Association between life events after diagnosis of breast cancer and metastasis

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Abstract *The objective was to examine the association between life events post diagnosis of breast câncer and metastasis. Cross-sectional study with 300 women attending a reference hospital in oncology in the Espírito Santo. Was used the instrument Life Events Units-LEU/VAS to evaluate life events reported by women. Data were analyzed by using the nonparametric Wilcoxon and chi-square tests. It was performed odds ratio calculation for the variables associated with metastasis. It was found that 21% of the sample reported at least one life event post diagnosis. Of the 46 women who developed metastases, 20 reported one or more life events (p = 0.001). The odds ratio calculated shows that having life events post diagnosis increases by 2.59 (1,37 – 4,91; p = 0,003) times the chance of developing metastasis. When considering the time between diagnosis and the onset of metastasis there was a median of 18.0 months. The study shows a relationship between life events and metastasis, however emphasize the importance of a more complex analysis to better understand the impacts of these events on the onset and progression of breast cancer.*
Key words *Breast neoplasms, Life change events, Stress, Neoplastic metastasis*

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Introduction

Do stressful life events cause breast cancer and/or its progression? Many studies have tried to answer this question in recent decades. Taking into account that the relationship between the mind and the body is complex, the results of investigations have been inconsistent and contradictory.

Authors[1-3] suggest that psychosocial factors have powerful modulatory effects on the course of cancer. Although this conception is the subject of some controversy, it is not unacceptable, since variability in the progression of the neoplasm is determined not only by aspects related to the tumor, but also by particularities of the host[4].

Stressful life events can favor growth of cancer and metastasis, through modulation of the nervous, endocrine and immunological systems[5], and researchers[3,6-8] have sought to improve knowledge of this association.

Further, some researchers[9,10] on stress, and the process of facing it, have shown an action on the immune system intermediated by stress causing a reduction of 'natural killer' cells and consequently progression of cancer.

All prolonged exposure to stress causes an activation of the endocrine system through the Hypothalamus-Hypothesis-Adrenal (HHA) system, and as a consequence results in an increase in the production of cortisol. This process of increase in the level of cortisol prejudices the organism in the exercise of its activities over the long term and causes immunosuppression of the body, leaving it susceptible to a variety of threats[3].

The body has been programmed in such a way that moments of stress, followed by a physical reaction of the fight-or-flight type, cause little damage. However, when physiological response to stress is not discharged, a cumulative effect in the body begins. In the short term, stress hormones are essential to human survival[11,12]. However, a continuously maintained response to stress, that is to say, chronic stress, causes permanent disorders[13].

The objective of this study was to examine the association between metastasis and life events after diagnosis of breast cancer in women attended by a reference hospital in the state of Espírito Santo, Brazil.

Methodology

This was a cross-sectional study, made in the *Ylza Bianco* outpatient unit of the *Santa Rita de Cássia* Hospital (HSRC), maintained by the Feminine Association for Education on and Combating Cancer (*Associação Feminina de Educação e Combate ao Câncer*) in the city of Vitória, capital of the Brazilian state of Espírito Santo. HSRC is a philanthropic entity recognized throughout the state as a reference in cancer treatment, which also makes available general specialties.

The *Epidat* program was used to calculate the size of sample for estimating prevalence of at least one event taking place after diagnosis in women with breast cancer. Considering a target population of 2,000 women, expected prevalence of 50%, sampling error of 5.5% and level of significance of 5%, the minimum size of the sample was 274 patients. The researcher executed a sampling plan, considering the five working days and the morning and afternoon shifts randomly in the period of collection. Women were approached randomly, comprising a total of 300 women in the sample.

The criteria for inclusion were: women, aged 18 or more, with diagnosis of breast cancer. As a criterion for exclusion: patients who presented cognitive deficits preventing them from understanding the study.

Data were collected during the months of September and December 2014. The questionnaire was applied at one single moment. The sample included women with recent diagnosis, women who were in treatment and women who were already cured.

