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Negative Valence Life Events Promote Breast Cancer Development

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Abstract

The contribution of life events (LEs) to breast cancer risk is unclear. The present case-control study of 664 cases and 203 controls demonstrates that adverse events cumulatively increase breast cancer risk and positive events attenuate this increased risk. Assessing LEs on a negative to positive gradient will allow for a more fine-tuned understanding of how personal LEs influence breast cancer risk.

Background: The influence of stress on breast cancer risk remains unknown. The goal of the present study was to determine the effect of stress in the form of salient positive and negative valence life events (LEs) on primary invasive breast cancer risk. We hypothesized that salient negative LEs would increase breast cancer risk and salient positive LEs would attenuate this increased risk.

Patients and Methods: We used a case-control design with 664 cases identified through the Cancer Surveillance Program of Orange County and 203 population-based controls. Participants completed a risk factor questionnaire, which included a LE section. Fourteen salient LEs of positive or negative valence were used to quantify stress exposure. A baseline model was constructed, and odds ratios (ORs) were calculated using multivariate unconditional logistic regression.

Results: Negative LEs were associated with increased breast cancer risk. The OR for ≥ 4 negative LEs showed a 2.81-fold increase in breast cancer risk (OR, 2.81; 95% confidence interval [CI], 1.47–5.36). A significant dose–eresponse relationship between lifetime negative valence LEs and breast cancer risk was found. Previous personal illness increased breast cancer risk by 3.6-fold (OR, 3.60; 95% CI, 2.50–5.20). In contrast, abortion was associated with a 45% decrease in breast cancer risk (OR, 0.55; 95% CI, 0.34–0.89). Salient positive LEs did not have a significant effect on breast cancer risk. However, they seemed to buffer the adverse effect of salient negative LEs on breast cancer risk.

Conclusion: The findings from the present study support the role of salient negative LEs in promoting breast cancer development, with a possible buffering effect of salient positive LEs.

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Disclosure

The authors declare that they have no competing interests.

Keywords

Breast cancer; Case-control study; Epidemiology; LEs; Stress

Introduction

Breast cancer is the most common non-skin cancer in women, comprising 30% of newly diagnosed cancers.[1] Approximately 12% (1 in 8) of women will develop invasive breast cancer in the United States.[2] Invasive breast cancer is the second most common cause of cancer mortality in women. Research has shown that approximately 85% of women develop breast cancer sporadically, with no family history of breast cancer.[1–3] Despite advances in understanding breast cancer risk factors, such as reproductive variables, obesity, alcohol consumption, and genetics, it has been estimated that ≤ 60% of the variability in a woman's breast cancer risk cannot be explained by these factors.[4] Therefore, the investigation of additional factors associated with breast cancer risk will expand our understanding of breast cancer etiology and is expected to lead to better methods of prevention, diagnostic tools, and treatment options.

Despite years of debate concerning the link between mind and body in breast cancer risk, this relationship remains unknown and is currently under active investigation.[5,6] Breast cancer patients continually express concern regarding psychological stress contributing to their breast cancer. A meta-analytical study by Dumalaon-Canaria et al[7] reviewed the perceived causes of breast cancer in studies reported from 1982 to 2012. They showed that survivors reported stress as 1 of the main contributors to the development of their breast cancer.[7] Because patients with breast cancer are more likely to remember previous experiences and exposures that could explain the development of their breast cancer, the possibility for recall bias is strong. The present study used different intervals when analyzing life events (LEs) to best overcome this limitation.

Understanding of the intricate communication of the nervous system with the immune and endocrine systems is slowly unfolding. Through extensive molecular, cellular, animal, and human research, the link between psychological and physiologic stress and cancer initiation and progression is becoming apparent.[8–10] In vitro and in vivo experiments have demonstrated a clear relationship between stress signaling and breast cancer pathogenesis. Animal models of breast cancer have indicated that prolonged activation of the physiologic stress response contributes to breast carcinogenesis.[11] In addition, stress signaling impairs DNA repair capabilities and causes direct DNA mutagenesis.[12]

