

PSYCHOLOGICAL STRESS AND BREAST CANCER INCIDENCE: A SYSTEMATIC REVIEW

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Abstract

Objective. Breast cancer is the world's leading cause of cancer mortality in women. Stress is an imminent risk factor with a documented negative impact on neuro-endocrine and immune system. Numerous epidemiological studies have investigated the link between stress and cancer, reporting contradictory results from no association to a close causal link. The impact of the topic and the lack of conclusion compelled this systematic review.

Methods. A systematic review was carried out, including all literature studies from 1966 to 2016, investigating the relationship between stress and the occurrence of breast cancer. Of the 1813 articles identified in the PubMed/Medline database, 52 were eligible and included in the analysis.

Results. A number of 17 retrospective, 20 limited prospective and 15 prospective studies were analyzed. The number of patients exceeded 29,000, for a total number of more than 700.000 women recruited from hospital, screening cohorts or population registers. We identified 26 positive articles linking personal traits, stressful events and breast cancer, 18 negative articles that did not confirm their hypothesis and 8 articles that could not be classified. Facing heterogeneity, all possible misguiding factors such as: study design, information gathering, stress type, moment of exposure, individual susceptibility and personality, were discussed independently.

Conclusions. Qualitative analysis of articles has revealed a possible association between stress and cancer, especially regarding stressful life events. In the absence of a meta-analysis and taking into account the methodological heterogeneity of the studies, the results are difficult to interpret and the role of chance is difficult to exclude.

Keywords: breast cancer, incidence, life events, stress

Background and aims

Breast cancer represents the leading cause of death by cancer in women [1]. Only around 50% of mammary carcinoma can be attributed to a physiological, behavioral or genetic risk factor [2]. Additionally, new risk factors have been studied, including psychological stress, smoking and nutrition: their management and exclusion may offer great benefit.

Mind-body symbiosis has its roots in antique Greece through the writings of Hippocrates and Galen who

observed an increase in breast cancer incidence among the melancholic compared with the sanguine women. The connection between "psyche" and cancer remains mostly anecdotal till the end of 19th century, when Dr. Snow [3] reported in his paper that 156 out of 200 women with breast cancer had suffered a traumatic life event, usually the loss of a dear person.

The knowledge accumulated in the 20th century regarding stress and its mechanism of action combined with the enthusiasm regarding the impact of stress hormones in cancer development has led to numerous research studies. Strong, but empirical hypotheses sustaining stress cancerogenesis have appeared. However,

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results from epidemiologic studies have been conflicting and ranged from no association between stress and breast cancer, with an OR=0.95 [4] up to a close link between the two with OR=11.6 [5]. Moreover, the meta-analyses [6-12] completed over the years have resulted in the same inconstancy and failed to provide a creditable conclusion.

The main objective of the present systematic review is to examine the relationship between psychological stress and the risk of breast cancer. The question we want to answer is: Are women exposed to stress more prone to develop breast cancer than women who are non-exposed?

Methods

A search was conducted on the PubMed database, using various combinations of the following keywords: “stress”, “psychological stress”, “life events” and “breast or mammary cancer, carcinoma or neoplasm”. Search interval had no temporal limits. All published articles identified, with no time limit, were then screened based on title and abstract. The potential eligible studies were then obtained in full-text and verified in order to meet the inclusion and exclusion criteria. The reference list of these articles was also consulted in order to identify studies that were not initially found or had been omitted. In order to evaluate the methodological quality of the studies, each article was subjected to the Downs and Black control list [13].

The inclusion and exclusion criteria are listed below:

Inclusion criteria: 1. Case-control, cohort or randomized studies 2. Studies conducted on women older

than 18 years, diagnosed with primary breast cancer 3. Prospective studies with a minimum 5 years follow-up 4. Studies that included a quantitative or semi-quantitative method of stress measurement 5. Studies written in English, Romanian or French.

