Maturitas 191 (2025) 108143

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Menopausal symptoms in breast cancer survivors on adjuvant endocrine therapy compared with those of menopausal women

Giorgia Asinaro [a,b,1], Claudia Massarotti [a,b,1], Anjeza Xholli [a], Ambrogio P. Londero [b,c], Matteo Lambertini [d,e], Paola Anserini [a], Lucia Del Mastro [d,e], Angelo Cagnacci [a,*]

[a] IRCCS Ospedale Policlinico San Martino, Largo R. Benzi 5, 16132 Genoa, Italy
[b] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DINOGMI Department), University of Genoa, Largo R. Benzi 5, 16132 Genoa, Italy
[c] Obstetrics and Gynecology Unit, IRCCS Istituto Giannina Gaslini, via G. Gaslini 5, 16147 Genoa, Italy
[d] Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genoa, Largo R. Benzi 5, 16132 Genoa, Italy
[e] Department of Medical Oncology, UO Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi 5, 16132 Genoa, Italy

ARTICLE INFO

Keywords:
Breast cancer
Aromatase inhibitors
Tamoxifen
Endocrine adjuvant therapy
Menopause symptoms
Hot flushes
Depression
Anxiety

ABSTRACT

Objectives: To compare menopausal symptoms of breast cancer survivors on adjuvant endocrine therapy with those of menopausal women.
Study design: In a retrospective nested case-control study menopausal symptoms were compared of breast cancer survivors in pre-, peri- or post-menopause at the time of diagnosis, on tamoxifen or an aromatase inhibitor, plus a gonadotrophin-releasing hormone analogue, if pre- or peri-menopausal, and age-matched control women either in the late peri-menopause, or in surgical or in physiological post-menopause on no hormone replacement therapy. Differences between women on tamoxifen and those on aromatase inhibitors were also evaluated. Weighted and non-weighted *t*-tests, chi-square tests, and linear or logistic regressions were applied as appropriate.
Main outcome measures: Score on the Greene's Climacteric Scale and so of its subscales evaluating vasomotor, anxiety, depression, somatisation and sexuality symptoms.
Results: A total of 99 breast cancer survivors (45 on tamoxifen, 54 on aromatase inhibitors) and 554 controls (173 in late perimenopause, 353 in natural and 28 in surgical menopause) were enrolled. The score on the Greene's Climacteric Scale was similar in cases and controls (means ± standard deviation) (21.3 ± 10.4 vs. 22.8 ± 11.5, $p = 0.199$), as were the subscale scores for vasomotor symptoms, anxiety, and somatisation. The depression score was lower (4.63 ± 3.3 vs. 5.98 ± 3.8; $p = 0.001$) in breast cancer survivors on adjuvant endocrine therapy, mainly due to a lower score of −2.132 (95 % confidence interval − 3.858/−0.407; $p = 0.016$) for users of aromatase inhibitors. The sexuality score was higher (1.76 ± 1.1 vs. 1.50 ± 1.1, $p = 0.011$) than in controls. Differences remained significant when corrected for age, menarche, body mass index, menopausal status (peri- or post-), type of menopause (natural, surgical), use of gonadotrophin-releasing hormone analogues, years of amenorrhea, smoking, alcohol use, and for breast radiotherapy, chemotherapy, tamoxifen or aromatase inhibitors. Among breast cancer survivors, women on aromatase inhibitors had lower scores for anxiety (5.75 ± 2.5vs.5.75 ± 2.5; $p = 0.045$) and depression (3.89 ± 2.5 vs. 5.13 ± 3.6; $p = 0.046$) than women on tamoxifen.
Conclusions: In breast cancer survivors, adjuvant therapy induces symptoms similar in type and intensity to those of symptomatic menopausal women. Compared with menopausal women, breast cancer survivors, particularly those on aromatase inhibitors, appear to experience less severe depressive symptoms.

* Corresponding author at: Academic Unit of Obstetrics and Gynecology, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi, 5, 16132 Genoa, Italy.
E-mail address: angelo.cagnacci@unige.it (A. Cagnacci).
[1] GA and CM share first authorship.

https://doi.org/10.1016/j.maturitas.2024.108143
Received 29 April 2024; Received in revised form 23 September 2024; Accepted 27 October 2024
Available online 30 October 2024

1. Introduction

1.1. Background

Female breast cancer is the leading global cancer in women, registering an estimated 2.3 million new cases for the year 2020 and constituting 11.7 % of all cancer diagnoses [1]. Over the past decades, treatment of hormone receptor-positive breast cancer of postmenopausal women has mainly switched from use of tamoxifen to a preference for an aromatase inhibitor (AI). Thereafter in premenopausal women adjuvant therapy have switched to suppression of ovarian activity by a Gonadotrophin Releasing Hormone (GnRH) analogue associated with either tamoxifen or AI [2,3]. AI reduces circulating estradiol to levels that are much lower than those of the natural menopause, by inhibiting testosterone conversion to estrogens in extra-gonadal tissue [4]. The related adverse effects of adjuvant endocrine therapy lead to hypoestrogenic side effects and therapy interruption up to 30–35 % of cases [5–7]. Women on tamoxifen report more vasomotor symptoms, than those on AI, and this effect is particularly evident in premenopausal women [2,8–10]. Women on AI report more genitourinary symptoms, a greater loss of sexual interest, of being aroused, a higher prevalence of arthralgia and a greater likelihood of therapy discontinuation [2,5,11]. The condition created by adjuvant therapy is likely different by natural menopause or even ovariectomy, for its rapid onset due to drug administration, for the inhibition of extragonadal sources of estrogen by AI, or for the pharmacological blockade of estrogen receptors, by tamoxifen. Symptoms should develop more rapidly and with a higher intensity than in natural conditions. Yet no specific study has investigated this issue. Many data have linked the presence and the severity of menopausal symptoms with long-term negative cardiovascular, bone and cognitive consequences [12–14]. Thus, in breast cancer survivors eventual more severe menopausal symptoms may indicate a higher risk of long-term non-oncological consequences, to be considered in patients' management and counselling [15,16].

