Self-Reported Stress and Risk of Breast Cancer

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BACKGROUND. Many women attribute the development of their breast cancer to psychosocial factors such as stress and depression. Yet investigations of the relationship between breast cancer and stressful life events have had inconsistent outcomes, due in part to studies with small sample sizes and reliance on hospital-based populations.

METHODS. As part of a population-based, case–control study of breast cancer etiology, we evaluated the association between stressful life events and the risk of breast cancer among 258 breast cancer patients and 614 randomly selected population-based controls. Information on 11 stressful life events was collected in telephone interviews with women aged 50–79 who were participating in the ongoing study.

RESULTS. Breast cancer patients and controls experienced the same number of stressful life events in the five years prior to diagnosis or an equivalent reference date (controls), averaging 2.4 and 2.6 events, respectively. After adjustment for known breast cancer risk factors, there was no association between weighted stressful life event scores and the risk of breast cancer (odds ratio [OR] = 0.90 per unit increase; 95% confidence interval [CI], 0.78–1.05). Only one life event, death of a close friend, was significantly more often reported by controls (OR = 0.72; 95% CI, 0.52–1.00). Other life events were inconsistently and nonsignificantly associated with breast cancer risk.

CONCLUSIONS. The results of this retrospective study do not suggest any important associations between stressful life events and breast cancer risk. *Cancer* 1996; 77:1089–93. © 1996 American Cancer Society.

KEYWORDS: breast cancer, psychosocial factors, stress, life events.

Clinical observations have long suggested an association between severe emotional trauma and the occurrence of cancer.[1] From the humoral theory of the Middle Ages to 19th-century physicians who based their conclusions on years of clinical experience, the relation between severe emotional trauma and cancer incidence has been easily accepted. More recently, investigators have suggested biologic mechanisms that might support an association between stressors and physical health.[2-4] In fact, direct experimental evidence indicates that psychologic stress increases the risk of the common cold.[5]

Some epidemiologic investigations have supported an association between cancer incidence and psychosocial stress, noting that patients with cancer had experienced more stressful events prior to the onset of their disease than noncancer patients.[6-11] These studies found an association between stressful life events and breast cancer,[6-8] gastric cancer,[9] and certain childhood cancers.[11] However, nearly as many population-based studies have found no such significant associations.[12-16] Three of these were studies of breast cancer incidence.[12,14,16]

Importantly, women themselves report that they believe "stress" or "depression" was a factor in the development of their breast cancer.[17]

This finding suggests that clinicians may need to assist their patients in understanding the role of stressful life events in the onset of disease. To this end, the current study uses a population-based, case–control design to investigate the relationship between self-reported life events, as a surrogate for exposure to psychosocial stressors, and a diagnosis of breast cancer in women.

MATERIALS AND METHODS

All women in the study were residents of Wisconsin between the ages of 50 and 79. The women completed a standardized interview over the telephone as part of a multicenter study of cancer in women. The study was conducted according to an institutionally approved protocol; agreement to proceed with the telephone interview constituted informed consent. In Wisconsin, the study site from which the current sample was drawn, the ongoing investigation has enrolled 4000 breast cancer patients and 4000 population-based controls. Ninety percent of eligible breast cancer patients and 89% of eligible controls have been enrolled.

Patients for the current evaluation were identified through the Wisconsin Cancer Reporting System in 1993. This is a population-based cancer incidence reporting program. Controls younger than 65 years old were identified from the Wisconsin Department of Transportation as licensed drivers; controls aged 65 years and older were identified through the Health Care Financing Administration. The controls were sampled to have an age distribution similar to the breast cancer patients, but otherwise the selection was made at random.

