European Journal of Oncology Nursing 52 (2021) 101953

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

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

Anxiety and depression after breast cancer: The predictive role of monoamine levels

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ARTICLE INFO

Keywords:
Breast cancer survivors
Depression
Anxiety
Age
Monoamines

ABSTRACT

Purpose: Despite the fact that the prevalence of anxiety and depression in breast cancer survivors is higher than in the general female population, the psychobiological substrate of this phenomenon has yet to be elucidated. We aimed to examine the predictive role of peripheral dopamine (DA), noradrenaline (NA), serotonin (5-HT) and kynurenine (KYN) in anxiety and depression among breast cancer survivors.
Method: We evaluated 107 women using the Hospital Anxiety and Depression Scale, and monoamine levels were analyzed via high-performance liquid chromatography.
Results: High *KYN* levels predicted both disorders, while low NA and DA predicted anxiety and depressive symptoms, respectively. A negative conditional effect of 5-HT was found for anxiety and depression among younger women only, while being both middle-aged and younger influenced the negative conditional effect of *DA* on depression.
Conclusion: Monoamine variations may render breast cancer survivors more vulnerable to anxiety and depression, with young women being especially vulnerable to the detrimental effect of low *DA* and *5-HT*. Assessing subclinical psychobiological markers allows mental health nurses to identify vulnerable survivors prior to the onset of anxiety and depression, and to adjust nursing interventions accordingly.

1. Introduction

With survival rates of over 85% at 5 years from diagnosis (Allemani et al., 2015), therapeutic efforts related to breast cancer are currently aimed not only at overcoming the disease, but also at preventing its burden during survivorship. Life changes derived from the disease, such as those in the personal, family and professional fields, may condition survivors' (in)adaptation to their new situation after medical discharge, leading to anxiety and depression, stress-related disorders that often co-occur and precede each other, especially in women (Rodgers et al., 2016). Furthermore, the prevalence of anxiety and depression is higher among breast cancer survivors than among women with no prior history of cancer (Carreira et al., 2018), and depression has been associated with a higher risk of cancer recurrence (Mallet et al., 2018; Smith, 2015).

As defined in the conceptual model developed by Callista Roy, adaptation is a positive response to internal or external stimuli, in which the individual switches on psychosocial and physiological mechanisms in order to promote personal integrity (Roy, 2009). However, when distress is too high, or biopsychosocial resources are not accurately managed in the face of chronic challenges, individual health is impacted, leading to a sub-clinical dysregulation state known as allostatic load (McEwen, 1998). If sustained over time, this cumulative effect may contribute to disease and senescence (Stewart, 2006).

According to the monoaminergic hypothesis of depression, the stress-induced deficiency of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in the synaptic cleft may lead to depressive symptoms, inasmuch as these neurotransmitters are involved in the regulation of emotions and cognition (Dremencov, 2014; Hirschfeld, 2000). A dysregulation in monoamine activity has also been observed in anxiety disorders, characterized mainly by serotonin depletion and noradrenergic hyperfunction (Curran and Chalasani, 2012; Yamamoto et al., 2014). Consequently, most currently available antidepressants and

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https://doi.org/10.1016/j.ejon.2021.101953
Received 26 November 2020; Received in revised form 18 March 2021; Accepted 21 March 2021
Available online 26 March 2021

anxiolytics are based on monoamine transporters or receptors, but the association between monoamines and anxiety and depressive symptoms is rather complex, and not all evidence supports the theory of monoamine depletion (Curran and Chalasani, 2012; Liu et al., 2017). For instance, serotonin and noradrenaline reuptake inhibitors take several weeks to take effect, and healthy subjects do not develop depression when serotonin concentrations in their synaptic cleft are lowered due to tryptophan depletion (Ruhe et al., 2007) or an increase in serotonin transporter (Kasper and McEwen, 2008). Long-term exposure to selective serotonin reuptake inhibitors (SSRIs) reduces anxiety, while acute exposure (first 2 weeks of treatment) is often accompanied by anxiety-inducing behavior (Grillon et al., 2007). For its part, the kynurenine (KYN) metabolic pathway has become increasingly relevant in the monoaminergic framework of anxiety and depression over recent years. The conversion of tryptophan (the primary amino acid precursor of serotonin) to KYN may reduce the availability of tryptophan for serotonin synthesis, and the KYN metabolism may also lead to the formation of neurotoxic products (Dantzer, 2017).