Exclusion criteria: 1. Studies that analyzed stress caused by lifestyle, work environment or posttraumatic stress disorder. 2. Studies that analyzed stress in women with a medical psychiatric history. 3. Studies that implied the role of stress in the recurrence or in the prognosis of breast cancer. 4. Studies that involved treatment as a stress factor. 5. Studies that included the use of non-conventional therapy (massage, reflexology, acupuncture, mindfulness) for stress reduction. 6. Reviews, meta-analysis and editorials.

Results

Using the search strategy described above, from 1966 to March 2016, a number of 1813 articles were screened with a total of 52 articles selected for the final analysis (Figure 1). The articles were case-control or cohort studies, having level II or III of evidence [14]. All studies received a satisfactory DB evaluation, were considered qualitative and were included. Selected articles were reviewed and the main data were summarized. For each article included in the present study, the year of publication, type of study, number of patients/controls, the type of stress and the time period evaluated, as well as the main results were extracted (Table I-III).

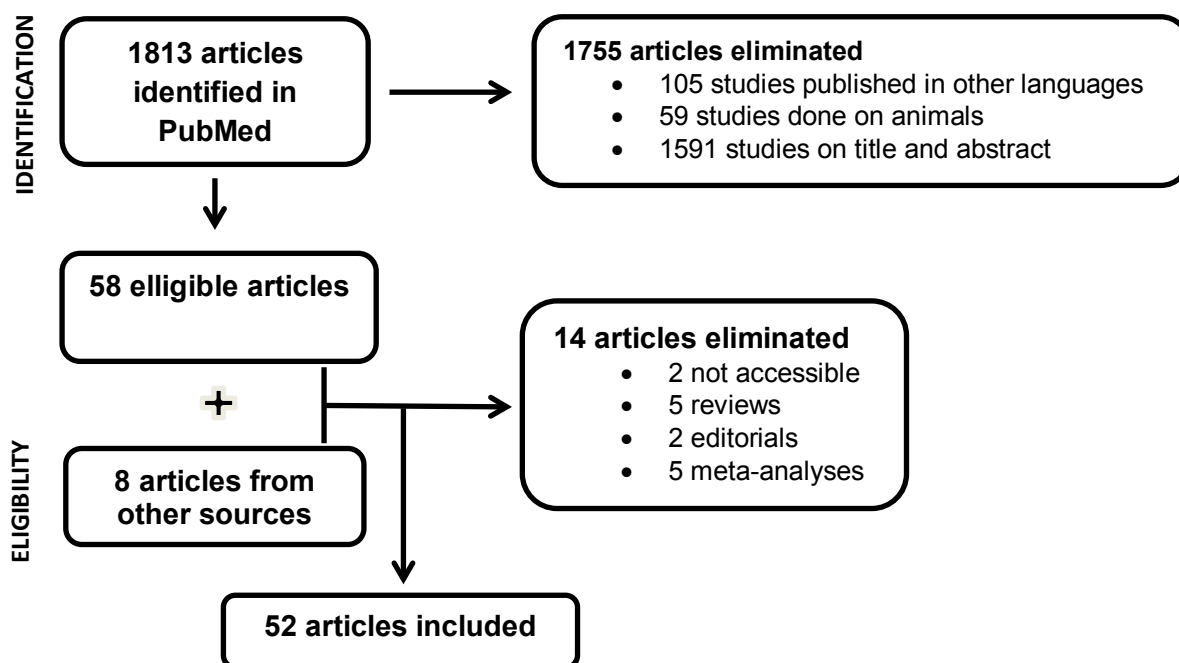


Figure 1. Diagram of article selection.

Table I. Summary of retrospective studies.