The instrument used was Life Events Units – LEU/VAS, which is based on Holmes and Rahe's[14] Social Readjustment Rating Scale – 1967, adapted and validated by Vasconcellos et al.[15]. It is based on the idea that the difficulty required for the person to readjust to society, after significant changes in the person's life, pleasant or otherwise, generates a wear-and-tear factor that can lead to illnesses.

The LEU/VAS is a list of 51 events that measure the intensity and duration of the time necessary for adaptation to a life event and is based on the concept that any change, pleasant or unpleasant, is considered to be a stressful factor. The instrument also presents the possibility of including other life events that are not part of the original list, but which can be mentioned by the women during the interview. The participants were questioned as to the occurrence and repetition of some significant event with marked effect in their lives, as to: the date (year) of the episode; the aspect of the event (positive or negative); the impact caused on their respective lives (on a scale

from 10 to 100); and whether the episode had happened to them or to another person.

Although the LEU/VAS considers the possibility of the event having occurred more than once, this study considered only the first occurrence of the events, since the majority of the women related occurrence of each event only one time. Further, only events taking place after the cancer diagnosis were used.

Data on the socio-demographic and clinical variables were also collected through the SIS-RHC (Health Information System Hospital Cancer Records [*Sistema de Informação em Saúde – Registro Hospitalar de Câncer*]), as a source of secondary data of the hospital. Medical records of some patients were used to complete material information that was not found in the database.

For analysis, the data were organized in the program Microsoft Office Excel 2007 for Windows, and analyzed using the Social Sciences Statistics Package (*Pacote Estatístico para Ciências Sociais* – SPSS), version 20.0. The results were analyzed using calculations of frequency, average, median and standard deviation. The non-parametric Wilcoxon test was also applied for comparison of the data obtained at different moments (verification was not made of the normality of the data which was constituted on a mark from zero to 10); and the chi-squared test was used to verify the association between the variables of the process and the number of life events. Associations were tested for the variable metastasis; and odds ratio was calculated for the variable number of life events. The level of significance adopted was 5%.

The study was submitted to and approved by the Research Center of the *Santa Rita de Cássia-Afecc* Unit, and the Research Ethics Committee of the Health Sciences Center of the Federal University of Espírito Santo, as research project Nº. 804020.

Results

Table 1 presents the social-demographic, clinical and risk characterization of the women. It is seen that 63% of the sample are aged 50 or more, and that there is predominance of the *non-white* race/color variable (65%), and women with less than eight years' schooling (64%).

It is noted that 54% of the women were married or in a stable union (n = 162), 43% had remunerated activity, 190 reported living on up to two times the minimum wage (63%), 187 lived in

Greater Vitória (62%), 166 lived in a house with three or more other people (55%) and 292 had some religious or spiritual belief (97%).

Table 1. Socio-demographic, clinical and risk characteristics of women with breast cancer attended by the Santa Rita de Cássia Hospital/Afecc, Vitória, 2014.

Variables	n	%
Age group		
Up to 39	27	9.0
40 to 49	84	28.0
50 to 59	104	35.0
60 to 69	65	22.0
70 and over	20	6.0
Race/color		
White	105	35.0
Non-white	195	65.0
Years of schooling		
Up to 7	193	64.0
8 and more	107	36.0
Marital status		
Single	52	17.0
Married/stable union	162	54.0
Divorced/separated	46	15.0
Widowed	40	13.0
Family income		
Up to 2 x minimum wage	190	63.0
3 to 4 x minimum wage	81	27.0
Over 4 x minimum wage	29	10.0
Physical activity		
None	242	81.0
1 or 2 times per week	16	5.0
3 or more times per week	42	14.0
Consumption of alcoholic beverages		
Never	154	51.0
Rarely/socially/weekend	12	4.0
Former consumer	134	45.0
Smoking		
Non-smoker	204	68.0
Ex-smoker	84	28.0
Present smoker	12	4.0
Family breast cancer history		
Yes	95	32.0
No	205	68.0
Stage of the disease		
Initial (I and II)	140	47.0
Advanced (III and IV)	160	53.0
Metastasis		
Yes	46	15.3
No	254	84.7

As to physical activity, a large part of the sample (81%) were sedentary (n = 242). It was observed that 154 women had never ingested alcoholic beverage (51%), 204 were non-smokers (68%), and 205 (68%) had no family history of breast cancer. Most of them were at a late stage (53%) with absence of metastasis (84.7%).

