

ACTIVE AND PASSIVE COPING STRATEGIES COMPARING PSYCHOLOGICAL DISTRESS, CORTISOL, AND PROINFLAMMATORY CYTOKINE LEVELS IN BREAST CANCER SURVIVORS

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Abstract

Background: Breast cancer survivors can suffer psychological distress, such as anxiety and depressive symptoms, long after the treatment has ended, and the development of such negative affective states has been related to the coping strategy used by the subject. Additionally, coping strategies can affect the immune and endocrine systems, which are linked in turn to the onset of anxiety and depressive symptoms. **Objectives:** This pilot study aims to determine whether different coping strategies are associated with differences in psychological distress, cortisol and TNF- α in breast cancer survivors. **Methods:** Fifty-four breast cancer survivors completed the Stress Coping Questionnaire and the Hospital Anxiety and Depression Scale, and provided a blood sample for cortisol and proinflammatory cytokine measures. **Findings:** Passive coping strategy were associated with higher psychological distress, cortisol and TNF- α levels. Given that the coping style is a modifiable risk factor that influences a range of biological factors and health outcomes, it must be a target variable in preventive strategies and therapeutics.

Keywords: psychological distress, coping, cortisol, TNF- α , breast cancer survivors

Introduction

Breast cancer is the most common cancer in women worldwide. Although cancer survival rates have increased in recent years, survivors often face additional mental health problems,

such as anxiety or depression, long after treatment has ended (Bower, 2008). These disorders lead to a poorer quality of life and compromises patient health outcomes (Smith, 2015). Depression is a clear predictor of reduced survival and facilitate cancer progression, probably through changes in hypothalamic-pituitary-adrenal (HPA) axis and immune system (Feller et al., 2019) . Thus, physiopathology of anxiety and depression is characterized by a HPA axis dysregulation (Ju et al., 2018) and an inflammatory response (Furtado & Katzman, 2015a, 2015b; Gerritsen et al., 2019). In this regard, an important and modifiable risk factor for the development of anxiety and depressive symptoms can be the coping strategy (Geyikci, Cakmak, Demirkol, & Uguz, 2018; Reich & Remor, 2010). Coping styles has been defined as the way we face a threat or a challenge in an attempt to prevent or reduce associated distress (Ghanem et al., 2019) and are commonly categorized as active coping versus passive/avoidant coping (Nielsen and Knardahl, 2014). Active coping is generally associated with more adaptive adjustment, and characterized by strategies such as problem-focused coping, whereas passive coping is defined as maladaptive strategies when faced with stressful situations, such as negative self-targeting and avoidance (Wood & Bhatnagar, 2015). Some authors proposed that coping co-determine the immune and endocrine responses to stress (Diaz, Aldridge-Gery, & Spiegel, 2014; Hoyt et al., 2014; Tripathy, Tripathy, Gupta, & Kar, 2019). Specifically, an avoidance coping strategy, in contrast to active coping, has been related to poorer immune response and flatter cortisol diurnal slope (Dougal, Biglan, Swanson & Baum, 2013; Hoyt et al., 2014). Accordingly, a meta-analysis reported that positive psychological traits are associated with reduced HPA reactivity in healthy population (Chida & Hamer, 2008) and in cancer patients (Diaz et al., 2014) .

Focusing on breast cancer, patients who exhibit more psychological distress, such as anxiety and depressive symptoms, are those that show ineffective coping strategies, such as negation or avoidance (Alcalar, Ozkan, Kucucuk, Aslay, & Ozkan, 2012; Donovan-Kicken & Caughlin,

