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Perception matters: Stressful life events increase breast cancer risk

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Abstract

Objective: The relationship between psychological stress and breast cancer risk is unclear. The present study sought to understand how stressfulness appraisal of salient Life Events (LEs) influences breast cancer risk.

Methods: A case-control design was used and included 664 female cases identified through the Cancer Surveillance Program of Orange County, CA and 203 female population-based controls. A LE questionnaire determined if events occurred prior to breast cancer diagnosis and if these events were considered to be stressful or not. Multivariate unconditional logistic regression was used to calculate ORs while adjusting for known breast cancer covariates.

Results: Cumulative adverse LEs perceived as stressful were associated with increased breast cancer risk in a dose response fashion (OR = 1.63, 95% CI = 1.00–2.66, P_{trend} = 0.045). Conversely, events perceived as non-stressful did not have a significant impact on breast cancer risk. Previous personal illness was directly related to increased breast cancer risk, whether perceived as stressful (OR = 2.84, 95% CI = 1.96–4.11) or non-stressful (OR = 3.47, 95% CI = 1.34–8.94). Abortion and relocation were observed to have a protective effect on breast cancer risk only when reported as stressful (OR = 0.54, 95% CI = 0.32–0.92; OR = 0.63, 95% CI = 0.43–0.93, respectively). Pre/Peri-menopausal women who were nulliparous or who had their first child at ≥30 years of age were especially prone to the effects of appraised stress on increased breast cancer risk.

Conclusions: This study underscores the importance of stressfulness appraisal when determining the effect of major LEs on breast cancer risk. Our results support incorporating assessments of perceived stressfulness in future epidemiological investigation of this topic.

Keywords

Breast cancer; Life events; Stress appraisal

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Conflicts of interest

The authors declare no competing interests.

1. Introduction

Breast cancer is the most common female malignancy in the United States and worldwide [1,2]. Breast cancer is the leading cause of cancer mortality among women in developing countries and the second leading cause of cancer mortality among women in the United States [3]. Known breast cancer risk factors include increased age, family history of breast cancer, post-menopausal obesity, hormone replacement therapy and reproductive characteristics mostly pertaining to increased estrogen exposure such as early age at menarche, nulliparity, and late menopause [4,5]. Genetic determinants of breast cancer have been increasingly the focus of breast cancer research. However, an estimated 85% of breast cancers are sporadic in nature, with no known familial or genetic contributions [6]. Further, an estimated 60–70% of breast cancer patients do not have known breast cancer risk factors [7]. Therefore, there is paramount importance to studying additional breast cancer risk factors.

1.1. Stress as a potential breast cancer risk factor

Psychosocial stress as a risk factor for cancer and breast cancer specifically has been subject of research investigation for centuries [8]. Nevertheless, the association between psychological stress and breast cancer risk in human populations remains unclear. Many breast cancer survivors attribute past experiences of stress as major contributors to their cancer development [9]. However, despite many studies examining the role of stress in breast carcinogenesis, firm conclusions have yet to be reached.

Studies examining whether LEs influence breast cancer risk have reached conflicting conclusions. Some epidemiological studies found that LEs are associated with increased breast cancer risk [10–13], while other studies did not supported this conclusion [14–16]. One of the main challenges in stress research is measuring the level of stress. When analyzing the effect of stress due to LEs on breast cancer risk, researchers have attempted to standardize measurement of stress exposure. The main measures of stressful LEs utilized in epidemiological studies thus far have been the Holmes and Rahe Social Readjustment Rating Scale [11–14] and the Brown and Harris LEs and Difficulties Schedule (LEDS) [15,17]. However, in both of these measures individual stress appraisal is not directly addressed [18,19].

2. Stress carcinogenesis

The carcinogenic properties of the stress hormones cortisol, epinephrine and norepinephrine have been demonstrated in cell culture and animal models [24–27]. Cortisol shifts the immune response from Th1 to Th2 dominated. Decreased IFN-gamma production and a decline in natural killer cells have also been observed in response to increased HPA axis signaling. These alterations impair the ability of the immune system to identify and neutralize cancer cells [28,29]. With prolonged stress, tissues become insensitive to cortisol regulation contributing to an inflammatory state [30]. This state is characterized by increased cell proliferation and elevated reactive nitrogen and oxygen species that contribute to DNA damage, dysplasia and resultant neoplasia [31]. Consistently, the pro-inflammatory cytokine Interleukin-6 (IL-6) is elevated in various cancers [32].

2.1. Stress appraisal

Psychological stress arises when a person appraises the environmental demands to overwhelm his/her ability to cope with the situation [33]. The stress researcher Selye, M.D. was the first to recognize that the individual is the one to determine based on their perception of the situation whether it is eustressful or distressful. When a stressor is appraised to be positive, beneficial or desired, it leads to eustress. In contrast, when a stressor is appraised to be negative, unwanted or exceeding coping abilities, it will cause a state of distress [34,35]. Personal perception of stress has been shown to be important in determining how stressors impact physiology [36].