Despite the wide prevalence of anxiety and depression among breast cancer survivors, studies exploring the relationship between monoamine levels and such disorders in this population are scarce and inconclusive (Li et al., 2020). Pertl et al. (2013) found no association between depression and KYN levels either during cancer treatment or six weeks after finishing chemotherapy or radiation therapy. Conversely, Lyon et al. (2018) found that increased serum KYN levels were associated with depression after the last chemotherapy infusion among 19 individuals with breast cancer, while no associations were found regarding serotonin. Furthermore, the treatment of hot flushes in breast cancer survivors using the SSRI escitalopram and the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine hydrochloride was found to improve depressive symptoms (Biglia et al, 2005, 2018), although no monoamine levels were measured. In relation to anxiety, to our knowledge, only one study has been carried out with breast cancer patients, finding an increase in the proportion of kynurenine/tryptophan (Hüfner et al., 2015).

The clinical value of studying monoamine levels in breast cancer survivors lies not only in testing the monoaminergic hypothesis of depression in a vulnerable population, but also in the fact that such physiological indicators may signal overload early enough to enable a timely clinical response, thereby preventing adverse outcomes.

Thus, the aim of the present study was to explore the predictive role of plasma noradrenaline, serotonin, dopamine and kynurenine in anxiety and depression among breast cancer survivors.

2. Methods

A cross-sectional descriptive design was used to study the influence of some monoaminergic variables and age on anxiety and depressive symptoms.

Participants were 107 female breast cancer survivors recruited from the Onkologikoa Fundazioa Hospital by their oncologists and nurses in a biannual review. The inclusion criteria for this study were: (1) age 30–70 years; (2) having completed all active cancer treatments (surgery, chemotherapy, or/and radiotherapy) and (3) at least one year and no more than five years having elapsed since the end of the treatment. The exclusion criteria were: (a) women with metastases and (b) those with current medical conditions or medication that would affect inflammation. Medical treatments not affecting inflammation were allowed. Women who met the inclusion criteria were informed of the study procedures and those who agreed to participate received an informed consent form with enough time for due consideration. Next, participants were called in one morning for blood extraction and an individual psychological interview by a research clinician. Participants' written consent was obtained prior to any data collection. This work was carried out in accordance with the Declaration of Helsinki, and all procedures were approved by the Clinical Research Ethics Committee of the Basque Country and the Ethical Committee of the Basque Country University.

2.1. Psychological and physiological variables

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) is used to identify psychological distress in the hospital setting. This test is divided into two subscales: anxiety and depression. Responses to the 7 questions contained in each subscale are given on a 4-point Likert-type scale, which generates a total score for each subscale, ranging from 0 to 21. The reliability coefficient was 0.839 for anxiety symptoms and 0.777 for depressive symptoms.