Name of first author and year of publication	Study design	Number of cases/ control1/ control2	Period of time evaluated	Type of stress/ role of personality	Results (Personality traits of patients)	Downs Black Score (DB)
Snell [25] 1971	Case-control	352/670	5 years	Life events	No differences between groups in separations, divorces, family illness or a range of other life events.	9
Jansen [20] 1984	Case-control	69/71/82	?	Personality	Timid, non-assertive, non-competitive, calm, less aggressive, easy-going, and keeping anger inside	14
Watson [21] 1984	Case-control	30/27	?	Personality	Tendency to control anger, repressive coping style, less curious, no difference in trait anxiety and anger	13
Priestman [22] 1985	Case-control	100/100/100	3 years	Life events	No difference between cases and controls in life events; Controls reported more life events than other two groups.	12
Bremond [23] 1986	Case-control	50/105	5 years	Life events	More negative events in the case group. Tendency to suppress feelings, commitment to social norms,	12
Ewertz [26] 1986	Case-control	1782/1738	3-15 years	Divorce and husband death	RR=0.9 (0.7-1.2) divorce RR=0.8 (0.7-1.0) husband death	13
Scherg [31] 1988	Case-control	508/1563	>10 years	Life events	OR=1.10 father's death early in life OR=1.71 mother's death early in life OR=1.45 divorce or husband's death	13
Forsen [24] 1991	Case-control	87/87	6 years	Life events	RR=5.02 (1.72-14.7) important emotional losses	13
Roberts [4] 1996	Case-control	258/614	5 years	Life events	OR=0.9 (0.78-1.05) stressful life events	15
Ginsberg [19] 1996	Case-control	99/99	2 & 10 years	Life events	RR=2.24 (0.92-5.44) distress score > 210 than those with <70 at 10 years 4.67 (1.33-16.41) change score >210, than those with <70 at 10 years	15
Kruk [27] 2004	Case-control	257/565	> 5 years	Life events	OR = 3.70 (2.61-5.26) major life events	15
Peled [28] 2008	Case-control	255/367	Any period	Life events	OR= 1.62 (1.09-2.40) more than one stressful event	14
Keinan [32] 2009	Cohort	11822/315544	~44 years	Holocaust	RR = 2.44 (1.46-4.06) for the youngest birth cohort	14
Tas [29] 2012	Case-control	276/492	1year	Life events	Stressful events of patient vs control (41.9% vs. 31.7%, P = 0.04)	13
Kruk [30] 2012	Case-control	858/1085	>5 years	Life events	OR=3.95 (2.39-6.55) severe personal illness OR=3.74 (1.99-7.03) legal problems OR=3.14 (2.18-4.54) death of a close friend/relative	15
Toleutay [17] 2013	Case-control	114/196	?	Chronic and familial stress	OR=3.61 (1.75-7.45) chronic stress OR=4.86 (2.59-9.12) stress in the family	14
Wang [16] 2013	Case-control	157/314	1 month	Stress in general	OR = 1.65 (1.10-2.47) high perceived stress	15

Table II. Summary of limited-prospective studies.