Epidemiologic studies using LE stress such as the death of a spouse or serious illness as quantified measures of stress exposure have shown a stronger association with breast cancer risk compared with that from employment or daily stress.[13] Nevertheless, the role of LEs in breast cancer pathogenesis remains ambiguous, given that some studies have indicated a direct relationship between a history of LEs and breast cancer risk,[14–16] but others have found no such relationship.[17–19] A recent cohort study reported in 2016 concluded that no relationship exists between adverse LEs and breast cancer risk.[20] However, that study had had a relatively short follow-up period (average 6 years), had focused on the LEs in the

previous 5 years, had not inquired about cumulative lifetime events, and had included a relatively young cohort (average age 46.6 years).[20] Another study that found a null association had used hospital controls with a suspicious breast lump; therefore, their results have limited generalizability.[19] An additional study with negative findings had examined the effect of individual LEs on breast cancer risk without examining the cumulative effect of these events.[18] The present case-control study included a large sample of breast cancer patients and population-based controls and examined the effect of cumulative lifetime LE measures, in addition to individual LEs, on breast cancer risk. We have also included information about LEs spanning ≥ 40 years. Furthermore, the present study sought to understand how to better quantify the stress resulting from LEs by addressing the importance of LE valence. Thus, the results from the present study will allow for a better understanding of the stress-breast cancer relationship by overcoming the limitations of previous studies.

Our working hypotheses were that salient negative valence, undesirable LEs would increase breast cancer risk in a dose–eresponse fashion, and positive valence, desirable LEs would moderate this increased risk. Positive valence LEs were hypothesized to allow a break in the stress response, allowing restoration of hormone levels and immune function to baseline and therefore protecting against the deleterious effects of negative, undesirable LEs on breast cancer risk.

Patients and Methods

Study Population

We included population-based incident primary invasive breast cancer cases and population-based controls who were a part of the Hereditary Breast and Ovarian Cancer study of the University of California, Irvine (approval no. CA58860).[21,22] Breast cancer cases were identified through the population-based cancer registry of the Cancer Surveillance Program of Orange County. The institutional review board of the University of California, Irvine, approved the study protocol. All the participants provided written informed consent (approval nos. HS91–137 and HS96–496).

The cases included incident breast cancer diagnoses among women aged 24 to 75 years from March 1, 1994 to February 28, 1995. After informing physicians about the study, the patients were contacted with an initial introductory letter explaining the purpose of the study and requesting their consent to participate. Female controls of similar age with no history of cancer were randomly selected from the residents of Orange County using random digit dialing from December 1997 to February 1999. The cases and controls were asked to complete an epidemiologic risk factor questionnaire (RFQ) that included extensive information regarding personal, social, medical, and family history, in addition to a section querying about LEs.

A total of 1019 invasive breast cancer cases were eligible for participation in the study, 809 of which completed the RFQ (79%). Of those who completed the RFQ, 719 were aged 24 to 75 years. Of these 719 women, 664 completed the LE section and were included in the present analyses (92%). Most cases (94%) completed the questionnaire within 3 years of the

breast cancer diagnosis. Given that the format of the RFQ changed midway through the study and no longer included a LE section, the number of controls for which we had information about LEs was smaller than that for the cases. A total of 226 population-based controls in the appropriate age interval completed the RFQ. Of these, 203 completed the LE section and were included in the present study (90%).

Measures

The LE measures in the RFQ were determined from a subset of the Holmes and Rahe scale,[23] along with additional LEs we had identified as potentially causing significant stress, including abortion, marriage of an offspring, and buying a house. The participants were queried about LEs that had occurred before their breast cancer diagnosis or the corresponding reference age for the controls, defined as their age at questionnaire completion. The questionnaire prompted participants to identify their age at which each event had occurred using the following intervals: 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and ≥ 60 years. LEs were operationally defined by 16 salient events that are commonly encountered during one's life. These included (1) marriage, (2) marriage of an offspring, (3) death of a spouse, (4) death of an offspring, (5) death of a close person (eg, sister, brother, relative, or friend), (6) death of a parent, (7) abortion, (8) job loss, (9) relocation, (10) separation or divorce, (11) buying a house, (12) foreclosure of a mortgage loan or bankruptcy, (13) pregnancy, (14) pregnancy of a child, (15) illness, and (16) illness in the family.