Blood was collected in serum separator tubes (Vacutainer SST II Advance), centrifuged for serum acquisition, and stored at −80 °C. To determine the monoaminergic variables, dopamine (DA), noradrenaline (NA), serotonin (5-HT) and kynurenine (KYN) levels were analyzed using high-performance liquid chromatography (HPLC). The HPLC equipment comprised an Agilent 1200 LC system (Agilent Technologies, Madrid, Spain) equipped with a vacuum degasser, quaternary pump, cooled autosampler, thermostatted column compartment, and fluorescence and variable wavelength detectors. The chromatographic separation was performed on a Poroshell 120 EC-C18 column (100 × 4.6 mm, 2.7 μm) protected by a cartridge guard column (Agilent Technologies). The mobile phase comprised 0.05% trifluoroacetic acid (solvent A) and acetonitrile (solvent B). The flow was maintained at a constant rate of 0.5 ml/min. The gradient elution program was as follows: from 0 to 8 min, 2% solvent B (v/v); from 8 to 13 min, 6% solvent B (v/v); from 13 to 16 min, 8.4% solvent B (v/v); from 19.5 to 23 min, 20% solvent B (v/v); and from 23 to 27 min, 2% solvent B (v/v). The column was maintained at 32 °C during the analysis, and the samples were maintained at 4 °C in an autosampler unit. The effluent was monitored with the fluorescence detector at an emission wavelength of 320 nm for dopamine, noradrenaline and 5-HT. For these analyses, the excitation wavelength was 283 nm. The kynurenine effluent was monitored with a variable wavelength detector set at 230 nm. The total sample analysis time was 27 min.

For sample preparation, the serum was homogenized in a 300 μl solution (1% formic acid in acetonitrile) and immediately vortexed for 5 min (Vortex Genie-2; Scientific Industries, Bohemia, NY, USA). The supernatants were dried for 30 min with compressed air to concentrate the samples and were then reconstituted with 50 μl of 0.05% trifluoroacetic acid. Subsequently, the samples were centrifuged for 20 min at 15,000×*g* and 4 °C. Finally, supernatant was injected into the HPLC system for analysis. The final data were expressed as ng/ml.

2.2. Statistical analysis

Before carrying out the statistical analysis, all study variables were transformed into Z-scores in order to eliminate range disparity. Once it had been established that the variables did not follow a normal distribution, we transformed them using the Bloom transformation offered as part of the SPSS 24.0 statistical package, which is one of the best transformations for dealing with asymmetric distributions (Rodriguez and Ruiz, 2008). The variables were normalized to mitigate the violation of the normality assumption and to enable the subsequent parametric analyses to be carried out. The Pearson correlation coefficient was used to test for possible associations between the different variables analyzed in the study. Regression analyses were conducted to study the influence of age, biological variables, and their interactions on anxiety and depressive symptoms, controlling for the effect of type of medical treatment, hormonotherapy and time since the end of treatment. In order to ensure the robustness of the analyses, subject quantity-range was estimated for each of the variables included in the regression model (Field, 2009). Finally, we assessed those interactions that were found to be significant, using the moderation analyses described by Hayes with the Johnson-Neyman technique (Hayes, 2013). No significant effects of sociodemographic variables on anxiety and depressive

symptoms were found. All statistical analyses were conducted using the SPSS 24.0 statistical package.

3. Results

Demographic characteristics and descriptive statistics for the psychological and biological variables are presented in Tables 1 and 2, respectively.

3.1. Correlation analyses

Pearson correlations were conducted to explore the relationship between psychological distress and monoaminergic variables. As shown in Table 3, depressive symptoms were found to correlate negatively with dopamine, and positively with anxiety symptoms. Furthermore, noradrenaline correlated positively with kynurenine and age. Finally, a positive correlation was found between dopamine and kynurenine.

3.2. Effects of the interaction between monoamines and age on depressive symptoms

In order to assess the interactions between dopamine, noradrenaline, serotonin, kynurenine and age and their interactions on depressive symptoms, a number of regression analyses were conducted. First, depressive symptoms were introduced as dependent variable and monoamines, age and their interactions were introduced as predictors, along with type of medical treatment, hormonotherapy and time since the end of treatment. Next, with the aim of improving the model, interactions that were not significant were removed from the model. Given the lack of statistically significant differences between the two models (original and simplified), the most parsimonious option which explained the highest percentage of variance was chosen in each case (Cohen et al., 2003). The general regression model obtained was found to be significant ($R^2 = 0.208$, $F_{(10,97)} = 2.541$, $p < .01$). Statistically significant direct effects were observed for dopamine and kynurenine, and the interactions age x 5-HT and age x DA were also found to be statistically significant (Table 4). To analyze these interactions, simple slopes tests were conducted as described above.

