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VARIACIÓN DIURNA DEL CORTISOL Y SU RELACIÓN CON ESTRÉS, OPTIMISMO Y ESTRATEGIAS DE AFRONTAMIENTO EN MUJERES CON CÁNCER DE MAMA

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Resumen

El ritmo diurno del cortisol se ha visto alterado en los pacientes con cáncer. Factores como el avance de la enfermedad y los niveles de estrés se han considerado para explicar esta condición; sin embargo, los resultados no son claros. El objetivo de este estudio fue evaluar y determinar si existen diferencias en los niveles de cortisol en mujeres con cáncer de mama en diferentes estadios, y analizar la relación entre los niveles de cortisol y el estrés, el optimismo y las estrategias de afrontamiento. Se recolectaron muestras de cortisol salival durante dos días, y se aplicaron cuestionarios psicológicos de estrés percibido (PSS), optimismo disposicional (LOT-R) y estrategias de afrontamiento (MAC) a 17 mujeres con cáncer de mama en estadio I, II y III. Los resultados muestran que las pacientes con cáncer de mama en los tres estadios presentan un ritmo diurno de cortisol normal y no difieren significativamente en los niveles de cortisol. Respecto a las variables psicológicas, solo difieren en la variable de optimismo. Las estrategias de afrontamiento - espíritu de lucha y evitación cognitiva - son las variables que tienen más influencia en los niveles de cortisol, y explican un 55% de la varianza. Se discuten las implicaciones de estos resultados.
Palabras Clave: cortisol, estrés, ritmo diurno del cortisol, estrategias de afrontamiento.

DIURNAL CORTISOL VARIATION AND ITS RELATIONSHIP WITH STRESS AND COPING STRATEGIES IN WOMEN WITH BREAST CANCER

Abstract

Diurnal cortisol rhythm is affected in patients with cancer. Factors such as disease progression and stress levels are regarded as possible causes of this condition, however results are not clear. The aim of this study was to assess and determine whether there are differences in cortisol levels in women with breast cancer in different stages and analyze the relationship between cortisol levels and stress, optimism and coping strategies. Salivary cortisol samples were collected for two days and psychological questionnaires of perceived stress (PSS), dispositional optimism (LOT-R) and coping strategies (MAC) were administered to 17 breast cancer women in stage I, II and III of the disease. The results show that patients with breast cancer in the three stages have a normal diurnal cortisol rhythm and do not differ significantly in cortisol levels. Regarding the psychological variables, they differ only in the optimism. Coping strategies such as fighting spirit and cognitive avoidance are the variables that have more influence on the cortisol levels, explaining 55% of variance. The implications of these results are discussed.
Key Words: cortisol, stress, diurnal cortisol rhythm, coping strategies.

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VARIAÇÃO DIURNA DO CORTISOL E SUA RELAÇÃO COM O ESTRESSE: OTIMISMO E ESTRATÉGIAS DE ENFRENTAMENTO EM MULHERES COM CÂNCER DE MAMA

Resumo

O ritmo diurno do cortisol vem sendo visto alterado nos pacientes com câncer. Fatores como o avanço da doença e os níveis de estresse estão sendo considerados para explicar essa condição; contudo, os resultados não são claros. O objetivo deste estudo foi avaliar e determinar se existem diferenças nos níveis de cortisol em mulheres com câncer de mama de diferentes estágios, bem como analisar estratégias de enfrentamento. Foram coletadas amostras de cortisol salival durante dois dias e aplicados questionários psicológicos de estresse percebido, otimismo disposicional e estratégias de enfrentamento a 17 mulheres com câncer de mama em estágio I, II e III. Os resultados mostram que as pacientes com esse câncer nos três estágios apresentam um ritmo diurno de cortisol normal e não se diferenciam significativamente na variável de otimismo. A respeito das variáveis psicológicas, só diferem na variável de otimismo. As estratégias de enfrentamento —espírito de luta e evitação cognitiva— são as variáveis que têm mais influência nos níveis de cortisol e explicam 55% da variação. Discutem-se as implicações desses resultados.
Palavras-chave: cortisol, estresse, ritmo diurno do cortisol, estratégias de enfrentamento.