Figure 1 shows the total of life events experienced by subjects after the diagnosis of breast cancer. It is seen that 21% reported having experienced at least one life event and 79% did not report any event.

As to the time elapsed between diagnosis of breast cancer and the life events, and to whom the event happened, Table 2 shows that the event 'death in the family' was the most reported by the subjects (7.7%), with only negative classification. In relation to the time between diagnosis and the event, a median of 4.0 and a standard deviation of 3.0 was observed. We further note that, in all the cases, it was the women themselves who experienced this event.

The event 'Prison', also with classification only negative, was reported by 17 women (5.7%). The time elapsed between diagnosis and the event had a median of 3.0 (SD = 3.7) and in all the cases, the event happened to other people.

It is found that the conjugal events 'death of conjugal partner' and 'divorce' are among those most quoted by the women. 'Death of partner' was reported by six women (2%), and all of them classified it as a negative event. The median of the time between diagnosis and the event was 7.0 (SD = 5.5). 'Divorce' was cited by five patients (1.7%), all with negative classification, the median being 1.0 (SD = 1.3) for the time elapsed between diagnosis of the breast cancer and the respective life event.

The event 'change in financial condition' was also among the most reported (2%). It presented only a negative classification and the median of time elapsed between diagnosis and the event was 1.0 (SD = 1.2), in all cases experienced by the patients themselves.

Table 3 examines the impact that the event caused on the life of the woman when it happened and the possible impact that it could still exercise at the moment of the interview. The patients who reported 'death in the family', when questioned about the burden of the event on a scale from 10 to 100, presented a median of 100.0 (SD= 16.5) and for the burden that the event could still exercise in their life at the moment of the interview, a median of 50.0 and standard deviation of 38.5 (p = 0.001).

In relation to 'prison' the median of burden at the moment when the event took place in fact was 100.0 (SD= 23.4), and when questioned at the moment of the interview the median was 10.0 (SD= 30.6), showing a considerably significant reduction (p = 0.001).

The event 'death of conjugal partner' first presented a median of 100.0 (SD = 25.8), and underwent a not very strong reduction to 65.0 (SD = 37.6), there being no statistical significance.

There was a significant reduction of burden in relation to the event 'Divorce', in that the median moved from 100.0 (SD =11.0) to 10.0 (SD = 39.7), in spite of not having been significant.

The variables of the profile were associated with the number of life events, but the results were not significant, with the exception of the variable metastasis. It was observed that in the group without events, 26 women (11.0%) presented metastasis, and that this percentage rose to 31.7% (total of 20 women) in the group with one event or more (p = 0.001). The time elapsed between the diagnosis and occurrence of metastasis in the 46 women had a median of 18.0 months (SD = 36.9).

On the basis of this result the association of possible factors of confusion for the outcome metastasis was calculated. Table 4 shows the association between profile variables, clinical variables and the number of life events, and the variable metastasis. The results indicate the stage factor of the disease as a possible confusion factor, but all the metastasis occurred in the advanced stage, it not being possible to use multivariate models. Through the calculation of the odds ratio it was
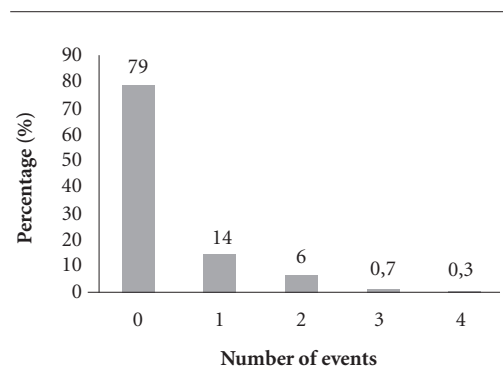
Figure 1. Total of events (%) experienced by women with diagnosis of breast cancer attended at Santa Rita de Cássia Hospital – Vitória, Brazil, 2014.