First, the Johnson-Neyman technique was used to analyze the interaction between age x 5-HT. The visual plot of the interaction is shown in Fig. 1. The conditional effect of 5-HT on depressive symptoms was statistically significant when age was $M \leq -0.71$. In other words, being younger influenced the negative conditional effect of 5-HT on depressive symptoms.

Next, the same approach was used to analyze the age × DA interaction. The visual plot of the interaction is shown in Fig. 2. The conditional effect of dopamine on depressive symptoms was statistically significant when age was $M \leq 0.59$. In other words, being middle-aged or younger influenced the negative conditional effect of dopamine on depressive symptoms.

Table 1
Demographic characteristics of the sample.

Variables (n = 108)	Mean ± SD
Age	56.1 ± 8.61
Time since the end of treatment (years)	2.61 ± 1.26
Marital status	
Single/married/divorced/widow (%)	6.25/77.5/12.5/3.75
Household composition	
Single/Partner/Children/Partner and children/ Parents/Partner and Parents/Partner, children and parents/Siblings (%)	7.4/29.6/4.6/50.9/ 0.9/0.9/2.8/2.8
Education level	
Secondary/tertiary or higher (%)	59.3/40.7
Labor situation	
Employed/Unemployed/Time off work/Retired (%)	52.8/25/4.6/17.6

Table 2
Descriptive data for the psychological and biological variables studied.

Variables (n = 108)	Mean ± SD
Depressive symptoms	
Normal/clinically significant (%)	72.2/27.8
Anxiety symptoms	
Normal/clinically significant (%)	73.1/26.9
NA	262.89 ± 16.19
DA	0.31 ± 0.26
5-HT	0.05 ± 0.06
KYN	255.48 ± 101.94

5-HT, Serotonin; DA, Dopamine; KYN, kynurenine and NA, Noradrenaline.

Table 3
Correlations between anxiety and depressive symptoms, monoaminergic variables and age.

	DA	5-HT	KYN	Age	Anxiety symptoms	Depressive symptoms
NA	,145	-,142	,448**	,189*	-,127	-,091
DA		-,083	,263**	-,172	-,079	-,287**
5-HT			-,056	-,075	-,058	,011
KYN				,132	,083	,072
Age					-,179	-,042
Anxiety symptoms						,690**

5-HT, Serotonin; DA, Dopamine; KYN, kynurenine and NA, Noradrenaline.

Table 4
Regression analysis for depressive symptoms.

	Beta	t	Sig
NA	-.192	−1.735	.086
DA	-.362	−3.483	.001
5-HT	-.077	-.797	.427
KYN	.272	2.512	.014
Age	-.075	-.773	.441
Age x NA	.115	1.017	.312
Age x DA	.216	2.017	.046
Age x 5-HT	.222	2.175	.032
Age x KYN	-.116	−1.030	.305
Hormonotherapy	.086	.922	.359

5-HT, Serotonin; DA, Dopamine; KYN, kynurenine and NA, Noradrenaline.

3.3. Effects of the interaction between monoamines and age on anxiety symptoms

In order to assess the interactions between dopamine, noradrenaline, serotonin, kynurenine, age and their interactions on anxiety symptoms, a number of regression analyses were conducted. First, anxiety symptoms were introduced as dependent variable and monoamines, age and their interactions were introduced as predictors, along with type of medical treatment, hormonotherapy and time since the end of treatment. Next, with the aim of improving the model, interactions that were not significant were removed from the model. Given the lack of statistically significant differences between the two models (original and simplified), the most parsimonious option which explained the highest percentage of variance was chosen in each case (Cohen et al., 2003). The general regression model obtained was found to be significant ($R^2 = 0.191$, $F_{(11,96)} = 2.065$, $p < .05$). Statistically significant direct effects were found for noradrenaline and kynurenine, and the interaction age x 5-HT was also found to be statistically significant (Table 5). To analyze this interaction, a simple slopes test was conducted as described above.