INTRODUCTION

Cortisol is a glucocorticosteroid of the adrenal cortex which has effects on the protein, carbohydrates and lipid metabolism. Concentration levels of cortisol are high in very early hours of the morning (6a.m.-8a.m.) and decrease slowly and progressively until it gets to a minimum activity in hours after the afternoon (4p.m.-6p.m.). This pattern is present in healthy people and is considered as a circadian rhythm (Fischbach & Dunning, 2009; Kronfol, Nair, Zhang, Hill & Brown, 1997). Cortisol changes also depend on the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which responds homeostatically in different stressing challenges. The constant activation due to chronic stress can cause biochemical imbalance and impairment in different body systems, including the immune system, increasing vulnerability to disease and the neuroendocrine system which alters the circadian rhythms (Moscoso, 2009; Sephton & Spiegel, 2003; Young & Welsh, 2005).

Stress and cancer are related from the moment a person feels vulnerable to developing the disease. The effects of the perception of risk and uncertainty involved in diagnosis are observed in the biological and psychological stress response (Barroilhet, Forjaz & Garrido, 2005; Dettenborn, James, Valdimarsdottir, Montgomery & Bovbjerg, 2006; Lang, Berbaum & Lutgendorf, 2009). The stress response also depends on psychological variables called coping strategies and their effects are observed in the modulation of the stress response through mechanisms people use to face situations they assess as stressful, diminishing the biological response through: 1) less perception or less feeling of vulnerability of the threat and 2) a more effective handling when the threat is detected (Taylor et al.2008).

The interaction of these variables with cortisol is important because patients with different types of cancer have altered circadian endocrine function which is mainly observed at low values and less variability in cortisol levels (Touitou, Bogdan, Lévi, Benavides & Auzéby, 1996; Abercrombie et al., 2006; Mazzoccoli, Vendemiale, De Cata, Carughi & Tarquini, 2010, Mazzoccoli, Tarquini, Durfot & Francoise, 2011; Weinrib et al., 2010). These alterations have been associated with short periods of survival (Septhon, Sapolsky, Kraemer & Spiegel 2000; Septhon et al., 2012).

However, other studies on breast cancer patients have reported that a normal diurnal cortisol rhythm comparable to healthy groups is observed (Haus et al. 2001; Garland et al. 2004; Vedhara, Tuin, Miles, Sanderman & Ranchor, 2006; Carlson et al. 2007; Mazzoccoli, Giuliani & Sothern, 2012). Furthermore, the variables that have been considered to explain the diurnal cortisol alteration as the progression of the disease, are contradictory or in the case of stress, the results are little or null (Touitou et al, 1995; Porter et al, 2003 ; Nakaya et al., 2005; Garland et al., 2004; Carlson et al., 2007; Vedhara et al, 2003, 2006). Therefore, the aim of this study was to compare the cortisol levels in women with breast cancer from different stages of the disease, and examine the relationship between cortisol levels and stress, optimism and coping strategies.

METHOD

Type of study

This study used a non-experimental design with a non-probability sample (by convenience).

Participants

The patients were referred by an oncologist and contact with them was established at the Breast Clinic of the Bernardo Sepúlveda Hospital. The inclusion criteria were: women diagnosed with breast cancer and scheduled for chemotherapy, who had signed the participation consent. Patients with bilateral cancer, previous cancer and in hormonal treatment were excluded. The elimination criteria were data with incomplete or contaminated samples, insufficient amount of saliva or incomplete questionnaires. Out of 25 patients who agreed to participate, two of them did not attend and three were excluded. 20 patients were assessed and three were eliminated.

