Association between stress and breast cancer in women: a meta-analysis

Associação entre estresse e câncer de mama feminino: metanálise

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Abstract

The objective of the current meta-analysis was to verify the association between stressful life events and primary breast cancer incidence in women. A total of 618 studies from 1982-2007 were found in the PubMed, LILACS, and Cochrane Library databases. Methodological quality was evaluated according to the Downs & Black criteria. Eight studies were selected (six case-controls and two cohorts). The studies were grouped in three analyses, two of which based on the categories widowhood and divorce and the other based on self-rated intensity and frequency of stressful events. Relative risks were: widowhood 1.04 (95%CI: 0.75-1.44; p = 0.800); divorce 1.03 (95%: 0.72-1.48; p = 0.850); and intensity/frequency of stress 1.73 (95%CI: 0.98-3.05; p = 0.059). We conclude that stressful life events as a whole are not associated with risk of breast cancer in women. However, it is not possible to rule out high-intensity stress as a risk factor for breast cancer.

Life Change Events; Psychological Stress; Breast Neoplasms

Introduction

Breast cancer in women is one of the main public health problems worldwide, due to its magnitude (high morbidity and mortality) and transcendence (high social and economic cost). It has thus been the subject of extensive international discussion on risk evaluation [1,2].

Various risk factors for breast cancer have been established in both the Brazilian and international literature [3,4]. Among these factors, age is definitely the most important, followed by family history. Researchers agree that such factors have been the main focus for both the prevention and early diagnosis of breast cancer [4,5,6].

However, cancer in women has a multifactorial etiology and can originate from a combination of genetic, environmental, and lifestyle factors that make women susceptible to breast cancer [4,7].

Secondary factors like stress could have a less pronounced association, and would thus not necessarily be identified as risk factors in primary studies. A positive association between stress and breast cancer was observed in cohort studies [8,9] and some case-control studies [9,10,11,12,13,14,15], while other case-control studies do not indicate evidence of such an association [16,17].

A growing number of studies [18,19,20,21,22,23] have been conducted to investigate this possible causality, specifically linked to stressful life events: divorce, death of husband or child,

friend's illness, personal health problems, change in marital status (separation, divorce, or widowhood), change in financial status, or death of close relatives.

Two recent studies show conflicting results concerning the target event. A prospective cohort study concluded that stressful life events in women are associated with increased incidence of breast cancer [8]. There is a biological plausibility to this correlation, since high estrogen concentration is characterized as a risk factor for breast cancer, that is, inhibition of estrogen synthesis induced by chronic stress could explain the increased incidence of breast cancer in women exposed to high degrees of stress. Meanwhile, a case-control study indicated no correlation between stress and breast cancer incidence [20].

Thus, this possible association has not been based on sufficient clinical and epidemiological evidence, thereby leading to conflicting results. The findings from the above-mentioned studies motivated us to conduct the current systematic review, with the aim of searching the literature for evidence of an association between stressful life events and primary breast cancer incidence in women.

Methods

A systematic review and meta-analysis were conducted with primary cohort and case-control studies, with the following basic question: are women exposed to stressful life events at increased risk of developing breast cancer?

Search strategy

A systematic review was according to the Cochrane Handbook model produced by the Cochrane Collaboration [24]. We searched the MEDLINE (PubMed), LILACS (Latin American and Caribbean Health Sciences Literature), and Cochrane Library electronic databases to identify studies published from 1982 to July 2007.

The database search strategy used the Medical Subject Headings (MesSH) terms and proximity operators (* ; "") with the following combinations of terms and key words: *life events*, *adverse life events*, *breast cancer*, *female*, *stress*, *stressful*, *change events*, *case-control studies*, *cohort study*.

