone receptor-positive BC. AIs treatment has been associated with adverse events such as increased bone loss, musculoskeletal pain, impaired lipid profile and cardiovascular risk, but also with mood disturbances, anxiety and memory deficit [6–8]. Physical and psychological side effects seriously impair women’s psychological balance and perceived QoL and may negatively influence the participation in medical care and adherence to every fundamental prescription [9–17]. In fact, several studies demonstrate the importance played by traumatic factors both on mental health and mood which could also lead to an increased suicidal risk and cognitive decline [18–24]. A recent evidence demonstrates the role of motivation and its relationship with anxiety, depression and QoL in subjects with chronic diseases [25–30].

Several studies examined the impact of ET on cognitive functioning in BC survivors (BCSs) detected at different times from diagnosis and according to various treatments and duration. Some evidence suggested that hormonal changes during specific treatments do not provoke cognitive decline in patients BCSs in the first years from diagnosis [31]. The occurrence of severe perceived cognitive deficits have been noted, above all in attention and memory, and worse QoL in BCSs who were undergoing adjuvant therapy, which are disruptive for BCSs in their work life because of lack of performance [32,33].

Previous studies have highlighted the physical adverse effects in BCSs being treated with AIs, focusing on emotional distress [10, 34,35].

Bidstrup et al. observed that a young age, not having a partner, less education, and receiving chemotherapy but not radiotherapy might identify BCSs whose psychological distress lasted
eight months after BC diagnosis [36]. Vance et al. reported also that symptoms of physical and psychological distress may be associated with weight change after treatment [37].

Nevertheless, personality and physical complaints resulting from adjuvant treatment distinguished different distress trajectories [38].

High patient-perceived burden from physical symptoms, and high coping self-efficacy suggest a transient, self-limiting distress trajectory, while patients experiencing chronic distress, and those developing distress following treatment completion only cannot be identified by a single initial assessment. [39–42].

Ho et al. underlined the key role of timely recognition of anxiety and depression, during the treatment and survivorship phases of BC trajectory [43].

Takei et al. studied psychological distress, and adverse events in BCSs who received ETs, finding that HRQoL was better in BCSs treated with tamoxifen than those treated with exemestane or anastrozole [44]. Moreover, Donovan et al. suggested a large prevalence of persistent depressive symptoms at the start of adjuvant treatment, focusing the relevance of psychological screening during the therapy [45].

Conversely, Schilder et al. [46] detected depressive symptoms in BCSs treated with ET and found no significant differences in comparison with healthy controls.

In BCSs, AIs physical adverse effects (e.g. hot flushes, palpitation, bone or joint pain, muscle stiffness) are commonly reported as well as psychological effects (e.g. anxiety and depressive symptoms) [10].

As many BCSs perceive a range of symptoms as a consequence of ET, Rosenberg et al. (2015) suggested attention to these symptoms may improve adherence and QoL, optimizing survival [10].

Ates et al. (2016) described the psychosocial and medical characteristics of BCSs initiating ET and evaluated emotional distress according to their psychosocial and medical characteristics, highlighting that these patients’ features were related to emotional distress[34]. Schilder et al. (2009) detected depressive symptoms in BCSs treated with different ET and found no significant differences in comparison with the healthy group[46]. Differently, Maas et al. (2015) found a higher prevalence of depressive symptoms among BCSs than in the general female population, while they didn’t find an increased prevalence of anxiety[35].

It is well known that emotional distress is reported in postmenopausal women who have a greater risk of developing both BC and osteoporosis[47].

On the basis of this data we aimed at exploring emotional distress, in an Italian sample of postmenopausal BCSs assessed for osteoporosis, focusing on anxiety levels, depressive symptoms and health related QoL before starting therapy and 6 months after initiation of AIs treatment.

**Materials and methods**

**Participants**

We recruited a group of postmenopausal women with a diagnosis of BC and a group of healthy controls. Both groups were referred to the Outpatients Clinics at the Department of Clinical and Experimental Medicine, University Hospital of Messina, Italy, for BMD evaluation by DXA-scanning. Research eligibility criteria included: postmenopausal age, graduation from primary school or higher; newly diagnosed early BC staged 0, I, II, or IIIA; non-metastatic hormone receptor positive BC; completed surgical treatment; concluded chemotherapy and radiation therapy when prescribed. All treatments ended 3 months before the start of the study.

