BMJ 1995;311:1527-1530 (9 December)

Papers

Adverse life events and breast cancer: case-control study

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Abstract

Objective: To investigate the strength of association between past life events and the development of breast cancer.
Design: Case-control study. A standardised life events interview and rating was administered before a definitive diagnosis.
Setting: Breast Cancer Screening Assessment Unit and surgical outpatient clinics at King's College Hospital, London.
Subjects: 119 consecutive women aged 20-70 who were referred for biopsy of a suspicious breast lesion.
Main outcome measures: Odds ratio of the risk of developing breast cancer after life events in the preceding five years after adjustment for confounders.
Results: 41 women were diagnosed as having malignant disease while the remainder had benign conditions. Severe life events increased the risk of breast cancer. The crude odds ratio was 3.2 (95% confidence interval 1.35 to 7.6). After adjustment for age and the menopause and other potential confounders this rose to 11.6 (3.1 to 43.7). Multiple logistic regression analysis showed that all severe events and coping with the stress of adverse events by confronting them and focusing on the problems significantly predicted a diagnosis of breast cancer. Non-severe life events and long term difficulties had no significant association.
Conclusion: These findings suggest an aetiological association between life stress and breast cancer.

Key messages

- Key messages
- Women with breast cancer have more severe life events in the five years before diagnosis
- The way a woman deals with stress may also affect the risk of breast cancer
- Longer prospective studies are needed to confirm these findings

Introduction

Is life stress a cause of breast cancer? Many have tried to answer this question, but their studies have been prone to bias,[1][2][3] or errors of measurement.[4][5] To answer the question properly stress must be assessed objectively and independently of physical illness. Few studies have met these prerequisites. Ramirez et al compared 50 women at first clinical recurrence of breast cancer with matched controls in remission for the prevalence of life events and difficulties by means of a standardised interview.[6] Their results showed that severe life events and difficulties increased the risk of relapse significantly (odds ratio 5.7 (95% confidence interval 1.6 to 37.2) for severe events; odds ratio 4.7 (1.6 to 19.1) for severe difficulties). Barraclough et al failed to replicate this result.[7] Geyer compared the onset of disease in 39 women with breast cancer and 58 with benign breast disorders on the eve of biopsy and found that life stress during the eight years before diagnosis had a significant association with cancer.[8] As the importance of life events in breast cancer is controversial we tried to replicate Geyer's result in a larger sample that included symptom free women identified through screening. We also assessed psychological and behavioural strategies for coping with stressful life events to examine whether these too play a part in increasing the risk of cancer.

Subjects and methods

Subjects were recruited from two groups. The first group comprised women who had been recalled after screening mammography because of a suspicious lesion and who were about to undergo fine needle biopsy at a local breast cancer screening unit. The second group comprised women with symptoms of breast cancer who were awaiting the results of a biopsy at King's College Hospital in London; these women had been referred to an outpatient clinic. One hundred and forty consecutive women aged from 20 to 69 were approached; 119 agreed to participate (85%). The 21 non-responders were of similar age and were as likely to have benign or malignant diagnoses as the participants. Seventy two participants were recruited from the breast screening unit and 47 from the surgical outpatient clinic. Their mean age was 52 (SD 12) years. Most (85) were married; 72 were employed.

DIAGNOSIS OF CANCER

Diagnosis of cancer was confirmed by histopathological results in biopsy specimens of breast tissue. Subjects were then classified as having cancer or as being controls with no disease or benign disease.

ASSESSMENT OF LIFE EVENTS

The life events and difficulties schedule was used to collect detailed information about the occurrence and context of adverse life events during the five years before the positive result on screening or discovery of breast symptoms.[9] [10] This is a semistructured interview concerning discrete events and ongoing long term difficulties. Each category of event or difficulty is extensively defined. The exact date of an event or difficulty was searched and recorded during the interview. The threat of each life event was rated on a four point scale, 1 indicating a great threat, 2 a moderate threat, 3 some threat, and 4 little or no threat. If a moderate event affected the subject herself it was classed as an important moderately threatening event. The rater, patients, and clinical staff were blind to the exact diagnosis. Only events and difficulties that were logically independent of the effects of breast cancer were included in the analysis. The investigator (CCC) presented 70 events chosen at random to one of the schedule's originators[9] [10] and the reliability was high ((kappa) coefficient 0.81).