Table 2. Time, in years, between diagnosis of breast cancer and life events, and the person to whom the event happened – Vitória, Brazil, 2014.

Life events	Classification of the event	Total		Time in years from diagnosis to event			To whom event happened	
		N	%	Average	Median	SD	You	Others
1. Death in the family	Negative	23	7,7	4,4	4,0	3,0	23	0
2. Prison	Negative	17	5,7	4,5	3,0	3,7	0	17
3. Death of a conjugal partner	Negative	6	2,0	7,3	7,0	5,5	6	0
4. Change in financial condition	Negative	6	2,0	1,7	1,0	1,2	6	0
5. Divorce	Negative	5	1,7	1,8	1,0	1,3	5	0
6. Accident/illness	Negative	5	1,7	3,8	4,0	1,9	2	3
7. Illness in the family	Negative	4	1,3	8,3	8,5	3,3	4	0
8. Family problems	Negative	4	1,3	3,5	3,0	3,0	4	0
9. Death of intimate friend	Negative	3	1,0	3,7	5,0	2,3	3	0
10. Birth of child	Negative	1	0,3	4,0	4,0	-	0	1
	Positive	1	0,3	5,0	5,0	-	1	0
11. Child leaves home	Negative	2	0,7	6,0	6,0	1,4	2	0
12. Loss of job	Negative	1	0,3	6,0	6,0	-	1	0
13. Reconciliation with partner	Positive	1	0,3	1,0	1,0	-	1	0
14. Retirement	Positive	1	0,3	2,0	2,0	-	1	0
15. Separation of couple	Negative	1	0,3	4,0	4,0	-	1	0

SD = Standard deviation.

Table 3. Comparison of burden caused by life event at the moment when it happened and at moment of interview - Vitória, Brazil, 2014.

Life events	Classification of the event	Score at that time				Score at interview				Wilcoxon p-value
		N	Average	Median	SD	N	Average	Median	SD	
1. Death in the family	Negative	23	90.9	100.0	16.5	23	51.3	50.0	38.5	0.001
2. Prison	Negative	17	86.5	100.0	23.4	17	27.1	10.0	30.6	0.001
3. Death of a conjugal partner	Negative	6	83.5	100.0	25.8	6	61.7	65.0	37.6	0.066
4. Change in financial condition	Negative	6	100.0	100.0	0.0	6	56.7	60.0	42.3	0.066
5. Divorce	Negative	5	92.0	100.0	11.0	5	36.0	10.0	39.7	0.066
6. Accident/illness	Negative	5	86.0	100.0	21.9	5	36.0	10.0	39.7	0.068
7. Illness in the family	Negative	4	77.5	80.0	26.3	4	50.0	45.0	37.4	0.180
8. Family problems	Negative	4	100.0	100.0	0.0	4	80.0	85.0	24.5	0.180
9. Death of intimate friend	Negative	3	83.3	100.0	28.9	3	46.7	50.0	35.1	0.109
10. Birth of child	Negative	1	90.0	90.0	-	1	90.0	90.0	-	0.180
	Positive	1	100.0	100.0	-	1	100.0	100.0	-	0.180
11. Child leaves home	Negative	2	100.0	100.0	0.0	2	65.0	65.0	7.1	0.180
12. Loss of job	Negative	1	90.0	900.0	-	1	10.0	10.0	-	0.180
13. Reconciliation with partner	Positive	1	100.0	100.0	-	1	10.0	10.0	-	0.180
14. Retirement	Positive	1	10.0	10.0	-	1	10.0	10.0	-	0.180
15. Separation of couple	Negative	1	100.0	100.0	-	1	50.0	50.0	-	0.180

SD = Standard deviation.

concluded that having life events after diagnosis of breast cancer increased the chance of developing metastasis by 2.59 times (1.37 – 4.91; p = 0.003).