Inclusion and exclusion criteria

The following inclusion criteria were adopted for the studies: (a) type of study – prospective and historical cohort study and case-control study; (b) type of sample – women 18 years or older with first occurrence of breast cancer in cohort studies and in case-control studies with the appearance of the first breast cancer; (c) mean follow-up time – minimum of ten years in cohort studies, while in case-control studies no limit was set on the period between exposure and diagnosis; (d) type of variable – studies in which the stress variable was measured quantitatively; stress measured with a numerical scale, questionnaire, and checklist; stress measured against frequency of exposure and intensity of the event; (e) statistical type and analysis – studies that calculated relative risk (RR) for the first episode of breast cancer in relation to the stress variable, adjusting for the following confounding factors (age, use of oral contraceptives, any type of hormone replacement, menopause, alcohol intake, smoking, socioeconomic status, and family history of breast cancer).

The exclusion criteria for studies were: (a) articles on work-related or environmental stress or daily activities, post-traumatic stress; lifestyle and daily stress; (b) studies focusing on the association between breast cancer and personality type and anxiety; social, psychological, and psychosocial support; (c) stress in women with a psychiatric history; (d) breast cancer recurrence and other diseases of the breast; (e) surgical and clinical intervention (radiotherapy and chemotherapy); and (f) literature review articles and editorials.

Strategy for article identification and selection and data collection

First, the article titles and abstracts were evaluated by three reviewers, verifying each primary study that addressed the systematic review's underlying question. The abstracts were grouped into selected versus not selected.

The selected articles were retrieved, read in full, and screened for those indexed in more than one source or in another language.

In the next phase, data from the selected studies were assigned to an instrument to verify whether they met the inclusion and exclusion criteria, and discrepancies were resolved by discussion and consensus. Studies for which there was no agreement as to inclusion were analyzed by a fourth reviewer.

Data from the case-control and cohort studies were assigned to a structured form containing: author's name, year of publication, study's country of origin, type of study, adjustment for confounding factors, and odds ratios (OR) and respective 95% confidence intervals (95%CI). The data were reviewed by the four reviewers.

Methodological quality

Methodological quality was evaluated using the scale proposed by Downs & Black [25]. The instrument was a checklist consisting of 27 items distributed in five subscales: (1) communication (9 items) – whether the information provided by the article was sufficient to allow the reader to detect biases in the study's results; (2) external validity (3 items) – in which the study's results can be generalized to the population from which the subjects came; (3) internal validity – bias (7 items) – whether there is bias in measuring the intervention and the result; (4) internal validity – confounding factors/selection bias (6 items) – whether there is bias in subject selection; (5) power (1 item) – whether negative findings can be related to chance; and (6) validation of the study's power (1 item). Each study was scored from 0 to 1 on each answer, with the exception of the first item, communication, scored from 0 to 2, and the last item, study power, scored from 0 to 5. The instrument's maximum total score is 31.

We thus analyzed the cohort studies based on 19 items (1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 16, 17, 18, 20, 21, 22, 25, 26, 27) and the case-control studies based on 17 items (1, 2, 3, 5, 6, 7, 10, 11, 12, 16, 17, 18, 20, 21, 22, 25, 27). Items 9 and 26 were not used in the evaluation of case-control studies since they contain questions that do not apply to this type of study. Items 4, 8, 13, 14, 15, 19, 23, and 24 were not scored because they pertain to intervention studies, since no publication included in this review was of the experimental type.

Other items that were evaluated included: whether the study provided estimates of the random variability in the main findings; whether losses to follow-up were described; whether the probability values for the main outcomes were specified; whether the sample of subjects invited to participate in the study was representative; whether the sample of subjects included in the study was representative; if the results were not based on a priori hypotheses, whether this was made clear; in trials and cohort studies, whether the analysis was adjusted for different follow-up times, or in case-control studies, whether the intervention and outcome time was the same for cases and controls; whether the statistical tests used to measure the principal outcomes were appropriate; whether the measurements of the principal outcomes were accurate (valid and reliable); whether the patients in different groups were recruited from the same population; whether the patients in different groups were recruited during the same time period; whether the analysis included adequate adjustment for the main confounding factors; whether losses to follow-up were considered; and whether the study had sufficient power to detect an important effect with 5% significance.

