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Stressful Life Events and Risk of Breast Cancer in 10,808 Women: A Cohort Study

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The authors prospectively investigated the relation between stressful life events and risk of breast cancer among 10,808 women from the Finnish Twin Cohort. Life events and breast cancer risk factors were assessed by self-administered questionnaire in 1981. A national modification of a standardized life event inventory was used, examining accumulation of life events and individual life events and placing emphasis on the 5 years preceding completion of the questionnaire. Through record linkage with the Finnish Cancer Registry, 180 incident cases of breast cancer were identified in the cohort between 1982 and 1996. The multivariable adjusted hazard ratio for breast cancer per one-event increase in the total number of life events was 1.07 (95% confidence interval (CI): 1.00, 1.15). This risk estimate rose to 1.35 (95% CI: 1.09, 1.67) when only major life events were taken into account. Independently of total life events, divorce/separation (hazard ratio (HR) = 2.26, 95% CI: 1.25, 4.07), death of a husband (HR = 2.00, 95% CI: 1.03, 3.88), and death of a close relative or friend (HR = 1.36, 95% CI: 1.00, 1.86) were all associated with increased risk of breast cancer. The findings suggest a role for life events in breast cancer etiology through hormonal or other mechanisms.

breast neoplasms; cohort studies; life change events; stress, psychological

Abbreviations: CI, confidence interval; HR, hazard ratio.

Life events and accompanying psychological and behavioral reactions frequently have an impact upon people's daily lives and are believed to predispose them to disease. Observational studies have established that stressful life events, often defined as an accumulation of ordinary life events or bereavement, increase the risks of mental disorders (1, 2), acute infections such as the common cold (3), and total and cause-specific mortality (4). Life events have also been suggested to contribute to various other diseases, including cardiovascular diseases (5, 6), cancer (6–9), asthma (10), and rheumatoid arthritis (11).

Several case-control studies (7, 12–17) and one small prospective cohort study (18) have reported an increased risk of breast cancer among women with a high number of life events or women with one or more major life events such as bereavement. However, the few available record-linkage studies on the relation between single major life events and breast cancer risk have reported null or negative findings (9, 19–23). Thus, the epidemiologic evidence on the role of life events in breast cancer etiology has remained inconclusive.

We investigated prospectively the relation between the number and nature of self-reported life events and risk of breast cancer in women from a population-based Finnish cohort, the Finnish Twin Cohort, who were followed from 1982 to 1996. Our a priori hypothesis was that the accumulation of life events, as well as major life events alone (i.e., the death of a husband, divorce/separation, and the death of a close relative or friend), would increase breast cancer risk.

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We first investigated these relations using methods of standard cohort analysis and then using a nested case-control analysis of twin pairs who were discordant for breast cancer. Because twins in a pair share all or some of their genes and usually had the same childhood environment, the latter analysis examined whether the relation between life events and breast cancer risk was explained by familial factors.

MATERIALS AND METHODS

Study population

The Finnish Twin Cohort was established to examine the genetic, environmental, and psychosocial determinants of chronic diseases. It includes all Finnish same-sex twin pairs born before 1958 in which both co-twins were alive in 1975 (24). Data collection was approved by the national authorities and the ethics committee. The cohort members were mailed a baseline health questionnaire in 1975 (response rate = 89 percent), a first follow-up questionnaire in 1981 (response rate = 84 percent), and a second follow-up questionnaire in 1990 (the last questionnaire targeted only twins born between 1930 and 1957; response rate = 77 percent). The life event inventory was included in the 1981 questionnaire, and this served as the baseline for the present study; the 1990 questionnaire was used to update information on some covariates. The study group consisted of the 10,808 women (out of a total of 11,069 respondents) who completed at least one item in the life event inventory. These women were aged 24 years or older in 1981 (mean age = 41.1 years; standard deviation, 14.0), and approximately 30 percent of them were members of monozygotic twin pairs.