Data from 17 women with breast cancer were analyzed, the mean age was 50.65 years (SD = 8.3). 11 of them were married, three were single, two were cohabiting and one was a widow. Only four of them were working at the time of the study. 14 of them had had surgery and the other three, had not had it. Concerning the stage of the disease, six of the patients were in stage I, six in stage II, four in stage III, and one datum was not available.

Instruments

The Oral Swab Method (*Salimetrics* ®) was used to collect samples of salivary cortisol. It consists of placing and maintaining a cotton swab under the tongue for 2 minutes and then placing it in a storage tube. This method is adequate and easy to use for the cortisol recollection and it has the advantage of filtrating mucus and other material of the sample, which favors better immunoassay results (Salimetrics, 2012).

Perceived Stress Scale. It was developed by Cohen, Kamarck and Mermelstein (1983) to assess the degree to which situations in one's life are appraised as stressful. In this study, the cultural adaptation done in Mexico by González and Landero (2007) was used. It has 14 items and a Cronbach's alpha coefficient of 0.83. Cronbach's alpha obtained for this sample was 0.86. The scores range from never -0- to very often -4- with a total score in the range of 0 to 56. The highest score corresponds to the greatest perceived stress.

Life Orientation Test (Scheier, Carver & Bridges, 1994). It assesses widespread individual differences of optimism versus pessimism. The Spanish version by Otero, Luengo, Romero, Gómez and Castro (1998) was used, composed of 10 items and with a Cronbach's alpha of 0.79. In this sample, Cronbach's alpha was 0.64. Scores of items written in the negative are reversed and a total score oriented towards the pole of optimism is obtained. The score range goes from 6 to 30. A high score indicates greater optimism.

Mental Adjustment to Cancer Scale. It was developed to assess the extent to which patients adopt certain responses to adjust to the diagnosis of cancer and its treatment. The Spanish translation by Caro and Ibáñez (Watson et al, 1988) was used, consisting of 40 items divided into five sub-scales: hope-hopelessness, anxiety-concern, fighting spirit, cognitive avoidance and fatalism, which have a score range from 6 to 24, 9 to 36, 16 to 64, 1 to 4 and 8 to 32, respectively. It obtained a Cronbach's alpha of 0.84, and in this sample the alpha was 0.64.

Procedure

This study was conducted in three phases: Phase 1. After the approval of the bioethics committees of the institutions Bernardo Sepúlveda Hospital of the Ministry of Health and the Center for Development Research in Health Sciences (CIDICS) UANL, the patients were contacted at the Hospital's Breast Clinic. Those who met the criteria were called and invited to be briefed about the study.

Phase 2. Patients who agreed to participate signed the informed consent and spent two consecutive days at the Psychology Unit of the CIDICS, during which six samples of saliva were collected at the following times: before sleeping, on awakening, 30 and 60 minutes after awakening, and at 12 and 16 hours. The regular sleep-awake schedule of patients was respected to detect the natural diurnal rhythm. During data collection it was indicated and monitored to avoid tooth-brushing and consuming chewing gum, food or beverages high in sugar or acid, and alcohol, for 12 hours before collection (Salimetrics, 2012). The psychological data were assessed during the two days after breakfast.

Phase 3. Saliva samples were labeled and frozen (-20 ° C) before sending them to the Salimetrics Inc. laboratory for analysis.

Data Analysis

Cortisol levels were determined by an enzyme immune-assay carried out by Salimetrics, Inc. The sensitivity of the essay lies within a rank from 0 to 0.007 µg/dL. The intra-assay variation coefficients ranks go from 4 to 7% and those of the inter-assay go from 3 to 11% (Salimetrics, 2013).

Data were captured and analyzed with the SPSS program. The Shapiro-Wilk normality test was applied where four cortisol samples were found significant ($p < .01$) and the subscales scores of fighting spirit and cognitive avoidance ($p < .01$). For this reason it was decided to use nonparametric tests. Averages for each salivary sample were obtained to

analyze the diurnal cortisol rhythm and a plot was made in order to observe changes in cortisol secretion. The Friedman test was performed to validate the changes in time.