2.2. Stress appraisal and breast cancer risk

The subjective reporting of daily stress and breast cancer incidence has been investigated previously [20]. In a large prospective cohort study investigating the influence of perceived daily stress on subsequent breast cancer risk during 24 years of follow-up, a 2-fold increase in breast cancer risk was observed for women who reported high levels of stress compared to women who reported no or minimal mental stress [20]. Conversely, another prospective study focusing on perceived daily stress found a protective relationship between higher stress levels and breast cancer risk [21]. However, these studies quantified stress based on reports of nervousness and anxiety in everyday life and did not address stressfulness of more salient LEs such as death of a close relative or serious illness. Within human studies focusing on stress and breast cancer etiology, there is more substantial evidence toward the role of stress in the form of salient LEs as opposed to daily stress [22]. Our recent work supports the role of negative valence LEs in promoting breast cancer development [23].

To our knowledge, the relationship between perceived stressfulness of salient LEs and breast cancer risk has not been directly addressed. Higher perceived stress has been linked to increased cortisol levels [37] and therefore can provide easily ascertained information regarding HPA perturbations resulting from LEs. Recent work has revealed that higher perceived stress is linked to higher resting amygdalar activity [38], a key component of the physiological stress system. The synergistic influence of a stressor and the perception that ‘stress influences health outcomes’ on increasing mortality, further supports the importance of stress perception [39].

2.3. Modulators of stress appraisal

Antoni et al. [27], developed a bio-behavioral model for the relationship between psycho-social factors and cancer incidence and progression. Based on this model, the cancer “macroenvironment” is comprised as a result of the interaction between environmental stress and an individual’s attitudes toward the stressor, perception of treat, and coping abilities [27]. When the state of appraised distress persists chronically, it is more likely to activate neuroendocrine stress systems leading to secretion of stress hormones and neuropeptides that contribute to cancer growth [40]. Recently, blocking the effects of physiological stress in mice models by antagonizing the ß-adrenergic receptor was shown to protect against breast tumor dissemination through lymphatic spread [41]. The individual’s internal working model and attachment style are important factors in modulating perceived stressfulness, which contributes to subsequent activation of the physiological stress response facilitating

the tumor microenvironment [42]. A recent study found that an “optimal” relationship with at least one parent leading to a secure attachment style reduced the likelihood of LN involvement of breast malignancies by 62% [43].

2.4. Importance of life event stress appraisal in breast cancer risk

To better study the effects of stress in the form of LEs, we sought to understand if a woman’s personal stress appraisal influences the association between LEs and breast cancer risk. As discussed, perceived stress is associated with elevated cortisol levels [37], and higher resting amygdalar activity [38]. Considering our understating of the plausible role of cortisol in cancer initiation and progression [24–27], we hypothesize that the perception of stress resulting from major life events will increase cortisol signaling and hence impair immune surveillance [28,29] and contribute to breast cancer risk. The aim of the present analysis is to investigate whether LEs increase breast cancer risk depending on the individually reported experience of stress. Understanding how to better epidemiologically measure and quantify stress is expected to allow a more accurate assessment of whether stress influences breast cancer development.

3. Methods

3.1. Study population

Population-based primary invasive breast cancer cases and population-based controls were identified as part of the Hereditary Breast and Ovarian Cancer (HBOC) study of the University of California, Irvine (CA58860) [44,45]. Cases were identified via the population-based cancer registry of the Cancer Surveillance Program of Orange County (CSPOC). The Institutional Review Board of the University of California, Irvine approved the study protocol and written informed consent was obtained from participants of the study (IRB numbers HS91–137 and HS96–496) [45].

Data from incident breast cancer diagnoses among females aged 24–75 years, between March 1st, 1994 and February 28th, 1995 was used. Female controls of similar age and race/ethnicity that had no history of cancer were randomly selected from residents of Orange County using random digit dialing between December 1997 and February 1999. Cases and controls were asked to answer an epidemiological risk factor questionnaire (RFQ) that included extensive information regarding personal, social, medical and family history in addition to a section querying about LEs.

Seven hundred and nineteen breast cancer cases between 24 and 75 years of age completed a risk factors questionnaire (RFQ). Six hundred and sixty four of these women completed the life event (LE) section of the RFQ and were included in the present analyses. The majority of cases (94%) completed the questionnaire within 3 years of breast cancer diagnosis. Two hundred twenty six population-based controls in the appropriate age interval completed the RFQ, out of which 203 completed the LE section and were included in the analyses.

3.1.1. Measures—LE measures in the RFQ were based on a subset of the Holmes and Rahe scale [18]. LEs from the Holmes and Rahe scale that were inquired about here were: 1) marriage, 2) death of a spouse, 3) death of an offspring, 4) death of a close person: sister,

brother, relative or friend, 5) death of a parent, 6) job loss, 7) relocation, 8) separation/divorce, 9) foreclosure of a mortgage loan or bankruptcy, 10) pregnancy, 11) pregnancy of a child, 12) illness and 13) illness in the family. We also asked participants about a history of abortion, marriage of an offspring, and buying a house. Participants were asked whether specific LEs occurred prior to their breast cancer diagnosis or corresponding reference age for controls, defined as age at questionnaire completion. We further assessed if events that occurred were individually perceived as "stressful" or "non-stressful". The questionnaire prompted participants to identify their age at which each event occurred using the following age intervals: 10–19, 20–29, 30–39, 40–49, 50–59 and ≥60.