Assessment of life events

We constructed the 21-item life event inventory after reviewing the life event inventories available around 1980. We selected life events with the goal of gathering information on a wide range of life experiences (from common events such as a change in residence to major events such as the death of a spouse) yet maintaining an inventory size that was manageable in a large-scale postal questionnaire. We also attempted to capture experiences that are typical in Finland. For instance, the present study's life event inventory came to include 17 items comparable to those on the widely known 43-item Holmes and Rahe scale (25) and four additional items (see individual items listed in table 4). The women were asked to indicate which life events they had encountered and to specify the timing of those events in relation to baseline (response alternatives: "during the previous 6 months," "during the previous 5 years," "earlier," or "never").

In addition to separately examining the effects of individual life events, we formulated three kinds of summary life-event variables: 1) the total number of life events; 2) a weighted life change score that aimed to account for the magnitude of life change related to each event (the Holmes and Rahe method; see definition below); and 3) various numbers of major life-event variables that would capture five, eight, or 10 life events with the highest impact (based on the Holmes and Rahe life-event weights; see table 4 for weights). The purpose of the summary life-event variables was to investigate whether the effects of life events might be cumulative because of (hypothetical) biologic mechanisms shared by all or most life events.

To calculate the total number of life events, we identified which life events each subject had recorded for the 5 years preceding the 1981 baseline and added up the number of events (theoretical range, 0–21). This variable was formulated for subjects who had completed at least 18 of the 21 scale items on the questionnaire (n = 9,569). Missing values were replaced by a score of 0 in the final statistical analyses; replacing them with the mean number of reported events or excluding subjects with missing values did not affect the results.

The life change score was formulated by weighting the life events with the Holmes and Rahe life-event weights (25). These weights were derived from a community-based US study of 394 adults who were asked to rate 43 life events in terms of the extent of life change the event was generally assumed to produce in one's usual way of life, as compared with marriage, which was given a fixed value of 50 (25). By adding together the individual event weights (see table 4), we calculated the life change score for subjects who had completed at least 15 of the 17 life event items comparable to those on the Holmes and Rahe scale (n = 9,473; theoretical range, 0–702).

Assessment of covariates

Data on known or suspected breast cancer risk factors were derived from the 1981 questionnaire, except data on zygosity and birth years for children, which were derived from the 1975 questionnaire (the latter was supplemented with Central Population Register data for the years 1976–1981). For the subgroup of women born between 1930 and 1957, the 1990 questionnaire provided updated data on body mass index (weight (kg)/height $(m)^2$) and alcohol use.

To obtain data on the subjects' self-perceptions of their psychological state at baseline, we used three psychosocial scales from the 1981 questionnaire, as follows. First, assessment of the *stress of daily activities* was based on the respondent's own judgment as to how well four items measuring i) feelings of tension and nervousness, ii) stress or iii) demand associated with daily activities, and iv) daily mental and physical exhaustion described her (26, 27). Each item was rated on a four-point scale, with the total score varying from 4 to 16. Second, the four-item *life satisfaction scale* assessed a woman's satisfaction with her own life on the basis of the fit between her personal goals and her achievements (total score, 4–20) (28, 29). Correlation between this scale and the Beck Depression Inventory is 0.63, suggesting that the scale also measures aspects of depressiveness. Third, *neuroticism* (emotional lability) was measured with 10 items answered in a yes/no format (total score, 0–10), using the short form of the widely known Eysenck Personality Inventory (30). In previous studies of the Finnish Twin Cohort (31–33), each of the three above scales has been found to have at least adequate reliability (Cronbach's α: all superior to 0.70; 6-year test-retest reliability: all superior to 0.40). In

addition, as we reported previously, none of the measures, individually or in combination with the others, was related to subsequent breast cancer risk in this cohort (26, 33).

Follow-up data

Through record linkages with the Central Population Register and the Finnish Cancer Registry, we obtained, respectively, data on dates of death and emigration and data on invasive and in-situ cases of breast cancer (34). Reporting of every cancer case to the Finnish Cancer Registry has been compulsory since 1961, and information is received independently from multiple sources such as hospitals, policlinics, physicians, pathology laboratories, and death certificates (35). Registration of newly diagnosed breast cancers in Finland is considered to be practically complete (36).