1.2. Objectives

The aim of the present study was to compare the severity of menopausal symptoms, evaluated by the Greene's Climacteric Scale, of symptomatic breast cancer survivors on adjuvant endocrine therapy and symptomatic menopausal women.

2. Methods

2.1. Subjects

Women were evaluated during their initial visit at the outpatient service for menopause between January 2020 and December 2023. Patients with breast cancer were referred to our outpatient service of a university hospital by their treating oncologists (our service is regional referral center) for a long-term gynecologic follow up, as a part of a larger oncofertility collaborative project [17]. Eligibility criteria for breast cancer survivors were to be on treatment with tamoxifen or AI, and not having changed the treatment since its beginning. In addition, all women that at time of adjuvant therapy, were in premenopause (regular menstrual cycles) or in perimenopause (FSH values above 25 IU/L and irregular menstrual cycle with an interval between cycles >60 days at least once in the last year), accordingly to the STRAW criteria [18] received concomitantly with tamoxifen or AI a GnRH analogue to induce a medical menopause (2,3). Exclusion criteria were incomplete hormonal suppression, i.e. pre- or peri-menopausal patients not receiving a GnRH-analogue, or not in amenorrhea. Utilization of treatments for climacteric symptoms was an additional exclusion criterium.

The control group was made by the women in the late perimenopausal period, in the early menopause and in surgical menopause (bilateral ovariectomy), not receiving menopausal hormonal therapies or non-hormonal therapies for the treatment of climacteric symptoms. Women in pre-menopause, hysterectomized but with ovarian conservation and with an unclear determination of menopausal stage were not included in the analysis. Among cases and controls women with insufficient comprehension of the Italian language to complete the questionnaire and women with symptoms of fibromyalgia, autoimmune disease, chronic fatigue and psychiatric disorders were excluded.

2.2. Study design

A nested case-control study was performed within a well-defined cohort of women breast cancer survivors and non-breast cancer survivors. A random selection process was used to choose seven matched controls for each case based on age categories. The age categories were determined through a discretization process that divided the entire range of age into three intervals of equal width. Moreover, this subdivision was in accordance with the local distribution of premenopausal status ages under 44 years, menopausal age between 44 and 59 years, and advanced postmenopausal age, i.e., over 59 years of age. The selection of controls was weighted to ensure proper representation across the defined age strata.

All patients provided an informed consent for the use of their anonymized data for clinical research and the regional ethics committee approved data publication (n. 484/21) The manuscript was prepared according to the STROBE guidelines. At time of initial evaluation data of each woman of our outpatient service were collected and saved in an electronic database for subsequent scientific analyses.

2.3. Data collection

For each woman demographic and clinical data were collected, including detailed gynecologic and oncologic history. The following parameters were collected: age, age at menarche, menopausal status (peri- or post-), type of menopause (natural, surgical), being a breast cancer survivor (yes or not), years of amenorrhea (years since menopause or initiation of GnRH analogue), smoking habit, use of alcoholic beverages, body mass index (BMI) (kg/m^2) and for breast cancer survivors use of radiotherapy, chemotherapy, tamoxifen or AI and GnRH analogue.

During the visit, patients were asked to complete the Greene's Climacteric Scale questionnaire. The questionnaire comprises 21 items. Items 1 to 11 evaluate psychological symptoms and in particular items 1 to 6 evaluate anxiety symptoms, and items 7 to 11 depressive symptoms. Items 12 to 18 evaluate somatic symptoms, items 19 and 20 evaluate vasomotor symptoms and item 21 is a probe for sexual dysfunction. Each item requires choosing an option between "not at all" (0), "a little" (1), "quite a bit" (2), or "extremely" (3). The scores of each item were then added up to obtain the total Greene's Climacteric Scale total score, where a higher score indicates more intense and bothersome menopausal symptoms.

2.4. Sample size

The primary outcome of the study was to compare the score of Greene's Climacteric scale between breast cancer survivors on adjuvant endocrine therapy and controls. Secondary outcome was to explore differences among women treated with tamoxifen and AI.