COPING STRATEGIES

Subjects' general coping style with previous adverse experiences was assessed by the coping strategies inventory.[11] This consists of 72 items divided into several subscales. It measures two main strategies: engagement and disengagement, each consisting of secondary coping strategies focused on problems and emotions. Engagement means actively confronting the stressful situation. This can be done through working out a plan of action (focusing on problems) and by seeking emotional support (focusing on emotions).

OTHER PSYCHOSOCIAL VARIABLES

General psychological morbidity and personality traits were assessed before diagnosis by the 12 item general health questionnaire and the Eysenck personality inventory, respectively.[12] [13]

STATISTICS

We used χ^2, t, and Fisher's exact tests when appropriate. We also used Mantel-Haenszel estimation and logistic regression analysis to calculate odds ratios and examine the predictive effect of adverse life events on the risk of breast cancer.

Results

In 41 cases the biopsy results showed malignancy; the remaining 78 patients were diagnosed as having benign breast disorders. Tables 1 and 2 show sociodemographic characteristics of the two groups. The women with cancer were significantly older than the women with benign disorders, and more were postmenopausal. These two and other potentially confounding factors were therefore controlled in the analysis. Nineteen out of 41 patients with cancer compared with 15 out of 78 controls experienced at least one greatly threatening life event in the five years before diagnosis (odds ratio 3.63 (95% confidence interval 1.58 to 8.34)). Life events that were important moderate threats also increased the risk of breast cancer: 20 of the 41 women with cancer had one or more such event during the five years before diagnosis compared with 29 of the 78 controls (odds ratio 2.39 (1.10 to 5.17)). When these two types of event were combined and categorised as severely threatening they were significantly associated with the risk of breast

cancer (odds ratio 3.21 (1.35 to 7.60)). After adjustment for potential confounders these associations remained significant, the odds ratios increasing (table 3). There were no significant associations between breast cancer and life events or long term difficulties that were of little or no threat.

Table 1--Sociodemographic characteristics of the two groups. Values are numbers (percentages)

Variables	Cancer (n=41)	Control (n=78)	All (n=119)	Statistics
Mean (SD) age (years)	57 (7)	50 (12)	52 (12)	t=3.3, P=0.001
Employment:				
Employed	20 (49)	52 (67)	72 (61)	χ^2=4.5, P=0.1
Housewife or retired	19 (46)	21 (27)	40 (34)	
Other	2 (5)	5 (6)	7 (6)	
Marital status:				
Married or cohabiting	27 (66)	58 (74)	85 (71)	χ^2=4.0, P=0.1
Separated, divorced, or widowed	11 (27)	10 (13)	21 (18)	
Never married	3 (7)	10 (13)	13 (11)	
Socioeconomic status*:				
Middle class	27 (66)	58 (74)	85 (72)	χ^2=0.9, P=0.3
Working class	14 (34)	20 (26)	34 (29)	

*Adapted from Goldthorpe and Hope.*RF 13a*

Table 2--Comparison of risk factors for breast cancer between two groups. Values are numbers (percentages) of women unless stated otherwise

Risk factor	Cancer (n=41)	Control (n=78)	All (n=119)	Statistics
Menopausal state:				