Cortisol levels were obtained through the indicator area under the curve (AUC) which is used in endocrinology to estimate the hormonal changes and assess the overall discharge over a period of time. Its formula is based on the trapezoid method comprising the sum of triangles and rectangles based on the information obtained from the repeated measurements. Calculation of the AUC enables simplifying statistical analysis without sacrificing measurements and increases the tests power by reducing the need to adjust the significance level. For this study, two AUC indicators were obtained: a) the area under the curve with respect to the base (AUCg) is the area that takes into account all measurements and represents the total cortisol concentration and b) the area under the curve with respect to the increase (AUCi), calculated with reference to the baseline measurement and does not take into account the zero distance for all measurements and represents the increase in cortisol over time (Fekedulegn et al., 2007; Pruessner, Kirshbaum, Meinlschmid & Hellhammer, 2003). The Kruskal-Wallis test was used to assess the differences in cortisol levels by stage (AUC) and the psychological variables. The Spearman's correlation coefficient was used for correlation analysis. Finally, a multiple regression analysis with the successive steps method was conducted to assess the variables that explain the dependent variable (AUCi AUCg cortisol).

RESULTS

In this section results are presented according to the objectives of this study.

Diurnal cortisol rhythm by stage of cancer

The mean of each cortisol sample per day was obtained. Data indicate that the three stages analyzed (I, II, III) show a normal diurnal cortisol rhythm during the two days (Figure 1), an increase from the sample taken before sleep (1) to the sample taken upon awakening (2) and a decrease in the secretion of cortisol from the sample taken half an hour after awakening (3). These variations in cortisol concentrations were significant for all three stages during day 1: Stage I (Friedman = 24.4, p = .000), stage II (Friedman = 23.5, p = .000) and stage III (Friedman = 18.2, p = .003) and during Day 2: stage I (Friedman = 26.6, p = .000), stage II (Friedman = 19.3, p = .002) and stage III (Friedman = 17.4, p = .004). These data validate the diurnal variation in the three stages.

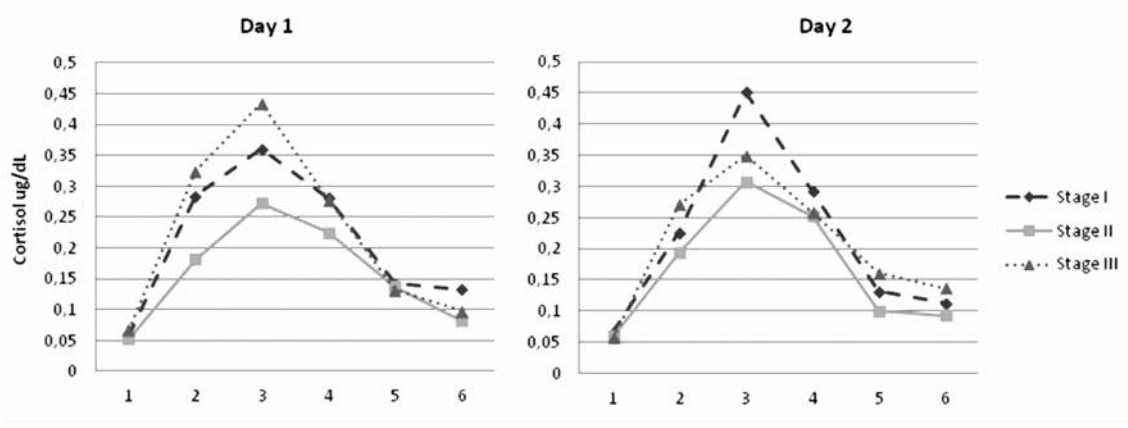

Figure 1. Diurnal cortisol rhythm by cancer stage.
Stage I n=6, stage II n=6, stage III n=4.
1. Before going to bed, 2 . Awaking, 3. 30 min after awaking 4. 60 min after awaking
5. at noon, 6. 4 pm.