Name of first author and year of publication	Number of cases/ control1/ control2	Period of time evaluated	Type of stress/ Role of personality	Results	DB Score
Schonfield* [46] 1975	27/85	3 years	Life events	Controls reported more events, no differences regarding deaths	13
Greer* [42] 1975	69/91	5 years	Personality and Life events	No differences in type or amount of stress. Abnormal release of emotions: suppression of anger.	14
Morris* [43] 1981	17/33	? years	Personality and Life events	Patients experience less frequently: anger, losing control in anger, neuroticism	14
Scherg* [47] 1981	100/100/69	3 years	Life events	Cases report more deaths of close relative than controls (46% v. 31%).	13
Wirsching* [50] 1985	18/38	?	Personality	Patients are inaccessible, altruistic, suppressing feelings, rationalizing, harmonizing, optimistic	13
Cheang* [34] 1985	46/75/42	2 years	Life events	Cases had higher life events scores than controls; Cases report more illness events than controls (78% v. 50%).	13
Scherg* [48] 1987	75/75	Any period	Personality	Patients show less anxiety, less pattern A, more social desirability, more war experiences	12
Grassi* [41] 1988	41/35	?	Personality	Patients present less state hostility and irritability. More emotional suppression.	12
Todarello* [49] 1989	13/187	?	Alexithymia	Patients have more alexithymic traits	13
Cooper* [35] 1989	171/1265/727	2 years	Life events	Husband's or close friend's death are related with the occurrence and severity of disease	13
Edwards* [37] 1990	79/505/397	2 years	Life events	No difference on life event scales, coping, Type A or social support	14
Anagnostopoulos* [33] 1993	180/156/112	?	Alexithymia	No differences	15
Cooper* [36] 1993	171/1265/727	2 years	Life events	Loss-related events are associated with increased risk of cancer	13
Geyer* [40] 1993	33/59	8 years	Life events	Cases report more severe 'contextual threats' (48%) than controls (10%) and more severe loss events (45% v. 12%) than controls.	13
Fox* [39] 1994	20/488/266	2 years	Life events and loneliness	Patients have more often experienced the death of a spouse or close family member	15
Chen* [5] 1995	41/78/50	5 years	Life events	OR=7.08 (2.31-21.65) great threat OR= 11.64 (3-10 to 43-66) severe threat	15
Protheroe* [45] 1999	106/226	5 years	Life events	OR=0.91 (0.47-1.81) more than 1 severe life event OR=0.86 (0.41-1.81) life difficulties	14
Price* [18] 2001	239/275	2 years	Life events	OR=9.39 (1.90-46.42) highly threatening stress without emotional social support	15
Ollonen* [44] 2005	34/28/53	10 years	Life events	Association found for very severe and severe losses (P = 0.02) and greater number of moderate or severe losses (P = 0.0009)	14
Eskelinen* [38] 2010	34/28/53	10 years	Difficult childhood and adolescence	Association found for deficit in childhood (P <0.05) or severe deficit in childhood (P = 0.02)	14

* case-control

Table III. Summary of prospective studies.

Name of first author and year of publication	Design	Number cases/ controls- cohort	Period of follow up	Type of stress/ role of personality	Results	DB Score
Hagnell [15] 1966	Case-control	9/ 2550	10 years	Personality	No associations between cancer risk and validity, solidity, and capacity;	9
Reynolds [55] 1990	Cohort	71/ 6848	17 years	Social support	Association between social isolation and breast cancer	14
Scherg [54] 1993	Case-control	48/ 2874	11 years	Personality	No association with: personality factors and background factors. Association with: health-related problems	13
Kvikstad [52] 1994	Case-control	4491/ 44910	?	Divorce and husband's death	OR=0.83 (0.75-0.92) divorce OR=1.13 (0.94-1.36) husband's death	14
Bleiker [53] 1996	Case-control	131/ 9705	5 years	Personality	Weak association between: anti-emotionality and breast cancer incidence.	15
Johansen [57] 1997	Cohort	198/ 5716	1-50 years	Cancer and child's death	No relation between cancer in child and cancer in parent	16
Jacobs [56] 2000	Cohort	39/ 1213	>20 years	Parent's death and other events	OR = 2.56 (1.59-4 .35) mother's death in childhood	18
Helgesson [59] 2003	Cohort	49/ 1462	24 years	Life events	RR = 2.1 (1.2-3.7) stress	18
Lillberg [58] 2003	Cohort	180/ 10808	14 years	Life events	HR = 2.26 (1.25-4.07) divorce HR = 2.00 (1.03-3.88) husband's death HR = 1.36 (1.00-1.86) close relative or friend's death	18
Kroenke [61] 2004	Cohort	1700/ 69886	8 years	Nursing	RR = 1.19 (0.87-1.62) >15hours of nursing/ week	16
Lambe [51] 2004	Case-control	617/ 141798	34 years	Child's death	OR = 2.65 (1.06 -6.60) loss of a child between the ages of 1 and 4 for uniparous	15
Nielsen [62] 2005	Cohort	251/ 6689	16-18 years	Daily stress	HR = 0.60 (0.37 -0.97) high stress	18
Surtees [63] 2009	Cohort	313/ 11467	9 years	Life events	HR = 1.02 (0.91-1.16) difficulties in childhood HR = 0.99 (0.89 -1.11) life events	16
Metcalfe [60] 2007	Cohort	62/ 991	30 years	Daily stress	HR = 2.16 (1.00 - 4.71) moderate stress HR = 1.92 (0.81 - 4.55) high stress	18
Michael [64] 2009	Cohort	2481/ 84334	8 years	Life events	HR = 1.12 (1.0 -1.25) one life event	18