Exclusion criteria were: known neurological or psychiatric diseases, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria [48] which could interfere...
with the study; previous bone fractures; previous cancer; autoimmune and endocrine diseases; cardiovascular, respiratory, liver or kidney failures; psychopharmacological therapy and use of steroid, hormone treatment or any active bone agents; already started adjuvant aromatase inhibitor administration.

Ethics statement
The study was approved by the Institutional Ethical Committee of the University Hospital “Gaetano Martino”, University of Messina, Italy. The research was conducted with respect for the rights of all participants and data was analysed entirely anonymously. Participants were evaluated by researchers in Clinical Psychology in collaboration with physicians. All subjects were thoroughly informed about the research aim of the study and gave written informed consent in accordance with the Declaration of Helsinki [49] and its subsequent revisions. All intervention, including rating scales administration and physical parameters detection were performed as a part of daily clinical assessment of patients.

Measures

Demographical and medical data. Data on each participant data regarding age, age at menopause, smoking habits, alcohol consumption and BMI was collected. Medical information comprised data on vitamin D status, BMI, BMD and data on subclinical vertebral fractures.

Clinical psychological evaluation. A gold standard interview to detect patient’s mental status was performed by a researcher in clinical psychology in a confidential setting [50–52]. This gold standard interview was complementary combined with the psychodiagnostic administration of the following self-report scales and questionnaires: Beck Depression Inventory Second Edition (BDI-II), Hamilton Anxiety Rating Scale (HAM-A), the Italian version of Short Form-36 (SF-36) questionnaire. Particularly, BDI-II, consisting of 21 items, was administered to detect the presence and severity of depressive symptoms, based on a range from 0 to 63, with higher scores reflecting more severe symptoms [53]. In the present study the reliability (Cronbach’s α) for the total score was .89.

HAM-A comprising 14 items, was used to detect anxiety levels. Each item is scored from 0 to 4, depending on the severity of perceived anxiety. It measures both psychological and somatic anxiety. In the area of psychic anxiety it measures anxious moods, tension, fears, insomnia, intellectual and depressed mood. In the area of somatic symptoms it measures the sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic and observed behaviour at the time of interview [54]. In the current study the reliability (Cronbach’s α) was .87 for the total score, and .83 and .77 for psychological and somatic anxiety respectively.

The Italian version of the SF-36 survey was administered to detect participants’ health perceived QoL [55,56] exploring the following eight dimensions: physical functioning, social functioning, role limitations because of physical problems, role limitations because of emotional problems, health, vitality, pain, and general health perception. Each dimension was scored from 0 to 100 points, with higher scores indicating lower limitations and better perceived QoL. Physical Component Summary (PCS) and Mental Component Summary (MCS) were also evaluated [57] to analyze both physical and mental well-being. In the present study the reliability (Cronbach’s α) was .83 and .82 for PCS and MCS respectively, with acceptable values for each dimension as follows: physical functioning (.85), role-physical (.78), bodily pain (.71), general health (.80), vitality (.79), social functioning (.72), role-emotional (.77), and mental health (.82).
Clinical characteristics. Physical evaluation was conducted measuring height and weight, according to standard procedures, and vitamin D status was assessed by HPLC, measuring 25(OH)D serum concentrations; BMD was measured at the lumbar spine (mean of L1-L4) in anteroposterior projection, and at femoral neck by dual-energy X-ray absorptiometry (DXA) (Hologic Discovery) [58]. A dorso-lumbar X-ray scan was applied in lateral projection, according to Genant’s classification, to exclude previous subclinical vertebral fractures [59].

BCSs and controls were compared at baseline and 6 months for all explored parameters, except for 25(OH)D and BMD.

Statistical analysis
Statistical analysis was performed using the MedCalc software (version 10.2.0.0; Mariakerke, 173 Belgium). Comparisons between groups were performed by an unpaired t-test or Mann-Whitney test and within-group comparisons were determined by paired t-test or Wilcoxon matched paired rank sum test for paired data as appropriate. The $\chi^2$ test was performed to calculate differences in the proportion of categorical variables. Spearman’s coefficient was used to measure the degree of association between two variables. Multiple regression was performed to analyse the association between a dependent variable and one or more explanatory variables. Values of $p \leq 0.05$ indicated statistical significance. All reported $p$ values were two-sided.