Figura 1. Diurnal cortisol rhytm by cancer stage

Difference in cortisol levels and psychological variables as cancer stage

Stages I, II and III were analyzed, comparing cortisol AUCg, AUCi without obtaining significant differences. Regarding the psychological variables, only optimism was significant (Table 1).

Table 1.
Difference of cortisol levels and psychological variables as stage of cancer

Variable Mean (SD)	Stage I n=6	Stage II n=6	Stage III n=4	Kruskal-Wallis Ch2 (p)
AUCg1	183.4(46.9)	136.8(51.4)	192.6(58.9)	3.01(221)
AUCg2	167.8(38.6)	139.0(57.4)	180.6(66.7)	1.69(429)
AUCi1	122.9(47.6)	82.9(47.5)	124.0(47.8)	3.11(210)
AUCi2	100.5(39.9)	78.6(61.3)	122.2(50.7)	1.83(339)
Stress	18(4.8)	26.5(11.9)	29.2(6.2)	4.08(.130)
Optimism	43.1(4.3)	38.5(6.1)	35(1.8)	7.40(.025)*
Fighting Spirit	59.0(2.4)	53.6(5.2)	53(5.4)	3.93(.140)
Hope-Hopeleness	7.8(1.7)	9.1(3.4)	11.0(3.5)	2.31(.315)
Anxiety-worry	23.0(3.7)	24.3(5.4)	28(6.9)	1.57(.456)
Fatalism	18.0(4.0)	21.5(4.1)	21.5(5.9)	1.59(.451)
Cognitive avoidance	2.0(1.5)	2.0(1.5)	2.2(.95)	.291(.864)

Note: SD: Standard deviation, AUCg1: Area under the curve ground of day 1, AUCg2: Area under the curve ground of day 2. AUCi1: Area under the curve increase of day 1, AUCi2: Area under the curve increase of day 2.

Relationship between cortisol AUC and psychological variables

The mean AUC relative to the base (AUC g) and the mean AUC regarding increased (AUCi) were obtained to relate psychological variables with cortisol levels. As shown in Table 2, the cortisol AUCg significantly negatively correlated with stress, indicating that the higher the stress, the lower the total cortisol secretion. The AUCg showed a positive and significant correlation with the coping strategy of fighting spirit and avoidance, indicating that the greater the use of fighting spirit and cognitive avoidance strategies, the higher the total cortisol secretion. Similarly, the AUCi cortisol is related positively and significantly with the strategies of fighting spirit and avoidance, which indicates that the greater the use of these strategies the higher the increase of cortisol reactivity.

Table 2.
Correlation between cortisol AUC and psychological variables

Variable	AUCg rs(p)	AUCi rs(p)
Stress	-.593 (.012)*	-.447 (.072)
Optimism	.127 (.628)	-.022 (.933)
Fighting Spirit	.642 (.005)**	.490 (.046)*
Hope-Hopeleness	.133 (.612)	.172 (.508)
Anxiety-worry	-.183 (.482)	-.172 (.508)
Fatalism	-.130 (.620)	-.002 (.992)
Cognitive avoidance	.537 (.026)*	.566 (.018)*

Note: rs: Spearman correlation, p: statistical significance, ** p<.01, * p<.05

Regarding the relationship between psychological variables, stress showed a negative and significant relationship with optimism (r= -.618, p=.008) and with fighting spirit (r= -.809, p=.000). Optimism correlated positive and significantly with fighting spirit (r= .663, p=.004).