The sample size for the nested case-control study was determined on the primary outcome through a preliminary analysis of the original cohort, with the intention of enabling multivariate analysis. There is no published studies comparing the Greene's Climacteric Scale score of breast cancer survivors and control. Yet by evaluating literature [20–23] data involving breast cancer survivors with different scales and Greene's questionary subscales it was observed a median effect size (d) of 0.5 that corresponds to the Cohen's moderate effect size. Accordingly, the primary outcome of our study is a continuous numerical value, and we have

assumed that the effect size (d) is 0.5. The alpha level was set at 0.001 and the power (1-β) at 0.9, assuming a two-sided alternative hypothesis. The calculation was conducted using an initial sample size of 99 cases. Based on the power analysis, it was determined that we would require around 568 controls to attain the desired level of statistical power. To compensate for missing values and guarantee adequate statistical power, we increased this figure by 20 %, yielding a total sample size of 682 control subjects. The outcome of this calculation indicates a ratio of approximately 7 controls for every case. The total number of controls after extraction was 544 because of the weighted selection to ensure proper representation across the defined age strata, that increased the weight of specific less represented controls. The weights were derived as the inverse probability of being included in the sample, conditional on the group (cases vs. controls) and matched variables.

2.5. Statistical analysis

The population was initially characterized based on the primary attributes of the subjects. The presentation of continuous variables included their means and standard deviations, while categorical variables were expressed as percentages. A weighted two-tailed Student's *t*-test was used to compare continuous data, while the weighted chi-square test was employed to compare frequencies. The Greene's scale and subscales scores were adjusted through weighted multiple regression analysis, considering patient age, age at menarche, BMI, case or control status, length of time in amenorrhea, smoking habits, consumption of alcoholic beverages, and use of tamoxifen, AI, or GnRH analogue. Only the variables with a *p*-value below 0.100 were included in the multivariate analysis. For the sexuality subscale a weighted logistic regression was used. The sexuality scale was categorized through a discretization process that divided the entire range into intervals of equal width (score 0–1 and score 2–3). A sensitivity analysis was performed considering only women in natural post-menopause.

When analyzing only the group of individuals who have survived breast cancer, we also considered other factors that could affect the results, such as the use of radiotherapy and chemotherapy. In this case comparison were performed by the Student's *t*-test and by the chi squared test, for continuous data and frequencies, respectively, and by multiple linear regression analysis. The statistical software R (version 4.4.1) was used for all analyses and sample size assessment [19]. Before conducting statistical analysis, normality distribution of data was assessed by the Kolmogorov-Smirnov test. A significance level of $p < 0.05$ was deemed to have statistical significance. Continuous data were reported as mean ± standard deviation (SD).

3. Results

3.1. Participants

A total of 99 breast cancer survivors on adjuvant endocrine therapy and 554 controls were included. Among cases, 75 (75.8 %) had previously received chemotherapy, and at time of investigation, 45 (45.5 %) were on tamoxifen and 54 (54.5 %) on AI. Adjuvant endocrine therapy was initiated 4.7 ± 2.4 months after surgery. All patients with breast cancer who were premenopausal at the time of the diagnosis were also receiving a GnRH analogue ($n = 58$, of which 25 on tamoxifen and 37 on AI). Control women were either in the late perimenopause ($n = 173$, 31.2 %), in surgical ($n = 28$, 5.1 %) or in physiological ($n = 353$, 63.7 %) post-menopause.

Table 1 reports demographic and clinical data of the study population. Cases were younger (48.6 ± 9.1 vs. 51.8 ± 6.4 yrs., $p = 0.001$), with an earlier menarche (12.0 ± 0.4 vs. 12.5 ± 1.5 yrs.; p = 0.001) and for a shorter time in amenorrhea, suggesting a shorter time of low estrogen exposure (2.4 ± 4.9 vs. 3.9 ± 5.4 yrs.; 0.001).

Table 1
Demographic and clinical data of all women included in the study.

	Breast cancer (n = 99)	Control (n = 554)	P value (Breast cancer vs. control)	AI ± GnRHa	Tam ± GnRHa	P value (AI vs. Tam)
Age (yrs.)	48.6 ± 9.1	51.8 ± 6.4	**0.001**	46.9 ± 8.5	54.3 ± 8.5	**0.001**
Age at menarche (yrs.)	12.0 ± 0.4	12.5 ± 1.5	**0.001**	12.5 ± 2.8	12.1 ± 1.5	0.458
Length of amenorrhea (yrs.)	2.4 ± 4.9	3.9 ± 5.4	**0.001**	3.1 ± 9.9	5.20 ± 4.8	**0.015**
BMI (kg/m^2)	25.6 ± 3.9	26.1 ± 4.7	0.153	23.2 ± 3.6	22.9 ± 4.0	0.748
Smokers, n. (%)	0 (0)	166 (30.0)	**0.001**	0	0	/
Alcohol users, n. (%).	0 (0)	14 (2.5)	0.315	0	0	/
Greene total score	21.3 ± 10.4	22.8 ± 11.5	0.199	19.5 ± 7.5	22.3 ± 12.2	0.155
Vasomotor score	2.77 ± 2.0	2.93 ± 2.1	0.538	2.89 ± 1.9	2.58 ± 2.0	0.509
Anxiety score	6.47 ± 3.4	6.64 ± 3.9	0.656	5.75 ± 2.5	7.06 ± 4.0	**0.045**
Depression score	4.63 ± 3.3	5.98 ± 3.8	**0.001**	3.89 ± 2.5	5.13 ± 3.6	**0.046**
Somatization score	5.63 ± 3.9	5.78 ± 4.1	0.713	5.16 ± 3.2	5.89 ± 4.4	0.345
Sexuality score	1.76 ± 1.1	1.50 ± 1.1	**0.011**	1.83 ± 1.0	1.65 ± 1.1	0.400

AI: aromatase inhibitor; Tam: tamoxifen; GnRHa: GnRH analogue.
Notes: The values reported in the cells refer to mean ± standard deviation or absolute value and (percentage).
Comparison reaching a statistical significance are reported in bold.