Statistical analysis

Statistical analysis used the Stata program, version 9.0 (Stata Corp., College Station, USA).

To allow a meta-analysis of the eight selected studies, they were grouped into three distinct analyses. Two analyses referred to the three studies that calculated relative risk for breast cancer as a function of stressful life events: the categories widowhood and separation (divorce) [9,26,27].

Six studies calculated relative risk for breast cancer without considering categories, but rather self-rated intensity or frequency of stressful events, regardless of the situation that caused it [8,9,14,15,16,17]. We chose the RR related to the highest intensity in each article, ignoring the RR related to stressful events rated as less intense or less frequent.

Four studies classified intensity as rated by the subjects themselves [8,14,15,16].

Ginsberg et al. [15], using a system based on Tennant/Andrews, classified participants in four groups based on score: 0-70, 71-140, 141-210, > 210. We considered the result for participants scoring greater than 210.

Chen et al. [14] classified their sample in five groups: women who felt little or no threat from the events and those that felt slightly, moderately, or heavily threatened. We considered the result for women that felt heavily threatened.

Helgesson et al. [8] classified the stressful event dichotomously, as whether or not it had produced intense stress (yes or no). We considered the result for women that answered yes.

Protheroe et al. [16] used a 4-point scale of self-rated stress, with 1 to 2 points representing mild stress and 3 to 4 points reflecting severe stress. We only considered severe stress.

Two studies [9,17] investigated intensity using the number (frequency) of events, based on the logic that more events would be related to more stress (intensity): Lillberg et al. [9] used the modified Holmes-Rahe questionnaire, including the possibility of checking 21 stressful items, and classified the group in four: no event, one event, two events, and three or more (we considered the result for three or more events) and Robert et al. [17], including the possibility of 11 events and comparing the observed frequencies between cases and controls (we considered the mean score between the two groups of patients). Thus, the total number of studies is greater than eight, because one study calculated RR for both the category and the intensity of stress [9].

We used the Q test to evaluate the heterogeneity among studies and the random effects model to calculate the combined effect, i.e., the RR of the meta-analysis. Due to the small number of studies, we did not conduct sensitivity or bias analyses. The studies' level of evidence was classified as proposed by Melnyk & Fineout-Overholt [28].

Results

The search strategy identified 619 titles and abstracts. Of these articles, 554 were excluded after reading the titles and abstracts. We selected 65 abstracts whose full texts were obtained for analysis and application of the inclusion and exclusion criteria, and 57 articles were excluded for the following reasons:

Two studies [10,20] did not present the RR and 95%CI for the association between stressful life events and breast cancer. These missing data were requested from the authors by e-mail, but the latter did not reply.

Seventeen studies [29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45] described risk factors related to psychiatric, psychological, or social disorders; six referred to other types of stress (stress and work [46,47]; stress and daily activities [48,49]; post-traumatic stress [50]; stress and lifestyle [51]). Fourteen [12,21,22,23,52,53,54,55,56,57,58,59,60,61] evaluated the psychosocial approach, and there were six editorials [62,63,64,65,66,67] and three literature reviews [68,69,70].

We also excluded an update study [71] on the relationship between stress and breast cancer; five studies on personality and breast cancer [72,73,74,75,76]; and three meta-analyses, on the relationship between stressful events and breast cancer [18]; the association between breast cancer and life events in general [19]; and psychosocial factors and breast cancer [77].

As for level of evidence, the eight studies were classified as level IV, referring to evidence from well-designed cohort and case-control studies [28].

The majority of the studies showed satisfactory methodological quality according to the Downs & Black classification [25]. The cutoff point for characterizing the studies as having a high methodological score was the median value of the studies, or 17 (Table 1). According to the Downs & Black criteria [25], the maximum possible total score was 20 points for cohort studies and 18 points for case-control studies. Due to the limited variation in scores, the eight studies were considered representative and were included in the systematic review and selected for the meta-analysis.