Results
102 postmenopausal women were recruited and completed the study according to the protocol. We screened 146 postmenopausal women, of whom 62 were diagnosed with BC and 84 were healthy controls. Due to inclusion and exclusion criteria we enrolled only 51 BCSs (82%) and 51 healthy controls (60%).

Before entering the study the BCSs had received surgical treatment (100%), chemotherapy (60%) and radiotherapy (90%), in accordance with routine oncological prescription. The 51 BCSs received daily AIs and bimonthly cholecalciferol 25,000 UI whereas the 51 controls solely received bimonthly cholecalciferol 25,000 UI.

The main clinical characteristics of the 102 participants at baseline are shown in Table 1.

At the baseline, we found no significant differences between the two groups regarding age, age at menopause, BMI, smoking habits, alcohol consumption, serum 25(OH)D concentration and BMD. The two groups showed significant differences at HAM-A, both in somatic and psychic scores. Mainly, BCSs obtained the highest HAM-A scores, reflecting higher anxiety levels in comparison with controls. The two groups also showed a significant difference at BDI-II, as the BCSs demonstrated higher scores, reflecting higher depressive symptoms in comparison with controls. Moreover, the two groups showed a significant difference at SF-36 scores for each of the eight explored domains. Particularly, there were lower scores for each domain in BCSs, in comparison with controls, reflecting BCSs’ worse perceived QoL.

Psychological features after 6 months are shown in comparison with the baseline in Table 2. Particularly, BCSs showed a significant difference of anxiety levels between the baseline and 6 month detections, with decreased anxious symptoms at the end of the study. Moreover, we noticed that at 6 months BCSs showed decreased depressive symptoms, even if it was not significantly different in comparison with baseline. Also BCSs at 6 months showed a statistically significant better perceived QoL in comparison with baseline. Additionally, controls showed a significant reduction of anxiety levels at 6 months in comparison with the baseline and they also presented decreased depressive symptoms, which were not significantly different from the baseline, as we observed instead in BCSs. Furthermore, controls had a significantly different perceived QoL, with higher scores at the end of the study.
The main outcome, at 6 months, consisted of higher anxious and depressive symptoms and lower perceived QoL in BCSs as compared to controls (Fig 1).

Table 1. Baseline main clinical characteristics of all participants, breast cancer survivors (BCSs) and controls.

|                         | Total (n = 102) | BCSs (n = 51) | Controls (n = 51) | p value |
|-------------------------|----------------|--------------|------------------|---------|
| Age (yr.)               | 66.5±9.1       | 66.9±8.7     | 66±10.9          | NS      |
| Age at menopause (yr.)  | 47.3±5.4       | 47.4±4.8     | 47.5±5.1         | NS      |
| BMI (Kg/m²)             | 24.4±4.9       | 24.5±5.5     | 24.4±4.2         | NS      |
| Current smoking [n(%)]  | 10 (10)        | 5 (10)       | 5 (10)           | NS      |
| Alcohol ≥ 3 units/day   | 0              | 0            | 0                | NS      |
| S-25(OH) D (ng/ml)      | 26.9±10        | 25.1±7.4     | 28.7±11.7        | NS      |
| Bone mineral density    |                |              |                  |         |
| Lumbar spine T-score (SD) | -2 ± 1        | -2.1 ± 1     | -1.9 ± 0.9       | NS      |
| Femoral neck T-score (SD) | -1.8 ± 0.6     | -1.8 ± 0.6   | -1.8 ± 0.7       | NS      |
| Anxiety levels          |                |              |                  |         |
| HAM-A score             | 27.8±7.11      | 33.2±4.1     | 22.3±5          | <0.0001 |
| HAM-A somatic symptom score | 11.9±3.9    | 14.5±2.8    | 9.3±3.2         | <0.0001 |
| HAM-A psychic symptom score | 15.9±3.8 | 18.7±2.4 | 13±2.9         | <0.0001 |
| Depression severity     |                |              |                  |         |
| BDI-II score            | 7.2±3.1        | 8.6±2.6      | 5.9±3.1          | <0.0001 |
| Perceived Quality of Life–SF-36 |            |              |                  |         |
| Mental health           | 28 (20 to 52)  | 28 (17 to 32)| 44 (21 to 56)   | 0.001   |
| Role emotional          | 0 (0 to 33)    | 0 (0 to 0)   | 33 (0 to 66)    | <0.0001 |
| Social functioning      | 50 (25 to 62)  | 37 (25 to 50)| 50 (37 to 62)   | 0.0003  |
| Vitality                | 35 (25 to 50)  | 30 (20 to 40)| 40 (30 to 55)   | 0.0008  |
| General health          | 40 (25 to 52)  | 30 (20 to 40)| 45 (35 to 52)   | 0.0011  |
| Bodily pain             | 41 (22 to 52)  | 30 (22 to 41)| 41 (22 to 74)   | 0.004   |
| Role physical           | 0 (0 to 50)    | 0 (0 to 0)   | 25 (0 to 75)    | 0.0001  |
| Physical functioning    | 55 (30 to 75)  | 35 (20 to 55)| 75 (55 to 90)   | <0.0001 |