3.2. Main results

The Greene's Climacteric Scale score was similar in cases and controls (Table 1) along with the score of vasomotor, anxiety and somatization subscales (Table 1). The sexuality score was higher ($p = 0.011$), while the depression score was significantly lower ($p = 0.001$) in cases than controls.

When all the data were entered into a weighted multiple regression model, breast cancer, chemotherapy and radiotherapy, and the related endocrine therapies (GnRH-analogue, tamoxifen, AI), were not significantly related to the Greene's climacteric scale score. Being a smoker was associated with a higher (worse) Greene's Climacteric scale score (Table 2).

The analyses of the Greene's sub-scale indicated that depression had a lower (better) score ($p = 0.001$) in breast cancer survivors than in controls (Table 1). Upon multiple regression analysis, use of AI was independently associated with a lower depression score of −2.132 (95 % Confidence Interval (CI) −3.858/−0.407; $p = 0.016$) (Table 2). The sexuality score was higher in breast cancer survivors than in controls ($p = 0.011$). This was mainly due to length of amenorrhea ($p = 0.001$) and the use of a GnRH-analogue (p = 0.001) (Table 2).

A sensitivity analysis was performed including only women in natural menopause as controls (mean age 54.5 ± 3). The Greene's Climacteric Scale score (22.29 ± 10.9) and the subscale scores of vasomotor (3.18 ± 2.1), anxiety (6.38 ± 3.8), and somatization (5.52 ± 3.8) were not different from the scores observed in breast cancer survivors on adjuvant endocrine therapy. Depression score (5.47 ± 3.7) remained significantly higher ($p = 0.013$) in controls than in breast cancer survivors. Upon multiple regression analysis, use of AI was independently associated with a lower depression score of −1.586 (95 % Confidence Interval (CI) −2.923/−0.249; $p = 0.02$). The sexuality score of controls was no more significantly different from that of breast cancer

Table 2
Analysis by weighted multiple linear regression or multiple logistic regression (*) of factors independently related to the score of the Greene's climacteric scale and of its vasomotor, anxiety, depression, somatization and sexuality sub-scales.

Variables	CR	95 % CI	P value
Greene *R2 0.01; p = 0.042*			
Smoking (y/n)	2.016	0.075/3.956	0.042
Vasomotor *R2 0.02; p = 0.001*			
Smoking (y/n)	0.585	0.235/0.936	0.001
Perimenopause (y/n)	−0.377	−0.725/−0.029	0.034
Anxiety *R2 0.001; p = 0.11*			
No factor independently related			
Depression R2 0.03; p = 0.001			
Age (yrs.)	−0.061	−0.106/−0.015	0.009
BMI (kg/m^2)	0.078	0.016/0.14	0.013
Aromatase Inhibitors (y/n)	−2.132	−3.858/−0.407	0.016
Somatization *R2 0.01; p = 0.097*			
No factor independently related			
Sexuality (0–1 reference vs. 2–3) *R2 0.016* (*)			
Length of amenorrhea (yrs.)	1.05	1.03/1.07	0.001
GnRH-analogue (y/n)	2.55	1.44/4.49	0.001

CR: Coefficient of regression; CI: Confidence Interval. OR: Odds Ratio.
R2 is the R-squared the extent of the factor variation induced by the model, and the associated p value refers to the F-statistic p-value and shows the whole model's statistical significance.
Considered factors were breast cancer survivor (y/n), age (yrs.), smoking habit (y/n), use of alcohol (y/n), BMI (kg/m^2), age at menarche (yrs.), type of menopause: (natural (y/n), surgical (y/n), GnRH-analogue induced (y/n) or perimenopause (y/n), age at menopause (yrs.), chemotherapy (y/n) or radiotherapy (y/n) for breast cancer, use of aromatase inhibitors (y/n) or tamoxifen (y/n) after breast cancer, years in amenorrhea (yrs.) after either menopause or adjuvant endocrine therapy.

survivors on adjuvant therapy (1.75 ± 1.06 vs. 1.80 ± 1.07; $p = 0.799$).

3.3. AI and tamoxifen in breast cancer survivors

Women on AI were younger (46.9 ± 8.5 vs. 54.3 ± 8.5 yrs.; $p = 0.001$) and with less years in amenorrhea (3.1 ± 9.9 vs. 5.2 ± 4.8 yrs.; $p = 0.015$) than women on tamoxifen (Table 1). The Greene's Climacteric scale score, and the score of the vasomotor, somatic and sexuality subscales were similar in the two groups (Table 1). The score of anxiety (5.75 ± 2.50 vs. 7.06 ± 4.04, $p = 0.045$) and depression (3.89 ± 2.54 vs. 5.13 ± 3.56, $p = 0.046$) was lower in women on AI than on tamoxifen (Table 1). When corrected for confounding, including the use of GnRH analogues the Greene's climacteric scale score, and the scores of the somatic, vasomotor and sexuality subscales were not different between women on AI and tamoxifen. The use of AI remained significantly related to a lower score of anxiety (CR-1.367, 95%CI −2.69/−0.04; $p = 0.044$), but not of depression (CR-1.22, 95%CI −2.45/0.009; $p = 0.052$). The use of the GnRH analogue was not independently related to the Greene's Climacteric Scale score or to its subscales.