In order to analyze if perceived event stressfulness was impacted by event valence, we used the Paykel et al. [46]. LE Scale to dichotomize events based on whether they were more likely to be desirable or undesirable, i.e. of positive or negative valence. Events that were at the top half of the scale were determined to be of negative valence, while events at the bottom half of the scale determined to be of positive valence [46] (Fig. 1). LEs included in our study but not in the Paykel scale were not assigned valence.

3.1.1.1. Negative valence LEs.: A subset of LEs that were identified as being more likely to be undesirable and unpredictable and therefore have negative valence were: 1) death of a spouse, 2) death of an offspring, 3) death of a sister, brother, close relative or friend, 4) death of a parent, 5) job loss, 6) foreclosure of a mortgage loan or bankruptcy, 7) illness and 8) illness in the family.

3.1.1.2. Positive valence LEs.: A subset of LEs that were identified as being more likely to be desirable and predictable and therefore have positive valence were identified: 1) marriage, 2) marriage of an offspring, 3) relocation, 4) buying a house, 5) pregnancy, 6) pregnancy of a child.

3.1.1.3. Stressful/non-stressful life events.: Participants were asked if the above life events, whether positive or negative, brought about a "moderate to severe" amount of stress. If "yes", the life event was considered a 'stressful life event' (SLE), if "no", the life event was considered a 'non-stressful life event' (NSLE) (Fig. 1). In a similar fashion described for LEs, age interval at SLE/NSLE was determined. Three different SLE/NSLE parameters were used to evaluate the effect of SLEs/NSLEs on breast cancer risk: (1) *SLE/NSLE occurrence*: (yes/no), (2) *negative valence SLE/NSLE sum*: 0, 1, 2, 3 and ≥4 events, and (3) *positive valence SLE/NSLE sum*: 0, 1, 2–3, 4–5 and ≥6 events.

For the *SLE/NSLE occurrence* variable, the LE category received a value of "0" if the event did not occur and "1" if any number of events happened in the same category (if someone was pregnant twice, the "pregnancy" *occurrence* variable obtained a value of "1"). The grouping of the sum of positive/negative valence *SLEs/NSLE*s was based on creating a zero event baseline and dividing the remaining distribution of events in the control group into quartiles. Here each event in a LE category contributed an unweightd value of "1" to the sum (if a women was pregnancy twice, "2" LEs would be added to the *SLE/NSLE sum*. For the *SLE sum*, LEs that were appraised as non-stressful (NSLEs) were included in the zero event

baseline and for the *NSLE sum*, LEs that were appraised as stressful (SLEs) were included in the zero event baseline.

3.1.2. Data analysis—Descriptive statistics were calculated for cases and controls. Means and standard deviations were computed for continuous variables, whereas frequencies and percentages were computed for categorical variables. Additional descriptive statistics were generated in a stratified analysis according to occurrence of events appraised as stressful or non-stressful.

Candidate variables for model building were selected based on a literature review of breast cancer covariates. A standard stepwise model building process with statistical threshold for inclusion into the model of $P_{entry} = 0.25$ and $P_{\text{stay}} = 0.3$ was performed in selection of a baseline model for the multivariate analyses. The final multivariate logistic regression model adjusted for *age* (age at diagnosis for cases and age at RFQ completion for controls), *smoking history* (ever smoked/never smoked), *race/ethnicity* (non-Hispanic white/all other groups), *education* (less than college/some college or more), *family history* (yes/no) (determined based on family history of breast cancer in first degree relative), *hormone replacement therapy* (*HRT*) (ever use/never use), *age at menarche* (≤11, 12–13 and ≥14), *age at first full term pregnancy* (*FFTP*): (< 25, 25–29 and ≥30), *menopausal status* (pre-menopausal/peri-menopausal/post-menopausal) and *physical activity* (not active/moderately active/very active). To examine potential confounding, we examined the estimates for the covariates in the model when including negative life events and when not including negative life events. The estimates of the ORs associated with covariate coefficients did not differ by > 5% and therefore we conclude that there is no significant association between stress in the form of life events and the breast cancer covariates examined in the model.

SLE and NSLE parameters were evaluated in separate univariate and multivariate analyses. Univariate associations between breast cancer and *SLE/NSLE occurrence* parameters, *negative valence SLE/NSLE sum, positive valence SLE/NSLE sum* and *total SLE/NSLE sum* were determined. Frequency tables and χ^2 statistics were used to compare *SLE/NSLE* variables among cases and controls. Likelihood of an event being “stressful” was determined based on the fraction of (SLEs)/(total LEs) reported for cases and controls.