The Paykel life event scale[24] was used to operationally define which events were more likely to result in positive valence or negative valence. This scale includes 61 LEs rated on a scale of 0 to 20 for the degree of distressfulness. In general, events in the top one half of the scale are considered more distressing and hence, operationally, defined as having a negative valence. Events in the bottom one half of the scale are considered less distressing and more likely to be desirable and hence defined as having a positive valence.[24] Events that were inquired about but did not match the categorization of events used by Paykel et al[24] were abortion and divorce or separation. Because abortion could have been induced or spontaneous and, therefore, have equivocal valence, it was not included as a positive or negative valence LE. Similarly, because divorce is more likely to have a negative valence and separation not due to argument more of a positive valence, separation/divorce was not included as a positive or negative valence LE.

Negative Valence LEs.—A subset of LEs identified as being more likely to be undesirable and unpredictable and therefore to have a negative valence were identified and analyzed separately. The LEs included in this analysis 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.

Positive Valence LEs.—A subset of LEs identified as being more likely to be desirable and predictable and therefore to have a positive valence were identified and analyzed

separately. The LEs included in this analysis were (1) marriage, (2) marriage of an offspring, (3) relocation, (4) buying a house, (5) pregnancy, and (6) pregnancy of a child.

Sum Total LEs.—To test the buffering hypothesis of positive valence salient LEs on the effect of negative valence LEs on breast cancer risk, they were analyzed together as the sum total LEs. Abortion and separation/divorce were excluded because they had been determined to be of equivocal valence and hence not easily categorized as either positive or negative valence.

Four different LE parameters were used to evaluate the effect of LEs on breast cancer risk: (1) LE occurrence (yes vs. no), (2) negative valence LE sum (0 [baseline], 1, 2, 3, and ≥ 4 events), (3) positive valence LE sum (0 [baseline], 1, 2–3, 4–5, and ≥ 6 events), and (4) total LE sum (0 [baseline], 1–3, 4–5, 6–8, and ≥ 9 events). The grouping of the sum of positive and negative valence LEs and the total LE sum was determined by creating a 0 event baseline and dividing the remaining distribution of events in the control group into quartiles.

Statistical Analysis

Descriptive statistics were calculated for the cases and controls. For continuous variables, the mean ± standard deviation was computed; for categorical variables, the frequencies and percentages were computed. Covariates identified in the published data as breast cancer risk factors and candidates for baseline model inclusion included age (age at diagnosis for cases and age at RFQ completion for controls), smoking history (ever smoked vs. never smoked), alcohol use (none vs. any), body mass index (BMI; underweight [BMI < 18.5 kg/m^2], normal weight [BMI ≥18.5 but ≤ 24.9 kg/m^2], overweight [BMI ≥ 25 but ≤ 29.9 kg/m^2], and obese [BMI ≥ 30]), race/ethnicity (non-Hispanic white [European ancestry], Hispanic, non-Hispanic black [African American ancestry], Asian, and other), education (less than college vs. some college or more), family history (yes vs. no; determined by family history of breast cancer in a first-degree relative), hormone replacement therapy (ever vs. never used), age at menarche (≤ 11, 12–13, and ≥ 14), age at first full-term pregnancy (< 25, 25–29, and ≥ 30 years), parity (nulliparous vs. parous), menopausal status (premenopausal vs. perimenopausal vs. postmenopausal), and physical activity (not active vs. moderately active vs. very active). A stepwise unconditional logistic regression selection process was used, and goodness of fit diagnostics were evaluated in the selection of the baseline model used in the multivariate unconditional logistic regression.

Univariate analyses were performed on LE parameters with a dependent measure of breast cancer and the independent measures including individual LE occurrence parameters, negative valence LE sum, positive valence LE sum, and total LE sum. Frequency tables and χ^2 statistics were used to compare the LE occurrence, negative valence LE sum, positive valance LE sum, and total LE sum among the cases and controls. The influence of LE parameters on the breast cancer odds ratios (ORs) was determined using simple unconditional logistic regression, with ORs and 95% confidence intervals (CIs) computed. Significant LE parameters were then included 1 at a time into the baseline multivariate regression model, and adjusted ORs and 95% CIs were determined using multivariate unconditional logistic regression. The negative valence LE sum was also included in the

logistic regression model as a continuous variable, and Wald χ^2 statistics were used to test for trend.