Among the eight studies included in the meta-analysis, six were case-controls [14,15,16,17,26,27] and two were cohort studies [8,9]. The eight studies included a total of 66,612 women.

The two cohort studies included in the meta-analysis were from Sweden [8] and Finland [9]. Their combined population consisted of 12,270 women. The mean age for the sample in the first study was 47.2 years, and the second was limited to women older than 24 years. The types of stress measured in the two studies were stressful events and divorce and widowhood, respectively. The six case-control studies [14,15,16,17,26,27] were from Denmark, England, Norway, Australia, and the United States. The combined population consisted of 54,342 women. The types of stress measured were: life events, stressful life events, and divorce and widowhood (Table 1).

The Q test showed heterogeneity in the three analyses for the risk factors widowhood ($Q = 7.634$; $p = 0.020$), divorce ($Q = 9.591$; $p = 0.008$), and stress intensity ($Q = 24.688$; $p < 0.001$). We used the random effects model to calculate the combined effect, i.e., the RR of meta-analysis.

The first analysis considered studies on the association between widowhood and breast cancer [9,26,27] (Figure 1). These three studies were used in the second analysis with divorce as the risk factor (Figure 2). The third analysis included studies with self-rated intensity of stress as the risk factor, considering the RR for the highest intensity in the studies [8,9,14,15,16,17] (Figure 3).

Among the three studies included in the meta-analysis on widowhood as risk factor, none was conclusive [9,26,27]. The meta-analysis showed a lack of association between widowhood and breast cancer risk, with RR = 1.04 (95%CI: 0.75-1.44; $p = 0.800$), as shown in Figure 1.

Among the three studies included in the meta-analysis on divorce as risk factor [9,26,27], the study by Lillberg [9] concluded that divorce is a risk factor for breast cancer (RR = 2.07; 95%CI: 1.16-3.67). However, our meta-analysis showed no association between divorce and breast cancer, with RR = 1.03 (95%CI: 0.72-1.48; $p = 0.850$), as shown in Figure 2.

Among the six studies [8,9,14,15,16,17] on the association between high-intensity stress and breast cancer, two [8,14] conclusively showed such an association: Chen et al. [14], with RR = 7.08 (95%CI: 2.31-21.6), and Helgesson et al. [8], with RR = 2.1 (95%CI: 1.2-3.7). However, the other four were inconclusive [9,15,16,17]. According to our meta-analysis, there was only a borderline risk of breast cancer due to intense stress: RR = 1.73 (95%CI: 0.98-3.05; $p = 0.059$), as shown in Figure 3.

Table 1

Characteristics of studies included in the meta-analysis and score on Downs & Black scale [25].

Authors	Country/Year	Design	Sample size	Age (mean)	Type of stress	Result RR ** (95%CI)	Downs & Black score [25]
Ewertz [27]	Denmark/1986	Case-control	1,782/1,738	< 70 *	Divorce Widowhood	0.9 (0.7-1.2) 0.8 (0.7-1.0)	14
Kvikstad et al. [26]	Norway/1994	Case-control	4,491/44,910	40-60 *	Divorce Widowhood	0.83 (0.75-0.92) 1.13 (0.94-1.36)	17
Chen et al. [14]	England/1995	Case-control	41/78	57.0/50.0	Life events	7.08 (2.31-21.65)	18
Ginsberg et al. [15]	Australia/1996	Case-control	99/99	-	Stressful life events	2.24 (0.92-5.44)	17
Roberts et al. [17]	United States/1996	Case-control	158/614	64.8/62.4	Stressful life events	0.9 (0.78-1.05)	18
Protheroe et al. [16]	Australia/1999	Case-control	106/226	61.6/51.8	Stressful life events	0.91 (0.47-1.73)	17
Helgesson et al. [8]	Sweden/2003	Cohort	1,462	47.2	Stressful events	2.1 (1.2-3.7)	20
Lillberg et al. [9]	Finland/2003	Cohort	10,808	> 24 *	Divorce Widowhood	2.07 (1.16-3.67) 1.64 (0.84-3.19)	20

95%CI: 95% confidence interval; RR: relative risk.

