


# Breast cancer: Is grief a risk factor?

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## SUMMARY

*Cancer is characterized by the disordered growth of cells that have high capacity of invasion to the tissues and organs. One of the types of tumour that has national incidence and high mortality is breast cancer. Studies show that in addition to hereditary factors, lifestyle and environmental factors, there are factors related to emotional distress (mourning), which interfere with the development of breast cancer. Thus, it is necessary to investigate if the experience of mourning can trigger the appearance of the tumour. For this, an integrative review was performed to verify the existence of the relationship between mourning and development of breast cancer, which presented contradictory results. Methodological errors and lack of access to important information, such as alcohol and tobacco use, were pointed out as the main causes of the contradiction found. A possible mechanism involving cortisol release has been proposed, but more research is needed to make it clear whether the association between mourning and breast cancer really exists, and by what path.*

**KEYWORDS:** Mourning. Death. Risk factors. Breast neoplasms.

## INTRODUCTION

Characterized by a set of more than 100 diseases that have in common the disordered growth of cells that invade tissues and organs, cancer accounts for one of the highest death rates in the world. Among its different types, breast cancer is the one with the highest incidence and mortality among women<sup>1,2</sup>.

The causes of this pathology are varied, being external or internal to the organism, both being interrelated. The main factors associated with breast cancer are age, family history, use of contraceptives, alcohol consumption, smoking, previous breast disease, radiation exposure and obesity<sup>3</sup>. In addition, emotional state, stress, depression and be-

reavement have also been investigated as risk factors for this type of cancer<sup>4</sup>.

For Angerami-Camon<sup>5</sup>, the conflicts and emotional problems experienced, such as the loss of a relative and separation between spouses may affect emotional health and come to determine the illness. In this sense, research indicates that the appearance of the tumour is attributed to the inadequate way of coping with traumas experienced in the past<sup>4,6</sup>. As reported by the patients, the tumour physically externalized many painful experiences that were “stored” by them.

As a possible physiological explanation, Li et al.<sup>7</sup> state that the balance of neuroendocrine hormones in women is easily affected by psychological trauma

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and that long-term adverse emotional experience can cause hyperplasia in mammary epithelial cells, leading to tumour development. In this sense, the definition of a cellular mechanism that establishes the relationship between these variables (psychological trauma, neuroendocrine hormones and development of breast cancer) will bring new perspectives for the preventive treatment of this disease, and may introduce, in the traditional care plan, special attention to the mourner.

This study aimed to verifying if it is possible to affirm, based on existing data, that there is an association between mourning and breast cancer. In addition, to alert the societies of medicine and psychology to the need for new research on the subject and the inclusion of questions about mourning in the anamnesis of patients with breast cancer.

## METHODS

This work was developed from an integrative review, using the descriptors bereavement, grief and mourning, crossed with risk, risk factors and breast cancer to survey the population and define the sample. The database used was PubMed and the population obtained was 39 articles, which were read and analysed (Table 1, page 18). According to the inclusion and exclusion criteria adopted by the study, only nine articles were selected for the sample and one was added by reverse search (Table 2, page 19).

Inclusion criteria were approach to grief as a risk factor for the development of breast cancer and the availability of articles on the internet in its entirety. The exclusion criterion adopted was articles written in languages other than English and Portuguese.

**TABLE 1** – SEARCH STRATEGY

| Source                           | Search strategy   | Population | Sample |
|----------------------------------|---|------------|--------|
| PubMed                           | <i>risk factors AND breast cancer AND bereavement</i>                                 | 13         | 6      |
| PubMed                           | <i>risk factors AND breast cancer AND grief</i>                                       | 12         | 4      |
| PubMed                           | <i>risk factors [MeSH Terms] AND breast cancer [MeSH Terms] AND mourning</i>          | 7          | 2      |
| PubMed                           | <i>((risk[MeSH Terms]) AND breast cancer[MeSH Terms]) AND bereavement[MeSH Terms]</i> | 7          | 3      |
| Articles excluded per repetition | -   | -          | 6      |
| Reverse search                   | -   | -          | 1      |
| Total                            | -   | 39         | 22*    |

\* The sample was only nine articles since some of them were found in more than one search.