To reduce the potential for recall bias and determine the influence of the timing of LEs on breast cancer risk, 2 different analyses were performed. The first analysis included all lifetime events, including those in the decade of the reference age, to determine whether LEs occurring in this decade influenced breast cancer risk. A probability weighting process was used when including LEs in the decade of reference age such that only the events occurring before reference age would be included in the analysis because the timing of the LEs was at 10-year intervals (ie, 20–29, 30–39). To minimize the possibility of information bias arising from cases overreporting their recent breast cancer diagnosis as a severe LE, the second analysis included only LEs that had occurred before the decade of the reference age and therefore did not include the period in which the breast cancer diagnosis had occurred. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

The demographic data and characteristics among the cases and controls are listed in Table 1. Overall, the cases were slightly older than the controls, with a mean age of 55.6 years for cases and 53.6 years for controls. The cases were also more likely to have a positive family history for breast cancer (24.7%) compared with the controls (15.3%). Both cases (88.9%) and controls (87.7%) were predominantly of white ethnicity. The mean age at the first full-term pregnancy was significantly younger for the controls (23.7 years) than for the cases (25.2 years). The cases were more active than the controls, with 60.6% of cases compared with 49.3% of controls reporting being moderately or very active. No significant differences were found between cases and controls for the following parameters: mean BMI, age at menarche, parity, number of children, menopausal status, hormone replacement therapy, education level, smoking history, or alcohol history.

The univariate analysis of lifetime events showed that abortion, personal illness, death of a parent, and the negative valence LE sum were significantly associated with breast cancer risk (Table 2). The significant results from the univariate analysis and the adjusted estimates in the multivariate logistic regression model are provided in Table 3. After adjusting for covariates, abortion was significantly associated with a 45% decrease in breast cancer risk (OR, 0.55; 95% CI, 0.34–0.89). Personal illness before the reference age was associated with a 3.6 times increase in breast cancer risk (adjusted OR, 3.60; 95% CI, 2.50–5.20), and relocation was significantly associated with a 33% reduction in breast cancer risk (adjusted OR, 0.67; 95% CI, 0.47–0.97; Table 3).

After adjusting for covariates in the multivariate analysis, negative valence LEs remained significantly associated with increased breast cancer risk in a dose–eresponse fashion (Table 4). Breast cancer risk approximately tripled in the highest category of negative valence LE sum (≥ 4) compared with the baseline of negative valence LEs (OR, 2.81; 95% CI, 1.47–5.36). The *P* value for trend in the univariate ($P = .0065$) and multivariate ($P = .0334$) logistic regression models indicated a statistically significant monotonic increase in the association between an increasing number of negative valence LEs and breast cancer risk.

Positive valence LEs were not significantly associated with breast cancer risk (Table 2). However, the individual OR estimates for positive valence LE sum showed a trend < 1, suggesting a mild protective effect of the positive valence LEs on breast cancer risk. The increased risk of breast cancer resulting from the negative valence LEs disappeared when the positive and negative valence LEs were summed (*P* values for all values of sum total events were not statistically significant [*P* > .05]), suggesting a moderating effect of positive valence LEs on the detrimental negative valence LEs in breast cancer risk.

Similar to the inclusive analysis with all lifetime events, when excluding the decade of breast cancer diagnosis, the same LE occurrence parameters significantly influenced breast cancer risk. A history of personal illness was associated with an approximately double risk of breast cancer (adjusted OR, 2.15; 95% CI, 1.46–3.17), and abortion (adjusted OR, 0.57; 95% CI, 0.35–0.93) and relocation (adjusted OR, 0.65; 95% CI, 0.45–0.95) had protective effects (Table 3). The effects of cumulative LEs on breast cancer risk were more modest when the only LEs occurring before the decade of reference age were included (Table 4). The highest category of negative valence LEs (≥ 4 events compared with 0 events) evaluated in the univariate analysis showed a significant increase in breast cancer risk (OR, 1.66; 95% CI, 1.03–2.66). However, this effect was no longer significant on multivariate analysis (adjusted OR, 1.49; 95% CI, 0.86–2.57).