Premenopausal	2 (5)	28 (36)	30 (25)	χ^2=19.2, P<0.0001
Perimenopausal	2 (5)	11 (14)	13 (11)	
Postmenopausal	37 (90)	39 (50)	76 (64)	
Mean (SD) age at menarche (years)	13.0 (1.7)	13.0 (1.4)	P=0.9	
Mean (SD) when first child born (years)*	25.5 (4.7)	25.6 (4.9)	P=0.9	
Mean (SD) age at menopause (years)+	54.2 (12.9)	51.8 (9.7)	P=0.4	
Alcohol use:				
Yes	4 (10)	11 (14)	15 (13)	χ^2=0.46, P=0.5
No	37 (90)	67 (86)	104 (87)	
Tobacco use:				
Yes	21 (51)	32 (41)	53 (45)	χ^2=1.13, P=0.3
No	20 (49)	46 (59)	66 (55)	
Family history of breast cancer:				
Yes	5 (12)	8 (10)	13 (11)	χ^2=0.10, P=0.7
No	36 (88)	70 (90)	106 (89)	
Mean (SD) score++:				
General health questionnaire	2.8 (3.8)	3.5 (3.3)	3.3 (3.5)	P=0.3
Eysenck personality inventory:				
Extroversion	10.1 (3.4)	9.8 (4.1)	9.9 (3.9)	P=0.7
Neuroticism	10.8 (5.8)	10.7 (4.8)	10.8 (5.9)	P=0.8

*Applies to 28 women with cancer and 52 controls.
+Applies to 36 women with cancer and 37 controls.
++Applies to 41 women with cancer and 77 controls.

Table 3--Odds ratios for life events of different threat and risk of breast cancer after adjustment for potential confounding factors* by logistic regression

Life event	Regression coefficient	SE	Odds ratio (95% confidence interval)	P value

Great threat	1.96	0.57	7.08 (2.31 to 21.65)	<0.001
Important moderate threat	1.43	0.53	4.17 (1.47 to 11.86)	0.007
Moderate and important moderate threat	0.28	0.49	1.32 (0.51 to 3.47)	0.567
Some or no threat	-0.89	0.92	0.41 (0.07 to 2.51)	0.409
Severe threat+	2.45	0.68	11.64 (3.10 to 43.66)	<0.001
Non-severe threat	-0.70	0.77	0.50 (0.11 to 2.24)	0.363

*Includes age, menopausal state, age at menarche, family history of breast cancer, tobacco and alcohol use, and score on general health questionnaire and Eysenck personality inventory.
+Moderate and important moderate threats combined.

The average annual rate per subject of severely threatening life events was 1.42 for cases and 1.69 for controls with no significant variation over the five successive years (multiple analysis of variance showed no main effect for year ($F(4,468)=0.78$, $P=0.54$) and no significant interaction of diagnosis and year ($F(4,468)=1.20$, $P=0.31$)). There was no apparent increase in the year before diagnosis in either group. Had this occurred we would have suspected recall bias.

We hypothesised that women who used different coping strategies to deal with stress would have different relative risks of breast cancer. Generally we found little support for this. However, among 73 women who experienced one or more severe life event in the five years before diagnosis those who were used to coping with stress by confronting it and working out a plan of action (focusing on problems) had a higher risk. The odds ratio was 3.11 (1.18 to 8.19).

There were no significant differences in the mean score on the general health questionnaire and subscores of the Eysenck personality inventory between the two groups.

We used multivariate logistic regression to examine independent predictors of a diagnosis of cancer. All possible risk factors were entered, including age, family history of breast cancer, age at menarche, use of cigarettes and alcohol, menopausal state, coping strategy, score on the general health questionnaire, subscores on the personality inventory, and events of all degrees of threat. The five factors that each independently predicted a positive diagnosis of cancer were life events that were great or important moderate threats, menopausal state, coping with stress by confronting it and focusing on problems, and cigarette smoking (table 4).

Table 4--Multiple logistic model analysis showing significant predictors of breast cancer

	Odds ratio

Factors	(95% confidence interval)
Severely threatening life event	15.00 (3.74 to 60.44)
Important moderately threatening life event	9.70 (2.45 to 38.17)
Being postmenopausal	9.13 (1.47 to 56.42)
Problem focused means of coping with stress	5.12 (1.46 to 17.89)
Use of:	
Tobacco	3.82 (1.22 to 11.90)
Alcohol	0.25 (0.03 to 2.26)
Family history of breast cancer	1.42 (0.29 to 6.94)
Age	0.99 (0.43 to 2.26)
Score on:	
General health questionnaire	0.89 (0.75 to 1.07)
Eysenck personality inventory:	
Extroversion	0.86 (0.74 to 1.02)
Lie	1.23 (0.92 to 1.66)
Neuroticism	1.05 (0.93 to 1.18)

Deviance=log likelihood statistic=98.74, df=106, P<0.0001.

