PLOS ONE

RESEARCH ARTICLE

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

Gabriella Martino[1☯]*, Antonino Catalano[1☯], Rita Maria Agostino[2], Federica Bellone[1], Nunziata Morabito[1], Carmen Giulia Lasco[1], Carmelo Mario Vicario[3], Peter Schwarz[4‡], Ulla Feldt-Rasmussen[4‡]

1 Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy, **2** Unit of Medical Oncology, Grand Metropolitan Hospital Bianchi Melacrino Morelli, Reggio-Calabria, Italy, **3** Department of Cognitive Sciences, Psychology, Education and Cultural Studies, University of Messina, Messina, Italy, **4** Department of Medical Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* martinog@unime.it

Citation: Martino G, Catalano A, Agostino RM, Bellone F, Morabito N, Lasco CG, et al. (2020) Quality of life and psychological functioning in postmenopausal women undergoing aromatase inhibitor treatment for early breast cancer. PLoS ONE 15(3): e0230681. https://doi.org/10.1371/journal.pone.0230681

Editor: Debashis Ghosh, State University of New York Upstate Medical University, UNITED STATES

Received: November 16, 2019

Accepted: March 5, 2020

Published: March 26, 2020

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

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.

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.±4.8	47.5±5.1	NS
BMI *(Kg/m^2)*	24.4±4.9	24.5±5.5	24.4±4.2	NS
Current smoking *[n(%)]*	10 (10)	5 (10)	5 (10)	NS
Alcohol ≥ 3units/day *[n(%)]*	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.

https://doi.org/10.1371/journal.pone.0230681.t001

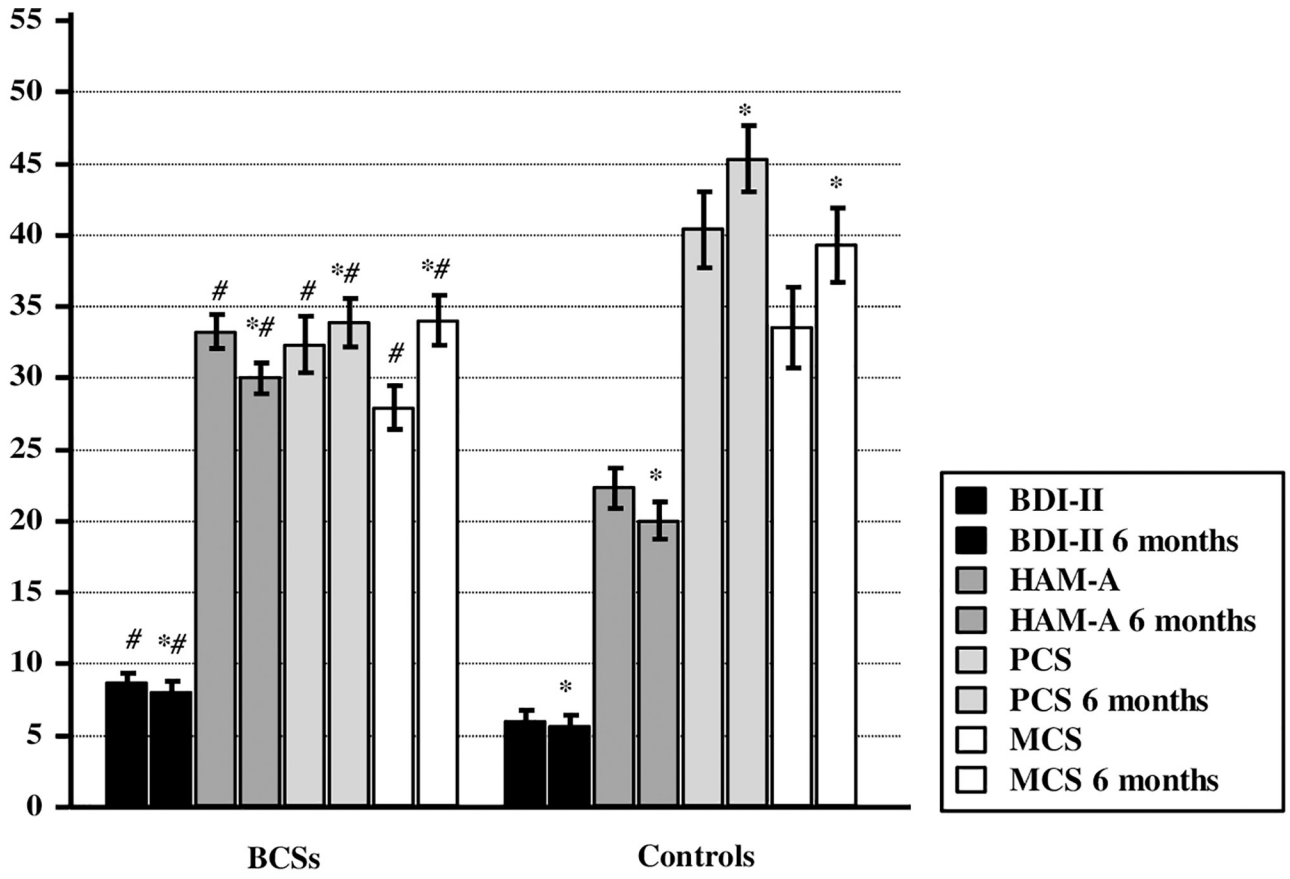
The main outcome, at 6 months, consisted of higher anxious and depressive symptoms and lower perceived QoL in BCSs as compared to controls (Fig 1).