Statistical analysis

In the cohort analyses, person-time at risk was computed for each study subject from January 1, 1982, to the date of diagnosis of breast cancer, death, emigration, or December 31, 1996, whichever came first. Cox regression models (37) were used to obtain hazard ratios for breast cancer (and 95 percent confidence intervals) according to life events. The summary life event variables were analyzed as continuous variables; the individual life events were analyzed as dichotomous variables ("within the past 5 years" vs. "never/earlier"). A test for nonlinear trend was performed with the total number of life events treated as a squared continuous variable.

Results of the analyses were first adjusted only for age (continuous variable). The next set of analyses examined whether the age-adjusted estimates were confounded by zygosity (monozygotic or dizygotic), marital status (unmarried or married), social class (blue-collar, intermediate, or white-collar), age at first full-term pregnancy (<25 years or ≥25 years), number of children (0, 1–2, or ≥3), use of oral contraceptives (never or ever), body mass index (<25, 25–29, or ≥30), alcohol use (0, 1–399, or ≥400 g/month), smoking (never smoker, occasional smoker, ex-smoker, or current smoker), and physical activity during leisure time (sedentary, occasional exerciser, or conditioning exerciser). Further adjustment was made for the stress of daily activities (three categories), life satisfaction (three categories), and neuroticism (three categories). In the analyses of individual life events, we also adjusted for the total number of life events. We retained subjects with missing values for any of the covariates by including them in the reference category for the relevant covariate. For most of the variables, there were very few subjects with missing data; most of the missing data were on the use of oral contraceptives (13 percent missing data).

We used generalized estimating equations (38) to obtain correct standard errors for the estimated hazard ratios in the presence of possible correlations between twins in a pair. The cohort analyses were performed using Stata statistical software (release 7.0; Stata Corporation, College Station, Texas).

In the nested case-control analysis, twins who were diagnosed with breast cancer during follow-up were compared with their co-twins without breast cancer in terms of the number and nature of life events recorded at baseline. Because twins share either all (monozygotic twins) or half (dizygotic twins) of their genes and usually lived in the same childhood environment, this type of analysis can examine whether a relation between life events and breast cancer risk is explained by genetic or other familial factors that could be antecedents of both a stressful environment and breast cancer in adult life. In the case of no familial selection, the results of a nested case-control analysis would be expected to be similar to those of a cohort analysis. Of the twin pairs that became discordant for breast cancer during follow-up from 1982 to 1996, we studied pairs in which the twin without breast cancer was alive at the time her co-twin was diagnosed with breast cancer and remained free of breast cancer until the end of follow-up. We used conditional logistic regression analysis (39) with SAS software (SAS Institute, Inc., Cary, North Carolina) to estimate odds ratios for breast cancer (and 95 percent confidence intervals) according to life events.

RESULTS

Cohort analyses

The characteristics of the 10,808 study women are given in table 1. The mean number of life events reported for the 5 years prior to baseline assessment was 4.0 (range, 0–18; standard deviation, 2.7). Total number of life events and age were negatively correlated (Pearson correlation coefficient (r) = –0.37). After adjustment for age, total life events showed weak correlations with increasing alcohol consumption (r = 0.07), decreasing life satisfaction (r = 0.15), high neuroticism (r = 0.14), and a high level of stress in daily activities (r = 0.23) (table 1). The mean total number of life events was slightly higher among ever users of oral contraceptives than among never users, and it was higher in smokers than in never smokers.

During 15 years of follow-up (155,622 person-years), 180 incident breast cancers were diagnosed in the study cohort. The relations between summary life-event variables and breast cancer risk are given in table 2. After adjustment for age, the hazard ratio for breast cancer per one-event increase in the total number of life events was 1.05 (95 percent confidence interval (CI): 0.98, 1.13); the risk estimate for the life change score was slightly higher (table 2). When we restricted the number of life events to the 10, eight, and five events considered a priori to cause the most change in a person's life (according to the Holmes and Rahe weights), there was a clear tendency toward a higher risk of breast cancer with an increasing impact of the events (table 2). The age-adjusted hazard ratio for breast cancer was 1.31 (95 percent CI: 1.06, 1.61) per one-event increase in the five major life events (death of a husband, divorce/separation, personal illness or injury, death of a close relative or friend, and loss of a job). After adjustment for potentially confounding factors, the aforementioned risk estimates increased slightly (table 2). In one additional analysis, we

