Papers

Stressful life events and difficulties and onset of breast cancer: case-control study

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Abstract

Objective To determine the relation between stressful life events and difficulties and the onset of breast cancer.

Design Case-control study.

Setting 3 NHS breast clinics serving west Leeds.

Participants 399 consecutive women, aged 40-79, attending the breast clinics who were Leeds residents.

Main outcome measures Odds ratios of the risk of developing breast cancer after experiencing one or more severe life events, severe difficulties, severe 2 year non-personal health difficulties, or severe 2 year personal health difficulties in the 5 years before clinical presentation.

Results 332 (83%) women participated. Women diagnosed with breast cancer were no more likely to have experienced one or more severe life events (adjusted odds ratio 0.91, 95% confidence interval 0.47 to 1.81; $P = 0.79$); one or more severe difficulties (0.86, 0.41 to 1.81; $P = 0.69$); a 2 year severe non-personal health difficulty (0.53, 0.12 to 2.31; $P = 0.4$); or a 2 year severe personal health difficulty (2.73, 0.68 to 10.93; $P = 0.16$) than women diagnosed with a benign breast lump.

Conclusion These findings do not support the hypothesis that severe life events or difficulties are associated with onset of breast cancer.

Introduction

The belief that the onset of cancer may be associated with a stressful experience is found in the British, French, and United States medical literature at least as far back as 1701.[1] In a recent survey of South Australian women, 40% reported that they believed that stress was a cause of breast cancer.[2] Research into the association, however, has methodological weaknesses.[3]

Four recent studies of breast cancer have used the life events and difficulties schedule, a semistructured interview of proved reliability[4]: two examined the association between stress and relapse, and two examined the association between stress and onset of breast cancer.[5–8] The results are not clear cut. In the most recent study, Chen et al found that severe life events were associated with breast cancer, with an odds ratio of 11.6 after adjustment for confounders. The result provoked speculation about biological mechanisms for

the effect,[9] and widespread media coverage of the association between stress and cancer followed.[10]

We have attempted to replicate the findings of Chen et al, but with improvements in five areas of study design. Firstly, we included a larger sample of women presenting with a suspicious breast lump. Secondly, we obtained a consecutive series of women from a defined geographical area presenting with a breast lump, to reduce selection bias. Thirdly, we examined more social and physical risk factors for breast cancer to correct for potential confounding. Fourthly, we used two researchers who held regular consensus rating meetings to reduce observer bias. Finally, we examined the effect of the participant's knowledge of diagnosis on reporting of severe life events.

Participants and methods

Participants

Outpatient services for diagnosing suspicious breast lumps in Leeds were provided by two NHS trusts at the time of the study (September 1996 to February 1998). The two services were similar, and we identified no obvious systematic bias in general practitioners' referral patterns to the two units. We therefore sited the study in the three clinics that form the service for the west of Leeds. We recruited all women attending breast clinics at Leeds General Infirmary, Chapel Allerton Hospital, and Wharfedale General Hospital, Otley who were to have tissue checked from a suspicious breast lump. Women aged between 40 and 79 years residing at a Leeds address were asked to participate by their surgeon. Exclusions were previous breast cancer and inability to comply with an interview owing to poor English or serious physical or mental illness. We obtained research ethics approval for our study.

Study protocol

The women were introduced to the research interviewer (DP or KT) immediately after the surgical consultation, and a home interview was arranged— usually for the next day. Written consent was obtained. The life events and difficulties schedule was administered to cover a 5 year period before the clinical presentation. Social and physical risk factors for breast cancer were recorded, and the participants were asked to predict their diagnosis. The women completed the Beck depression inventory.[11] If the interview reminded them of painful emotional issues, they were offered

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appropriate professional counselling. Weekly consensus rating meetings were held, and borderline or unusual events and difficulties were rated over the telephone with one of the originators of the life events and difficulties schedule.

Cancer diagnosis

Cancer was diagnosed by cytological examination of breast tissue and confirmed by histopathological examination. Participants diagnosed with cancer were cases and those whose biopsy showed normal breast tissue or benign breast disease were controls.