The influence of *SLE/NSLE* parameters on breast cancer odds ratios (ORs) was determined using simple unconditional logistic regression where ORs and 95% confidence intervals (CIs) were computed. Significant *SLE/NSLE* parameters were then included one at a time into the baseline multivariate regression model and adjusted ORs and CIs were determined using multivariate unconditional logistic regression. The *negative valence SLE/NSLE sums* were also included in the logistic regression model as continuous variables and Wald χ^2 statistics were used to test for trend.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

4. Results

4.1. Demographics and characteristics among breast cancer cases and controls

Descriptive characteristics of cases and controls are presented in Table 1. Cases were slightly older than controls with a mean age of 55.6 years for cases and 53.6 years for controls. Cases were more likely to have a positive family history of breast cancer (24.7%) compared to controls (15.3%). Both cases (88.9%) and controls (87.7%) were primarily of white ethnicity. Mean age at first full term pregnancy was significantly younger for controls (23.7) compared to cases (25.2). The majority of controls had children at the age of ≤24 years (60.8%) in comparison to 49.8% in the case group. No significant differences between cases and controls were observed for the following parameters: BMI, age at menarche, parity, number of children, menopausal status, hormone replacement therapy, education level, smoking history and alcohol history.

4.2. Descriptives of cases and controls who perceived events as "stressful"

Pre-menopausal or peri-menopausal women who appraised at least one event as stressful were more likely to be cases ($P = 0.002$). Similarly, nulliparous women ($P = 0.043$) and women who had their first child at age ≥ 30 and appraised at least one event as stressful were more likely to have had breast cancer ($P = 0.024$). There were no significant differences observed among cases and controls on the following parameters: age, BMI, race/ethnicity, age at menarche, number of children, HRT, family history of breast cancer, education level, smoking history and alcohol history (Table 2).

4.2.1. Likelihood of events being "stressful"—The pattern of stressfulness of individual *LE occurrence* variables did not differ among cases and controls (Fig. 2). As expected, negative valence LEs were more likely to be perceived as stressful compared to positive valence LEs. On average, 85% of the time negative LEs were categorized as "stressful" among cases, as compared to 89% of the time among controls. On the other hand, positive LEs were categorized as "stressful" only 61% of the time among cases and 64% of the time among controls. Job loss and foreclosure were the negative valence LEs most likely to be reported as "stressful" among cases (89%) and controls (100%).

4.2.2. Stressful/non-stressful LEs and breast cancer risk—In the univariate and multivariate analyses, relocation (OR = 0.65, 95% CI = 0.44–0.95) and abortion (OR = 0.54, 95% CI = 0.32–0.91) were associated with decreased breast cancer risk only when perceived as stressful. History of personal illness was associated with increased breast cancer risk both when appraised as stressful (OR = 2.80, 95% CI = 1.94–4.04) and non-stressful (OR = 3.40, 95% CI = 1.32–8.75) (Table 3).

Negative valence LEs were associated with a significant dose-response increase in breast cancer risk only when perceived as stressful ($P_{trend} = 0.049$). The highest category of negative valence SLEs was associated with a 62% increase in breast cancer risk after adjusting for breast cancer covariates (OR = 1.62, 95% CI = 0.99–2.63) (Table 4). Conversely, positive valence LEs were cumulatively associated with a non-significant trend

toward decreased breast cancer risk only when events were perceived as stressful (data not shown).

5. Discussion

The results presented here suggest that LEs differentially influence breast cancer risk according to stress perception. This result is consistent with previous research indicating the importance of stress appraisal in altering the physiological stress system [37]. Prior research supports this finding given that LEs were overall perceived as more impactful among breast cancer patients as compared to controls [47].

Our results are in line with those reported by Helgesson et al. [20] where perceived stress was associated with an approximately 2-fold increase in breast cancer risk. However, in this study stress was determined based on experiencing daily stress “occasionally or more” during the past 5-years and did not address LE stress [20]. Likewise, a recent study that focused on perceived stress in daily life and increased breast cancer risk in a cohort of 29,098 Japanese women showed that women who reported “high perceived stress”, had a 1.71 (95% CI = 1.02–2.85) increased risk of developing breast cancer prospectively [48]. It is possible that women who reported higher perceived stress also had more negative valence LEs that they perceived as stressful since these measures are significantly correlated [49].

Our findings support the need to examine salient LEs in combination with other factors influencing perception of stress such as coping style and social support [50]. We found that repeated exposure to negative valence LEs perceived as “stressful” increased the risk of breast cancer. Therefore, it is likely that negative LEs cumulatively contribute to appraised overload of environmental demands compared to available coping mechanisms leading to a state of distress [34,35,40]. Consistently, a significant interaction was observed between LEs perceived as highly stressful and social support in predicting breast cancer risk, with the highest risk observed for those with highly stressful events and low social support [50].

As expected, we found that negative valence LEs were those to have the greatest likelihood of being perceived as “stressful” (Fig. 2). Therefore, negative valence, cumulative LEs perceived as stressful seem to be most influential in increasing breast cancer risk. Interestingly, “relocation” was the positive valence event to be reported as “stressful” most often and was the only positive LE to be significantly associated with decreased breast cancer risk. Therefore, it seems that to experience the benefits of positive stress, an event needs to be salient enough to induce significant eustress. Consistent with this hypothesis, the cumulative benefit of positive valence LEs on decreasing breast cancer risk was only observed when events were perceived as stressful.