TABLE 1. Selected characteristics of 10,808 study subjects and their relation to stressful life events based on information obtained from a 1981 health questionnaire, Finnish Twin Cohort Study

Characteristic	Mean (n = 10,808)	Correlation with total no. of life events*	Correlation with the five major life events*
Age (years) at baseline	41.1	–0.37	0.065
Age (years) at first full-term pregnancy	24.6	0.050	–0.053
No. of children	1.6	0.045	0.016
Body mass index†	23.2	–0.021	0.036
Alcohol use (g/month)	117	0.071	0.015
Stress of daily activities score (range, 4–16)	6.9	0.23	0.057
Life satisfaction score (range, 4–20)‡	8.5	0.15	0.079
Neuroticism score (range, 0–10)	4.3	0.14	0.052
	%	Mean no. of total life events§	Mean no. of the five major life events§
Social class			
Blue-collar	31.7	3.6	0.7
Intermediate	61.1	4.1	0.7
White-collar	7.2	4.7	0.6
Use of oral contraceptives			
Never user	52.1	3.9	0.7
Ever user	47.9	4.5	0.7
Smoking			
Never smoker	62.5	3.8	0.7
Occasional smoker	2.0	4.2	0.7
Ex-smoker	15.9	4.2	0.7
Current smoker	19.6	4.3	0.8
Physical activity			
Sedentary	13.0	4.1	0.7
Occasional exerciser	79.7	4.0	0.7
Conditioning exerciser	7.3	4.0	0.6

* Age-adjusted Pearson correlation coefficient for the relation between life events and subject characteristics. Five life events were identified as major on the basis of the life event weights on the Holmes and Rahe scale (25); they included the death of a husband, divorce/separation, personal illness or injury, the death of a close relative or friend, and loss of a job.

† Weight (kg)/height (m)^2.

‡ An increasing score indicates decreasing life satisfaction.

§ Mean values were adjusted for age.

indirectly accounted for potential confounding by family history of breast cancer by excluding cases from twin pairs concordant for breast cancer (n = 12) and subjects who reported a history of "change in the health of a family member" (n = 2,031). This did not affect the results (results not shown).

Further analyses of the shape of the relation between life events and breast cancer risk gave some suggestion that the risk in relation to total life events might begin to clearly rise only after accumulation of eight or more life events (hazard ratios for one to seven events ranged from 1.04 to 1.50, whereas those for eight, nine, and 10–18 events were 2.68, 2.86, and 2.05, respectively), but the test for nonlinear trend was not significant (p = 0.67). The tendency toward a linear trend between the five major life events and increased risk of breast cancer (p = 0.005) is displayed in figure 1. Compared with women with no major life events, the adjusted hazard ratios for breast cancer were 1.29 (95 percent CI: 0.89, 1.87), 1.97 (95 percent CI: 1.23, 3.17), and 2.02 (95 percent CI: 0.61, 6.72) for women with one, two, and three or more major life events, respectively.

The increase in breast cancer risk in relation to life events was slightly higher during 1982–1988 (i.e., soon after the women had completed the questionnaire) than during 1989–1996 (table 3). Lifetime life events were also related to increased risk of breast cancer, but to a slightly lesser degree than life events confronted within the 5 years prior to questionnaire completion (table 3).