4. Discussion

4.1. Key results

Present results indicate that the total Greene's scale score and its vasomotor subscale do not exhibit any significant difference between breast cancer survivors on adjuvant endocrine therapy and women in late perimenopause, natural or surgical post-menopause. The data are also not influenced by the use of chemotherapy, radiotherapy or GnRH analogues. This implies that the suppression of the hormonal signal associated with breast cancer therapies induces symptoms comparable to those experienced by women with symptomatic menopause, even if in breast cancer patients the increase of vasomotor symptoms is more rapid and almost concomitant with the initiation of the adjuvant endocrine therapy [7]. Depressive symptoms appeared less bothersome in women with breast cancer than in healthy menopausal women. The burden of depressive symptoms in breast cancer survivors is unclear. It was hypothesized that because of the estrogen decline, depressive symptoms are more prevalent after breast cancer than after other types of tumours [24]. A high prevalence of depression after breast cancer was reported in studies that lacked a control group [25–27], using healthy non-menopausal women as controls [20], or in which survivors from breast cancer were mixed with survivors from other gynecologic cancers [27]. Vice-versa other uncontrolled studies indicated that breast cancer survivors do not suffer from depression but mainly from anxiety due to the psychological distress of having the disease [28] particularly when it is metastatic [29]. Higher levels of anxiety and lower levels of depression were also reported in survivors from different types of tumours, among which breast cancer, in comparison to healthy men and women [22].

In our study the burden of depression was lower in breast cancer survivors on adjuvant endocrine therapy than in control women. Breast cancer survivors were younger than controls, but controlling for age did not change the result. Thus, a difference between the two conditions can be suggested. In rats, some GnRH analogues showed anxiolytic and antidepressant effects [30]. However, in our analysis, the use of the GnRH analogue did not impact on the depression or anxiety scores.

Only the use of AI was associated with less depressive symptoms, while women on tamoxifen showed depressive and anxiety symptoms like those of healthy menopausal women. It is noteworthy that some AI, especially exemestane and its metabolites, have mild androgenic properties [31]. Yet in premenopausal women higher circulating androgens were associated with worse depressive symptoms. This did not apply to hypoestrogenic women. Thus, the role of androgens with different estrogen milieu is not fully elucidated and would require additional studies. Vice-versa, the negative impact of BMI on depressive symptoms, herein observed, confirm previous associations found in pre- and post-menopausal women [32]. The estrogenic/antiestrogenic effect of tamoxifen, on the brain is still unclear [33]. Decreased cognitive functions, of areas rich of estrogen receptors, such as the hippocampus and the frontal lobes, were observed during tamoxifen [34,35], and anxiety and depression-like behaviours were documented in animal treated with tamoxifen [36]. In the TEXT study, administration to young premenopausal women of AI associated with a GnRH agonist did not induce depressive symptoms different from tamoxifen given alone or in association with a GnRH analogue [3]. The different experimental protocol and the different scales used to evaluate mood states can probably explain the different results obtained in our study.

The sexuality score was higher in breast cancer survivors. More years in amenorrhea and the use of GnRH analogues contributed to increase (worsen) the score. Notably, GnRH analogues were used in younger individuals, that probably perceived these symptoms as more debilitating. Indeed, the sexuality score of breast cancer survivors was not any more different from controls when only women after menopause were used in the sensitivity analysis.

4.2. Strength and limitations

The strength of this study lies in the use of a validated questionnaire for menopausal symptoms administered in a gynecologic outpatient service. It has been reported that women under-report adverse effects of adjuvant endocrine therapy when investigated in an oncological setting [5]. The symptoms of breast cancer survivors on adjuvant endocrine therapy were compared with those of women in different menopausal conditions because the trajectory of menopausal symptoms encompass the *peri* and the postmenopausal period. Yet the sensitivity analysis restricted only to control women in natural menopause mostly confirmed the data obtained in the entire group of control women. Prospective case-control studies are warranted to further evaluate this topic. Measurement of symptoms at a single time point, limited the evaluation of their trajectory on time and may have reduced the

possibility to find differences among groups. The analysis was corrected by years in amenorrhea. The length of time in amenorrhea did not influence the results, except for the sexuality score, that increased with time. Prospective studies should be set to have a better evaluation of these issues. Similarly, a better definition of circulating estrogens in breast cancer survivors and menopausal women would better clarify eventual differences between the groups. At the time of data collection no one of the cancer survivors included was using psycho-oncological counselling, but a psycho-oncological support was indeed offered at the time of breast cancer diagnosis and during chemotherapy. While we cannot exclude that it could have been a source of empowerment that resulted in lower depression rates later, we must note that women came to our attention at a mean of 3.59 ± 3.7 years after the start of adjuvant endocrine therapy, when they were back to their regular life and work. Moreover, this possible confounding does not explain the different results in women observed with AI and tamoxifen. Yet dedicated studies are necessary to further address the impact that a psychological support may have on long-term menopausal, psychological symptoms and quality of life of these women. The study was not designed to test symptoms prevalence in the two populations. It is known that many menopausal women do not suffer from bothersome symptoms, and women attending our services may be those with the most intense symptomatology. Yet the present study indicates that when symptoms are present, they appear, on average, to be similar in menopausal women and in breast cancer survivors on adjuvant endocrine therapy. We found that several different factors may influence the intensity of menopausal symptoms evaluated by the Greene's Scales and its subscales, but the analysis indicates that these factors can only slightly modulate the intensity of menopausal symptoms. Yet being a breast cancer survivor, as well as the use of adjuvant therapy, are not among these subtle modulators. We made the comparisons considering the Greene's Climacteric Scale and its defined subscales. Accordingly, we cannot define whether single items of the scale for example that evaluating arthralgia are different between cases and controls.