History of personal illness, defined as ‘serious illness or injury of oneself’ was significantly associated with increased breast cancer risk both when perceived as stressful and when perceived as non-stressful. In line with our findings, a higher incidence of major personal illness has been reported in the past among breast cancer patients than among controls [12,47]. In a separate validation analysis, fibrocystic breast disease and gallstones were more commonly reported among breast cancer cases than among controls ($P < 0.05$). This may

indicate the possibility of physical illness contributing to immune system breakdown and facilitation of a pro-cancer microenvironment, regardless of individual psychological stress perception. Consistent with this finding, previous research has shown that physical and psychological stressors activate the HPA stress axis in a similar fashion and independently contribute to immune system breakdown [51]. Pre-existing immune system function and HPA reactivity from transgenerational [52] or early-childhood [43] experiences may predispose women to both physical illness and breast cancer.

Younger women seem to be more impacted by the effects of perceived stress. Our results suggest that stressful LEs have a stronger influence on pre/peri-menopausal breast cancer risk than on post-menopausal breast cancer risk. In the only study identified focusing on breast cancer in young women, LEs were cumulatively associated with a 62% increase in breast cancer risk [53]. It is possible that LE stress has a stronger impact on basal estrogen levels during reproductive years.

Estrogen causes proliferation of breast tissue and may promote the progression from normal cellular proliferation to hyperplasia and neoplasia [54]. Further, estrogen metabolites are directly genotoxic [55,56]. Premenopausal women have higher average levels of estradiol [57,58]. In a mouse model of LE stress, tail shock and forced swim tests resulted in increased estrogen levels and persistently thereafter [59]. Consequently, decreased estrogen metabolism resulting from LE stress [60] likely more substantially contributes to increased premenopausal estrogen exposure.

Further, LE stress seems to influence breast cancer risk specifically among nulliparous women and women who delayed childbirth. Many studies have shown that the younger a woman is at her first full term pregnancy, the lower her risk of breast cancer [61]. It is hypothesized that the mammary gland undergoes complete differentiation during pregnancy, leading breast tissue to increased resistance against carcinogenic initiation [62]. Therefore, young women who are nulliparous or had an older age at first full-term pregnancy, not only have the highest endogenous estrogen levels, but their breast tissue is also the most susceptible to mutagenic changes. Hence this population is hypothesized to be the most vulnerable to the effects of LE stress on breast cancer risk. Future studies examining the interaction between parity/age at first full term pregnancy and negative valence LEs would deepen our understanding of this observation and the interplay between reproductive and psychological factors in breast tumorigenesis.

Premenopausal breast cancer tends to be more aggressive with estrogen-independent tumors being more common [63]. Further, approximately 30% of female breast malignancies are diagnosed among women younger than 50 years of age [64]. We are limited in our understanding of etiologic and mechanistic contributors to this disease. A study from 2016 achieved significance for the population attributable fraction when considering known risk factors for post-menopausal breast cancer but not premenopausal breast cancer [65]. Therefore, this research has important implications toward understanding contributing factors to development of breast malignancy in young women.

Breast cancer cases and controls did not exhibit a different pattern of LE stress perception. Stressfulness perception followed a predictable trend among cases and controls. The likelihood of an event being reported as “stressful” followed our valence categorization based on the Paykel scale (1971) [46]. Negative valence LEs were more often perceived as stressful as compared to positive valence LEs. These findings implicate that cases and controls do not differ in what events they perceive as stressful. However, given the cumulative effect of stressful events on breast cancer risk, it seems that cases are experiencing more stress through negative valence LEs and possibly are not as well equipped to cope with stress compared to the control group.

6. Future directions

Additional research focusing on the effect of perceived LE stress on breast cancer risk among premenopausal women is needed. Incorporating assessments of cortisol, catecholamines and estradiol would allow researchers to better understand the mechanism behind the proposed alterations in neuroendocrinological processes accelerating breast carcinogenesis. Further investigating the contributing factors that distinguish cases and controls in their response to stressful situations should be considered. Controls may be more likely to find meaning in their stressful situations and as a result gain resiliency, while cases are perhaps more debilitated in the face of stress.

Epidemiological studies examining the relationship between LEs and breast cancer risk thus far do not directly incorporate individualized stress appraisal measures. Questionnaires and structured interviews are currently widely used in an attempt to standardize stress exposure [11–13,15,17]. However, this approach ignores the importance of an individual’s interaction with their environment along with their coping mechanisms and resulting appraised stress [66,67]. Higher scores on the most commonly used measure of stress appraisal, the Perceived Stress Scale (PSS), have been associated with prior occurrence of LEs and the presence of somatic and depressive symptomology [49]. However, this measure addresses perceived stress in the preceding 30 days. Our results support the utilization of an adapted PSS in future research focusing on LEs and breast cancer risk. Consistent with this recommendation, studies incorporating self-ratings of event stressfulness were superior predictors of health outcomes compared to studies that did not incorporate this information [68,69].

7. Limitations and strengths

When interpreting our findings, it is important to consider study limitations. Firstly, this is a case-control study, where information was ascertained retrospectively and hence the possibility of recall bias. However, since LEs are reported with high reproducibility [70], it is unlikely that cases were over-reporting the occurrence of LEs. Reflective of the population of Orange County, the majority of participants were of White ethnicity. Therefore, generalizability to other racial/ethnic groups is questionable. Additional studies examining a more diverse population are warranted. Because we asked about an additional 3 events not included in the validated Holmes and Rahe scale [71], we did not sum events according to

assigned weights. A further limitation to our study pertains to the use of a dichotomized assessment of stressfulness and assignment of positive/negative valence to LE categories.