Table 4 gives the results concerning individual life events for the previous 5 years. The five highest age-adjusted

TABLE 2. Hazard ratios for breast cancer according to number of stressful life events and life change score, Finnish Twin Cohort Study, 1982–1996*

Variable	Age-adjusted HR†	95% CI†	Multivariable HR‡	95% CI	HR further adjusted for psychosocial factors§	95% CI
Total no. of life events	1.05	0.98, 1.13	1.06	0.99, 1.13	1.07	1.00, 1.15
Life change score	1.09	0.98, 1.21	1.09	0.99, 1.21	1.12	1.01, 1.25
10 major life events¶	1.09	0.96, 1.23	1.09	0.97, 1.24	1.12	0.99, 1.27
Eight major life events¶	1.16	0.99, 1.35	1.16	1.00, 1.36	1.19	1.02, 1.39
Five major life events¶	1.31	1.06, 1.61	1.33	1.08, 1.64	1.35	1.09, 1.67

* Hazard ratios are for a one-event increase in the number of life events or a 50-point score increase in the life change score. The life change score is the number of life events weighted by the Holmes and Rahe life event weights (25).

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for age, zygosity, marital status, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity. Further adjustment for age at first full-term pregnancy among parous women did not change the results.

§ Further adjusted for stress of daily activities, life satisfaction, and neuroticism.

¶ Major life events were chosen on the basis of the life event weights on the Holmes and Rahe scale (25). The 10 major life events were the death of a husband, divorce/separation, personal illness or injury, the death of a close relative or friend, loss of a job, change in the health of a family member, the gain of a new family member, sexual difficulties, financial problems, and a change to a different kind of work. Of these, the first five life events and the first eight life events are the five and eight major life events, respectively.

hazard ratios were observed for divorce/separation (hazard ratio (HR) = 2.07, 95 percent CI: 1.16, 3.67), the death of a husband (HR = 1.64, 95 percent CI: 0.84, 3.19), the death of close relative or friend (HR = 1.44, 95 percent CI: 1.05, 1.96), the gain of a new family member (HR = 1.44, 95 percent CI: 0.97, 2.13), and an interrupted pregnancy in the family (HR = 1.44, 95 percent CI: 0.91, 2.28). After adjustment for potentially confounding factors, the risk estimates for divorce/separation and the death of a husband became somewhat higher (table 4). The risk estimate for an interrupted pregnancy in the family and risks for some other events decreased slightly after adjustment for psychosocial factors (including total number of life events) (table 4).

To reduce the possibility of residual confounding by obesity/weight change, alcohol use, and physical inactivity, we repeated all of the main analyses 1) with adjustment for body mass index and alcohol use (g/month) as continuous variables, 2) with body mass index and alcohol use analyzed as time-dependent covariates in the Cox models using updated data from the 1990 questionnaire, and 3) with adjustment for leisure-activity metabolic equivalent index as an indicator for total volume of leisure physical activity (40). The results of these analyses did not materially differ from those given in tables 2 and 4.

Discordant-pair analyses

Table 5 shows results of the analyses conducted within twin pairs discordant for breast cancer. The adjusted odds ratio for breast cancer related to a one-event increase in the total number of life events was 1.14 (95 percent CI: 0.99, 1.32). Similarly to the cohort analyses, this estimate clearly rose when only the major life events were taken into account; the adjusted odds ratio for a one-event increase in the

TABLE 3. Hazard ratios for breast cancer according to number of stressful life events, with stratification by timing of the life events and length of follow-up, Finnish Twin Cohort Study, 1982–1996

	Follow-up period 1982–1988		Follow-up period 1989–1996	
	Multivariable HR*,†	95% CI*	Multivariable HR†	95% CI
Reported for the past 5 years in 1981‡				
Total no. of life events	1.09	0.96, 1.23	1.05	0.97, 1.13
Five major life events§	1.69	1.13, 2.51	1.22	0.96, 1.56
Reported for lifetime in 1981¶				
Total no. of life events	1.04	0.95, 1.14	1.03	0.97, 1.09
Five major life events§	1.23	0.85, 1.78	1.27	1.04, 1.56

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age, zygosity, marital status, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity.

‡ Accounts for events that each subject had reported for the past 6 months or the past 5 years.

§ The five major life events are given in the last footnote of table 1.

¶ Accounts for events that each subject had reported for the past 6 months, the past 5 years, or earlier.