Regression analysis

In the multiple regression analysis, having the cortisol mean AUCg as dependent variable, and stress, avoidance and fighting spirit strategies as independent variables, two models were obtained (Table 3): The first one, in which the fighting spirit explains 40.5% of the variance. And the second one, where the fighting spirit and cognitive avoidance strategies explain 57.8% of the variance of the total cortisol concentration. Both models obtained a Durbin-Watson value of 1,110 and therefore are considered adequate.

Likewise, in the multiple regression analysis with the cortisol mean AUCi, two models were obtained: One in which the fighting spirit variable explains 33.3% of the variance. In the second one fighting spirit and avoidance explain 55.8% of the variance of cortisol levels. Both models were adequate and obtained a Durbin-Watson value of 1.634.

Table 3.
Multiple Regression Analysis cortisol AUC

Variable	R2aj	F	B	Beta	T
AUCg					
Model 1	.405	11.89**	6.403	.665	3.449**
Fighting Spirit					
Modelo 2					
Fighting Spirit	.578	7.13*	5.657	.588	3.561**
Cognitive avoidance			16.969	.441	2.671*
AUCi					
Model 1	.333	8.97**	5.351	.612	2.996**
Fighting Spirit					
Model 2			4.588	.525	3.107**
Fighting Spirit	.558	8.66*	17.376	.497	2.943*
Cognitive avoidance					

Note: AUCg: Area under the curve ground, AUCi: Area under the curve increase.
** p < .01, * p < .05

DISCUSSION

The main results of this study are a normal diurnal cortisol rhythm, with a higher cortisol secretion in the morning and decrease throughout the day in patients with breast cancer in the three stages of the disease. These results are different to the ones published elsewhere (Sephton et al., 2000; Touitou et al., 1996) in which patients show low levels and irregular increases or decreases of cortisol, as assessed in blood and saliva. This difference may be because in these studies some patients had metastases or had undergone chemotherapy or hormone treatments such as megestrol, altering HPA axis and reducing cortisol secretion (Morrow, Hickok, Andrews & Stern, 2002; Raeder et al., 2003). In this study, patients were assessed prior to chemotherapy treatment for controlling the cytotoxic effect on the functioning of the HPA axis.

This is important, as it has been reported that in patients with ovary cancer who did not receive chemotherapy but only surgical treatment, between six and twelve months after surgery, the diurnal cortisol rhythm normalizes, which is observed in a decrease in cortisol levels in the

morning, afternoon and night (Schrepf et al. 2013). This suggests that the alteration of the diurnal cortisol rhythm in patients with cancer may arise in specific phases of the disease, that is, before or after surgery, or before or after chemotherapy treatment.

Although patients show a normal cortisol rhythm, it was observed that those in stage III had increased secretion in some samples, like patients in stage I who show increased secretion on day 2. This is similar to the findings of other studies showing that patients with different types of cancer who had high levels of cortisol in the morning or at night, had a normal diurnal cortisol rhythm (Lissoni et al., 2007; Mazzoccoli et al., 2010). This may indicate that while cancer patients have higher cortisol secretion, it does not necessarily represent an alteration in the diurnal cortisol rhythm. Although it is unclear whether this long-term condition can alter the diurnal cortisol rhythm, it would be important to conduct follow-up studies with those who had higher than normal levels.

Due to the variability in the statistical analysis approaches used in different studies, there are difficulties in making comparisons between the results (Powell, Liossi, Moss-Morris & Schlotz, 2013). However, results regarding the relationship between psychological variables and cortisol AUC are discussed below.

When a comparative analysis of the area under the cortisol curve by stages was performed, no significant differences were observed. However, stage III has a higher mean than stages I and II. Similarly, Weinrib et al. (2010) reported not having found differences between early and advanced stages in cortisol concentration. When comparing the psychological variables, only significant differences in optimism were found, and patients in stage III were those with a lower level of this variable. They also had higher levels of stress, hopelessness and anxiety. Although these were not significant they may reflect the uncertainty of not having received any treatment unlike other stages.