The 52 studies were spread over a period of 47 years, the oldest dating back to 1966 [15] and the newest being published in 2013 [16,17]. With some exceptions [16,18,19] most studies came from European countries or from the USA. All articles were published in English.

We divided the studies based on design, identifying 16 retrospective case-control studies [4,16,17,19-31], 1 retrospective cohort study [32], 20 limited-prospective studies [5,18,33-50], 5 prospective case-control studies [15,51-54] and 10 prospective cohort studies [55-64]. There were two cases of 2 studies that analyzed the same population [35,36,38,44], but because they measured different variables and had different results, were considered as individual studies. The total number of breast cancer cases analyzed was 29,057 for a total participation of almost 700,000 women.

Regarding participant selection, cases were selected either from the hospital for 9 studies [16,20-25,29,31] or from the general population for 22 studies [4,15,17,19,26-

28,30,32,51,52,54-64]. Patients were also selected from a cohort of women with suspicious lesion in 18 studies (5,33-46,48-50) or from a screening cohort for 3 studies [18,47,53]. For the case-control studies the control group was selected from the hospital [16,20,21,23,25,27-31,54] or from the general population [4,15,17,19,22,24,26,52,53,32,55-54].

In the case of limited prospective studies, 10 were conducted on women that were scheduled for biopsy of a suspicious breast lesion [5,18,34,40-43,45,46,50], 3 on women that were waiting for a prophylactic or symptom-directed mammography [37,39,49] and 5 on women that were having a routine check-up with or without symptoms [33,35,36,38,44].

As an investigation method, 42 of 52 researchers used questionnaires accompanied or not by a medical consultation, 5 used exclusively the interview [15,25,42,50,56], and 5 retrieved information from population-based registries [26,32,51,52,57]. The scales utilized for results quantification varied from study to

study, no comparison being able to be made.

More than two-thirds of the articles analyzed stress produced by important life events, such as: the death of a husband, child, parent or close friend, divorce, financial problems, personal or familial medical problems and living in a political or cultural difficult period or region. Only two studies investigated daily stress [60,62] and 10 studies were based on highlighting the link between personality traits, the way of coping with stress and breast cancer [15,20,21,33,41,48-50,53,54].

In the retrospective studies participants were asked to remember stress exposure between 1 month [16] and any previous period [28]. The limited prospective studies had a minimum of two years between the stress exposure and diagnosis, whereas prospective studies had a minimum 5 years follow up. The longest periods analyzed were in the registries based studies, going up to 50 years [57].

We identified 26 positive articles that reported a link between stress and breast cancer, and 18 articles defined as negative that did not validate their hypothesis. The positive ones were 11 retrospective [16,17,19,23,24,27-32], 10 prospective limited [5,18,34-36,38-40,44,48] and 5 prospective [55,56,58-60]. The negative were 4 retrospective [4,22,25,26], 6 prospective limited [37,42,43,45,46,47] and 8 prospective [51,52,54,57,61-64].

Discussion

A number of 52 studies that analyzed the connection between stress and the risk of breast cancer development were identified. Of these, 26 validated their primary idea, concluding that a relation does exist between stress and cancer, whereas 18 did not sustain this hypothesis with sufficient data. The remaining 8 studies were focused on personality traits, and we considered it erroneous to appoint them as positive, even if there were differences between patients and controls personality. Regarding numerical power, the positive studies included more than 15,500 patients, with only around 13,000 patients in the negative group.