Discussion

We have confirmed our first hypothesis concerning the cumulative effect of salient negative valence LEs in increasing breast cancer risk. The time required from the stressful LEs to breast cancer manifestation is unclear.[25] In our study, the association between negative valence LEs and increased breast cancer risk was observed only when including LEs that had occurred in the 1 to 10 years before the age at diagnosis, in addition to previous LEs. Therefore, LEs seem to have a cumulative and promoting effect in the pathway to breast cancer pathogenesis. This observation is consistent with previous studies showing a positive relationship between breast cancer and severe LEs occurring in the 10 years before the diagnosis.[14–16,25,26]

As the number of lifetime salient negative valence LEs increased, so did the likelihood of breast cancer. This finding is supported by previous studies indicating the effect of distressing LEs in increasing breast cancer risk.[14–16] A recent meta-analysis by Lin et al[27] analyzed 7 studies reported from 1995 to 2012. The pooled OR was 1.51 (95% CI, 1.15–1.97; *P* = .003) for LEs and primary breast cancer.[27] This estimate was understandably discrepant with ours, because the valence/desirability of LEs summed in these studies was not considered.[14,15,18,25] Previous research that considered the desirability of LEs and the risk of psychological and physical illness supports our findings by showing a consistent positive relationship between negative valence LEs and disease and no consistent effect of positive valence LEs on disease.[28]

LEs might increase breast cancer risk by suppressing immune function and tumor surveillance, thus causing direct and indirect mutagenesis.[12,29–31] Cortisol, the main glucocorticoid in humans, impairs the ability of the immune system to identify and

neutralize cancer cells.[30] Cells treated with the stress hormones cortisol, epinephrine, or norepinephrine, showed a fivefold increase in DNA damage and impaired DNA damage repair.[29] Additionally, a rat model of LE stress showed that exposure to tail shock increased serum estradiol levels,[31] which directly and indirectly contribute to breast carcinogenesis.[32]

The results from the present study support the importance of a history of personal illness, defined as “serious illness or injury of oneself” as a major stress factor increasing breast cancer risk. This durable finding, even after excluding events in the decade of breast cancer diagnosis for the cases, makes it unlikely that this result is a mere artifact from overreporting by the cases. This result is consistent with previous results indicating that a history of personal illness increases breast cancer risk by 2.6-fold (OR, 2.6; 95% CI, 1.63–4.62).[15] In a validation analysis, cases more commonly reported a positive history of fibrocystic breast disease and gallstones compared with controls ($P < .05$). Personal illness contributes to both physical and psychological stress. Therefore, it is likely that these effects have an additive influence on the stress system and, thus, cumulatively contribute to breast cancer development.

The LEs abortion and relocation were shown to significantly reduce breast cancer risk. Abortion reduced breast cancer risk by 45% after adjusting for reproductive and other covariates. A plausible explanation for this finding is that abortion occurs during the reproductive years and that psychological stress resulting from abortion during this period reduces circulating estrogen levels and hence moderates breast cancer risk. Nevertheless, more studies are needed to verify this stipulation.

The second hypothesis concerning the negative relationship between salient positive valence LEs and breast cancer risk was not supported. However, these events seemed to have a buffering effect that moderated the adverse effect of negative valence LEs. The significant dose–eresponse relationship between negative valence LEs and breast cancer risk disappeared when the positive and negative valence LEs were summed in the total LE sum. It is possible that negative valence LEs are severely distressing and, therefore, perturb reproductive and immune function[24] and that positive valence LEs promote the recovery of these systems. This finding emphasizes the importance of including the valence or desirability of events in studies of how LEs influence breast cancer risk.[24,33] These results provide comfort and reassurance to women who have faced hardships, because it is likely that desirable, salient positive lifetime events moderate the effect of stressful and distressing undesirable events. Women are advised to continue to engage in meaningful, prolific lives despite negative valence LEs, given that their physiology and tumor microenvironment are likely influenced by both the positive and negative events occurring in their lives.