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**		**Baseline**	**6 months**	
Anxiety levels			p value			p value
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.

https://doi.org/10.1371/journal.pone.0230681.t002



*Bars = mean values; Error bars = 95% CI for means; * = p<0.05 vs baseline; # = p<0.05 vs controls; BCSs = Breast Cancer Survivors; BDI-II = Beck Depression Inventory II edition; HAM-A = Hamilton Anxiety Rating Scale; PCS = Physical Component Summary; MCS = Mental Component Summary.*

Fig 1. Clinical psychological features and comparison at baseline (*Left column of each signature*) and after 6 months (*Right column of each signature*). Bars = mean values; Error bars = 95% CI for means; * = p<0.05 vs baseline; # = p<0.05 vs controls; BCSs = Breast Cancer Survivors; BDI-II = Beck Depression Inventory II edition; HAM-A = Hamilton Anxiety Rating Scale; PCS = Physical Component Summary; MCS = Mental Component Summary.

https://doi.org/10.1371/journal.pone.0230681.g001

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.

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.

https://doi.org/10.1371/journal.pone.0230681.t003

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-colled "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 heath. 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 Δ HAM-A and Δ 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 subanalysis 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-hydrossi-vitamin D serum level; HAM-A = Hamilton Anxiety Rating Scale; BDI-II = Beck Depression Inventory II edition; SF-36 = Short Form Survey Instrument.
(DOCX)

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.
(DOCX)

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.
(DOCX)

Author Contributions

Conceptualization: Gabriella Martino.

Data curation: Gabriella Martino, Rita Maria Agostino, Federica Bellone.

Formal analysis: Gabriella Martino, Antonino Catalano.

Investigation: Gabriella Martino.

Methodology: Gabriella Martino.

Supervision: Nunziata Morabito, Carmelo Mario Vicario.

Visualization: Carmen Giulia Lasco.

Writing – original draft: Gabriella Martino.

Writing – review & editing: Peter Schwarz, Ulla Feldt-Rasmussen.