Values are expressed as mean ± SD or median (IQR) as appropriate. BMI = Body Mass Index; S-25(OH)D = 25-hydrossi-vitamin D serum level; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; SF-36 = Short Form Survey Instrument.

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The main outcome, at 6 months, consisted of higher anxious and depressive symptoms and lower perceived QoL in BCSs as compared to controls (Fig 1).

Table 2. Changes in psychological features in patients with breast cancer and controls at baseline and after 6 months of treatment with aromatase inhibitors.

|                         | BC (n = 51) | Controls (n = 51) |
|-------------------------|------------|------------------|
|                         | Baseline   | 6 months | p value | Baseline | 6 months | p value |
| Anxiety levels          |            |          |         |          |          |         |
| HAM-A score             | 33.2±4.1   | 30±3.7   | <0.001  | 22.3±5   | 20±4.4   | <0.001  |
| HAM-A somatic symptom score | 14.5±2.8 | 13.2±2.6 | 0.02    | 9.3±3.2  | 8.2±2.5  | 0.05    |
| HAM-A psychic symptom score | 18.7±2.4 | 17.2±2.2 | 0.002   | 13±2.9   | 11.9±2.8 | 0.04    |
| Depression severity     |            |          |         |          |          |         |
| BDI-II score            | 8.6±2.6    | 8±2.6    | 0.001   | 5.9±3    | 5.6±2    | NS      |
| Perceived quality of life |           |          |         |          |          |         |
| PCS                     | 32.3±7.2   | 33.8±6.1 | 0.006   | 40.5±9.1 | 45.4±8   | <0.001  |
| MCS                     | 27.9±5.4   | 34±6.2   | <0.001  | 33.5±9.8 | 39.3±9.2 | <0.001  |

Data is reported as mean ± SD. BC = Breast Cancer; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; PCS = Physical Component Summary; MCS = Mental Component Summary.

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Besides, at baseline and after 6 months there were statistically significant differences in both somatic and psychic anxiety in both patients and controls (Table 2).

Anxiety levels, depressive symptoms and perceived QoL were significantly associated at baseline in all participants, and they were also related with age (Table 3).

At baseline, the 25(OH)D serum concentration was inversely related with both age (r = -0.33; p = 0.001) and with the HAM-A score (r = -0.19; p = 0.05), while it was positively related to PCS (r = 0.23; p = 0.01). Furthermore, in BCSs an association between the 25(OH)D concentration and Δ PCS (r = -0.33; p = 0.02), as well as between Δ HAM-A and Δ MCS (r = -0.29; p = 0.03) was found. Finally, we performed stepwise multiple regression analysis assuming Δ MCS (model 1), and Δ PCS (model 2), as dependent variables in two distinct models, including age, age at menopause, serum 25(OH)D, Δ HAM-A score and Δ BDI-II score as explanatory variables. The Δ HAM-A score was the only predictor of Δ MCS (β = 0.55, p = 0.03, SE = 0.25) (model 1), while patient’s age was the only predictor of Δ PCS (β = 0.70, p = 0.005, SE = 0.24) (model 2). However, in the control group there were no significant associations in Δ values for any explored psychological variable.
The main finding of this study is that BCSs showed decreased anxiety levels and depressive symptoms, presenting a better perceived QoL after 6 months of AIs treatment, compared with the baseline.