2011; Malik & Kiran, 2013), and a problem-focused coping strategy have been associated with better psychological outcome (Büyükaşık-Çolak, Gündoğdu-Aktürk, & Bozo, 2012). Moreover, the persistent elevation of cortisol usually found in these women might be due to their failure to cope with stress during breast cancer survivorship (Hsiao et al., 2013), since ineffective emotion regulation may exacerbate the hypothalamic pituitary-adrenal axis, as well as the immune system activity (Appleton, Buka, Loucks, Gilman, & Kubzansky, 2014; Graham et al., 2006; Lam, Dickerson, Zoccola, & Zaldivar, 2009). In this regard, increased levels of both cortisol and the proinflammatory cytokines, such as tumor necrosis factor alpha (TNF- α) have been found in cancer patients with depression, including breast cancer patients (Cirulli et al., 2015; Bouchard et al., 2016; Smith, 2015). In addition, several works support the tumor-promoting effect of TNF- α (Cai et al., 2017; Ham, Fernandez, D'Costa, & Brodt, 2016). Korobeinikova et al., (2015) found that TNF- α -308 polymorphism might modulate the risk of breast cancer recurrence and metastasis of breast cancer patients. Interestingly, TNF- α levels were negatively correlated with active coping strategy in healthy people (Master et al., 2009), and positive associations between maladaptive coping styles and breast cancer incidence and other cancer outcomes have been reported (Svensson & Hansson, 2016; Watson, Homewood, & Haviland, 2012).

Despite the data indicated above, there are only a few studies concerning the relationship between the coping strategy, psychological distress (or anxiety and depressive symptoms) and changes in the immune and endocrine system. Some studies have shown that depressive symptoms have been associated with passive coping and increased saliva cortisol levels (Hohne et al., 2014), while strategies such as emotional acceptance moderate the associations between cytokines and sickness symptoms in breast cancer patients (Reed et al., 2016).

Purpose of the study

The purpose of this study is to examine whether adopting a certain coping style is associated with differences in psychological distress and physiological variables in breast cancer survivors. To this end, we pursue the followings specific aims:

- Classify breast cancer survivors' coping strategies into two categories: active and passive.
- Compare anxiety and depressive symptoms between active and passive coping women.
- Compare TNF- α and cortisol levels between active and passive coping women.

Method

Design

A cross-sectional descriptive design was used to identify different coping strategies used to face stressful situations in breast cancer survivors and its relationship with psychological distress, cortisol and TNF- α .

Sample and procedure

The participants were 54 female breast cancer survivors (age between 34 and 64 years, mean=51.6) recruited from different cancer associations through public talks or informative letters. The inclusion criteria for this study were: (1) age 30–65 years; (2) completing all active cancer treatments (surgery, chemotherapy, or/and radiotherapy) and (3) elapsing at least more than one year since the end of treatment. The exclusion criteria were: (a) women with metastases and (b) those that presented current medical conditions or medications that would affect inflammation, such as systemic corticosteroids or chronic inflammatory disease. Any other medical treatment was allowed. Those women that met the inclusion criteria for the study were called over two days, with a psychological interview being conducted in person on the first day and the second day being used for blood extraction. Participants were not compensated. Prior to any data collection, informed consent was obtained in accordance with

procedures approved by the Clinical Research Ethics Committee of the Basque Country and the Ethical Committee of the Basque Country University.

Psychological and Physiological Variables

The psychological measures used included the Stress Coping Questionnaire (SCQ) and the Hospital Anxiety and Depression Scale (HADS).

The SCQ (Sandin & Chorot, 2003) evaluates seven basic styles of coping used to face stressful situations: seeking social support (e.g., "I asked some family member or friend for advice to better cope with the problem"), open emotional expression (e.g., "I behaved in a hostile manner with others"), religion (e.g., "I prayed"), focusing on a problem's solution (e.g., "I tried to analyze the causes of the problem to be able to cope"), avoidance (e.g., "I tried to forget everything"), negative self-targeting (e.g., "I understood that I was the main cause of the problem") and positive reappraisal (e.g., "I tried to focus on the positive aspects of the problem"). The participants were asked to answer 42 questions on a 5-point Likert-type scale ranging from 0 (never) to 4 (almost always), which generated the scores for each subscale ranging from 0 to 24, with a higher score indicating a higher level of this type of coping style. The Cronbach's Alpha coefficients were: focusing on a problem's solution 0.786; negative self-targeting 0.802; positive reappraisal 0.713; open emotional expression 0.76; avoidance 0.752; seeking social support 0.855; religion 0,899.

The HADS (Zigmond & Snaith, 1983) is used to identify psychological distress in the hospital setting. This test is divided into two subscales: anxiety and depression. The total score for each subscale of 7 questions is obtained on a 4-point Likert-type scale, which generates the scores for each subscale, ranging from 0 to 21, with a higher score indicating a higher level of anxiety or depression. The total scores for both subscales gives psychological distress score. The Cronbach's Alpha coefficients were: psychological distress 0.845; anxiety subscale 0.801; depression subscale 0.792.