Information was collected using a standardized questionnaire administered over the telephone. The interview lasted about 35 minutes and consisted of close-ended questions designed to elicit information on a variety of known and suspected risk factors for breast cancer in women. Information was collected on physical activity, reproductive and other medical history, diet and alcohol intake, and family history of cancer. The life events section of the questionnaire was based on items drawn from the Holmes-Rahe social readjustment rating scale.[18] Some modifications were made to allow for both shorter time of administration and appropriateness to our study population (primarily older women). After extensive piloting, 11 specific events were included in the life events section of the questionnaire. Those reported included death of family/friends; change in health of family/friends; and life changes such as divorce, marriage, and retirement (See Appendix). A 12th item was also included as an open-ended query to collect "other" events that the respondent chose to report. These included, most commonly, difficult situations with children, marital problems, or difficult caretaking situations.

Respondents were asked to report specific life events occurring in the five years prior to an assigned reference date. For patients, this was the date of diagnosis; for controls, the reference date corresponded to the average length of time from diagnosis to interview for the patient group (about 12 months).

Odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression models. Conditional models were used to adjust for age.[19] Heterogeneity of the OR across age groups was assessed by examining the difference in the log likelihood between models with and without the cross-product terms.

RESULTS

Table 1 summarizes selected characteristics of the study population. Two hundred fifty-eight breast cancer patients and 614 controls participated in this life events evaluation over a 3-month period.

Patients and controls were similar in terms of race, smoking status, menopausal status, and current employment. Controls were more likely to be currently married. Patients tended to be slightly older than controls and have a higher level of education. As expected, patients had a later age at first birth and earlier menarche. These characteristics are similar to the larger study population of the ongoing study (unpublished data).

Table 2 presents the self-reported life events in rank order, beginning with the most frequently reported. Overall, regardless of disease status, the women most frequently reported experiencing the death of a close family member, a change in health of a close family member, and the death of a close friend.

The mean number of stressful life events reported by patients and controls was 2.4 and 2.6, respectively. The difference in these means was not statistically significant ($P = 0.13$).

Events were weighted to reflect relative "severity" of each life event. Based on investigations in populations similar to the one in the current study,[6,8] an event such as the death of a spouse received greater weight than newly married. There was no significant difference between the weighted mean scores of the patients and controls (1.6 and 1.7, respectively; $P = 0.08$). After adjustment for known breast cancer risk factors (age at first birth, parity, family history of breast cancer, body-mass index, and age at menarche). The OR per 1 unit increase in the weighted score was 0.90 (CI, 0.78–1.05). The relative OR per event reported was 0.95 (CI, 0.86–1.05).

After adjustment for known risk factors, none of the individual life events included in the 12-item questionnaire was reported differently by patients and controls, except death of a close friend by controls (OR = 0.72, CI 0.52–1.00).

A small group of open-ended "other" responses were coded and placed in post hoc categories such as "event

TABLE 1
Selected Characteristics of Study Population

Characteristic	Patients (%) (n = 258)	Controls (%) (n = 614)	P value[a]
Age			
40–59 years	32.5	38.6	
60–79 years	67.5	61.4	
(Mean age)	(64.8)	(62.4)	0.09
Menopausal status			
Premenopausal	8.9	7.5	
Postmenopausal	82.9	82.1	0.29
Family history of breast cancer			
Absent	75.6	85.2	
Present	18.2	11.9	
Don't know	6.2	2.9	0.02
Education			
Less than high school	19.4	16.0	
High school	41.9	52.4	
Some college	23.2	19.5	
College graduate	15.5	12.1	0.07
Race			
White	98.8	98.7	
Nonwhite	1.2	1.3	0.98
Marital status			
Never married	3.5	2.4	
Married	63.6	76.7	
Widowed/divorced	32.9	20.8	0.01
Parity			
Nulliparous	7.7	6.3	
1	12.8	6.2	
2	19	22.6	
3 or more	54.6	63.8	<0.0001
Age at first full-term pregnancy			
Younger than 20 years	13.9	19.9	
20–24 years	37.6	42.5	
25–29 years	19.4	17.7	
30 years or older	5.8	3.4	
Nulliparous/don't know	23.2	16.4	0.01
Age at menarche			
Younger than 12	18.6	18.6	
12	26	25.1	
13	26	25.7	
14 or older	22.9	29.8	
Don't know	6.6	0.8	<0.0001
Occupation			
Homemaker	19	19.4	
Full-time job	27.5	29.1	
Part-time job	11.2	16.3	
Retired	40.3	34.5	0.43
Hormone replacement therapy[b]			
Never	45.1	45.6	
Ever	54.9	54.3	0.53
Body mass index quartiles[b]			
I (<23.54 kg/m^2)	24.2	25.3	
II (23.54–25.83 kg/m^2)	18.5	24.5	
III (25.84–29.28 kg/m^2)	25.8	24.5	
IV (≥29.29 kg/m^2)	31.4	25.7	0.21