4.3. Generalizability

The study was performed in a single center on white women. The results cannot be completely applied to other setting or women of different ethnic groups. There are several methods to test menopausal symptoms and mood. We used the Greene's climacteric scale that gives an overall evaluation of menopausal symptoms [37], but it cannot be excluded that more specific and detailed instruments may achieve different results exploring different aspects of brain function.

4.4. Conclusions

Estrogen deprivation consequent to adjuvant endocrine therapy for breast cancer produces symptoms like those lamented by menopausal women. Gaining a more comprehensive understanding of the specific adverse effects encountered by breast cancer survivors on modern adjuvant endocrine therapy and their influence on overall quality of life is crucial. This knowledge will not only steer research but also inform clinical practice, aiming to enhance treatment adherence and achieve the highest possible quality of life throughout the treatment course.

Contributors

All authors contributed the conception and design of the study, and/or acquisition of data, and/or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content. All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Funding

No specific grant from funding agencies in the public, commercial, or not-for-profit sectors supported the publication of this study.

Ethical approval

This study was approved by IRB Regione Liguria (n. 484/21).

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Data sharing and collaboration

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

M. Lambertini reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Gilead; travel Grants from Gilead, Daiichi Sankyo, Roche; research funding (to the Institution) from Gilead all outside the submitted work. Prof. Lucia L. Del Mastro reports advisory role and/or speaker honoraria for Roche, Eli Lilly, Novartis, Pfizer, Pierre Fabre, Eisai, Gilead, Astrazeneca, Daiichi Sankyio, Gilead, Exact sciences, Agendia, Menarini Stemline, Olema, Ipsen, MSD; travel grants from Gilead, daiichi Sankyo, Astrazeneca, Roche; research funding (to the institution) from Pfizer, all outside the submitted work. The other authors declare no conflict of interest with the content of the present article.

Acknowledgements

We thank Marta Fiamberti, Valentina Musante and Beatrice Marchese for their contribution in patient management. Matteo Lambertini acknowledges the support by the Italian Association for Cancer Research Italian Association for Cancer Research ("Associazione Italiana per la Ricerca sul Cancro", AIRC; MFAG 2020 ID 24698) for pursuing his research efforts in the field of breast cancer in young women.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.

[2] J. Bernhard, W. Luo, K. Ribi, M. Colleoni, H.J. Burstein, C. Tondini, G. Pinotti, S. Spazzapan, T. Ruhstaller, F. Puglisi, L. Pavesi, V. Parmar, M.M. Regan, O. Pagani, G.F. Fleming, P.A. Francis, K.N. Price, A.S. Coates, R.D. Gelber, A. Goldhirsch, B. A. Walley, Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials, Lancet Oncol. 16 (2015) 848–858, https://doi.org/10.1016/S1470-2045(15)00049-2.

[3] P.A. Francis, O. Pagani, G.F. Fleming, B.A. Walley, M. Colleoni, I. Láng, H. L. Gómez, C. Tondini, E. Ciruelos, H.J. Burstein, H.R. Bonnefoi, M. Bellet, S. Martino, C.E. Geyer Jr., M.P. Goetz, V. Stearns, G. Pinotti, F. Puglisi, S. Spazzapan, M.A. Climent, L. Pavesi, T. Ruhstaller, N.E. Davidson, R. Coleman, M. Debled, S. Buchholz, J.N. Ingle, E.P. Winer, R. Maibach, M. Rabaglio-Poretti, B. Ruepp, A. Di Leo, A.S. Coates, R.D. Gelber, A. Goldhirsch, M.M. Regan, SOFT and TEXT investigators and the international breast Cancer study group. Tailoring adjuvant endocrine therapy for premenopausal breast Cancer, N. Engl. J. Med. 379 (2018) 122–137, https://doi.org/10.1056/NEJMoa1803164.

[4] E.J. Folkerd, P.E. Lønning, M. Dowsett, Interpreting plasma estrogen levels in breast cancer: caution needed, J. Clin. Oncol. 32 (2014) 1396–1400, https://doi.org/10.1200/JCO.2013.53.9411.