The blood extraction was done in rest conditions according to common procedures between 8:00 am and 10:00 am by a clinical nurse in conditioned room of the Basque Country University, time that coincides with the maximum peak of cortisol (Debono et al., 2009). The blood were collected into serum separator tubes (Vacutainer SST II Advance), centrifuged for serum acquisition, and stored at -80°C. The serum cortisol and TNF- α concentration was determined using a commercially available Elisa kit (Enzo, Switzerland and R&D Systems, USA, respectively) and an ELx 800 plate reader (BioTek, USA). The assay sensitivity of cortisol and TNF- α was 56.72 pg/ml and 0.106 pg/ml, and the intra- and inter-assay variation coefficients were 8.1-9.3% and 5.3–8.3%, respectively.

Statistical Analysis

Data obtained in this study were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Given that some variables not have a normal distribution, the cortisol, cytokine, anxiety, and depression levels were normalized using the Bloom transformation, 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, so as to enable the subsequent parametric analyses to be carried out. To classify the women in two groups depending on the coping strategy used, we conducted hierarchical cluster and multivariate discriminant analyses with the subscales obtained from the SCQ questionnaire. To study the differences between two groups in psychological and physiological variables were analyzed using multivariate analyses of covariance, taking into account the effect of age and hormonal treatment, due to its impact on the biological variables studied (Heaney et al., 2010; To et al., 2014). The relationships between the variables were examined using Pearson correlations. With the aim of analyzing the potential predictive role played by coping, cortisol and cytokine levels, regression analyses were conducted taking the psychological distress as the dependent variable. In order to ensure the robustness of the

analysis, the quantity-range of subjects was estimated for each of the variables included in the regression model (Field, 2009). Finally, we studied the effect of the pharmacological treatment, the years since the end of treatment and other sociodemographics variables on biological and psychological variables, and we did not find any significant differences.

Results

Demographic characteristics and descriptive statistics for psychological and biological variables are presented in table 1.

With the aim of being able to classify the participants based on the coping strategies in two groups, a cluster analysis using subscales of the SCQ questionnaire was carried out on all breast cancer survivors. This analysis resulted in two final clusters, and the multivariate discriminant analysis was done to confirm the statistical validity of the established groups. Cluster 1 (n=35), designated as “active group”, was characterized by a high level of focusing on a problem’s solution. Cluster 2 (n=19), the passive group, was characterized by women who exhibited negative self-targeting and avoidance behaviors. Passive group had more avoidance ($F[1,52]=10.385$; $p<0.01$) and negative self-targeting ($F[1,52]=39.172$; $p<0.001$) and less positive reappraisal ($F[1,52]=4.024$; $p<0.05$) and focusing on a problem’s solution ($F[1,52]=18.419$; $p<0.001$) (Fig. 1).

When analyzing the psychological data depending on the coping strategy to study the differences between these two groups, a significant effect was observed on anxiety symptoms levels ($F(1, 50) = 9.794$; $p < 0.01$), depressive symptoms levels ($F(1, 50) = 6.056$; $p < 0.05$), as well as on distress levels ($F(1, 50) = 9.592$; $p < 0.01$). Specifically, women with passive coping strategy presented higher levels of these variables (Fig.2).

In the case of physiological variables, the data revealed that there was a significant effect on cortisol ($F(1, 50) = 4.538$; $p < 0.05$) and TNF- α levels ($F(1, 50) = 4.061$; $p < 0.05$). Thus,

women with a passive coping strategy showed higher TNF- α and cortisol levels than women with an active coping strategy (Fig.2).

The analysis of the correlations observed between the different critical variables is shown in Table II. The correlations analysis revealed a negative relationship between TNF- α and focusing on a problem's solution and positive reappraisal. Similarly, psychological distress correlated negatively with positive reappraisal and positively with negative self-targeting. Negative self-targeting correlated negatively with focusing on a problem's solution and positive reappraisal. Finally, focusing on a problem's solution correlated positively with positive reappraisal. Regression analyses were conducted to assess the predictive role of coping and biological variables on psychological distress. First, psychological distress was introduced as the dependent variable, whilst subscales of the SCQ questionnaire, cortisol, and cytokine levels were introduced as predictors. Next, with the aim to obtain the most parsimonious option that could explain the highest percentage of variance (Cohen et al., 2003), not significant variables were removed (such as biological and psychological interactions). The general regression model obtained for psychological distress was significant ($R^2=.575$; $F=3.732$; $p=.002$) (see Table III).