It is known that during the so-called “re-entry” period, BCSs are usually distressed about the alteration of former roles, the decline in interpersonal support, and the lingering physical and psychological effects of diagnosis and treatment. This is in agreement with our findings that highlight a worse psychological state at the baseline evaluation, after completed surgical treatment and concluded chemotherapy and/or radiation therapy [60].

At the end of curative therapy, BCSs often receive long-term prophylactic AIs treatment to reduce BC relapses [6,61–63]. However, the treatment may be burdened by clinical psychological impairment due to estrogenic deprivation and their consequences on the brain [2–4].

The estrogenic actions on brain tissue and functioning has been intensively studied, including its activity on brain receptors, located in the hippocampus and cerebral cortex. Estrogen may have positive effects on neurotransmitters involved in cognitive processes and may also have a protective role against ischemic brain injuries through its anti-inflammatory action which enhances cell survival, improving blood flow and glucose transport in the brain [64–66]. There is also evidence suggesting estrogen could increase the risk of stroke and dementia [67,68]. However, there is conflicting data on the effects of both estrogen replacement and deprivation on cognitive function in clinical settings [68–71]. Bender et al. [72–77] highlighted decreased cognitive functioning in BCSs prior to initiation ET that did not appear to be influenced by treatment. Particularly, comparing anxiety levels between groups and exploring variation over time, they observed that women were more anxious at the baseline, while they were less anxious at 6 months. They found neither depressive symptoms nor fatigue were consistently associated with the cognitive function factors.

Aromatase inhibitor treatment, inducing estrogenic suppression, could provoke several adverse effects among which the aromatase inhibitor-associated musculoskeletal syndrome could adversely affect the health-related QoL of breast cancer survivors [8]. Conversely, in a recent multicenter study Taira et al. [78] suggested that neo adjuvant AIs induced a significant improvement of depressive and anxious symptoms and a better perceived QoL in a four month observation period in BCSs before surgical treatment.

In a recent cross-sectional descriptive and correlational study focused on psychosocial characteristics, Ates et al. [34] investigated the relationship between psychological and medical characteristics and self-reported emotional distress in BCSs who were treated with ET. Particularly they found that emotional distress was relatively higher among patients in the first two

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**Table 3. Correlation analysis at baseline between the studied variables of all participants.**

|            | Age          | Age at menopause | BMI           | HAM-A score | BDI-II score | PCS           | MCS           |
|------------|--------------|------------------|---------------|-------------|--------------|---------------|---------------|
| Age        | r = 0.13; p = 0.19 | r = 0.1; p = 0.28 | r = 0.15; p = 0.12 | r = 0.25; p = 0.01 | r = -0.52; p<0.001 | r = -0.34; p<0.001 |
| Age at menopause | r = 0.13; p = 0.19 | r = 0.11; p = 0.27 | r = -0.03; p = 0.74 | r = 0.07; p = 0.49 | r = -0.14; p = 0.16 | r = -0.14; p = 0.16 |
| BMI        | r = 0.1; p = 0.28  | r = 0.11; p = 0.27 | r = -0.12; p = 0.21 | r = -0.15; p = 0.12 | r = -0.08; p = 0.38 | r = -0.10; p = 0.31 |
| HAM-A score| r = 0.15; p = 0.12 | r = -0.03; p = 0.74 | r = -0.12; p = 0.21 | r = 0.63; p<0.001 | r = -0.49; p<0.001 | r = -0.53; p<0.001 |
| BDI-II score| r = 0.25; p = 0.01 | r = 0.07; p = 0.49  | r = -0.15; p = 0.12 | r = 0.63; p<0.001 | r = -0.54; p<0.001 | r = -0.46; p<0.001 |
| PCS        | r = -0.52; p<0.001 | r = -0.14; p = 0.16 | r = -0.08; p = 0.38 | r = -0.49; p<0.001 | r = -0.54; p<0.001 | r = -0.39; p<0.001 |
| MCS        | r = -0.34; p<0.001 | r = -0.14; p = 0.16 | r = 0.10; p = 0.31 | r = -0.53; p<0.001 | r = -0.46; p<0.001 | r = 0.39; p<0.001 |

BMI = Body Mass Index; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; PCS = Physical Component Summary; MCS = Mental Component Summary. Significant values (p<0.05) are reported in bold.