Discussion

The results show a significant aetiological association between severe life events and the development of breast cancer. These findings are consistent with a previous study that investigated a smaller sample.[8] The effect remained highly significant, and, in fact, increased after adjustment for potential confounders including age and menopausal state.

Unlike much previous research,[1 5] the measurement of life events and difficulties was carried out in strict accordance with the methods laid down by Brown and Harris[10]; these acknowledge the importance of context on the degree of threat and ensure maximum reliability and objectivity on the part of the rater. Furthermore, the method used guaranteed as far as possible that subjects and raters were blind to the eventual diagnosis. Assessment of life events was therefore independent of outcome. The wait for the result of a biopsy is an anxious time for women, and this could bias recall of life events. However, the effect should be the same for all women regardless of their eventual diagnosis.

SCREENED AND SYMPTOMATIC PATIENTS

Comparatively few women in the sample had cancer (41/119, 35%). This may be due to the fact that the local population had already been engaged in an active screening initiative.[14] We therefore recruited cases from among the screened women and the women with symptoms of breast cancer to ensure adequate statistical power. Nevertheless, when severe life events were analysed in the women without symptoms alone, the same significant association with breast cancer was observed (odds ratio=3.1 (1.1 to 8.3)). Hence, although a doctor could convey to a patient during a surgical consultation that malignant disease is expected--without saying so outright--this possibility is unlikely to explain entirely the positive association between life events and breast cancer. Furthermore, a few screened women may also have had some symptoms and perhaps an inkling of a sinister cause, although this was not recorded.

STRESS AND COPING

The ability to cope with stress is a crucial determinant of wellbeing.[15] Previous work has suggested that how women cope may influence the prognosis of breast cancer,[16 17] but little work has investigated the links between coping strategies, life stress, and the risk of cancer.[18] Studies indicate that actively and positively confronting difficult situations may be beneficial physically as well as psychologically,[16 17 19] while negative coping leads to a poorer outcome.[18 20] We tried to elucidate the correlation between coping strategy and development of breast cancer. The results support such a link but with an increased risk of breast cancer in the women who confronted a severe life stress. Cooper and Faragher found that the most harmful events are those that people have least control over, such as death of a relative or serious illness in the family.[18 20] We suggest that active confrontation in such severe events may not be beneficial. In an inescapable situation, an ineffective coping strategy may use up a person's resources, and, instead of attenuating the impact of stress, put him or her at greater risk. At such times withdrawal or disengagement may protect the person physically, although perhaps with a cost in terms of psychological wellbeing.[21] We should note that our data encompass reported coping style rather than actual behaviour.

POSSIBLE MECHANISMS

To account for this association with a biologically plausible mechanism is a formidable challenge. Cancer of the breast is probably present microscopically more than five years before it is clinically detectable. Hence, severe life events during this time may increase growth and multiplication of cancer cells through alteration of natural immune surveillance processes. This is presumably mediated through the endocrine system.[22 23] Alternatively, we may have studied women who had a long history of adverse life events, in which case the psychosocial stress may indeed predate the onset of cancer. However, chronic difficulties are not associated with breast cancer,[24] so the mechanism must incorporate the accumulation of separate stressful events over time. Finally, life events may be confounded by other, genuine risk factors, either environmental or constitutional, which are associated with both life stress and cancer. We are currently unaware of such factors and favour a direct relation between severe adverse events and malignant breast disease. Conformation using a truly prospective design without the possibility of recall bias is warranted.

We thank the counselling nurses, Karen Thompson, Sarah Lea, Edna Elias, and Carol Smith, for their help in arranging for subjects' interviews at the breast screening assessment unit. We also

thank Dr Tirril Harris of Bedford New College for her guidance on our life events ratings, and Patsy Mott for her work on the manuscript. Finally, we thank the Ministry of Education and National Cheng Kung University in Taiwan for granting the three year scholarship which enabled CCC to complete this study.

Funding: No additional funding.

Conflict of interest: None.

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