**TABLE 2** – ARTICLES SELECTED FOR THE SAMPLE

| Author            | Title   | Year | Source         | Reference |
|-------------------|---|------|----------------|-----------|
| Biondi et al.     | Can loss and grief activate latent neoplasia? A clinical case of possible interaction between genetic risk and stress in breast cancer.                       | 1996 | PubMed         | 19        |
| Cooper & Faragher | Psychosocial stress and breast cancer: the inter-relationship between stress events, coping strategies and personality  | 1993 | PubMed         | 9         |
| Hiller            | Breast cancer: a psychogenic disease?   | 1989 | PubMed         | 15        |
| Kvikstad et al.   | Death of a Husband or Marital Divorce Related to Risk of Breast Cancer in Middle-aged Women. A Nested Case-Control Study Among Norwegian Women Born 1935-1954 | 1994 | PubMed         | 10        |
| Lambe et al.      | Maternal breast cancer risk after the death of a child  | 2004 | PubMed         | 13        |
| Li et al.         | Cancer Incidence in Parents who Lost a Child  | 2002 | PubMed         | 11        |
| Li et al.         | Cancer survival in parents who lost a child: A nationwide study   | 2003 | PubMed         | 12        |
| Nakaya            | Effect of psychosocial factors on cancer risk and survival  | 2014 | PubMed         | 20        |
| Wellisch & Cohen  | The special case of complicated grief in women at high risk for breast cancer   | 2010 | PubMed         | 14        |
| Parkes            | Coping with loss: Bereavement in adult life.  | 1998 | Reverse search | 24        |

## RESULTS

Observations and personal impressions during the 18<sup>th</sup> century were the basis for the first statistical study conducted by Snow<sup>8</sup> at the London Cancer Hospital. He found that of the 250 cancer patients, 156 reported previous experience with the loss of close relatives. Likewise, Cooper & Faragher<sup>9</sup> identified a correlation between the prevalence of breast cancer and the impact of stress related to emotional trauma, such as mourning. However, Kvikstad et al.<sup>10</sup> did not identify a positive association between the bereavement caused by the husband's death or a divorce and the increased risk of developing breast cancer.

Trauma can be defined as an important and intense event in a person's life, where the inability to react to the event properly is the main factor. This incapacity correlates with the adverse effects that the traumatic event can cause in the psychic organization of the individual, generating an emotional state characterized by an increase in anxieties and fears, as well as an altered perception of the world and yourself<sup>6</sup>.

According to Li et al.<sup>11</sup>, the belief that psychological stress causes malignancies has a long history, but scientific evidence remains contradictory. This, according to the study, is the result of errors in the methodology used, such as the use of inadequate control, the carrying out of prospective studies with limited observation period due to patient loss, as well as data based on personal reports. Despite the caution with the definition of the methodology, the author clarifies that the lack of access to important information (lifestyle, alcohol and tobacco use) was responsible for the contradiction observed in two of his papers, in which the first one identified the increase for the risk of cancer in mothers who had lost children<sup>11</sup>, but not the second one<sup>12</sup>.

Lambe et al.<sup>13</sup> found a significant increase in the incidence of breast cancer in women who lost their only children between 1 and 4 years of age. In the study by Grzybowski, Schmidt & Borges<sup>6</sup>, breast cancer patients reported believing in the association between the development of neoplasia and previous emotional trauma, such as the death of a loved one. Wellisch & Cohen<sup>14</sup> investigated, in a population of women whose mothers developed breast cancer, bereavement as a risk factor for the disease. The study shows not only the presence of the relationship between chronic mourning and neoplasia, but also the

need that this group presents in relation to preventive healthcare.

According to Hiller,<sup>15</sup> for humans, emotional losses appear to be related to the immunosuppressive state. The author reports that clinicians have already described the role of depression, loss, sadness and anxiety in the aetiology of breast cancer in the 19<sup>th</sup> century. Galen (quoted by HILLER<sup>15</sup>) was the first clinician to report that women who had severe melancholia were more likely to develop breast cancer. Gendron (quoted by HILLER<sup>15</sup>) in 1701 noted that women suffering from depression and anxiety were prone to the development of cancer. Moreover, about 50 years later, Richard Guy (quoted by HILLER<sup>15</sup>) reported the case of a woman who developed breast cancer after a period of depression resulting from the loss of a child.