To gain a better understanding of the effect of perceived stressfulness on breast cancer risk, it would be more accurate to quantify stress appraisal on a gradient from non-stressful to extremely stressful. Further, it would be advised to include a positive-negative valence gradient for each event to better quantify the interplay of valence and stressfulness in breast cancer risk. Another limitation pertains to valence categorization of some events that did not perfectly match with the Paykel (1971) LE Scale categories [46]. For example, we could not differentiate the valence of our grouped category “separation/divorce” since based on our dichotomization “divorce” would be assigned negative valence and ‘separation not due to argument’ positive valence. Similarly, abortion could be desirable (terminating an undesirable pregnancy) or undesirable (spontaneous abortion) and therefore was not assigned valence.

This study provides novel insight into the relationship between LE stress and breast cancer risk. To our knowledge, this is the first study of its kind to investigate the influence of LE appraised stress on breast cancer risk. This assessment was facilitated by the information we had available to us on the personal categorization of events as “stressful”/’not-stressful’ by participants in the study. Further, our results shed light onto the effect of stress in the form of LEs on breast cancer risk in young women specifically. The use of population-based controls strengthens the external validity of our findings. Our rich dataset allowed for the adjustment of breast cancer covariates in our multivariate models, enabling a more accurate understanding of the influence of LEs on breast cancer risk while limiting the possibility of confounding.

8. Conclusion

This study demonstrates that stress appraisal should be addressed in future epidemiologic investigation of LEs and breast cancer risk. Negative valence LEs seem to increase breast cancer risk in a dose-response fashion only when perceived as stressful. Younger women, women who are nulliparous and women who delayed age at childbirth seem to be particularly sensitive to the effects of LE stress. Additional research should be performed specifically examining the effect of LE stress appraisal on premenopausal breast cancer risk according to breast cancer molecular subtypes.

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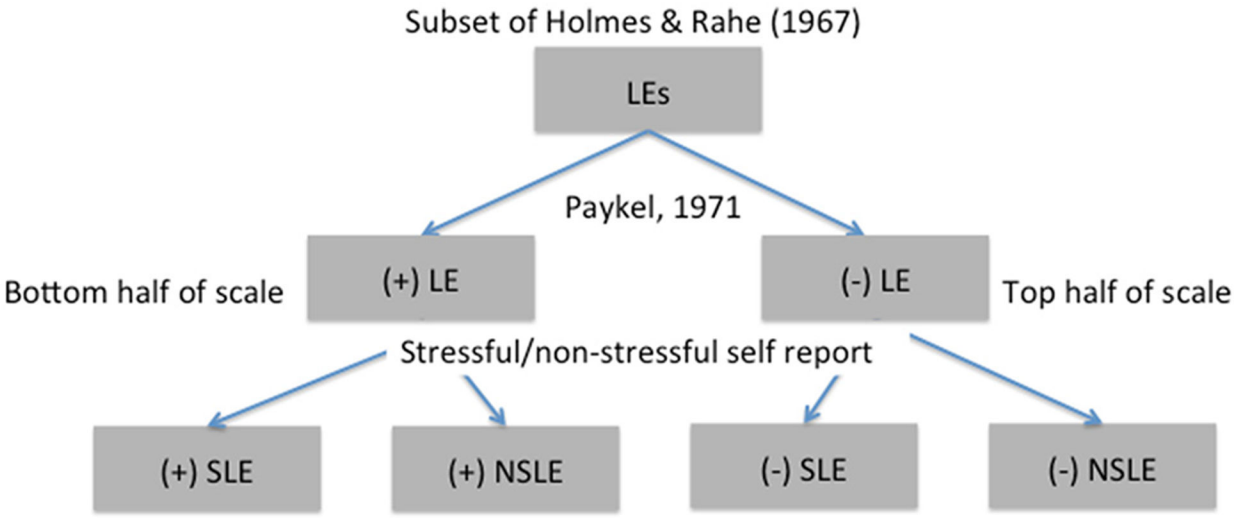

Fig. 1.

Categorization of Life Events according to valence and perceived stress.

LE: Life Event, SLE: Stressful Life Event, NSLE: Non-Stressful Life Event.

(+): Positive valence, (−): Negative valence.