The Johnson-Neyman technique was used to analyze the interaction between age x 5-HT. The visual plot of the interaction is shown in Fig. 3. The conditional effect of 5-HT on anxiety symptoms was statistically significant when age was $M \leq -0.22$. In other words, being younger influenced the negative conditional effect of serotonin on anxiety

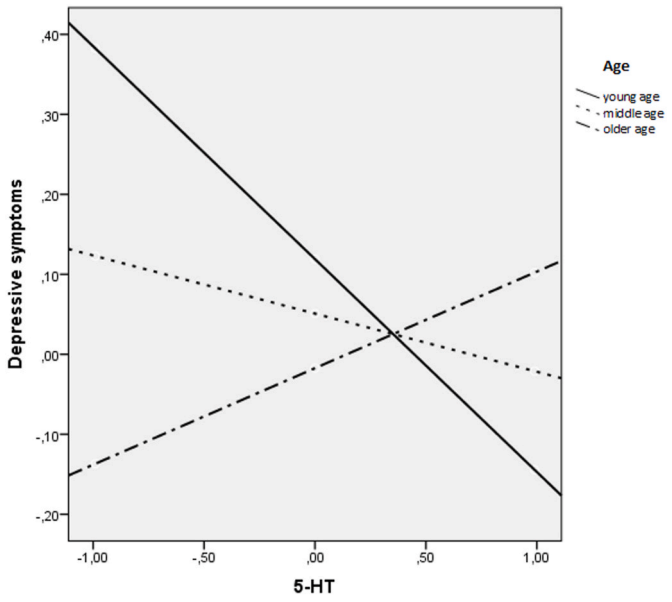

Fig. 1. Moderating effect of age on the relation between 5-HT and depressive symptoms.

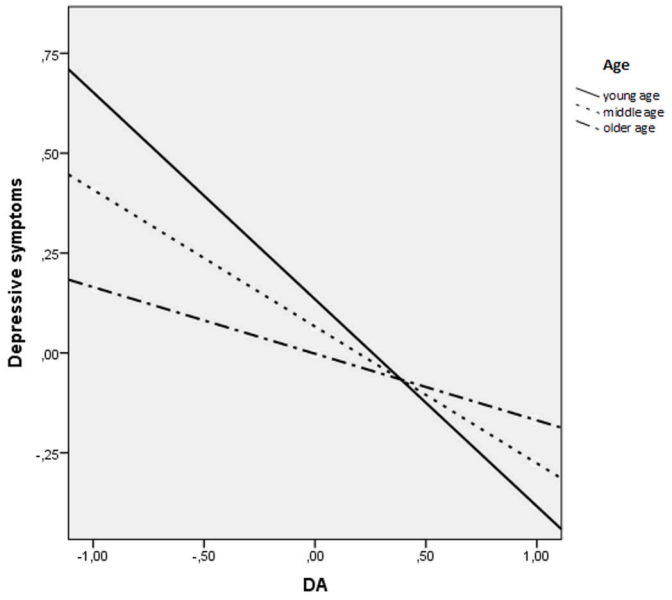

Fig. 2. Moderating effect of age on the relation between dopamine and depressive symptoms.

Table 5
Regression analysis for anxiety symptoms.