The observation that there was a personality type prone to the development of cancer and the existence of an association between an emotional state and breast cancer have been reported by other clinicians. The predisposition to the disease seems to be linked to women with a hysterical, melancholic, depressed, sexually inhibited profile and unable to discharge anger; such a correlation was not found when analysing a profile of women who have healthy life habits and who are more emotionally balanced<sup>15</sup>.

Cooper & Payne<sup>16</sup> reported that the relationship between psychosocial stress antecedents to the disease has been recognized for centuries. They also stated that most of the research was in the cardiovascular area, but more recently, it has been described in several types of cancer, including gastric, lung, breast and paediatric carcinomas. In addition, Cooper<sup>17</sup> adds that although studies in the area of oncology present methodological errors, they point to an important relationship between the occurrence of previous stress events (within a period of five years) and the subsequent diagnosis of breast disease.

Lerman & Schwartz<sup>18</sup> found that women at increased risk for breast cancer experienced specific or generalized psychological distress. Paget (quoted by BIONDI<sup>19</sup>) reported that the number of cancer patients reporting large losses and depressions prior to breast cancer is high, making clear the presence of an association between mental depression and the development of breast cancer.

However, the contradiction in the results found, coupled with the complexity of the disease and the lack of clarification about the cellular mechanisms

that proved the link between these risk factors and the development of breast cancer, resulted in an interest decline in the research of these psychological factors as cancer risk factor during the 20<sup>th</sup> century.

The reactivation of interest in the study of the connection between emotional losses and cancer, as well as in the relation between the mind, pathogenesis and progression of this disease, has been attributed to the emergence of research in the areas of psychoneurology and psychoneuroimmunology<sup>17</sup>. According to Li et al.<sup>12</sup>, emotional stress can alter immune function and influence tumour growth, metastasis and survival of cancer patients.

According to Nakaya,<sup>20</sup> psychosocial factors, such as personality types and depression, can also alter immune and endocrine function and thus affect the incidence and survival of cancer patients. Studies have reported the reduction of cellular immunity (immunosuppression) in women after the death of the partner<sup>21,21</sup>.

The effect on the immune system caused by stress seems to be of particular importance during childhood, at which point the neuroendocrine system is developing. In this sense, an increased risk for the development of cancer was identified among children who lost a close relative during the first 15 years of life, as well as an increased risk of this condition in children exposed to stress during the prenatal period<sup>23</sup>. However, Nakaya<sup>20</sup> did not find data that supported the hypothesis that personality and depression were risk factors for the development of cancer and survival of the patient in the face of the disease. They added that, if such an association exists, it is unlikely to have clinical or public health implications.

Parkers<sup>24</sup> and Cohen & Rabin<sup>25</sup> stated that the existence of physiological changes related to depression, particularly pain, induces the development of cancer or becomes a stimulus for the activation of pre-existing cancer (latent pathology). In this sense, Biondi, Constantini & Parisi<sup>19</sup> and Hiller<sup>15</sup> concluded that stress does not generate cancer, but it can activate latent pathology. As for Riley<sup>26</sup>, Bammer & Newberry<sup>27</sup> and Newberry, Gordon & Meehan<sup>28</sup>, emotional stress interferes with both the onset and progression of cancer.

In an interesting experimental study, Riley et al.<sup>29</sup> used a hybrid strain of female mice, in which the maternal parental line was inoculated with an onco-

genic virus. The development of the tumour, for the hybrid mice, only occurs between 8 and 18 months after birth in 80% to 100% of the cases. In the study it is possible to notice that, after stress induction, tumour development was altered in 92% of the animals when compared to the control group and that this result was mediated by the neuroendocrine and immunological systems.

In the present study, the authors report that emotional stress increased plasma corticosterone concentration (from 40 ng/mL to more than 700 ng/mL) and reduced the size of the thymus and number of natural killer (NK) cells, which participate of the body's natural defence against tumour cells<sup>29</sup>. According to Ben-Eliyahu,<sup>30</sup> these factors may lead to increased susceptibility to the development of breast cancer and metastasis.

For Hofer<sup>31</sup> and Irwin<sup>32</sup>, in addition to the reduction of NK cells, depression is also related to the constant activation of the hypothalamic-adrenal-pituitary axis and the high concentration of cortisol. It has been shown that neuroendocrine hormones (cortisol, adrenaline, and prolactin, among others) may influence the biology of cancer<sup>33</sup>.