Table 4. Association between profile variables, clinical variables and number of life events, and the variable *metastasis* – Vitória, Brazil, 2014.

Variable	Category	sim		não		χ² p-value	OR (CI 95%)**
		N	%	N	%		
Age group	Up to 39	3	11%	24	89%	0.451	
	40 to 49	16	19%	68	81%		
	50 to 59	18	17%	86	83%		
	60 to 69	8	12%	57	88%		
	70 and over	1	5%	19	95%		
Family income	Up to 2 x min. wage*	27	14%	163	86%	0.778	
	3 to 4 x min. wage	14	17%	67	83%		
	Over 4 x min. wage	5	17%	24	83%		
Years' schooling	Up to 7 years	21	14%	133	86%	0.402	
	8 years or more	25	17%	121	83%		
Race/color	White	16	15%	89	85%	0.973	
	Non-white	30	15%	165	85%		
Marital status	Single	8	15%	44	85%	0.277	
	Married/stable union	30	19%	132	81%		
	Divorced/separated	5	11%	41	89%		
	Widowed	3	8%	37	93%		
Diagnosis stage	Initial (I and II)	0	0%	140	100%	**0.001**	
	Late (III and IV)	46	29%	114	71%		
Life events	None	26	11%	211	89%	**0.001**	**2.59**
	1 or more	20	32%	43	68%		**(1.37 – 4.91)**

* min. wage = minimum wage. ** OR (CI 95%): Odds ratio (confidence interval 95%)

Discussion

The results of this study point to an association between life events and metastasis. It is a complex task to establish the exact dimension to which stress, rather than some other factor or combination of factors, is the element responsible for changes observed in the development of the breast cancer.

Breast cancer is the most common cancer in women. In spite of the relationship between psychological aspects and breast cancer being increasingly studied, few studies have dealt with the relationship between life events and relapse or metastasis.

Any cancer diagnosis, but especially breast cancer, is accompanied by great psychological suffering, and the majority of people believe that their psychosocial response, that is to say, the way in which they react to the diagnosis, affects their prognosis[16].

A stressful life event can affect the prognosis of breast cancer directly through alterations induced by stress of the immune system and neuroendocrine system, and indirectly through changes in health behavior, such as physical activity, consumption of alcohol, submission to treatment, and facing of the illness[17].

This study shows that 21% of the sample experienced at least one life event after the diagnosis of breast cancer. Further, the time elapsed between the diagnosis of the cancer and the occurrence of metastasis had a median of 18 months. In one case control study[7] with 100 women, the median time free of illness for the women who had a relapse or metastasis was 30.5 months.

When comparing a group of American women with breast cancer, some researchers[3] found an interval free of illness significantly greater among those who did not report traumatic or stressful life events (median = 62 months), compared to those who had experienced one or more stressful or traumatic event (median = 31 months).

In the sample of 300 women, 46 of them presented metastasis (15.3%). A result that was different, but not so distant, was found in a cohort

study[18] with 204 women, the objective of which was to assess whether adverse life events would shorten the time free of illness post-surgery in patients with breast cancer: the result found was that 23% of them presented metastasis. A cohort[8] of 202 women with breast cancer accompanied for five years in London confirmed a relapse of the illness in 54 of them (26.7%).

Another study[19], on a population basis, in which 708 Australian women with breast cancer were accompanied for approximately eight years, showed that 38% of the 638 women studied had a relapse.

The association between the variable metastasis and the number of life events showed that 20 of the women who presented metastasis experienced one or more life events (p = 0.001). In spite of having evaluated only women who had already evolved to metastasis, a retrospective study[3] with 94 women showed that 70.2% of them reported one or more stressful or traumatic event.