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**Discussion**

The main finding of this study is that BCSs showed decreased anxiety levels and depressive symptoms, presenting a better perceived QoL after 6 months of AIs treatment, compared with the baseline.

It is known that during the so-called “re-entry” period, BCSs are usually distressed about the alteration of former roles, the decline in interpersonal support, and the lingering physical and psychological effects of diagnosis and treatment. This is in agreement with our findings that highlight a worse psychological state at the baseline evaluation, after completed surgical treatment and concluded chemotherapy and/or radiation therapy [60].

At the end of curative therapy, BCSs often receive long-term prophylactic AIs treatment to reduce BC relapses [6,61–63]. However, the treatment may be burdened by clinical psychological impairment due to estrogenic deprivation and their consequences on the brain [2–4].

The estrogenic actions on brain tissue and functioning has been intensively studied, including its activity on brain receptors, located in the hippocampus and cerebral cortex. Estrogen may have positive effects on neurotransmitters involved in cognitive processes and may also have a protective role against ischemic brain injuries through its anti-inflammatory action which enhances cell survival, improving blood flow and glucose transport in the brain [64–66]. There is also evidence suggesting estrogen could increase the risk of stroke and dementia [67,68]. However, there is conflicting data on the effects of both estrogen replacement and deprivation on cognitive function in clinical settings [68–71]. Bender et al. [72–77] highlighted decreased cognitive functioning in BCSs prior to initiation ET that did not appear to be influenced by treatment. Particularly, comparing anxiety levels between groups and exploring variation over time, they observed that women were more anxious at the baseline, while they were less anxious at 6 months. They found neither depressive symptoms nor fatigue were consistently associated with the cognitive function factors.

Aromatase inhibitor treatment, inducing estrogenic suppression, could provoke several adverse effects among which the aromatase inhibitor-associated musculoskeletal syndrome could adversely affect the health-related QoL of breast cancer survivors [8]. Conversely, in a recent multicenter study Taira et al. [78] suggested that neo adjuvant AIs induced a significant improvement of depressive and anxious symptoms and a better perceived QoL in a four month observation period in BCSs before surgical treatment.

In a recent cross-sectional descriptive and correlational study focused on psychosocial characteristics, Ates et al. [34] investigated the relationship between psychological and medical characteristics and self-reported emotional distress in BCSs who were treated with ET. Particularly they found that emotional distress was relatively higher among patients in the first two
years of treatment, without any significant statistical difference in comparison with the following three years of treatment. To evaluate emotional distress, Ates and colleagues [34] administered the hospital anxiety and depression scale (HADs), a self-reported scale validated to detect the eventual presence of both anxiety and depressive states [79]. HADs is usually administered in clinical oncology and psychology services, but it does not allow clinicians to constructively discriminate between anxious and depressive symptoms, while it is more functional to measure the global entity of emotional distress [80,81].

Aromatase inhibitors may increase bone loss of up to 13% the first year of treatment and increase the risk of osteoporotic fractures risk as compared to healthy controls [58]. Bone fractures are by themselves associated with a higher risk of morbidity and mortality. The preventable increased risk of fractures due to the effects of AIs treatment in BCSs represents another source of worry which could further compromise their perceived QoL.

Maas et al. showed in their systematic literature review that the results on depression scales suggested an increase in risk of symptoms of depression, varying from 9.4% to 66%, in BCSs one year after the diagnosis, which then decreased over the following years. The prevalence of anxiety ranged from 17.9% to 33.3% [35].

The psychological features which characterize BCSs at baseline were probably related to their early BC diagnosis which induced severe emotional distress and deep awareness of their own survival. At the same time BCSs showed hyperarousal during the interview, disclosing great fears of both losing their lives and not being able to control the progress of their health. They were suffering from intense psychic and somatic anxious symptoms which impaired their perceived QoL. Particularly we found that perceived QoL in BCSs was lower at baseline as compared to controls, and it is conceivable that their oncologic pathology, even if after specific previous treatments, could lead to significant role limitations because of pain, anxiety and depressive symptoms [8,82–88].