TABLE 4. Hazard ratios for breast cancer according to individual stressful life events in descending order, beginning with the event with the highest age-adjusted hazard ratio, Finnish Twin Cohort Study, 1982–1996

Life event	Holmes and Rahe weight*	No. of subjects with the event	No. of subjects in the analysis	Age-adjusted HR†	95% CI†	Multivariable HR‡	95% CI	HR further adjusted for psychosocial factors§	95% CI
Divorce or separation	69	470	9,731	2.07	1.16, 3.67	2.23	1.25, 4.00	2.26	1.25, 4.07
Death of a husband	100	264	9,950	1.64	0.84, 3.19	1.78	0.90, 3.48	2.00	1.03, 3.88
Death of a close relative or friend	50	4,398	10,335	1.44	1.05, 1.96	1.43	1.05, 1.95	1.36	1.00, 1.86
Gain of a new family member	39	2,427	9,833	1.44	0.97, 2.13	1.54	1.04, 2.29	1.44	0.95, 2.16
Interrupted pregnancy in the family	—¶	1,355	9,872	1.44	0.91, 2.28	1.49	0.94, 2.36	1.35	0.85, 2.15
Family member leaving home	29	1,591	9,557	1.35	0.93, 1.95	1.39	0.94, 2.05	1.32	0.88, 1.98
Serious conflict in a close relationship	—¶	1,101	9,779	1.34	0.83, 2.18	1.34	0.82, 2.18	1.26	0.76, 2.07
Loss of a job	47	664	9,763	1.24	0.69, 2.23	1.26	0.70, 2.26	1.17	0.63, 2.18
Taking a loan	31	2,726	9,694	1.22	0.84, 1.77	1.19	0.82, 1.74	1.07	0.71, 1.59
Living away from husband due to work	—¶	543	9,687	1.20	0.59, 2.45	1.24	0.60, 2.56	1.12	0.54, 2.35
Increase in amount of work	20	2,994	9,575	1.15	0.80, 1.67	1.15	0.79, 1.66	1.00	0.65, 1.53
Change in residence	20	4,732	9,948	1.15	0.82, 1.62	1.13	0.80, 1.58	1.02	0.71, 1.48
Change to a different kind of work	36	2,265	9,729	1.15	0.75, 1.76	1.15	0.74, 1.77	1.02	0.63, 1.63
Personal illness or injury	53	1,702	9,874	1.07	0.72, 1.58	1.09	0.73, 1.61	1.01	0.66, 1.53
Interpersonal conflict at work	23	889	9,548	1.06	0.60, 1.88	1.02	0.57, 1.81	0.95	0.52, 1.75
Increase in responsibilities at work	29	2,371	9,694	0.96	0.63, 1.46	0.97	0.63, 1.48	0.80	0.49, 1.30
Positive change in life	—¶	3,514	9,752	0.94	0.66, 1.34	0.96	0.67, 1.38	0.80	0.53, 1.21
Change in the health of a family member	44	2,031	9,912	0.83	0.55, 1.27	0.81	0.52, 1.24	0.70	0.45, 1.09
Financial problems	38	1,674	9,862	0.80	0.49, 1.29	0.83	0.51, 1.34	0.74	0.42, 1.30
Change in the no. of arguments with husband	35	1,273	9,669	0.73	0.42, 1.27	0.77	0.43, 1.36	0.72	0.39, 1.32
Sexual difficulties	39	1,580	9,512	0.68	0.40, 1.15	0.68	0.40, 1.15	0.63	0.38, 1.07

* The weight of an individual event on the Holmes and Rahe scale (25), indicating the amount of life change that is generally assumed to be produced by the event (highest weight on the scale, 100; lowest weight, 11).

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for age, zygosity, marital status (except in the analyses of divorce or separation and death of a husband), social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity. Further adjustment for age at first full-term pregnancy among parous women did not change the results.

§ Further adjusted for total number of life events, stress of daily activities, life satisfaction, and neuroticism.

¶ Event not included in the Holmes and Rahe scale.

number of the five major life events was 1.88 (95 percent CI: 1.12, 3.13). The individual life events that were most strongly related to increased risk of breast cancer in the cohort analyses also increased the risk among twin pairs. Interactions between zygosity and any of the life-event variables were not statistically significant, but these analyses had low power to detect interactions.