Corroborating these results, Biondi et al.<sup>19</sup> verified that psychological stress and depression affect the endocrine and immune systems, and may contribute to neoplastic growth due to increased cortisol, prolactin and oestrogen, or by reducing the number and activity of lymphocytes and NK cells<sup>29,30</sup>.

In addition, behavioural studies have shown that people with a upset and depressed emotional state have higher consumption of alcohol and cigarettes, substances widely known as carcinogenic factors, that is, they are substances capable of interacting with the DNA molecule causing changes that allow the development of cancer<sup>34,35</sup>.

## CONSIDERATIONS AND CONCLUSION

A topic of general interest is the knowledge of how important changes in life may be related to the onset of cancer. Among these changes, to many the loss of a beloved one is experienced intensely, often accompanied by chronic stress and depression, and it has been associated with pathologies.

However, the intensity and duration of the state of stress or depression, as well as the consumption of alcohol and tobacco, whether or not due to this state, are different for each person and have been pointed

out as factors that may confuse and hinder proof of this hypothesis.

Errors in the methodology used, the limitation of the study due to patient loss, studies based on personal observation, inadequate control of confounding factors and the non-inclusion of important information are also pointed out as causes for this difficulty. In addition, stressed individuals are more likely to have health habits that put them at great risk of cancer, such as drug abuse, excessive alcohol consumption, less exercise, and poor diet. The lack of detailed information about individual behaviours such as smoking, physical activity, alcohol consumption and diet, can lead to a wrong association between death and cancer.

Another important point that compromises the validation of this hypothesis is the lack of definition of a cellular mechanism that links mourning to the development of breast cancer, that is, the identification of genetic and molecular changes resulting from this state. This has been attributed to a lack of appropriate technology, but with recent advances in knowledge, new possibilities for advancing this research are emerging.

The proposed biological mechanism for the risk of stress-related cancer includes neuroendocrine changes in the hypothalamic-adrenal-pituitary axis, which regulate the release of glucocorticoids, cortisol levels, catecholamine and reactive species that damage DNA. These substances may alter the cellular immune response to malignant

cells, as well as affect tumour angiogenesis and increase the risk of development and progression of the disease. However, despite pointing to a cellular mechanism, the results define only the beginning of a signalling pathway and, therefore, the need for more research.

## PERSPECTIVES

The results clearly showed that despite the resumption of research, the relationship between bereavement and risk of breast cancer was not clarified and errors in the methodology continue to be mentioned as the main factor. In this sense, in order to make an effective progress, special attention to the definition of the methodology to be used is necessary. The inclusion of questions about grief in the anamnesis of patients with breast cancer may contribute to the advancement of the research.

Another important point concerns the follow-up by psychologists of patients who face grief, so that they can have support in the process of accepting the loss.

Regarding the mechanism, cortisol seems to be a mediator of several chronic emotional states resulting from bereavement. Therefore, prolonged (chronic) treatment of normal and breast tumour cell may be the way to investigate the cellular mechanism that correlates bereavement to the development of breast cancer and the effect of emotional state on the development of cancer.

## RESUMO:

*O câncer é caracterizado pelo crescimento desordenado das células que possuem alta capacidade de invasão aos tecidos e órgãos. Um dos tipos de tumour que possui incidência nacional e alta mortalidade é o câncer de mama. Estudos mostram que, além dos fatores hereditários, ambientais e dos hábitos de vida, existem fatores relacionados a um trauma emocional (luto) que interferem no desenvolvimento do câncer de mama. Dessa forma, é necessário investigar se a vivência do luto pode desencadear o aparecimento do tumour. Para isso, realizou-se uma revisão integrativa para verificar a existência da relação entre o luto e o desenvolvimento do câncer de mama, que apresentou resultados contraditórios. Os erros metodológicos e a falta de acesso a informações importantes, como uso de álcool e fumo, foram apontadas como as principais causas da contradição encontrada. Um possível mecanismo envolvendo liberação de cortisol tem sido proposto, mas são necessárias mais investigações para que fique claro se a associação entre luto e câncer de mama realmente existe, e por qual mecanismo ocorre.*

**PALAVRAS-CHAVE:** Luto. Falecimento. Fatores de risco. Neoplasias da mama.

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