References

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The global burden of cancer 2013. JAMA Oncology. 2015 Jul 1; 1(4):505–27. https://doi.org/10.1001/jamaoncol.2015.0735 PMID: 26181261
2. Schagen SB, Vardy J. Cognitive dysfunction in people with cancer. The Lancet Oncology. 2007 Oct 1; 8 (10):852–3. https://doi.org/10.1016/S1470-2045(07)70287-5 PMID: 17913649
3. Ahles TA, Root JC, Ryan EL. Cancer-and cancer treatment–associated cognitive change: an update on the state of the science. Journal of Clinical Oncology. 2012 Oct 20; 30(30):3675. https://doi.org/10.1200/JCO.2012.43.0116 PMID: 23008308
4. Ganz PA, Petersen L, Castellon SA, Bower JE, Silverman DH, Cole SW, et al. Cognitive function after the initiation of adjuvant endocrine therapy in early-stage breast cancer: an observational cohort study. Journal of Clinical Oncology. 2014 Nov 1; 32(31):3559. https://doi.org/10.1200/JCO.2014.56.1662 PMID: 25267747
5. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. Journal of Clinical Oncology. 1999 May 1; 17(5):1474–81. https://doi.org/10.1200/JCO.1999.17.5.1474 PMID: 10334533
6. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005 Jan 1; 365(9453):60–2. https://doi.org/10.1016/S0140-6736(04)17666-6 PMID: 15639680
7. Rocha-Cadman X, Massie MJ, Du Hamel K. Aromatase inhibitors and mood disturbances. Palliative & Supportive Care. 2012 Sep; 10(3):225–7.
8. Roberts K, Rickett K, Greer R, Woodward N. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology. 2017 Mar 1; 111:66–80. https://doi.org/10.1016/j.critrevonc.2017.01.010 PMID: 28259297
9. Martino G, Catalano A, Bellone F, Russo GT, Vicario CM, Lasco A, et al. As Time Goes by: Anxiety Negatively Affects the Perceived Quality of Life in Patients With Type 2 Diabetes of Long Duration. Frontiers in Psychology. 2019; 10:1779. https://doi.org/10.3389/fpsyg.2019.01779 PMID: 31428028
10. Rosenberg SM, Stanton AL, Petrie KJ, Partridge AH. Symptoms and symptom attribution among women on endocrine therapy for breast cancer. The Oncologist. 2015 Jun 1; 20(6):598–604. https://doi.org/10.1634/theoncologist.2015-0007 PMID: 25933930
11. Marchini F, Caputo A, Napoli A, Balonan JT, Martino G, Nannini V, et al. Chronic illness as loss of good self: underlying mechanisms affecting diabetes adaptation. Mediterranean Journal of Clinical Psychology. 2018 Dec 20; 6(3). https://doi.org/10.6092/2282-1619/2018.6.1981

12. Settineri S, Frisone F, Merlo EM, Geraci D, Martino G. Compliance, adherence, concordance, empowerment, and self-management: five words to manifest a relational maladjustment in diabetes. Journal of Multidisciplinary Healthcare. 2019; 12:299. https://doi.org/10.2147/JMDH.S193752 PMID: 31118655

13. Martino G, Caputo A, Bellone F, Quattropani MC, Vicario C. Going Beyond the Visible in Type 2 Diabetes Mellitus: Defense Mechanisms and their Associations with Depression and Health-Related Quality of Life. Frontiers in Psychology. 2020 Feb; https://doi.org/10.3389/fpsyg.2020.00267 PMID: 32174865

14. Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. Neuroscience & Biobehavioral Reviews. 2018 Dec 10. https://doi.org/10.1016/j.neubiorev.2018.12.012 PMID: 30543906

15. Martino G, Bellone F, Langher V, Caputo A, Catalano A, Quattropani MC, et al. Alexithymia and Psychological Distress Affect Perceived Quality of Life in Patients with Type 2 Diabetes Mellitus. Mediterranean Journal of Clinical Psychology. 2019 Dec 12; 7(3).

16. Martino G, Langher V, Cazzato V, Vicario CM. Psychological factors as determinants of medical conditions. Frontiers in psychology. 2019; 10:2502. https://doi.org/10.3389/fpsyg.2019.02502 PMID: 31781002

17. Lenzo V, Sardella A, Martino G, Quattropani MC. A systematic review of metacognitive beliefs in chronic medical conditions. Front. Psychol. 10: 2875. https://doi.org/10.3389/fpsyg.2019.02875 2020 Jan 10. PMID: 31998178

18. Dell'Osso L, Stratta P, Conversano C, Massimetti E, Akiskal KK, Akiskal HS, et al. Lifetime mania is related to post-traumatic stress symptoms in high school students exposed to the 2009 L'Aquila earthquake. Comprehensive Psychiatry. 2014 Feb 1; 55(2):357–62. https://doi.org/10.1016/j.comppsych.2013.08.017 PMID: 24269194