A retrospective study[7] with 50 cases and 50 controls, in London, when evaluating the risk of relapse of breast cancer, showed that the relative risk of relapse associated with a serious life event was 5.67 (p = 0.004). A very different result was found in a cohort[8] of five years with 202 women with breast cancer, where those who had had one or more stressful life events in the five years after the diagnosis had a lower risk of recurrence (p = 0.03) than those who had not. Another study[6], which aimed to assess the relationship between life events and survival of 665 women after breast cancer, showed no association.

As to the types of life event experienced by the subjects, events involving death, conjugal or family problems and events related to the illness are the most reported. The studies that deal with this theme of life events and metastasis or relapse usually discuss only the presence or absence of events, often comparing the sub-categories (severe events, traumatic events, life events, absence of events), which tends to make a comparison of results on this aspect of the types of event more difficult.

A retrospective study referred to above[3] showed the types of events that the women with metastatic breast cancer reported: 19% reported rape, aggression or abuse in infancy; 16% survived a potentially fatal accident; 4% underwent a natural catastrophe; 9% were present at a traumatic event or a death due to the illness; 26% reported death of loved ones due to an accident or illness; 3% reported the death of a son; and 14% reported an event threatening the life of one or more loved ones due to accident or illness.

Isolated occurrence of a stressful event does not cause negative effects for the individual. The result of the effects will depend on how each person reacts to or confronts a given situation. Thus, it is the way of reacting to situations that makes the difference in susceptibility to the disease[20]. This endorses the importance of studying not only the life event, but also the impact caused by it.

As to the impact caused by the event at the moment of its occurrence and possible continuing impact at the moment of the interview, a considerable reduction was seen in a good proportion of the events, principally 'death in the family' and 'prison', which were significant (p = 0.001). It is inferred that the subjects, in spite of initially attributing very high scores to the event at the moment of its occurrence, were able to confront the situation experienced, thus reducing the burden over time.

An illness is not only a physical fact, but a problem that relates to the person as a whole, including not only the body, but also the emotions and the mind. Emotional and mental conditions carry out a fundamental activity both in relation to susceptibility to illness, including cancer, and in recovery from any illness[21]. Thus, every event experienced by an individual leads him/her to disappointments and feelings of loss, but the way in which the person will attribute significance to a given situation will also indicate the circumstance in which the organism will function. A simulation of the experience seems to be decisive in the emergence of illnesses and, essentially, in their progression.

We highlight that one of the principal limitations of this survey is its being cross-sectional, since researchers on this subject have given priority to cohort and case/control studies. Due to memory bias, the ideal situation would be a prospective cohort in which life events were observed over time, but this would call for time and funds. Also emphasized as a limitation is the low availability of present-day references on the subject of life events, principally when associated with metastasis.

Final considerations

Although there is a lot of discussion, and controversial results, on life events and cancer, this study shows a significant association between life

events after diagnosis of breast cancer and the appearance of metastasis.

Even though most life events cannot be simply avoided in people's daily lives, the results help to provide the scientific community with different possibilities for exploring this subject which still requires so many answers.

The results presented by this study emphasize the need for a more complex analysis, and also a qualitative approach, for better understanding of the impacts caused by life events in the growth and progression of breast cancer, and also the possible risks involved in this relationship.

Collaborations

CS Dourado worked on the design, design, analysis and interpretation of the data, as well as on the writing of the article, on the critical revision and approval of the version to be published. C Brandão de Souza worked on the writing of the article, on the critical revision and approval of the version to be published. DS Castro and MHMB Miotto worked on the critical review and approval of the version to be published. E Zandonade worked on the analysis and interpretation of data and approval of the version to be published. MHC Amorim worked on designing, designing, analyzing and interpreting the data, as well as writing the article, critically reviewing and approving the version to be published.

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