DISCUSSION

In this study of women from the Finnish Twin Cohort, we found a relation between the accumulation of life events during the 5 years before baseline assessment and an increased risk of breast cancer during 15 years of follow-up. Divorce/separation, death of a husband, and death of a close relative or friend—the individual life events of the greatest a priori interest—were each associated with increased risk. Discordant-pair analyses confirmed the results obtained from the cohort analyses, implying that familial factors are not important in the relation between life events and breast cancer. Our findings suggest a role for life events in breast cancer etiology through hormonal or other mechanisms.

The major strength of the present study is its prospective population-based study design. The reporting of life events

TABLE 5. Odds ratios for breast cancer according to number of stressful life events among twin pairs discordant for breast cancer, Finnish Twin Cohort Study, 1982–1996

Variable	No. of pairs			OR*,†	95% CI*	OR‡	95% CI
	Pairs concordant for life events	Pairs in which case twin had more life events	Pairs in which control twin had more life events				
Total no. of life events (112 pairs)	13	53	46	1.10	0.97, 1.24	1.14	0.99, 1.32
Five major life events (102 pairs)	45	40	17	1.59	1.06, 2.37	1.88	1.12, 3.13
Major life event	Control	Case					
		No	Yes				
Divorce or separation (115 pairs)	No	100	11	1.00		1.00	
	Yes	3	1	3.67	1.02, 13.1	6.72	1.38, 32.8
Death of a husband (115 pairs)	No	108	5	1.00		1.00	
	Yes	2	0	2.50	0.49, 12.9	3.19	0.36, 27.9
Death of a close relative or friend (130 pairs)	No	44	24	1.00		1.00	
	Yes	14	46	1.71	0.89, 3.31	2.35	1.05, 5.24
Gain of a new family member (117 pairs)	No	78	18	1.00		1.00	
	Yes	9	12	2.00	0.90, 4.45	2.65	0.91, 7.70
Interrupted pregnancy in the family (117 pairs)	No	91	10	1.00		1.00	
	Yes	6	10	1.67	0.61, 4.59	1.40	0.43, 4.54

* OR, odds ratio; CI, confidence interval.

† The study design inherently included total adjustment for age and also controlled for genetic and other familial factors.

‡ Adjusted for marital status (except in the analyses of divorce or separation and death of a husband), social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, and physical activity.

took place at baseline and thus was not susceptible to any selective remembering or reporting that might take place around the time of diagnosis (a crucial concern in case-control studies of this topic). Some randomly distributed underreporting of life events may have occurred, most likely of the kinds of events easily resolved by the respondents, but this would have the effect of underestimating the risk of breast cancer in relation to life events. Previous research has indicated that the death of a husband and divorce are generally not underreported to any considerable extent (41).

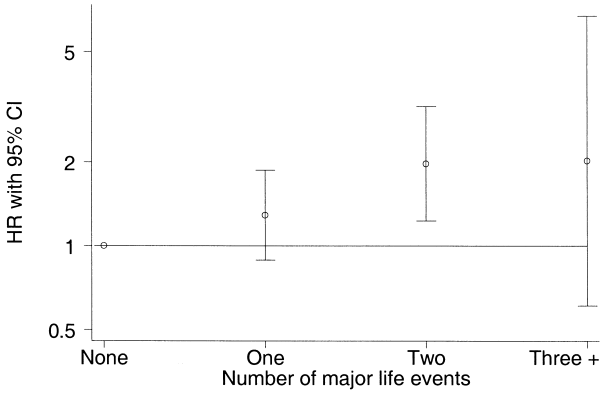

FIGURE 1. Adjusted hazard ratio (HR) for breast cancer according to the number of five major life events, Finnish Twin Cohort Study, 1982–1996. Bars, 95% confidence interval (CI). The five major life events included the death of a husband, divorce/separation, personal illness or injury, the death of a close relative or friend, and loss of a job. Hazard ratios were adjusted for age, zygosity, marital status, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, physical activity, stress of daily activities, life satisfaction, and neuroticism.