19. Dell'Osso L, Carmassi C, Rucci P, Ciapparelli A, Conversano C, Marazziti D. Complicated grief and suicidality: the impact of subthreshold mood symptoms. CNS Spectrums. 2011 Jan; 16(1):1–6. https://doi.org/10.1017/S1092852912000090 PMID: 24725296

20. Carmassi C, Shear MK, Massimetti G, Wall M, Mauro C, Gemignani S, et al. Validation of the Italian version Inventory of Complicated Grief (ICG): A study comparing CG patients versus bipolar disorder, PTSD and healthy controls. Comprehensive Psychiatry. 2014 Jul 1; 55(5):1322–9. https://doi.org/10.1016/j.comppsych.2014.03.001 PMID: 24721191

21. Piccinni A, Origlia N, Veltri A, Vizzaccaro C, Marazziti D, Catena-Dell'Osso M, et al. Plasma β-amyloid peptides levels: a pilot study in bipolar depressed patients. Journal of Affective Disorders. 2012 Apr 1; 138(1–2):160–4. https://doi.org/10.1016/j.jad.2011.12.042 PMID: 22310032

22. Martino G, Sardella A, Bellone F, Lasco C, Langher V, Cazzato V, et al. Executive functions and bone health: a focus on cognitive impulsivity and bone mineral density. Mediterranean Journal of Clinical Psychology. 2019 Aug 1; 7(2). https://doi.org/10.6092/2282-1619/2019.7.2167

23. Catalano A, Sardella A, Bellone F, Lasco CG, Martino G, Morabito N. Executive functions predict fracture risk in postmenopausal women assessed for osteoporosis. Aging clinical and experimental research. 2019 Nov 26:1–7.

24. Catalano A, Martino G, Bellone F, Papalia M, Lasco C, Basile G, et al. Neuropsychological Assessment in Elderly Men with Benign Prostatic Hyperplasia Treated with Dutasteride. Clinical drug investigation. 2019 Jan 31; 39(1):97–102. https://doi.org/10.1007/s40261-018-0720-7 PMID: 30367429

25. Barberis N, Quattropani MC, Cuzzocrea F. Relationship between motivation, adherence to diet, anxiety symptoms, depression symptoms and quality of life in individuals with celiac disease. Journal of psychosomatic research. 2019 Sep 1; 124:109787. https://doi.org/10.1016/j.jpsychores.2019.109787 PMID: 31443802

26. Marchi L, Marzetti F, Orrù G, Lemmetti S, Miccoli M, Ciacchini R, et al. Alexithymia and psychological distress in patients with fibromyalgia and rheumatic disease. Frontiers in psychology. 2019;10. https://doi.org/10.3389/fpsyg.2019.00010

27. Sheikh S, Dahiya S, Ansari AH, Kumar MM. The association of quality of life between anxiety and depression in patients with chronic rheumatic heart disease. Mediterranean Journal of Clinical Psychology. 2019 Aug 10; 7(2). https://doi.org/10.6092/2282-1619/2019.7.2164

28. Castelnuovo G, Pietrabissa G, Manzoni GM, Corti S, Ceccarini M, Borrello M, et al. Chronic care management of globesity: promoting healthier lifestyles in traditional and mHealth based settings. Frontiers in Psychology. 2015 Oct 15; 6:1557. https://doi.org/10.3389/fpsyg.2015.01557 PMID: 26528215

29. Rahnea Nița RA., Popescu M., Ciuhu AN., et al. The relationship between anxiety, depression and sense of illness understanding in palliative cancer patients. Archives of the Balkan Medical Union. 2016 51, 25–28.