* Age limit;

Figure 1

Relative risks and combined effect on breast cancer due to widowhood.

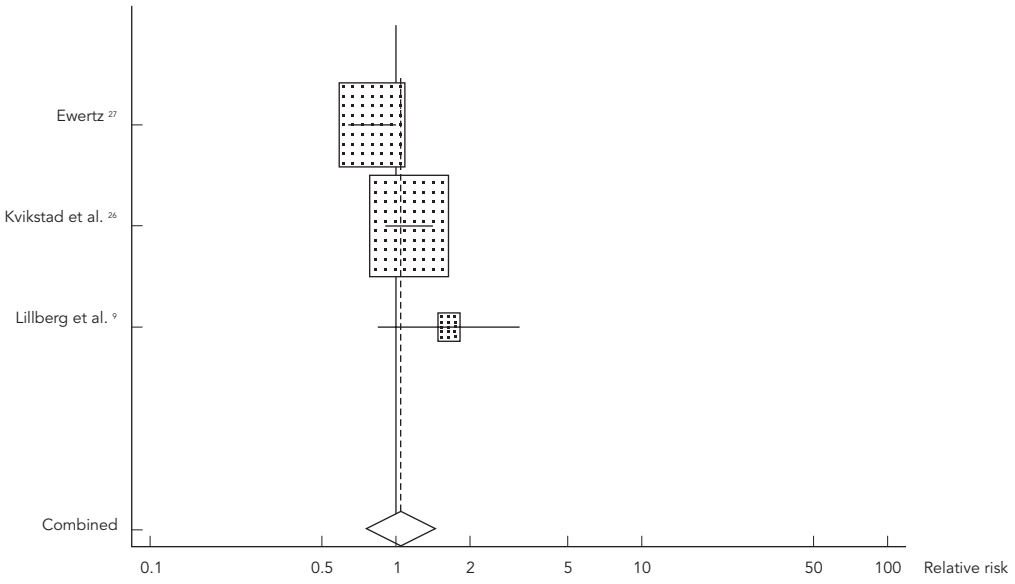


Figure 2

Relative risks and combined effect on breast cancer due to divorce.