Assessment of life stress

Events and difficulties were rated according to their severity and content, and difficulties were rated according to their duration. Life events were rated on a four point scale, and severity of difficulties lasting at least 4 weeks was rated on a six point scale. We followed the

usual convention in recording those events rated 1 or 2 and those difficulties rated 1 to 3 as severe.

The associations of prolonged periods of severe stress and prolonged periods of severe health problems with the onset of breast cancer were also examined. Severe difficulties, excluding the participant's own health problems, lasting 2 years or more were recorded as a third category ("severe 2 year non-personal health difficulties"). A fourth category, "severe 2 year personal health difficulties," was recorded. We excluded events and difficulties that were related to ovarian cancer, past and present breast problems, or a first degree relative's breast or ovarian cancer.

Analysis

We performed univariate analysis to calculate odds ratios and to examine the predictive effect of each factor on the risk of breast cancer. Those risk factors that were significant ($P < 0.25$) were entered into a forward selection multivariate logistic regression analysis,[12] either as continuous variables or categorised as quartiles.

Results

Participants and non-participants

In total, 409 women were eligible for our study. Ten women were not interviewed; six had severe mental or physical illness and four had poor English. Overall, 333 of 399 women agreed to participate (84%). We excluded one woman diagnosed with a lymphoma. One hundred and six women (32%) were diagnosed with breast cancer and 226 (68%) with benign breast disease. Forty six women (32 cancer, 14 benign) had been given a tissue diagnosis by the time of the interview

Of the 66 women who refused to participate, 18 (27%) were diagnosed with cancer and 48 (73%) with benign breast disease. No significant difference was found between participants and non-participants in the proportion of cancer and benign diagnoses, or in the age of cases or controls. There was no significant difference in the diagnoses of the women interviewed by each of the investigators.

Factors

Table 1 shows the characteristics of the cases and controls. Table 2 shows the risk factors for breast cancer, which were identified as potential confounders and entered into the multivariate analysis. The main risks for breast cancer were increasing age, postmenopausal status, later menopause, and increased body mass index. Factors associated with benign disease were history of benign breast lumps and exposure to the oral contraceptive pill. Factors that might have been expected to be associated with breast cancer but which were not were family history of breast cancer, nulliparity, and early menarche.

Stressors

Table 3 shows the final model, which includes results for the four categories of life stress. The most important risk factors for breast cancer were increasing age, increasing body mass index, and increasing alcohol consumption. Factors that predicted

Table 1 Characteristics of cases and controls. Values are mean (SD) unless stated otherwise

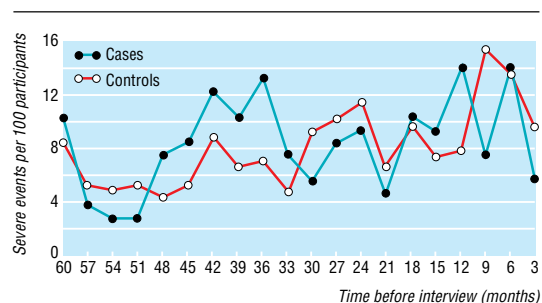| Variable	Breast cancer group (n=106)	Control group (n=226)	P value
Age	61.6 (10.9)	51.0 (8.5)	0.000*
Social class† (%):			
I	10 (10)	20 (9)	
II	38 (36)	82 (36)	
III non-manual	28 (26)	72 (32)	
III manual	13 (12)	24 (11)	0.094‡
IV	11 (10)	21 (9)	
V	3 (3)	2 (1)	
VI	3 (3)	4 (2)	
No of children (%):			
0	15 (14)	31 (14)	
1	16 (15)	31 (13.7)	0.97
2	42 (40)	84 (37)	
≥3	32 (31)†	80 (35)	
Age at birth of first child	21.3 (5.6)	20.5 (4.3)	0.500*
Age at menarche	12.8 (1.4)	13.0 (1.6)	0.200*
Menopausal state (%):			
Premenopausal	14 (13)	66 (29)	
Perimenopausal	9 (9)	43 (19)	0.000§
Postmenopausal	83 (78)	117 (52)	
Age at menopause	47.7 (4.5)	45.6 (5.2)	0.001*
Lifetime use of oral contraceptives (%)	38	61	0.000‡
No of years taking oral contraceptives	3.0 (5.4)	4.2 (5.0)	0.065§
No of months breastfeeding	(n=90)	(n=195)	
	7.4 (9.9)	7.4 (12.1)	0.990*
Lifetime use of hormone replacement therapy (%)	29 (27)	78 (35)	0.193§
Mean years of hormone replacement therapy	1.6 (3.7)	1.9 (4.0)	0.460*
Family history of ovarian cancer (%)	8 (8)	10 (4)	0.241§
History of benign breast disease (%)	15 (15)	105 (47)	0.000§
Family history of breast cancer¶ (%)	16 (15)	35 (16)	0.997§
Units of alcohol/week (%):			
0	38 (36)	59 (26)	
0-4	26 (25)	71 (31)	0.927‡
5-9	20 (19)	52 (23)	
≥10	22 (21)	44 (20)	
No of cigarettes/day:			
0	83 (78.3)	170 (75.2)	
1-9	8 (7.6)	14 (6.2)	0.383‡
≥10	15 (14.2)	42 (18.6)	
Body mass index (kg/m²)	26.8 (5.5)	24.8 (4.2)	0.001*