One of the main limitations of the present study, just as with other case-control studies, is the reliance on memory and, hence, the subjectivity to recall bias. However, highly salient events such as death in the family and marriage have been shown to be reported with high reproducibility and accuracy.[34] We have also shown that the same LE occurrence parameters were significant whether including events in the decade of the reference age or not. Therefore, it is unlikely that our results are an artifact of recall bias. Another limitation of the present study was that the classification of the desirability of events did not perfectly

match with that reported in the Paykel life event scale.[24] The scale created by Paykel et al[24] classifies divorce as a highly distressing event and therefore attributed to it a negative valence. Separation, although stressful, is potentially a desirable event and thus might be assigned a positive valence.[24] Because the LE questionnaire we used grouped these events into 1 category (separation/divorce), the data derived from this survey did not allow for the differentiation of these 2 salient LEs. Similarly, the LE abortion could be perceived as desirable if terminating an undesirable pregnancy (induced abortion) or undesirable if occurring spontaneously. Hence, we excluded these salient LEs from the positive and negative valence sums owing to the difficulty in matching the events to those in the Paykel scale. Finally, we acknowledge the limitation of having fewer controls than cases.

When assessing the effect of LEs on breast cancer risk, studies have generally focused on severe LEs measured using the Holmes and Rahe social readjustment rating scale.[14,15,18] A major limitation of this scale is that the events are weighted in a unidirectional dimension, such that all events are considered to increase disease risk with no consideration regarding the predictability or desirability of the events.[23] Vinokur and Selzer[35] argued that the desirability of events is a critical factor in determining the amount of stress resulting from LEs. Hoberman and Cohen[36] also suggested that positive or desirable LEs might serve as a buffer, moderating the effects of undesirable or negative LE stress by giving the body the time to restore its natural homeostasis. This buffering effect has been observed in subjects with depression, psychological disorder, and somatic symptoms such as headache.[36–38] Nevertheless, these studies were limited in scope because they primarily focused on daily positive valence LE but neglected to include more salient positive valence LEs such as marriage and childbirth.

To the best of our knowledge, ours is the first epidemiologic study to examine the effect of LEs on breast cancer risk with consideration of the valence of the salient LEs. The considered LEs were generally easily categorized as desirable or not using the Paykel scale.[24] We also included assessment of additional, less-studied LEs such as abortion.[14,16,25,26] The significant reduction in breast cancer risk resulting from abortion indicates that the scope of LEs investigated in the context of LEs and breast cancer risk should be expanded. The use of population-based controls increased the generalizability and external validity of our findings. The demonstration of a dose–eresponse relationship for the negative valence LE sum and breast cancer risk increases the likelihood that this association was not merely due to chance. Furthermore, our study included an extensive breast cancer risk factor data pool, allowing for the adjustment for known breast cancer risk factors. To the best of our knowledge, ours is the only study that has focused on the relationship of LEs and breast cancer risk in the population of Southern California.

Conclusion

The findings from the present study emphasize the importance of assessing the valence of LEs during the life course when evaluating the relationship between stress in the form of LEs and breast cancer risk. We have demonstrated that salient negative valence LEs are cumulatively associated with increased breast cancer risk. The additional finding that positive valence LEs might act as a buffer, thereby moderating the adverse effects of

negative valence LEs, points to the need to increase the understanding of how LE valence directly or indirectly moderates breast cancer risk. Assessments of LEs in the clinic, in conjunction with other breast cancer risk factors, such as alcohol, BMI, and diet, could allow a more targeted approach to understanding individualized breast cancer risk and guiding screening recommendations. We recommend expanding the categorization of major LEs and the modification of the LE scale into a scale with a −5 to +5 continuum. The evaluation of LEs on a gradient from a positive to negative valence will allow for a more personalized approach to evaluating a women's breast cancer risk in the context of her own personal experiences.

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Clinical Practice Points

- Breast cancer is the most common non-skin cancer in women, with a 1 in 8 lifetime risk in the United States. Only an estimated 40% of female breast cancer patients have known breast cancer risk factors; therefore, investigation of additional breast cancer risk factors is warranted.
- Breast cancer survivors have expressed concern that stress has contributed to the development of their breast cancer. In addition, convincing evidence from cellular and animal experiments supports the role of stress in breast cancer pathogenesis; however, human research is more complex, and the results from epidemiologic studies of the LE and breast cancer relationship have been contradictory.
- The present case-control study highlights the importance of LE valence in influencing breast cancer risk. Negative valence LEs cumulatively promote breast cancer development; however, positive valence LEs seemed to buffer this effect. A history of personal illness tripled the breast cancer risk, likely owing to a combination of mechanisms impairing the body's immunologic and endocrinologic homeostasis.
- Severe psychological stress resulting from salient negative valence LEs should be addressed in an effort to prevent breast cancer. Women who have experienced severe adverse LEs, especially those with other breast cancer risk factors, should be identified and targeted with psychological and, when necessary, pharmacologic interventions. Clinicians and public health educators could encourage women by bringing their attention to the beneficial effects of positive, desired events in buffering the effects of adverse events.
- The findings from the present study underscore the importance of treatment of the mind and body in everyday medical practice.