The information gathered tends to tip the balance toward an affirmative answer to our initial question. Yes, the women exposed to stress are at a higher risk of developing breast cancer than the non-exposed. This statement must be interpreted cautiously. In the absence of a meta-analysis, there are several elements that can induce judgment errors.

If the role of psychosocial factors is modest or even non-existent, does the inconsistency lie in the research methods? All the possible misleading factors must be taken into consideration. These are discussed separately below.

a. The Study design

The study design is well acknowledged to influence results. This is shown even in this particular area of research by the meta-analysis of Duijts [7] who reports differences in the calculated risk between retrospective and prospective studies. Retrospective studies have many drawbacks, the

most important being the recall error. The validity of results is mostly dependent on subject memory, which can sometimes be misleading. Even so, there are studies showing that the severity of the event is proportional with reporting reliability, because a major incident brings a deep remembrance [65]. Limited prospective studies obtain information just before a biopsy and the results can be biased by the reaction to the suspected diagnosis, usually overestimating the importance of an event. Real prospective studies are considered the most objective, but because of the long time required with an imminent loss of participants, some types of personality may be selected.

In our review we had only 15 prospective trials, and most of them were negative. Only 19% of positive studies were prospective, whereas, almost half of the negative ones had a prospective design.

b. Information gathering

Another major issue is represented by the large variety of methods used for obtaining information as well as by the method of data quantification which limits the objective comparison and interpretation of results. The questionnaires were extremely heterogeneous, with only a few validated forms used: Life events inventory [19,58], The Holmes–Rahe Social Readjustment Rating Scale [4,24,27,35,46] and the Brown-Harris Life Events and Difficulties Schedule (5,18,40,45). Questions with a Yes/No answer [23] as well as open answer questions [27] were present. For example [4] in one of the studies the great availability rate was considered to be due to the short and easy questionnaire: the abbreviated Life event inventory. Even if validated as a standardized tool [66] it represents a simplistic method to detect a relation between cancer and stress leaving results open to criticism. Moreover, gathering information over the phone seems unprofessional with a great probability of superficiality and biases. On the other hand, the interview, being open to much more subjectivity, is also far from the ideal way of collecting data.

Some studies [4,58] have used only the life events number, on the principle of more events = more stress, while others have included weighting scales for intensity measurement [19,46]. As an example, Protheroe [45] divided women into four groups using only one variable (1, 2- minor stress, 3, 4- major stress), while Ginsberg [19] used the Tennant/Andrews system. Similarly, other studies divided the researched group into five [5,38,44] or six [62] clusters based on stress level.

c. Stress type

Analyzing the same type of stress has led to opposed results. As an example: child death as a major stress has not influenced the risk of breast cancer in mothers, in Johansen's study [57], whereas the team conducted by Lambe [51] reported an increase of risk, valid just for the uniparous women whose child was 1 and 4 years at the time of death.

Other life events, like death of husband or divorce,

were the most frequently studied with a trend towards validating a link between stress and breast cancer. The most surprising positive study was the British one published by Chen [5] who reported an OR = 11, 6 for women subject to severe stress. Even if it is an accurately performed research, the study of Chen has long been debated, mostly because subsequent studies have not been able to reproduce its findings. The majority of positive articles relate an increase of around 2 times in the risk of breast cancer occurrence for women that experienced stressful life events. Controversially, there are several well conducted studies, such as Edwards's [37] or Michael's [64] that failed to show a relationship between stress and mammary carcinoma. These articles have drawn attention to the possibility of a complex psychosocial model, with a necessity to focus on biological and animal models.

d. Moment of exposure / Time period investigated

Taking into account the allostatic theory of McEwen [67] and the role of early stress as a risk factor of the allostatic load, as well as the doubling time of the tumor volume, which varies between 88 days and 2 years [68], for a psychological factor to be incriminated in oncogenesis, the stress must have acted a long time before diagnosis.