Concerning the relationship between cortisol levels and psychological variables, the relation between stress and AUC of cortisol was expected to be positive since research shows that when perceived stress is high, cortisol secretion increases as well (Fan et al. 2009, Schoofs, Hartmann y Wolf, 2008)). However, a negative direction was obtained. Other studies do not find any relationship between cortisol and variables such as distress, stress, depression and anxiety (Carlson et al., 2007; Porter et al., 2003, Septhon et al., 2000; Vedhara et al., 2003). Only one study shows a negative relation between stress and cortisol levels but it was not significant (Rosal, King, Yunsheng & Reed, 2004).

Some studies have suggested the possibility of a negative relationship between stress and cortisol levels, explaining that due to constant stressful situations, the body gets used and cortisol secretion decreases (Fries, Hesse, Hellhammer and Hellhammer 2005; Wüst, Federenko, VanRossum , Koper & Hellhammer, 2005). This can explain the negative relationship between stress and cortisol levels because although perceived stress was assessed, the patients who participated in this study had already experienced multiple stressful events like the diagnosis of a chronic disease and invasive procedures such as biopsy and mastectomy.

Regarding coping strategies, fighting spirit and cognitive avoidance are the variables that most influenced cortisol levels. There are few studies showing the relationship between coping strategies and cortisol levels and the results are contradictory (Sjögren, Leanderson & Kristenson, 2006; O'Donnell, Badrick, Kumari & Steptoe, 2008).

From a psychological point of view, the direction of the relationship between the coping strategy of fighting spirit and cortisol levels is unexpected, since this strategy is considered positive. The patients who use it have an optimistic view of cancer and take it as a challenge, with the determination to fighting the disease and not allowing their lives to be interrupted (Coyne & Tennen, 2010).

These results can be explained because assessing a condition as a challenge involves a perception of threat and a feeling of uncertainty as to what may happen in the future (Lazarus, 2000). Also, people who try to deal more effectively with stressful situations are more involved and this creates a potential stress for themselves (Mozkowitz & Folkman, 2004; Solberg, Segerstrom & Septhon, 2005).

The avoidance strategy is more used when an assessment of threat, damage or loss is done (Bigatti, Steiner & Miller, 2012) and, contrary to what was found in this study, it has been linked to increased anxiety and depression (Costanzo, Lutgendorf, Rothrock & Anderson, 2006; Donovan Kicken & Caughlin, 2011) and is not related to cortisol indicators (Dedert et al, 2012.), so it is important to conduct more studies to clarify the relationship obtained.

From a biological perspective, the relationship between cortisol levels and coping strategies of fighting spirit and avoidance is consistent with the classic behavioral response to a threatening condition, which is to fight or flight (McEwen, 2007). This is important since the activation of the HPA axis causes the secretion of cortisol to mobilize and make available the energy of the body so that it can respond to the demands of the environment.

The main limitations of this study are the amount of participants, the lack of a control group and the low internal consistency of the LOT and MAC instruments obtained in this

sample. To validate data in future investigations, a healthy control group and patients in stage IV must be included. However, the findings of this study are important because relationship between psychological variables such as stress and coping strategies was found a noted at the beginning, the relationships found in other studies are limited.

An important implication of the results of this study is the need to reassess the fighting spirit strategy and analyze its management in a psychological intervention. Although it is considered as a strategy for positive coping and generating a better adjustment to the cancer disease,- understanding this as less anxiety and depression (Cordova et al., 2003), other studies suggest that encouraging the fighting spirit sometimes is counterproductive in patients, because they do not know how to maintain this attitude throughout the process of the disease and sometimes this can be maladaptive (Spiegel, 2001; Watson, Haviland, Bliss & Davidson, 2000). Some studies also suggest that the avoidance strategy can be adaptive and allows the inhibition of cortisol information that is not relevant to the target (Master et al, 2009, Putman & Roelofs, 2011). This indicates that the studies on the interaction between these variables should be deepened.

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