[a] Mantel–Haenszel test of general association, adjusted by age.
[b] Postmenopausal women only (n = 715).

in child's life" (e.g., wedding, drug use, or child divorced), "business/work problems" (e.g., trouble on the job, new job, or trouble with boss), or "family event" (e.g., fight with sister-in-law, relatives married/divorced, or moved mother to nursing home). The relative frequency of the events reported as "other" appears in Figure 1. Although there was a notable proportion of women reporting some "other" stressful event (23% of patients, 21% of controls), there were no significant case–control differences. The small number of "other" responses in each of the post hoc categories made it difficult to compare them in any meaningful way within the 11 standardized event categories. The most frequently reported other stressful event reported by subjects fell into the category of "event in child's life" (45% patients, 49% controls).

DISCUSSION

Overall, we observed no association between life events, losses, and difficult life situations and disease status. Age-adjusted ORs, although slightly greater than 1 for some self-reported life events, were not statistically significant, nor did the scores weighted for "severity" of the individual events differ between patients and controls.

Prior studies investigating the relationship between breast cancer and stressful life events have had inconsistent results.[16] In a recent review of the role of psychosocial factors in the etiology of breast cancer, Hilakivi-Clarke et al conclude that the quantity of stressful life events is not associated with disease onset.[20]

Forsen used a case–control design similar to our own to evaluate the relationship between stressful life events and breast cancer.[7] Using all the items from the Holmes-Rahe social readjustment rating scale, Forsen concluded that breast cancer patients had significantly more life events, losses, and difficult life situations in the 6 years prior to the onset of disease than did population controls for an increase in events of two standard deviations (RR 3.06; CI, 1.13–8.25). The small size of the sample population (87 patients and 87 controls) however, necessarily limits the interpretation of this result.

Of the four studies using combined retrospective and prospective methods, two found few significant associations between psychosocial variables and breast cancer incidence,[12,16] whereas the other two studies found positive associations between breast cancer and stressful life events.[6,8] All these investigations used hospital series, asking patients to self-report on life events and other psychosocial variables prior to receiving the outcome of a breast biopsy. Although 2 of these investigations[8,16] provided large samples (more than 500 patients and 500 controls), these hospital-based samples are susceptible to bias and are generally not representative of the larger population.[21]

Our abbreviated life events inventory may have

TABLE 2
Self-Reported Life Events by Cases and Controls

Event	Patients (%) (n = 258)	Controls (%) (n = 614)	Odds ratio[a]	95% CI
Death of family member	46	51.3	0.80	0.58–1.09
Change in health of family member	46.3	49	1.00	0.73–1.37
Death of a close friend	36.2	44.5	0.72	0.52–1.00
Change in living conditions	25.2	20.6	1.35	0.93–1.97
Personal injury/illness	21.1	24.4	0.77	0.52–1.13
Change in financial status	21	23.2	0.96	0.66–1.41
"Other"	23.4	20.8	1.39	0.94–2.06
Husband retired/fired	14.8	23.1	0.81	0.53–1.26
Retired/fired	15.9	18.2	1.21	0.78–1.89
Death of husband	7.7	5.4	1.04	0.55–1.96
Newly married	2.3	2.5	0.91	0.32–2.61
Divorced or separated	1.5	1.5	1.11	0.29–4.22
Total Number of Events Reported Mean (standard deviation)	2.4 (1.7)	2.6 (1.7)	0.95[b]	0.86–1.05
Weighted Score for Events Reported Mean (standard deviation)	1.6 (1.1)	1.7 (1.1)	0.90[c]	0.78–1.05

CI: confidence interval.