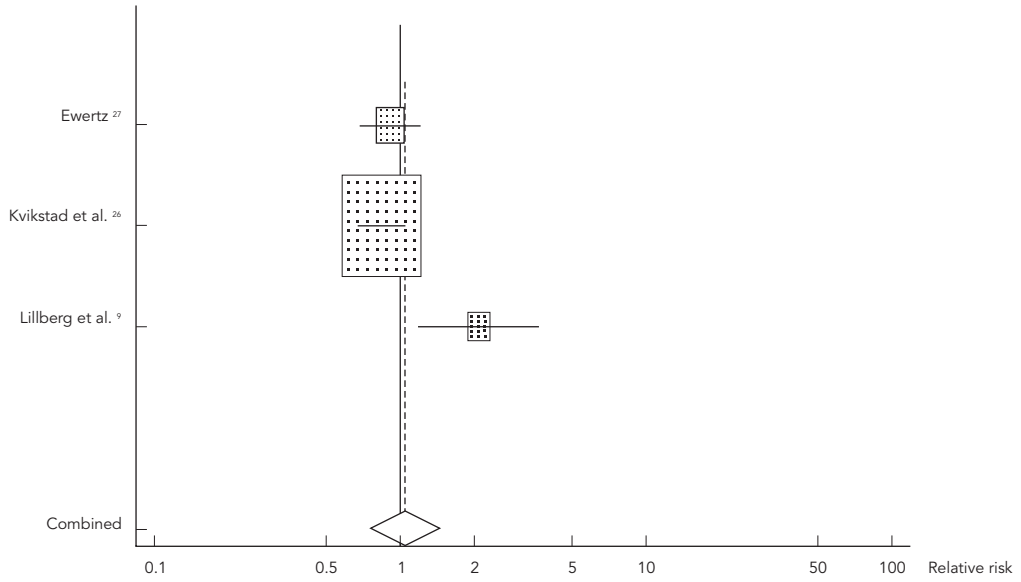
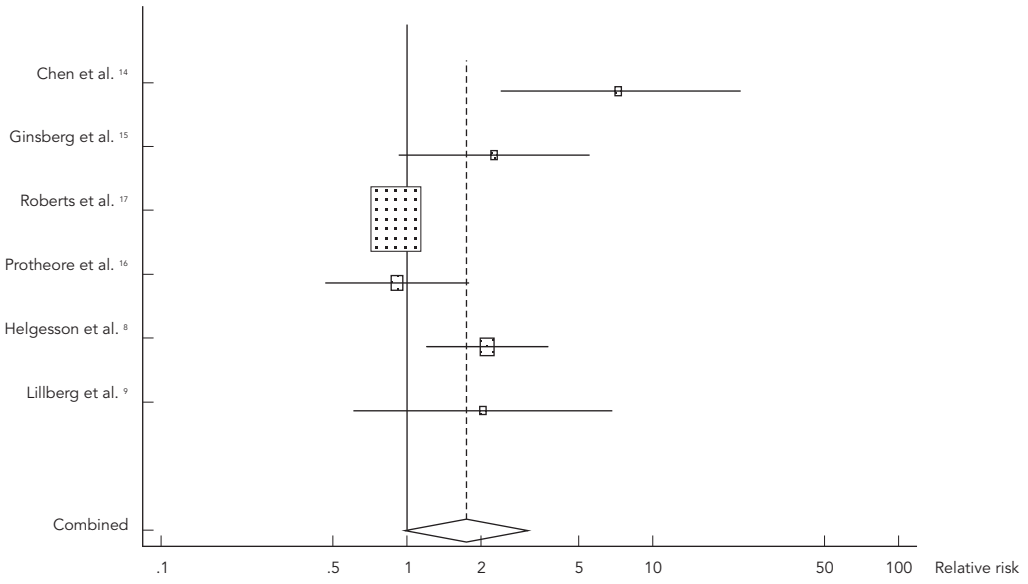


Figure 3

Relative risks and combined effect on breast cancer due to high-intensity stress.



Discussion

The results of the current meta-analysis do not show evidence of an association between stressful life events and primary breast cancer incidence in women. Similar findings were reported in two meta-analyses on the association between stressful events and breast cancer in women [18,19].

The first meta-analysis, with 29 studies, showed lack of support for a causal relationship between negative life events and breast cancer incidence (OR = 0.8; 95%CI: 0.96-1.06) [18]. According to the second, with 27 studies, which evaluated the categories death of husband, death of friend, health problems, financial problems, and change in marital status, there was no association between stressful events and breast cancer (OR = 1.77; 95%CI: 1.37-2.40), but there was a slight association between husband's death and risk of breast cancer (OR = 1.37; 95%CI: 1.10-1.71) [19].

Considering the methodological quality of the reviewed articles, the eight studies were methodologically homogeneous, with a mean score of 17 points out of a maximum of 20 points, according to the Downs & Black criteria [25]. These criteria have been used in meta-analyses [78,79] and systematic reviews [80,81] and provide an adequate instrument for use in systematic reviews like ours [82].

In the majority of the studies the event was investigated adequately, combining subjectivity and objectivity, with the application of instruments (scale, questionnaires, and checklist), thus reducing the possibility of recall bias [83,84]. They also considered the type of stressful agent by categories, intensity, and frequency of exposure, thus allowing the evaluation of the appropriate events from the point of view of the literature [84,85].