30. Rahnea-Nita RA, Paunica S, Motofei C, Rahnea-Nita G. Assessment of anxiety and depression in patients with advanced gynaecological cancer. Mediterranean Journal of Clinical Psychology. 2019 Aug 10;7(2). https://doi.org/10.6092/2282-1619/2019.7.2214

31. Hermelink K, Henschel V, Untch M, Bauerfeind I, Lux MP, Munzel K. Short-term effects of treatment-induced hormonal changes on cognitive function in breast cancer patients: results of a multicenter, prospective, longitudinal study. Cancer. 2008 Nov 1; 113(9):2431–9. https://doi.org/10.1002/cncr.23853 PMID: 18823033

32. Ribi K, Aldridge J, Phillips KA, Thompson A, Harvey V, Thürlimann B, et al. Subjective cognitive complaints one year after ceasing adjuvant endocrine treatment for early-stage breast cancer. British Journal of Cancer. 2012 May; 106(10):1618–25. https://doi.org/10.1038/bjc.2012.156 PMID: 22531635

33. Frank JS, Vance DE, Jukkala A, Meneses KM. Attention and memory deficits in breast cancer survivors: implications for nursing practice and research. Journal of Neuroscience Nursing. 2014 Oct 1; 46 (5):274–84. https://doi.org/10.1097/JNN.0000000000000078 PMID: 25099062

34. Ates O, Soylu C, Babacan T, Sarici F, Kertmen N, Allen D, et al. Assessment of psychosocial factors and distress in women having adjuvant endocrine therapy for breast cancer: the relationship among emotional distress and patient and treatment-related factors. SpringerPlus. 2016 Dec 1; 5(1):486.

35. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. Maturitas. 2015 Sep 1; 82(1):100 https://doi.org/10.1016/j.maturitas.2015.04.010 PMID: 25998574

36. Bidstrup PE, Christensen J, Mertz BG, Rottmann N, Dalton SO, Johansen C. Trajectories of distress, anxiety, and depression among women with breast cancer: Looking beyond the mean. Acta Oncol. 2015 May; 54(5):789–96. https://doi.org/10.3109/0284186X.2014.1002571 PMID: 25761086

37. Vance V, Mourtzakis M, Hanning R. Relationships Between Weight Change and Physical and Psychological Distress in Early-Stage Breast Cancer Survivors. Cancer Nurs. 2019 May/Jun; 42(3):E43–E50. https://doi.org/10.1097/NCC.0000000000000612 PMID: 29847347

38. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. Health Psychol. 2010 Mar; 29(2):160–8. https://doi.org/10.1037/a0017806 PMID: 20230089

39. Kant J, Czisch A, Schott S, Siewerdt-Werner D, Birkenfeld F, Keller M. Identifying and predicting distinct distress trajectories following a breast cancer diagnosis—from treatment into early survival. J Psychosom Res. 2018 Dec; 115:6–13. https://doi.org/10.1016/j.jpsychores.2018.09.012 PMID: 30470319

40. Junghaenel DU, Cohen J, Schneider S, Neerukonda AR, Broderick JE. Identification of distinct fatigue trajectories in patients with breast cancer undergoing adjuvant chemotherapy. Support Care Cancer. 2015 Sep; 23(9):2579–87. https://doi.org/10.1007/s00520-015-2616-x PMID: 25876159

41. Lam WW, Soong I, Yau TK, Wong KY, Tsang J, Yeo W, et al. The evolution of psychological distress trajectories in women diagnosed with advanced breast cancer: a longitudinal study. Psychooncology. 2013 Dec; 22(12):2831–9. https://doi.org/10.1002/pon.3361 PMID: 24038545

42. Stanton AL. What happens now? Psychosocial care for cancer survivors after medical treatment completion. J Clin Oncol 2012; 30:1215–1220. https://doi.org/10.1200/JCO.2011.39.7406 PMID: 22412133

43. Ho SS, So WK, Leung DY, Lai ET, Chan CW. Anxiety, depression and quality of life in Chinese women with breast cancer during and after treatment: a comparative evaluation. Eur J Oncol Nurs. 2013 Dec; 17(6):877–82. https://doi.org/10.1016/j.ejon.2013.04.005 PMID: 23727448

44. Takei H, Ohsumi S, Shimozuma K, Takehara M, Suemasu K, Ohashi Y, et al. Health-related quality of life, psychological distress, and adverse events in postmenopausal women with breast cancer who receive tamoxifen, exemestane, or anastrozole as adjuvant endocrine therapy: National Surgical Adjuvant Study of Breast Cancer 04 (N-SAS BC 04). Breast Cancer Res Treat. 2012 May; 133(1):227–36. https://doi.org/10.1007/s10549-011-1943-y PMID: 22234519