	Beta	t	Sig
NA	-.265	−2.324	.022
DA	-.195	−1.844	.068
5-HT	-.139	−1.403	.164
KYN	.266	2.417	.018
Age	-.173	−1.761	.081
Age x NA	.182	1.588	.116
Age x DA	.196	1.800	.075
Age x 5-HT	.223	2.091	.039
Age x KYN	-.179	−1.521	.132
Hormonotherapy	-.079	-.839	.404
Time since the end of treatment	-.092	-.932	.354

5-HT, Serotonin; DA, Dopamine; KYN, kynurenine and NA, Noradrenaline.

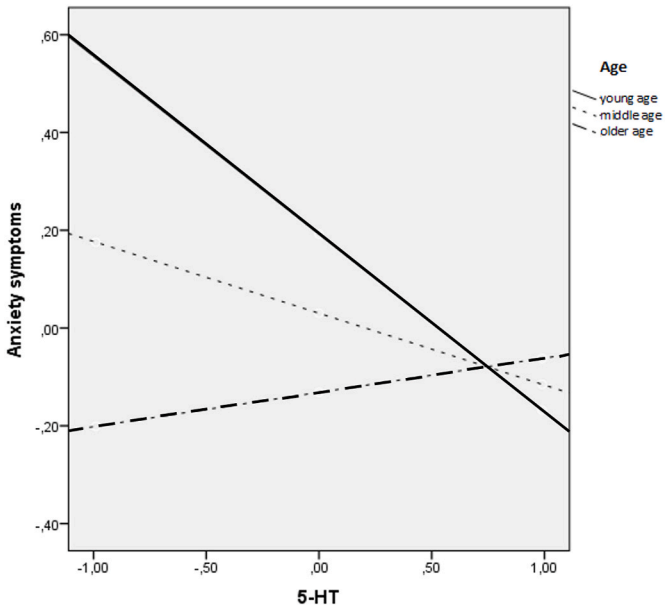

Fig. 3. Moderating effect of age on the relation between 5-HT and anxiety symptoms.

symptoms.

4. Discussion

The psychobiological approach proposed here constitutes a comprehensive view which takes into account the holistic functioning of the individual, analyzing whether interactions between biological variables and age are associated with anxiety and depression.

Although the monoamine hypothesis and kynurenine pathway framework have received growing attention in the field of major depressive disorder, our data are consistent with emerging evidence indicating that kynurenine pathway imbalance induces serotonin deficiency in anxiety disorders also (Kim and Jeon, 2018). Specifically, the regression models for anxiety and depression have been found to share a common physiological basis, with kynurenine positively predicting both disorders and 5-HT negatively predicting them in women aged under 46 years. Interestingly, Hüfner et al. (2015) found a heightened kynurenine/tryptophan ratio in breast cancer survivors with state anxiety. This type of monoaminergic pattern may be related to the fact that anxiety and depression are often overlapped in the female population (Rodgers et al., 2016). Decreased 5-HT levels may impair the cognitive performance of these women and lead to a poorer quality of life, since lowering central 5-HT concentrations via acute tryptophan depletion resulted in poorer episodic memory (delayed recall) and reduced motor speed among breast cancer survivors (Von Ah et al., 2012).

The crucial differences characterizing anxiety and depressive symptoms in our sample seem to lie in noradrenaline and dopamine levels. Low noradrenaline levels predict anxiety while low dopamine levels predict depression, especially among young and middle-aged women (under 46 and between 47 and 63 years, respectively). Moreover, dopamine levels were found to correlate negatively with depressive symptoms.

Low dopamine levels have been repeatedly linked to anhedonia, the core symptom of depression, characterized by a loss of pleasure for hedonic stimuli (Der-Avakian and Markou, 2012). As well as playing an important role in the reward system, dopamine is involved in a variety of neurological functions such as cognition and locomotor control (Bäckman et al., 2006). In this sense, Vitor et al. (2019) found that breast cancer survivors reporting cognitive deficits after chemotherapy had decreased dopamine release compared to healthy controls, suggesting

that chemotherapy-induced oxidative insult may alter dopamine system functioning. This effect may help explain the high prevalence of affective disorders among this population. However, no significant effects of the variable type of treatment were found in our sample.