Although the studies were classified as evidence IV according to the classification system used in this meta-analysis [28], it would not be possible to answer the question on stress and risk of breast cancer according to levels of evidence II and III, namely evidence derived from clinical trials. Observational studies are considered appropriate for conducting systematic reviews, according to members of the non-randomized studies in the Cochrane Collaboration, and are also the most adequate for determining risk factors [86,87], while emphasizing the importance of careful assessment of the studies' design.

As for the population, our findings refer to a total sample of 66,612 women participating in the eight studies. This ensures great statistical power. However, despite the significant sample size, we should point to some limitations in the current study. First, two studies identified in the initial systematic review [10,20] were excluded due to lack of data presented by the authors, and if used they might have been representative in the review, although they did not find an association between stress and breast cancer. Second, the inclusion of a larger number of studies might have allowed analyzing the studies for sensitivity and possible biases.

As for the electronic article search, we intentionally excluded articles that evaluated women with breast cancer relapse, since these women could present emotional responses that could lead to an increase in the target events, relating them to the risk of falling ill. We would thus prevent the findings from this meta-analysis from being conclusive as to the risk of stress leading to breast cancer, due to the woman's optimistic bias concerning her risk of developing this type of cancer.

When we analyzed the effect of high-intensity stressors, the meta-analysis suggests that an association may exist, and a statistically significant effect was observed in the studies with the largest sample size. This same result was not identified in other epidemiological studies and suggests that future research should further consider the evaluation of factors associated with breast cancer incidence in women.

This literature review identified a lack of Brazilian studies on the association between stress and breast cancer. Thus, the main sources of information were international studies, conducted mainly in countries with Nordic women, with a distinct cultural profile from that of Brazilian women. Future analyses are necessary to verify whether these findings will be corroborated in difference ethnic populations.

Conclusion

Research on stress and breast cancer has been documented by various studies published over the years. Data from the current study corroborate findings already published in the literature on the lack of evidence for an association between stressful life events (divorce and widowhood) and risk of breast cancer in women. However, our results point to high-intensity stress as having a borderline association with the development of breast cancer. Future studies are necessary to elucidate this relationship.

Resumo

O objetivo da presente metanálise foi verificar a associação de eventos de vida produtores de estresse com a incidência primária do câncer de mama entre as mulheres. Foram encontrados 618 estudos nas bases PubMed, LILACS e Biblioteca Cochrane Library, no período de 1982-2007. A qualidade metodológica foi avaliada pelos critérios de Downs & Black. Foram selecionados oito estudos, sendo seis caso-controle e dois de coorte. Os estudos foram agrupados em três análises, duas em virtude das categorias viuvez e divórcio, e uma considerando a intensidade autopercebida e freqüência de eventos. O risco relativo em relação à viuvez foi 1,04 (IC95%: 0,75-1,44; p = 0,800); ao divórcio foi 1,03 (IC95%: 0,72-1,48; p = 0,850), e em relação ao grau intensidade/freqüência de estresse foi 1,73 (IC95%: 0,98-3,05; p = 0,059). Concluímos que os eventos de vida produtores de estresse não têm associação de risco com câncer de mama feminino. O estresse de alta intensidade não permite eliminar a possibilidade de associação de risco para o câncer de mama.

Acontecimentos que Mudam a Vida; Estresse Psicológico; Neoplasias da Mama

Contributors

A. F. C. Fernandes oriented the study, participated in drafting the article, and approved the final version for publication. M. C. L. Santos contributed to the research project's conceptualization, data analysis and interpretation, drafting of the article, and final approval. B. L. Horta collaborated in the data analysis and interpretation and revision of the article. J. J. F. Amaral adjusted the research instrument to the project's design and revised the article. P. F. C. B. C. Fernandes adjusted the research project and revised the draft. C. M. Galvão conducted a critical review of the article's content.

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