Discussion

Our results showed two different types of coping strategies in the examined sample of fifty four breast cancer survivors. Passive group presented higher scores on negative self-targeting and avoidance, and lower scores on focusing on a problem's solution and positive reappraisal. The results also show differences in psychological distress depending on the coping strategy, finding higher anxiety and depression levels in women with passive coping. Furthermore, we found that lower scores on the avoidance and negative self-targeting and higher scores on positive reappraisal– both of which are characteristics of an active coping– as well as higher scores for seeking social support, was associated with lower levels of psychological distress.

In breast cancer patients, emotion regulation strategies that have been found to be effective in decreasing psychological distress include positive reappraisal (Kvillemo & Bränström, 2014), whilst avoidance coping strategy is associated with poor mood or depression (Bigatti, Steiner, & Miller, 2012; Malik & Kiran, 2013).

This study found that women with passive coping strategy had higher TNF- α and cortisol levels, and that measures of focusing on a problem's solution and positive reappraisal were inversely correlated with TNF- α levels in the examined sample. Very few studies have shown the relationship between coping and these biological variables. A recent study has shown that perceiving greater stress than usual was associated with elevations in cortisol, but only for adolescents who were below average on engagement coping or coping efficacy (Sladek, Doane, Luecken, & Eisenberg, 2016). Regarding breast cancer survivors, positive coping behaviors are related to normal cortisol responses (Sjögren, Leanderson, & Kristenson, 2006). On the other hand, limited emotion regulation may exacerbate the inflammation (Graham et al., 2006), whereas adaptive emotion regulation was associated with lower levels of inflammation (Appleton et al., 2012). In breast cancer patients, strategies such as emotional acceptance moderate the associations between cytokines, such as TNF- α , and sickness symptoms (Reed et al., 2016). In addition, elevated levels of pro-inflammatory cytokines, including TNF- α , and cortisol are associated with numerous adverse health outcomes, such as coronary artery disease, osteoporosis, arthritis, and certain cancers (Currier & Nemeroff, 2014), so our data suggest that women with passive coping could be more vulnerable to suffering certain pathologies. Epidemiological studies indicate that chronic inflammation predisposes individuals to various types of cancer including breast cancer, and underlying inflammatory responses are linked to 15-20% of all deaths from cancer worldwide (Mantovani, Allavena, Sica, & Balkwill, 2008). Chronic inflammation and chronic HPA-axis dysregulation have been associated with tumor

cell proliferation, angiogenesis and mortality (Currier & Nemeroff, 2014; Villasenor et al., 2015).

Relevance to Clinical Practice

Oncology nursing has made great advances on diagnostic and treatment periods of cancer, and the need for specific survivorship care delivery models is being claimed in recent times (Hebdon, Abrahamson, Griggs, & McComb, 2018; Sabiston et al., 2018). The findings presented in this manuscript may provide an integrative approach to the development of such care plans, since they suggest that different psychobiological profiles can be found between breast cancer survivors. Although more research is required, passive coping style may be a modifiable risk factor associated with inflammation, disrupted HPA axis and psychological distress in this population. Thus, the identification of survivors' maladaptive coping strategies by nurses and the subsequent personalized goal-directed support may meet the needs of these women, preventing, in turn, the hazardous stress-derived elevations of TNF- α and cortisol. Interestingly, coaching on active coping strategies seems to be closely related to the promising self-advocacy training for cancer survivors, since this last concept is defined as an individual's ability to get her needs and priorities met in the face of a challenge (Hagan et al., 2018; Hagan & Donovan, 2013). However, given the pronounced individuality of the survivorship experience (Hebdon et al., 2018), a better understanding of psychobiological factors in the emotional state of breast cancer survivors is critical to develop an integrative praxis on distress prevention and care-giving.

The limitations of this study include the convenience and size of the sample, which reduces intercultural reproducibility, and the lack of control group. In addition, further cortisol samples may have provided a more accurate picture of HPA axis function. However, it is difficult to frequently collect plasma samples of breast cancer survivors due to their poor compliance.