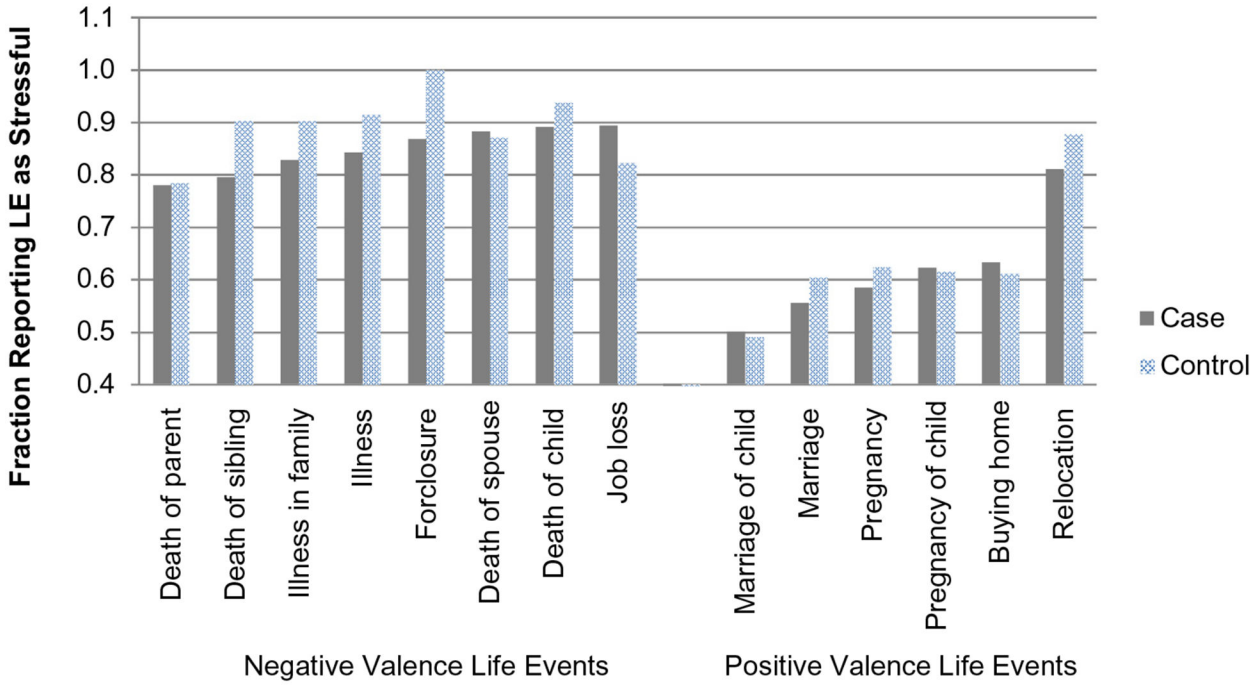

Fig. 2.

Likelihood of LEs being Perceived as "Stressful" among Breast Cancer Cases and Controls

LEs (LEs) were categorized into "positive" or "negative" valence based on the Paykel (1971) LE scale (see text for details). LEs are organized based on events least to most likely to be stressful among cases in both valence categories. The likelihood an event category to be classified as "stressful" was determined by the fraction: (# stressful LEs)/(total # of LEs).

Table 1

Distribution of demographics and other characteristics among 664 cases and 203 controls.

Characteristic	Cases (n = 664)		Controls (n = 203)		*P* value
Reference age, years: mean, s.d.	55.6	10.9	53.6	12.3	0.039
BMI: no. (%)					
Underweight	15	2.26	4	2	0.348
Normal weight	95	47.5	335	50.5	
Overweight	54	27	196	29.5	
Obese	47	23.5	118	17.8	
Race/ethnicity: no. (%)					
White	590	88.9	178	87.7	0.124
Hispanic	38	5.7	19	9.4	
Black	2	0.3	1	0.5	
Asian/Pacific Islander	34	5.1	5	2.5	
Age at menarche: no. (%)					
≤10 years	142	22.15	44	22.2	0.966
11–13years	349	54.45	106	53.5	
≥14 years	150	23.4	48	24.2	
Age at first full-term pregnancy: no. (%)					
≤24 years	277	49.8	104	60.8	0.042
25–29 years	184	33.1	44	25.7	
≥30 years	95	17.1	23	13.5	
Parity: no. (%)					
Nulliparous	107	16.1	32	15.8	0.865
Parous	556	83.7	171	84.2	
Number of children: mean., s.d	2.1	1.5	2.2	1.4	0.386
Menopausal status: no. (%)					
Pre/peri-menopausal	239	36.0	74	36.5	0.832
Post-menopausal	425	64.0	127	62.6	
Hormone replacement therapy: no. (%)					
Never	311	46.8	80	39.4	0.063
Ever	347	52.3	121	59.6	
Family history of breast cancer in first-degree relative: no. (%)					
No	499	75.2	172	84.7	0.005
Yes	164	24.7	31	15.3	
Education: no. (%)					
< College	419	63.1	121	59.6	0.357
Some college or more	241	36.3	81	39.9	
Smoking: no. (%)					
Never	332	50.0	112	55.2	0.240
Ever	326	49.1	91	44.8	
Alcohol use in year prior: no. (%)					

Characteristic	Cases (n = 664)		Controls (n = 203)		*P* value
None	243	36.6	69	34.0	0.533
Any	399	60.1	126	62.1	
Physical activity in previous year: no. (%)					
Not active	262	39.5	103	50.7	0.011
Moderately active	209	31.5	60	29.6	
Very active	193	29.1	40	19.7	

*Due to unknown values, subcategories may not sum to total numbers of cases and controls.