[a] Adjusted for age, age at first birth, parity, family history of breast cancer, body mass index, and age at menarche.

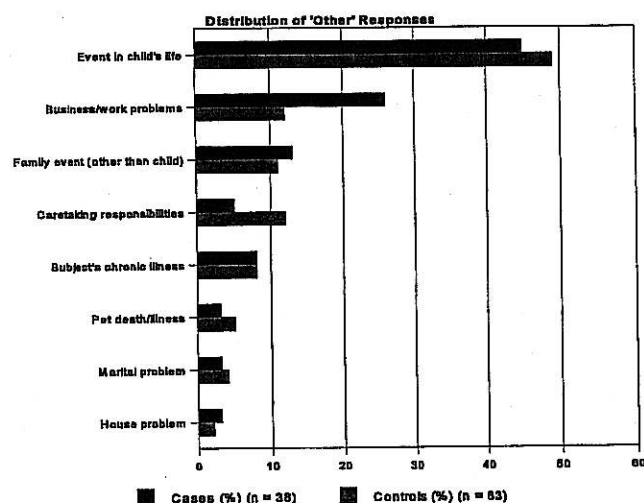[b] Per event.

[c] Per one unit increase in score.

FIGURE 1. Distribution of "other" responses by case–control status.

missed some areas in which patients could differ from controls in terms of exposure to stressful life events, however, the assessment tool was generally consistent in scope with other studies using inventories based on the Holmes-Rahe social readjustment rating scale.[7,8,14,16] Despite criticisms regarding the use of self-report life event checklist formats,[22] in theory this approach objectively segregates discreet events (death, relocation, divorce, etc.) from the perception of those events. In addition, this

approach, which has been validated in both full[23] and abbreviated versions,[24] provides a standardized instrument with which to compare study populations.

The possibility exists that our results were due in part to recall or selection bias. Recall is of particular concern because there appears to be some "fall off" over time of accurate reporting of life events.[25,26] However, Funch and Marshall note that the severity of an event is related to reporting reliability where severity refers to relative hardship or discomfort caused by the event.[26] Major life changes generally considered the most severe or disruptive (death in family, marriage, divorce, retirement) show little change in recall over time.[26] It is reassuring that in a 6-month retest of our survey instrument (among 35 patients and 35 controls, all randomly selected) there was 83% agreement overall between responses to the first and second administrations of the questionnaire. Major life events (e.g., death of spouse, marriage/divorce, retirement) showed much higher rates of reproducibility (91%–100% agreement).

Participation rates are very high in the ongoing study. In Wisconsin, the study site from which the current sample was drawn, 90% of eligible breast cancer patients and 89% of eligible controls have been enrolled. This provides reassurance that selection bias is not a substantial problem in this study. Thus, it is unlikely that our null results reflect differential participation rates by patients and controls with high rates of stressful life events.

The results of this retrospective study do not suggest any important association between stressful life events and the risk of breast cancer; this does not preclude, however, a more complex association between environmental/social stressors and the incidence of breast cancer in women. For clinicians, there is presently no evidence that commonly experienced difficult life events in any way constitute an increased risk of breast cancer for their patients.

APPENDIX: LIFE EVENTS QUESTIONNAIRE

In the five years from [five years prior to reference date] to [reference date], did any of the following events occur in your life:

1. The death of your husband?
2. The death of a close family member?
3. The death of a close friend?
4. A change in the health of a close family member?
5. A personal injury or illness (other than cancer diagnosis on reference date)?
6. Divorce or separation?
7. Newly married or living with a new partner?
8. A change in financial status?
9. Retired or fired from work?
10. Husband retired or fired from work?
11. A change in living conditions?
12. Any other stressful event in that five-year period?

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