45. Donovan KA, Gonzalez BD, Small BJ, Andrykowski MA, Jacobsen PB. Depressive symptom trajectories during and after adjuvant treatment for breast cancer. Ann Behav Med. 2014 Jun; 47(3):292–302. https://doi.org/10.1007/s12160-013-9550-2 PMID: 24158626

46. Schilder CM, Eggens PC, Seynaeve C, Linn SC, Boogerd W, Gundy CM, et al. Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: cross-sectional findings from the neuropsychological TEAM-side study. Acta Oncologica. 2009 Jan 1; 48(1):76–85. https://doi.org/10.1080/02841860802314738 PMID: 18777410

47. Catalano A, Martino G, Bellone F, Gaudio A, Lasco C, Langher V, et al. Anxiety levels predict fracture risk in postmenopausal women assessed for osteoporosis. Menopause. 2018 Oct 1; 25(10):1110–5. https://doi.org/10.1097/GME.0000000000001123 PMID: 29738418

48. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.

49. Rickham PP. Human experimentation. Code of ethics of the world medical association. Declaration of Helsinki. British Medical Journal. 1964 Jul; 2(5402):177. https://doi.org/10.1136/bmj.2.5402.177 PMID: 14150898

50. Fava GA, Tomba E, Sonino N. Clinimetrics: the science of clinical measurements. International Journal of Clinical Practice. 2012 Jan; 66(1):11–5. https://doi.org/10.1111/j.1742-1241.2011.02825.x PMID: 22171900

51. Conti C, Carrozzino D, Patierno C, Vitacolonna E, Fulcheri M. The clinical link between type D personality and diabetes. Frontiers in Psychiatry. 2016 Jun 21; 7:113. https://doi.org/10.3389/fpsyt.2016.00113 PMID: 27445869

52. Langher V, Caputo A, Martino G. What happened to the clinical approach to case study in psychological research? A clinical psychological analysis of scientific articles in high impact-factor journals. Mediterranean Journal of Clinical Psychology. 2017 Dec 30;5(3).

53. Beck AT, Steer RA, Brown GK. Beck Depression Inventory-II. San Antonio. 1996; 78(2):490–8.

54. Hamilton MA. The assessment of anxiety states by rating. British Journal of Medical Psychology. 1959 Mar; 32(1):50–5. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x PMID: 13638508

55. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical Care. 1992 Jun 1:473–83. https://doi.org/10.1097/00005650-199206000-00002

56. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. Journal of Clinical Epidemiology. 1998 Nov 1; 51(11):1025–36. https://doi.org/10.1016/s0895-4356(98)00094-8 PMID: 9817120

57. Martino G, Catalano A, Bellone F, Sardella A, Lasco C, Caprì T, et al. Vitamin D status is associated with anxiety levels in postmenopausal women evaluated for osteoporosis. Mediterranean Journal of Clinical Psychology. 2018 Apr 27; 6(1).

58. Catalano A, Gaudio A, Morabito N, Basile G, Agostino RM, Xourafa A, et al. Quantitative ultrasound and DXA measurements in aromatase inhibitor-treated breast cancer women receiving denosumab. Journal of Endocrinological Investigation. 2017 Aug 1; 40(8):851–7. https://doi.org/10.1007/s40618-016-0606-6 PMID: 28332172

59. Deleskog L, Laursen NØ, Nielsen BR, Schwarz P. Vertebral fracture assessment by DXA is inferior to X-ray in clinical severe osteoporosis. Osteoporosis International. 2016 Jul 1; 27(7):2317–26. https://doi.org/10.1007/s00198-016-3532-8 PMID: 26892040

60. Suppli NP, Johansen C, Christensen J, Kessing LV, Kroman N, Dalton SO. Increased risk for depression after breast cancer: a nationwide population-based cohort study of associated factors in Denmark, 1998–2011. J Clin Oncol 2014; 32:3831–3839. https://doi.org/10.1200/JCO.2013.54.0419 PMID: 25349294

61. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Journal of Clinical Oncology. 2000 Nov 15; 18(22):3758–67. https://doi.org/10.1200/JCO.2000.18.22.3758 PMID: 11078488

62. Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. Journal of Clinical Oncology. 2007 Feb 10; 25(5):486–92. https://doi.org/10.1200/JCO.2006.08.8617 PMID: 17200148

63. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. New England Journal of Medicine. 2004 Mar 11; 350(11):1081–92. https://doi.org/10.1056/NEJMoa040331 PMID: 15014181

64. Norbury R, Cutter WJ, Compton J, Robertson DM, Craig M, Whitehead M, et al. The neuroprotective effects of estrogen on the aging brain. Experimental Gerontology. 2003 Jan 1; 38(1–2):109–17. https://doi.org/10.1016/s0531-5565(02)00166-3 PMID: 12543268

65. Cholerton B, Gleason CE, Baker LD, Asthana S. Estrogen and Alzheimer's disease. Drugs & Aging. 2002 Jun 1; 19(6):405–27.

66. Cheng CM, Cohen M, Wang JI, Bondy CA. Estrogen augments glucose transporter and IGF1 expression in primate cerebral cortex. The FASEB Journal. 2001 Apr; 15(6):907–15. https://doi.org/10.1096/fj.00-0398com PMID: 11292650

67. Rossouw JE. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. Jama. 2002; 288:321–33. https://doi.org/10.1001/jama.288.3.321 PMID: 12117397

68. Shumaker SA. Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004; 291:2947–58. https://doi.org/10.1001/jama.291.24.2947 PMID: 15213206

69. Hurria A, Patel SK, Mortimer J, Luu T, Somlo G, Katheria V, et al. The effect of aromatase inhibition on the cognitive function of older patients with breast cancer. Clinical Breast Cancer. 2014 Apr 1; 14 (2):132–40. https://doi.org/10.1016/j.clbc.2013.10.010 PMID: 24291380

70. Matthews K, Cauley J, Yaffe K, Zmuda JM. Estrogen replacement therapy and cognitive decline in older community women. Journal of the American Geriatrics Society. 1999 May; 47(5):518–23. https://doi.org/10.1111/j.1532-5415.1999.tb02563.x PMID: 10323642

71. Hara Y, Waters EM, McEwen BS, Morrison JH. Estrogen effects on cognitive and synaptic health over the lifecourse. Physiological Reviews. 2015 Jun 24; 95(3):785–807. https://doi.org/10.1152/physrev.00036.2014 PMID: 26109339

72. Bender CM, Sereika SM, Ryan CM, Brufsky AM, Puhalla S, Berga SL. Does lifetime exposure to hormones predict pretreatment cognitive function in women before adjuvant therapy for breast cancer? Menopause. 2013 Sep; 20(9):922–9. https://doi.org/10.1097/GME.0b013e3182843eff PMID: 23481123

73. Bender CM, Merriman JD, Gentry AL, Ahrendt GM, Berga SL, Brufsky AM, et al. Patterns of change in cognitive function with anastrozole therapy. Cancer. 2015 Aug 1; 121(15):2627–36. https://doi.org/10.1002/cncr.29393 PMID: 25906766

74. Merriman JD, Sereika SM, Brufsky AM, McAuliffe PF, McGuire KP, Myers JS, et al. Trajectories of self-reported cognitive function in postmenopausal women during adjuvant systemic therapy for breast cancer. Psychooncology. 2017 Jan; 26(1):44–52. https://doi.org/10.1002/pon.4009 PMID: 26486371

75. Bender CM, Merriman JD, Sereika SM, Gentry AL, Casillo FE, Koleck TA, et al. Trajectories of Cognitive Function and Associated Phenotypic and Genotypic Factors in Breast Cancer. Oncol Nurs Forum. 2018 May 1; 45(3):308–326. https://doi.org/10.1188/18.ONF.308-326 PMID: 29683114

76. Bender CM, Sereika SM, Brufsky AM, Ryan CM, Vogel VG, Rastogi P, et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. Menopause. 2007 Nov-Dec; 14(6):995–8. https://doi.org/10.1097/gme.0b013e318148b28b PMID: 17898668

77. Bender CM, Merriman JD. Cancer- and treatment-related cognitive changes: what can we do now? What lies ahead? Oncology (Williston Park). 2014 Sep; 28(9):806–8.