In previous studies of the Finnish Twin Cohort involving many of the same subjects as the present study (26, 34), we observed increased breast cancer risk in relation to known breast cancer risk factors such as later age at first full-term pregnancy and nulliparity. In the present study, adjustment for these and other potentially confounding factors did not explain the relations observed between life events and breast cancer risk. Of the unmeasured risk factors, age at menarche and age at menopause are unlikely to have substantially confounded our results, since it has been estimated that breast cancer risk increases by only about 5 percent for each year of earlier menarche and about 3 percent for each year of later menopause (42). Hormone replacement therapy is unlikely to have confounded our results to a remarkable degree, since it was not commonly used in Finland prior to the 1980s. However, some residual confounding may still have affected the results.

The adjustment for psychosocial factors explored whether taking into account an individual's personality, experience of daily stress, and mood could affect the results. It could be argued that this adjustment was unnecessary, since we previously reported that these factors were not related to breast

cancer risk in this study cohort (26, 33). However, the adjustment seemed important, as it is generally agreed that it is an individual's reaction to life events rather than the events per se that might be predictively important.

In accordance with our results, several case-control studies (7, 12–17), but not all (43–47), have reported an increased risk of breast cancer among women with a high total number of self-reported life events and/or one or more major life events occurring 2–10 years before cancer diagnosis.

Among the few studies that have prospectively investigated this relation, a US cohort study of 1,213 women followed up for 15 years with interviews found a relation between maternal death in childhood (but not paternal death) and breast cancer in adulthood (odds ratio = 2.56, 95 percent CI: 1.59, 4.35) (18). In contrast, large-scale record-linkage studies from Scandinavia, the United Kingdom, and Israel have not detected risk increases in relation to other single major life events—that is, divorce (20, 22), death of a husband (19, 20, 22), death of offspring (9, 21), or cancer in offspring (23)—occurring several years to decades prior to breast cancer diagnosis. These record-linkage studies differed from our study in that they relied solely on register data; thus, the investigators had no information on several life events that only can be recorded by the individuals themselves, and they could not adjust for factors other than age (9, 19–23), parity (21, 22), or age at first birth (22). If we had investigated breast cancer risk in relation to one major life event only and without data on covariates other than age, we would not have found a statistically significant risk increase in relation to the death of a husband (age-adjusted HR = 1.64, 95 percent CI: 0.84, 3.19), but we would have detected the increases related to divorce/separation (age-adjusted HR = 2.07, 95 percent CI: 1.16, 3.67) and the death of a close relative or friend (age-adjusted HR = 1.44, 95 percent CI: 1.05, 1.96).

A relation between life events and breast cancer risk is biologically plausible in principle, but no studies have established a direct link between physiologic changes associated with life events and breast carcinogenesis. However, it has been suggested that the various changes observed in immunologic function among subjects with stressful life events (48–50) could enhance the development of breast cancer (48). The relation between life events and breast cancer risk could also have a hormonal basis, since stress-induced disruption of the functions of the neuroendocrine axes—for example, that axis relating the hypothalamus and pituitary to the gonads—can increase (or decrease) the secretion of various hormones (51, 52). Estrogens, for example, stimulate mitosis of breast epithelial cells in vitro and in vivo and also have an effect on breast carcinogenesis in humans (42, 53). Of the individual life events, the gain of a new family member (most often through the birth of one's own biologic child) is likely to have a direct biologic link with a transient increase in breast cancer risk through an increase in estrogen levels during pregnancy (42, 54).

In addition to direct biologic mechanisms, life events and the accompanying psychological reactions could also increase breast cancer risk by causing behavioral changes implicated in the etiology of breast cancer (51, 55). However, our data suggest that life events increase breast cancer risk independently of body mass index, weight change, alcohol use, smoking, and physical activity and that their effect is not mediated or modified by self-perceptions of daily stress, adverse personality, or suboptimal mood.

Future prospective studies are needed to confirm these findings of a relation between stressful life events and increased breast cancer risk and to further explore the potential role of an individual's behavioral and psychological coping styles in mediating or modifying the effects of life events.

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