Table 1

Distribution of Demographic Data and Other Characteristics[a]

Characteristic	Cases (n = 664)	Controls (n = 203)	*P* Value
Reference age, y	55.6 ± 10.9	53.6 ± 12.3	.039
BMI, kg/m^2	25.8 ± 5.3	26.5 ± 5.7	.134
Race/ethnicity			.124
White	590 (88.9)	178 (87.7)	
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, y	12.7 ± 1.6	12.8 ± 1.9	.422
Age at first full-term pregnancy, y	25.2 ± 5.0	23.7 ± 4.7	.001
Parity			.865
Nulliparous	107 (16.1)	32 (15.8)	
Parous	556 (83.7)	171 (84.2)	
Children	2.1 ± 1.5	2.2 ± 1.4	.386
Menopausal status			.832
Pre- or perimenopausal	239 (36.0)	74 (36.5)	
Postmenopausal	425 (64.0)	127 (62.6)	
Hormone replacement therapy			.063
Never	311 (46.8)	80 (39.4)	
Ever	347 (52.3)	121 (59.6)	
Family history in first-degree relative			.005
No	499 (75.2)	172 (84.7)	
Yes	164 (24.7)	31 (15.3)	
Education			.357
Less than college	419 (63.1)	121 (59.6)	
Some college or more	241 (36.3)	81 (39.9)	
Smoking			.240
Never	332 (50.0)	112 (55.2)	
Ever	326 (49.1)	91 (44.8)	
Alcohol use in previous year			.533
None	243 (36.6)	69 (34.0)	
Any	399 (60.1)	126 (62.1)	
Physical activity in previous year			.011
Not active	262 (39.5)	103 (50.7)	
Moderately active	209 (31.5)	60 (29.6)	
Very active	193 (29.1)	40 (19.7)	

Data presented as mean ± standard deviation or n (%).

Abbreviation: BMI = body mass index.

[a]Because of unknown values, subcategories might not sum to the total number of cases and controls.

Table 2

Breast Cancer Univariate Odds Ratios for Lifetime Life Event Parameters

Variable	Cases (n = 664)	Controls (n = 203)	OR	95% CI	*P* Value
Negative valence events					
Death of child	55 (8.28)	16 (7.88)	1.06	0.59 ± 1.89	.855
Death of parent	440 (66.27)	116 (57.14)	1.47	1.07 ± 2.03	.018
Death of sibling	288 (43.37)	93 (45.81)	0.91	0.66 ± 1.24	.540
Death of spouse	102 (15.36)	31 (15.27)	1.01	0.65 ± 1.56	.975
Foreclosure	53 (7.98)	16 (7.88)	1.01	0.57 ± 1.82	.963
Illness	393 (59.19)	59 (29.06)	3.54	2.52 ± 4.97	<.0001
Illness in family	383 (57.68)	113 (55.67)	1.09	0.79 ± 1.49	.612
Job loss	207 (31.17)	62 (30.54)	1.03	0.73 ± 1.45	.865
Positive valence events					
Buying home	340 (51.20)	103 (50.74)	1.02	0.74 ± 1.40	.908
Marriage	447 (67.32)	144 (70.94)	0.84	0.60 ± 1.19	.333
Marriage of child	188 (28.31)	53 (26.11)	1.12	0.78 ± 1.60	.539
Pregnancy	327 (49.25)	109 (53.69)	0.84	0.61 ± 1.15	.267
Pregnancy of child	119 (17.92)	39 (19.21)	0.92	0.61 ± 1.37	.677
Relocation	174 (26.20)	65 (32.02)	0.75	0.54 ± 1.06	.105
Equivocal valence events					
Abortion	76 (11.45)	34 (16.75)	0.64	0.41 ± 1.00	.047
Separation/divorce	253 (38.10)	81 (39.90)	0.93	0.67 ± 1.28	.645
Summary variables					
Sum negative valence events[a]					
0	25 (12.32)	38 (5.72)	1.00	NA	NA
1	30 (14.78)	108 (16.27)	2.37	1.24 ± 4.52	.009
2	44 (21.67)	103 (15.51)	1.54	0.83 ± 2.85	.169
3	39 (19.21)	125 (18.83)	2.11	1.14 ± 3.92	.018
≥4	65 (32.02)	290 (43.67)	2.94	1.66 ± 5.20	.000
Sum positive valence events					
0	111 (16.72)	29 (14.29)	1	NA	NA