[5] K.L. Smith, N. Verma, A.L. Blackford, J. Lehman, K. Westbrook, D. Lim, J. Fetting, A.C. Wolff, D. Jelovac, R.S. Miller, R. Connolly, D.K. Armstrong, R. Nunes, K. Visvanathan, C. Riley, K. Papathakis, N. Zafman, J.Y. Sheng, C. Snyder, V. Stearns, Association of treatment-emergent symptoms identified by patient-

reported outcomes with adjuvant endocrine therapy discontinuation, NPJ Breast Cancer. 8 (2022) 53, https://doi.org/10.1038/s41523-022-00414-0.
[6] N. Camejo, C. Castillo, C. Tambasco, N. Strazzarino, N. Requena, S. Peraza, A. Boronat, G. Herrera, P. Esperon, M. Cuello, G. Krygier, Assessing adherence to adjuvant hormone therapy in breast Cancer patients in routine clinical practice, World. J. Oncol. 14 (2023) 300–308, https://doi.org/10.14740/wjon1647.
[7] F. Balazard, A. Bertaut, É. Bordet, S. Mulard, J. Blanc, N. Briot, et al., Adjuvant endocrine therapy uptake, toxicity, quality of life, and prediction of early discontinuation, J. Natl. Cancer Inst. 12 (2023) djad109, https://doi.org/10.1093/jnci/djad109.
[8] N. Biglia, M. Cozzarella, F. Cacciari, R. Ponzone, R. Roagna, F. Maggiorotto, P. Sismondi, Menopause after breast cancer: a survey on breast cancer survivors, Maturitas 45 (2003) 29–38, https://doi.org/10.1016/s0378-5122(03)00087-2.
[9] E.B. Gold, S.L. Crawford, K. Leung, G. Greendale, K.W. Reeves, H. Joffe, N.E. Avis, Vasomotor symptoms in midlife women with incident breast cancer: pink SWAN, Breast Cancer Res. Treat. 191 (2022) 125–135, https://doi.org/10.1007/s10549-021-06425-y.
[10] P.F. Harris, P.L. Remington, A. Trentham-Dietz, C.I. Allen, P.A. Newcomb, Prevalence and treatment of menopausal symptoms among breast cancer survivors, J. Pain Symptom Manage. 23 (2002) 501–509, https://doi.org/10.1016/s0885-3924(02)00395-0.
[11] J. Baumgart, K. Nilsson, A. Stavreus-Evers, K. Kask, K. Villman, H. Lindman, T. Kallak, I. Sundström-Poromaa, Urogenital disorders in women with adjuvant endocrine therapy after early breast cancer, Am. J. Obstet. Gynecol. 204 (26) (2011) e1–e7, https://doi.org/10.1016/j.ajog.2010.08.035.
[12] N. Biglia, A. Cagnacci, M. Gambacciani, S. Lello, S. Maffei, R.E. Nappi, Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases? Climacteric 20 (2017) 306–312, https://doi.org/10.1080/13697137.2017.1315089.
[13] E.L. Yong, S. Logan, Menopausal osteoporosis: screening, prevention and treatment, Singapore Med. J. 62 (2021) 159–166, https://doi.org/10.11622/smedj.2021036.
[14] M. Sochocka, J. Karska, M. Pszczołowska, M. Ochnik, M. Fułek, K. Fułek, D. Kurpas, J. Chojdak-Łukasiewicz, A. Rosner-Tenerowicz, J. Leszek, Cognitive decline in early and premature menopause, Int. J. Mol. Sci. 31 (24) (2023) 6566, https://doi.org/10.3390/ijms24076566.
[15] S. Lello, I. Paris, A. Cagnacci, D. Sartori, S. Caruso, A. Iop, Vasomotor symptoms and management of women undergoing treatment for breast cancer: literature review with focus on the therapeutic potential of cytoplasmic pollen extract, Gynecol. Endocrinol. 39 (2023) 2162035, https://doi.org/10.1080/09513590.2022.2162035.
[16] C. Massarotti, G. Asinaro, M.G. Schiaffino, C. Ronzini, I. Vacca, M. Lambertini, P. Anserini, L. Del Mastro, A. Cagnacci, Vaginal oxygen plus hyaluronic acid on genito-urinary symptoms of breast cancer survivors, Climacteric 26 (2023) 129–134, https://doi.org/10.1080/13697137.2023.2167596.
[17] C. Massarotti, P. Scaruffi, M. Lambertini, F. Sozzi, V. Remorgida, P. Anserini, Beyond fertility preservation: role of the oncofertility unit in the reproductive and gynecological follow-up of young cancer patients, Hum. Reprod. 34 (2019) 1462–1469, https://doi.org/10.1093/humrep/dez108.
[18] S.D. Harlow, M. Gass, J.E. Hall, R. Lobo, P. Maki, R.W. Rebar, S. Sherman, P. M. Sluss, T.J. de Villiers, STRAW + 10 collaborative group. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging, J. Clin. Endocrinol. Metab. 97 (2012) 1159–1168, https://doi.org/10.1210/jc.2011-3362.
[19] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, 2nd ed., L. Erlbaum Associates, Hillsdale, N.J, 1988.
[20] M. Fafouti, T. Paparrigopoulos, Y. Zervas, A. Rabavilas, N. Malamos, I. Liappas, C. Tzavara, Depression, anxiety and general psychopathology in breast cancer patients: a cross-sectional control study, In Vivo 24 (2010) 803–810.
[21] A. Hinz, E. Brähler, Normative values for the hospital anxiety and depression scale (HADS) in the general German population, J. Psychosom. Res. 71 (2011) 74–78, https://doi.org/10.1016/j.jpsychores.2011.01.005.