To date, few clinical studies have explored catecholamine levels in cancer patients and their impact on anxiety, and those that have report inconsistent results. Thus, whereas Liu et al. (2017) found that anxiety may promote the release of catecholamines, such as noradrenaline, in liver cancer patients, other authors found no such significant association among cancer patients (Bastos et al., 2018; Davis et al., 2015). This issue requires further research due to the involvement of noradrenaline in the tumor-related immune response, including a reduction in the number and activity of natural killer (NK) cells and dysregulation in the production of cytokines by lymphocytes (Reiche et al., 2004; Lutgendorf et al., 2005).

Notably, age was not only found to have a predictive value in its own right, but also interacted with dopamine and 5-HT to predict depression and both disorders respectively. It can be inferred from these results that young breast cancer survivors are more vulnerable to the detrimental effects of low dopamine and 5-HT when developing stress-related disorders. Indeed, previous studies have found that those aged under 50 years are especially likely to report psychological distress (Champion et al., 2014; Howard-Anderson et al., 2012).

The results presented in this paper highlight the need for specific survivorship care delivery models targeted at women who have overcome breast cancer. Such approach is necessarily complex, since the stressors and/or maladaptive biobehavioral effects are complex and all patients are unique. However, according to our regression analyses, evaluating anxiety and depressive symptoms and measuring kynurenine, 5-HT, noradrenaline and dopamine may provide a near-term proxy for assessing and intervening at various stages of the allostasis–adaptation process (stress-response), thereby enabling interventions to be adjusted accordingly long before the long-term endpoint of morbidity. According to Rosemberg et al. (2017), the goal of this framework is not only to prevent the onset of disease originating from overload, but also to leverage adaptation for optimal health under the circumstances. Aligning this principle with our findings, although being younger seems to increase the risk of suffering from distress, it has also been reported that young breast cancer survivors may, in turn, benefit more from social support, improving coping skills and expanding opportunities for information-sharing (Chou et al., 2012; Perez-Tejada et al., 2019). Monoamine and metabolite levels may also be interpreted as modifiable risk factors, and not only via 5-HT and noradrenaline reuptake inhibitors. Physical exercise, for instance, increases the free tryptophan available for 5-HT synthesis (Chaouloff, 1997). Anxiety and/or depressive symptoms have also been attenuated by group-delivered cancer parenting programs and internet-based peer support groups (Lepore et al., 2019; Lewis et al., 2020).

Nevertheless, our study does have some limitations which should not be overlooked. It is important to point out that the sample was mainly comprised of white Caucasian women, which reduces intercultural reproducibility. Moreover, although kynurenine levels give some indication of kynurenine pathway activity, we were unable to detect other revealing metabolites, such as neuroprotectant kynurenic acid or the neurotoxic quinolinic acid (Meier et al., 2017).

In conclusion, the explanatory role of kynurenine in anxiety and depression suggests a shift in the tryptophan metabolism towards kynurenine production, which, coupled with low noradrenaline and dopamine, may render women more vulnerable to clinical alterations. Young breast cancer survivors seem to be especially vulnerable to the detrimental effects of low dopamine and 5-HT when developing stress-related disorders. These results provide a framework for assessing subclinical psychobiological markers and identifying vulnerable survivors prior to the onset of disorders.

CRediT authorship contribution statement

Joana Perez-Tejada: Conceptualization, Methodology, Formal analysis. **Ainitze Labaka:** Writing – original draft. **Oscar Vegas:** Funding acquisition, Supervision. **Aitziber Larraioz:** Investigation, Data collection. **Ane Pescador:** Investigation, Data collection. **Amaia Arregi:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this paper.

Acknowledgements

The authors would like to thank the women involved in the present study for their participation. This study was supported by the Basque Government Project: IT757-13 and by the University of Basque Country Projects: GIU18/103.

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