The dissonance between studies may be partially due to the time period taken into evaluation, a period that can be outside the relevant biological period. If we analyze the negative studies, we observe that 8 [4,22,25,37,42,43,45,47] of them investigated periods of less than 5 years. Nevertheless, the longest prospective follow-up considered, belong also to negative studies [57,62].

Another topic of discussion regards the impact of early stress. There are 4 studies [31,32,38,56] that investigated and confirmed that stress in childhood and adolescence –coinciding with the moment of mammary development - have a negative influence on breast cancer development later in life.

e. Interaction with other risk factors

One of the biggest problems in determining the role of stress is the difficulty in isolating it as a solitary variable. Breast cancer presents a large number of demographic or physiological risk factors. All these factors have the potential to increase or decrease the psychological impact and vice versa. As an example [28,42,43], stress has a more pronounced effect on young women, who tend to respond more severely to life events and who are also more prone to aggressive tumors. Social support is also implicated in stress management and therefore the lack of it can aggravate stress impact [18,40,64]. Smoking, alcohol consumption or obesity can also have a role in stress effect.

Essential risk factors as family history or other female physiological data are omitted in registry based studies. Such being the case, even if this type of studies have the highest degree of objectivity, their results must be regarded with suspicion. It is inaccurate to compare the

death of a husband at a young age in a close family with a death at an old age, after a long period of disease or in a dysfunctional family.

f. Individual susceptibility and personality

Cancer is not a homogenous disease, as stressors are not generic and their effect is not identical. Individual susceptibility offers one of the explanations for the heterogeneous results in epidemiological studies. One's particular manner of responding to stress brings frequently into discussion the idea of a genetic predisposition of stress induced cancer.

Personality is one of the potential risk factors investigated due to its stability in time.

After accepting the role of a type A or B personality in different diseases, the notion of a type C personality has more frequently been discussed. It is characterized by the incapacity of an emotional expression of anger and by the tendency of supporting the needs of others and ignoring their own. Women are shy, calm, less curious [20,21], and usually suppress their anger [42]. Taking into consideration personality traits, the biopsy results have been correctly predicted in 75% of cases, and the discriminative analysis correctly identified 77% of women with cancer and 87% of women without cancer [50].

To summarize our research, the significantly large number of studies, as well as the impressive number of approximately 700,000 women analyzed, guarantees a comprehensive overview on the subject. Our results are consistent with those reported by other reviews and meta-analyses [7,8].

Study limitations

Finally we acknowledge the shortcomings of our review. A single database was considered so there is the possibility of studies missed. We tried to exclude this error by also evaluating the list of references of the studies identified. There were two studies [69,70] that were not accessible in full text, both of which dated from 1986 and were published in less known journals. Even if not analyzed, the abstracts state a positive involvement of psychosocial factors in breast cancer, which further confirms our results. Moreover, a statistical analysis by conducting a meta-analysis would have brought more objectivity, but would have implied the exclusion of many studies which did not calculate risk. We could even say a meta-analysis including all 52 studies is impossible to achieve, given the heterogeneity of evaluated stress and the various methods used.

Clinical implications

Clinical impact of stress in women is a matter of great interest. Stressful life events are difficult to predict or prepare for, but their possible role in breast cancer development can bring new insights in the prevention and treatment of this disease. Controlling stress factors using various self-learned techniques or using professional help to deal early with negative feelings, should definitely have

a good effect on female health.

Conclusions

Stress is an imminent risk factor in our daily life and stressful events are real. A chronic exposure to stress has been linked to negative changes of body homeostasis. The role of stress in cancer has been extensively studied. Through this systematic review we focused on the epidemiological data regarding breast cancer. The qualitative analysis has shown a possible association between stressful events and breast cancer incidence. A final conclusion is difficult to be asserted because of the conflicting results. Elements of heterogeneity were discussed also. Possibly the role of experimental biology studies as a complementary method should be considered to measure the relationship between stressful life events and breast cancer development.

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