Variable	Cases (n = 664)	Controls (n = 203)	OR	95% CI	P Value
1	97 (14.61)	32 (15.76)	0.79	0.45 ± 1.40	.424
2–3	207 (31.17)	61 (30.05)	0.89	0.54 ± 1.46	.636
4–5	146 (21.99)	52 (25.62)	0.73	0.44 ± 1.23	.240
≥6	103 (15.51)	29 (14.29)	0.93	0.52 ± 1.66	.801
Sum total events					
0	21 (3.16)	8 (3.94)	1	NA	NA
1–3	134 (20.18)	48 (23.65)	1.06	0.44 ± 2.56	.891
4–5	157 (23.64)	46 (22.66)	1.30	0.54 ± 3.13	.558
6–8	176 (26.51)	54 (26.60)	1.24	0.52 ± 2.96	.626
≥9	176 (26.51)	47 (23.15)	1.43	0.59 ± 3.42	.426

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio.

[a] $P_{trend} = .0065$.

Table 3

Univariate and Multivariate Odds Ratios for Significant Life Event Occurrence Parameters

Life Event Occurrence	Cases (n = 664)	Controls (n = 203)	OR	95% CI	Adjusted OR[a]	95% CI
Including decade of reference age						
Abortion	76 (11.45)	34 (16.75)	0.64	0.41–1.00	0.55	0.34–0.89
Illness	393 (59.19)	59 (29.06)	3.54	2.52–4.97	3.60	2.50–5.20
Death of parent	440 (66.27)	116 (57.14)	1.47	1.07–2.03	1.43	0.98–2.08
Relocation	174 (26.20)	65 (32.02)	0.75	0.54–1.06	0.67	0.47–0.97
Excluding decade of reference age						
Illness	279 (42.02)	51 (25.12)	2.16	1.52–3.07	2.15	1.46–3.17
Abortion	71 (10.69)	32 (15.76)	0.64	0.41–1.00	0.57	0.35–0.93
Relocation	159 (23.95)	61 (30.05)	0.73	0.52–1.04	0.65	0.45–0.95

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio.

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

Table 4

Univariate and Multivariate Odds Ratios for Negative Life Event Sum

Lifetime Events	Cases (n = 664)	Controls (n = 203)	OR	95% CI	Adjusted OR[a]	95% CI
Including decade of reference age						
0	38 (5.72)	25 (12.32)	1	NA	1	NA
1	108 (16.27)	30 (14.78)	2.37	1.24–4.52	2.26	1.11–4.593
2	103 (15.51)	44 (21.67)	1.54	0.83–2.85	1.74	0.88–3.440
3	125 (18.83)	39 (19.21)	2.11	1.14–3.92	2.20	1.11–4.351
≥4	290 (43.67)	65 (32.02)	2.94	1.66–5.20	2.81	1.47–5.356
P_{trend}[b]			.0013		.0078	
Excluding decade of reference age						
0	103 (15.51)	38 (18.72)	1	NA	1	NA
1	117 (17.62)	35 (17.24)	1.23	0.73–2.10	1.25	0.70–2.22
2	94 (14.16)	42 (20.69)	0.83	0.49–1.39	0.92	0.52–1.63
3	103 (15.51)	33 (16.26)	1.15	0.67–1.98	1.12	0.62–2.03
≥4	247 (37.2)	55 (27.09)	1.66	1.03–2.66	1.49	0.86–2.57
P_{trend}[b]			.035		.193	

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio.

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

[b]P_{trend} determined by modeling negative events as a continuous variable in the logistic regression.