Implications for Practice

- Educate nurses on psychoneuroimmunology: coping skills modulate distress, and distress can lead to hazardous physical and psychological states.
- Assess breast cancer survivors for psychosocial and emotional needs, and identify active (positive reappraisal and focusing on a problem's solution) and passive (negative self-targeting and avoidance) coping strategies.
- Develop individualized coping-based survivorship plans.

Conclusion

In general, the results of this study show that the coping strategy is an important variable in determining psychological distress for breast cancer survivors. Moreover, immune and endocrine differences were found depending on coping used. Specifically, breast cancer survivors with passive coping had higher psychological distress and higher levels of TNF- α and cortisol, which might indicate a higher vulnerability to developing certain pathologies. In order to provide an integrative oncological care, it is necessary to understand the contribution of the coping styles and different physiological variables in the emotional state, which could help applying an individualized biopsychosocial approach for cancer survivors. These data potentially enable applications to be developed, such as psychological intervention for subjects with passive coping strategies aimed to modulate the risk of psychological distress or adopt a better multidisciplinary intervention for breast cancer survivors.

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Declaration of Conflicting Interests

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

Compliance with Ethical Standards

All procedures were in accordance with procedures approved by the Clinical Research Ethics Committee of the Basque Country and the Ethical Committee of the Basque Country University.

Author contributions

The first author provided the study design, conducted interviews, analyzed biological variables, interpreted the data and wrote the manuscript. The third author analyzed biological variables, interpreted the data and wrote the manuscript. The second and sixth authors provided the study design, contributed to the interpretation of the data, supervision, discussion of the findings and revising it critically. The fourth and fifth authors contributed to the interpretation of the data and discussion of the findings. All authors provided final approval of the manuscript submitted.

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Table I. Demographic characteristics and descriptive statistics for psychological and biological variables of the sample

Variables (n = 54)	Mean \pm SD
Age	51.6 \pm 6.79
Time since the end of treatment	4.22 \pm 1.3
Marital status	

Single/married/divorced/widow (%)	22.2/46.29/25.9/5.55
Educational level	
Secondary/tertiary or above (%)	50/50
Type of treatment	
Chemotherapy (%)	87
Radiotherapy (%)	68.5
Mastectomy surgery (%)	53.7
Hormonal treatment (%)	44.4
Psychological distress	12.72 ± 6.69
Coping style	
Focusing on a problem's solution	15.63 ± 4.61
Negative self-targeting	6.81 ± 3.54
Positive reappraisal	15.93 ± 4.33
Open emotional expression	8.85 ± 3.28
Avoidance	9.93 ± 4.94
Seeking social support	14.31 ± 5.31
Religion	3.67 ± 5.35

Table II. Pearson correlations between the subscales of the Stress coping questionnaire, psychological distress and the biological variables studied. *p<0.05 **p<0.01

	TNF- α	Focalized on problem's solution	Negative self targeting	Positive reappraisal	Psychological distress
Cortisol	.158	.095	.176	-.102	-.022
TNF- α		-.352**	.145	-.350**	.094
Focalized on problem's solution			-.332*	.339*	-.184

Negative self-targeting			-.374**	.404**
Positive reappraisal				-.312*

Table III. Regression analysis for psychological distress in order to analyze the potential predictive role played by coping, cortisol and cytokine levels: predictors were some subscales of SCQ questionnaire, cortisol and TNF- α . *p<0.05

	<i>Beta</i>	<i>t</i>	<i>Sig.</i>
Negative self-targeting	.292	2.202	.032*
Open emotional expression	-.103	-.817	.418
Avoidance	.258	2.044	.046*
Seeking social support	-.276	-2.366	.022*
Positive reappraisal	-.288	-2.103	.040*
Cortisol	.051	.444	.659
TNF- α	.115	.890	.378

Figure 1. Mean levels (\pm Standard Error of Measurement (SEM)) of subscales of the Stress Coping Questionnaire of the patients with passive and active coping strategies. *p<0.05

p<0.01 *p<0.001

Figure 2. Mean levels (\pm SEM) of anxiety symptoms, depressive symptoms, psychological distress, cortisol and TNF- α of the patients with passive and active coping strategies. * $p < 0.05$
** $p < 0.01$