[22] L. Inhestern, V. Beierlein, J.C. Bultmann, B. Möller, G. Romer, U. Koch, C. Bergelt, Anxiety and depression in working-age cancer survivors: a register-based study, BMC Cancer 17 (2017) 347, https://doi.org/10.1186/s12885-017-3347-9.
[23] Y.-C. Chang, G.-M. Lin, T.-L. Yeh, Y.-M. Chang, C.-H. Yang, C. Lo, C.-Y. Yeh, W.-Y. Hu, Impact of mindfulness-based stress reduction on female sexual function and mental health in patients with breast cancer, Support. Care Cancer 30 (2022) 4315–4325, https://doi.org/10.1007/s00520-021-06540-y.
[24] J.R. Fann, A.M. Thomas-Rich, W.J. Katon, D. Cowley, M. Pepping, B.A. McGregor, J. Gralow, Major depression after breast cancer: a review of epidemiology and treatment, Gen. Hosp. Psychiatry 30 (2008) 112–126, https://doi.org/10.1016/j.genhosppsych.2007.10.008.
[25] C. Burgess, V. Cornelius, S. Love, J. Graham, M. Richards, A. Ramirez, Depression and anxiety in women with early breast cancer: five year observational cohort study, BMJ 330 (2005) 702, https://doi.org/10.1136/bmj.38343.670868.D3.
[26] K. Tsaras, I.V. Papathanasiou, D. Mitsi, A. Veneti, M. Kelesi, S. Zyga, E.C. Fradelos, Assessment of depression and anxiety in breast Cancer patients: prevalence and associated factors, Asian Pac. J. Cancer Prev. 19 (2018) 1661–1669, https://doi.org/10.22034/APJCP.2018.19.6.1661.
[27] K. Ell, K. Sanchez, B. Vourlekis, P.J. Lee, M. Dwight-Johnson, I. Lagomasino, L. Muderspach, C. Russell, Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer, J. Clin. Oncol. 23 (2005) 3052–3060, https://doi.org/10.1200/JCO.2005.08.041.
[28] Ng CG, Mohamed S, Kaur K, Sulaiman AH, Zainal NZ, Taib NA; MyBCC Study group, Perceived distress and its association with depression and anxiety in breast cancer patients, PloS One 12 (2017) e0172975, https://doi.org/10.1371/journal.pone.0172975.
[29] E.M. Park, S. Gelber, S.M. Rosenberg, D.S.E. Seah, L. Schapira, S.E. Come, A. H. Partridge, Anxiety and depression in young women with metastatic breast cancer: a cross-sectional study, Psychosomatics 59 (2018) 251–258, https://doi.org/10.1016/j.psym.2018.01.007.
[30] G. Telegdy, A. Adamik, M. Tanaka, A.V. Schally, Effects of the LHRH antagonist Cetrorelix on affective and cognitive functions in rats, Regul. Pept. 159 (2010) 142–147, https://doi.org/10.1016/j.regpep.2009.08.005.
[31] E.A. Ariazi, A. Leitão, T.I. Oprea, B. Chen, T. Louis, A.M. Bertucci, C.G. Sharma, S. D. Gill, H.R. Kim, H.A. Shupp, J.R. Pyle, A. Madrack, A.L. Donato, D. Cheng, J. R. Paige, V.C. Jordan, Exemestane's 17-hydroxylated metabolite exerts biological effects as an androgen, Mol. Cancer Ther. 6 (2007) 2817–2827, https://doi.org/10.1158/1535-7163.MCT-07-0327.
[32] D. Stanikova, R.G. Zsido, T. Luck, A. Pabst, C. Enzenbach, Y.J. Bae, J. Thiery, U. Ceglarek, C. Engel, K. Wirkner, J. Stanik, J. Kratzsch, A. Villringer, S.G. Riedel-Heller, J. Sacher, Testosterone imbalance may link depression and increased body weight in premenopausal women, Transl. Psychiatry 9 (2019) 160, https://doi.org/10.1038/s41398-019-0487-5.
[33] Riggs BL, Hartmann LC. Selective estrogen-receptor modulators – mechanisms of action and application to clinical practice. N Engl J Med. 2003; 348:618–29. doi: https://doi.org/10.1056/NEJMra022219. Erratum in: N. Engl. J. Med. 2003;348 (12):1192.
[34] X. Chen, X. He, L. Tao, J. Li, J. Wu, C. Zhu, F. Yu, L. Zhang, J. Zhang, B. Qiu, Y. Yu, K. Wang, The working memory and dorsolateral prefrontal-hippocampal functional connectivity changes in long-term survival breast Cancer patients treated with tamoxifen, Int. J. Neuropsychopharmacol. 20 (2017) 374–382, https://doi.org/10.1093/ijnp/pyx008.
[35] P.R. Lee Meeuw Kjoe, J.M. Kieffer, B.J. Small, W. Boogerd, C.M. Schilder, E. van der Wall, E. Meershoek-Klein Kranenbarg, C.J.H. van de Velde, S.B. Schagen, Effects of tamoxifen and exemestane on cognitive function in postmenopausal patients with breast cancer, JNCI Cancer Spectr. 7 (2023) pkad022, https://doi.org/10.1093/jncics/pkad022.
[36] H. Azizi-Malekabadi, M. Pourganji, H. Zabihi, M. Saeedjalali, M. Hosseini, Tamoxifen antagonizes the effects of ovarian hormones to induce anxiety and depression-like behavior in rats, Arq. Neuropsiquiatr. 73 (2015) 132–139, https://doi.org/10.1590/0004-282X20140221.
[37] J.G. Greene, Constructing a standard climacteric scale, Maturitas 29 (1998) 25–31, https://doi.org/10.1016/s0378-5122(98)00025-5.