Table 2

Demographics and characteristics of women who appraised events as stressful.[a]

Characteristic	Cases[b]		Controls		[c]*P* value
Reference age, years: mean, s.d.	54.5	11.9	55.6	10.6	0.296
BMI: no. (%)					
Underweight	10	71.4	3	75.0	0.467
Normal weight	262	80.6	69	72.6	0.094
Overweight	163	84.9	42	77.8	0.215
Obese	95	83.3	42	89.4	0.466
Race/ethnicity: no. (%)					
Non-Hispanic White	479	83.5	139	78.1	0.103
Other	51	76.0	19	71.8	0.687
Age at menarche: no. (%)					
≤10 years	28	77.8	9	75.0	1
11–13 years	367	83.4	107	77.5	0.117
≥14 years	121	81.8	38	79.2	0.690
Age at first full-term pregnancy: no. (%)					
≤24 years	226	84.0	85	81.7	0.595
25–29 years	137	76.1	36	81.8	0.418
≥ 30 years	78	85.7	15	65.2	0.024
Parity: no. (%)					
Nulliparous	89	84.8	22	68.8	0.043
Parous	441	81.7	139	79.5	0.501
Number of children: mean., s.d	2.2	1.4	2.1	1.5	0.386
Menopausal status: no. (%)					
Pre/peri-menopausal	194	84.4	50	67.6	0.002
Post-menopausal	336	81.0	106	83.5	0.525
Hormone replacement therapy: no. (%)					
Never	244	80.8	61	76.3	0.368
Ever	282	83.4	97	80.2	0.416
Family history of breast cancer in first degree relative: no. (%)					
No	397	82.2	133	77.3	0.163
Yes	133	82.6	25	80.7	0.793
Education: no. (%)					
< College	331	80.7	95	78.5	0.590
Some college or more	197	84.9	62	76.5	0.086
Smoking: no. (%)					
Never	261	81.1	85	75.9	0.242
Ever	264	83.3	73	80.2	0.497
Alcohol use in year prior: no. (%)					
None	192	81.4	56	81.2	0.971
Any	324	83.7	97	77.0	0.087

Characteristic	Cases[b]		Controls		[c]*P* value
Physical activity in previous year: no. (%)					
Not active	207	81.5	78	75.7	0.219
Moderately active	172	84.7	46	76.7	0.145
Very active	151	80.3	34	85.0	0.492

(−) Test statistic could not be computed because of insufficient data.

[a]Appraised stressful events: had at least one event that was appraised as stressful.

[b]Table total values could be discrepant from the total cases and controls since some participants reported only NSLEs.

[c]*P* values were calculated based on χ^2 statistics unless cell counts were below 5 where fisher's exact test was used.

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Table 3

Univariate and multivariate odds ratios for significant stressful and non-stressful Life Event occurrence parameters.

	Cases (N = 664)		Controls (N = 203)		OR	95% CI		Adj OR[a]	95% CI	
	N	%	N	%						
LEs perceived as stressful										
Abortion	60	9.0	28	13.8	0.62	0.38	1.00	0.54	0.32	0.91
Illness	331	49.9	54	26.6	2.74	1.94	3.88	2.80	1.94	4.04
Relocation	141	21.2	57	28.1	0.69	0.48	0.99	0.65	0.44	0.95
LEs perceived as non-stressful										
Death of sibling	59	8.89	9	4.43	2.10	1.02	4.32	1.75	0.83	3.68
Illness	62	9.34	5	2.46	4.08	1.62	10.29	3.40	1.32	8.75
Illness in family	66	9.94	11	5.42	1.93	1.00	3.72	1.53	0.77	3.03

N: number of exposed; %: percent exposed.

[a]Adjusted for reference age, age at first full term pregnancy, menopausal status, family history of breast cancer, HRT use, smoking history, education level, race/ethnicity and physical activity.

Table 4

Univariate and multivariate odds ratios for sum negative Life Events.

	Cases (N = 664)		Controls (N = 203)		OR	95% CI		Adj. OR[a]	95% CI	
	N	%	N	%						
Stressful negative valence LEs										
0 events	123	18.5	45	22.2						
1 event	111	16.7	29	14.3	1.40	0.82	2.39	1.43	0.81	2.53
2 events	84	12.7	46	22.7	0.67	0.41	1.10	0.81	0.47	1.38
3 events	109	16.4	29	14.3	1.38	0.81	2.34	1.57	0.89	2.77
≥4 events	237	35.7	54	26.6	1.61	1.02	2.52	1.62	0.99	2.63
P trend[b]					0.042			0.049		
Non-stressful negative valence LEs										
0 events	526	79.2	161	79.3						
1 event	46	6.9	18	8.9	0.78	0.44	1.39	0.77	0.42	1.42
2 events	30	4.5	13	6.4	0.71	0.36	1.39	0.58	0.28	1.19
3 events	21	3.2	6	3.0	1.07	0.43	2.70	0.80	0.31	2.10
≥4 events	41	6.2	5	2.5	2.51	0.98	6.46	2.04	0.77	5.41
P trend[b]					0.227			0.760		

N: number of exposed; %: percent exposed.

[a]Adjusted for reference age, age at first full term pregnancy, menopausal status, family history of breast cancer, HRT use, smoking history, education level, race/ethnicity and physical activity.

[b]*P trend* computed by incorporating *negative valence LE* (*NSLE*) *sum* in the logistic regression model as a continuous variable.