78. Taira N, Iwata H, Hasegawa Y, Sakai T, Higaki K, Kihara K, et al. Health-related quality of life and psychological distress during neoadjuvant endocrine therapy with letrozole to determine endocrine responsiveness in postmenopausal breast cancer. Breast Cancer Research and Treatment. 2014 May 1; 145 (1):155–64. https://doi.org/10.1007/s10549-014-2935-5 PMID: 24692082

79. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983 Jun; 67(6):361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x PMID: 6880820

80. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Supportive Care in Cancer. 2011 Dec 1; 19 (12):1899. https://doi.org/10.1007/s00520-011-1251-4 PMID: 21898134

81. Norton S, Cosco T, Doyle F, Done J, Sacker A. The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. Journal of Psychosomatic Research. 2013 Jan 1; 74(1):74–81. https://doi.org/10.1016/j.jpsychores.2012.10.010 PMID: 23272992

82. Watt T, Hegedüs L, Bjorner JB, Groenvold M, Bonnema SJ, Rasmussen ÅK, et al. Is thyroid autoimmunity per se a determinant of quality of life in patients with autoimmune hypothyroidism?. European Thyroid Journal. 2012; 1(3):186–92. https://doi.org/10.1159/000342623 PMID: 24783018

83. Bové KB, Watt T, Vogel A, Hegedüs L, Bjoerner JB, Groenvold M, et al. Anxiety and depression are more prevalent in patients with graves' disease than in patients with nodular goitre. European Thyroid Journal. 2014; 3(3):173–8. https://doi.org/10.1159/000365211 PMID: 25538899

84. Catalano A, Martino G, Morabito N, Scarcella C, Gaudio A, Basile G, et al. Pain in osteoporosis: from pathophysiology to therapeutic approach. Drugs & Aging. 2017 Oct 1; 34(10):755–65.

85. Lauriola M, Tomai M, Palma R, La Spina G, Foglia A, Panetta C, et al. Intolerance of uncertainty and anxiety-related dispositions predict pain during upper endoscopy. Frontiers in Psychology. 2019; 10:1112. https://doi.org/10.3389/fpsyg.2019.01112 PMID: 31156518

86. Fiegl S, Lahmann C, O'Rourke T, Probst T, Pieh C. Depression according to ICD-10 clinical interview vs. depression according to the Epidemiologic Studies Depression Scale to predict pain therapy outcomes. Frontiers in Psychology. 2019; 10:1862. https://doi.org/10.3389/fpsyg.2019.01862 PMID: 31481912

87. Di Giuseppe M, Ciacchini R, Micheloni T, Bertolucci I, Marchi L, Conversano C. Defense mechanisms in cancer patients: A systematic review. Journal of psychosomatic research. 2018 Dec 1; 115:76–86. https://doi.org/10.1016/j.jpsychores.2018.10.016 PMID: 30470322

88. Di Giuseppe M, Ciacchini R, Piarulli A, Nepa G, Conversano C. Mindfulness dispositions and defense style as positive responses to psychological distress in oncology professionals. European Journal of Oncology Nursing. 2019 Jun 1; 40:104–10. https://doi.org/10.1016/j.ejon.2019.04.003 PMID: 31229199

89. Martino G, Catalano A, Bellone F, Langher V, Lasco C, Penna A, et al. Quality of life in postmenopausal women: which role for vitamin D?. Mediterranean Journal of Clinical Psychology. 2018 Aug 21; 6(2).

90. Husemoen LL, Ebstrup JF, Mortensen EL, Schwarz P, Skaaby T, Thuesen BH, et al. Serum 25-hydroxyvitamin D and self-reported mental health status in adult Danes. European Journal of Clinical Nutrition. 2016 Jan; 70(1):78. https://doi.org/10.1038/ejcn.2015.129 PMID: 26264349