We cannot explain this finding with a causal relationship between AIs treatment and psychological improvement, as we detected an improvement of the same psychological features in the control group too. Both groups suffered low baseline serum 25(OH)D levels and were treated by cholecalciferol supplementation at equal dosage from baseline to 6 months of observation. This vitamin D supplementation could contribute at least in part to the psychological improvement, as low levels of vitamin D in postmenopausal women are associated with depression, anxiety and low perceived QoL [47,57, 89,90], although the distance from surgical treatment could allow patients to elaborate mental processes, useful for helping them adapt better; moreover, we could consider the surgical cancer ablation made women feel free from a dramatic fear for their survival.

The awareness that their global health was at the centre of interest of both the clinical psychologist and physician probably had in part a positive influence on their emotional distress, also improving their perceived QoL. BCSs at the time of diagnosis commonly experience psychological trauma, but they could have resources to live their life with a healthier psychological approach. This could at least in part explain why they are able to benefit from other psychological sources, which could lead to useful adaptation to the stressful condition affecting them. Beyond suffering, psychological distress may also decrease the ability to find the best way to face and solve symptoms.

Furthermore, we observed that anxiety levels and perceived QoL changes in BCSs varied during the observational period in a directly proportional way. Particularly, HAM-A administration allowed us to highlight lower anxiety levels predicting a better perceived QoL, especially with regard to MCS, and independently from age, age at menopause, vitamin D status and depression.
In future research it could be valuable to plan a clinical psychological intervention strategy assisting patients to mentally integrate such chronic diseases, focusing on reducing psychological outcomes and improving QoL.

The strengths of the current study include a gold standard diagnostic interview which conferred specific objectivity to the performed surveys, and the complementary evaluation of clinical psychological features, in a homogeneous cohort of postmenopausal BCSs; the multiple regression analysis allowed us to highlight the association between $\Delta$ HAM-A and $\Delta$ MCS after multiple adjustment as depressive symptoms, age and serum 25(OH)D levels.

We must recognize that our research has some limitations as it was conducted solely in Italy, thus the findings may not be generalizable and it is based on a small sample size. Moreover, the control group consisted of postmenopausal women who had not previously suffered from BC or other malignancy, thus we could not exclude the possible effect of cancer and its treatment on the explored variables even relative to the comparison between different therapies among aromatase inhibitors. Also, adherence to AIs, side effects from AIs and participation in psychotherapy or counselling were not assessed. Further research should be conducted considering control groups of women with ER negative BC. A pain evaluation was not performed, excluding the possibility to directly apply associations between pain entity and changes in variables that could be expected in reference with PCS (e.g. for role limitation because of physical problems). Moreover, the small sample size did not allow separate sub-analysis of BCSs undergoing different AIs treatment, or even a separate analysis relative to previous therapies. Finally, the short 6- month observation period did not allow us to detect how the explored variables would change over time during these long-term prophylactic therapies.

**Conclusion**

Our study showed BCSs’ higher anxious and depressive symptoms compared to controls. Our findings revealed that 6 months of AIs treatment was associated with the improvement of clinical psychological features and better health related QoL in comparison with the baseline. This data could be useful to plan BCSs psychological intervention focused on health concerns as well as for assisting patients in reducing psychological and physical consequences due to this chronic disease and its treatments.

**Supporting information**

S1 Table. Baseline main clinical characteristics of all participants, breast cancer survivors (BCSs) and controls. Values are expressed as mean ± SD or median (IQR) as appropriate. BMI = Body Mass Index; S-25(OH)D = 25-hydroxy-vitamin D serum level; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; SF-36 = Short Form Survey Instrument.

S2 Table. Changes in psychological features in patients with breast cancer and controls at baseline and after 6 months of treatment with aromatase inhibitors. Data are reported as mean ± SD. BC = Breast Cancer; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; PCS = Physical Component Summary; MCS = Mental Component Summary.

S3 Table. Correlation analysis at baseline between the studied variables of all participants. BMI = Body Mass Index; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; PCS = Physical Component Summary; MCS = Mental Component.
Summary.

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