*Two sample t test.
†Data for one case missing.
‡χ^2 test for trend.
§χ^2 test.
¶No data for one control.

Rates of reporting of severe life events in 3 month intervals from time of interview over 5 years

Table 2 Odds ratios (95% confidence interval) of risk factors for breast cancer derived from univariate analysis entered into multivariate analysis

Risk factor	Odds ratio (95% CI)	P value
Age (years) v 40-49 years:		
50-59	1.79 (0.91 to 3.53)	0.000*
60-69	10.68 (5.12 to 22.30)	0.000*
70-79	16.40 (7.26 to 37.03)	0.000*
History of benign breast lumps	0.19 (0.10 to 0.35)	0.000*
Months breast feeding v no breast feeding:		
0.5-8	1.56 (0.88 to 2.77)	0.124*
>8	1.28 (0.74 to 2.22)	0.384
Menopausal status v premenopausal:		
Perimenopausal	0.99 (0.39 to 2.48)	0.977
Postmenopausal	3.34 (1.76 to 6.35)	0.000*
Age at menopause v premenopausal:		
28-40	1.54 (0.59 to 3.99)	0.377
41-49	2.81 (1.47 to 5.37)	0.002*
>50	5.82 (2.85 to 11.85)	0.000*
Age at hysterectomy v no hysterectomy:		
27-42	0.39 (0.16 to 0.98)	0.045*
>43	1.72 (0.87 to 3.37)	0.117*
Ever had hormone replacement therapy	0.71 (0.43 to 1.19)	0.194*
Years of hormone replacement therapy v never had hormone replacement therapy:		
0.2-4.5	0.64 (0.32 to 1.27)	0.203*
5.0-24.0	0.79 (0.41 to 1.50)	0.470
Past use of oral contraceptive pill	0.39 (0.24 to 0.62)	0.000*
No of years taking oral contraceptive pill v never taken oral contraceptive pill:		
0.25-6.5	0.35 (0.19 to 0.62)	0.000*
7.0-22.0	0.44 (0.24 to 0.79)	0.007*
Body mass index (kg/m^2) v 17.0-22.0 kg/m^2:		
22.1-24.2	0.67 (0.50 to 0.97)	0.008*
24.3-47.0	1.46 (1.08 to 1.97)	0.013*
Units of alcohol/week v 0 units/week:		
1-4	0.57 (0.31 to 1.04)	0.068*
5-9	0.60 (0.31 to 1.15)	0.124*
≥10	0.78 (0.40 to 1.49)	0.448

*P<0.25; variable entered into multivariate analysis.

Table 3 Final main effects model of risk factors for cancer

Covariate	Odds ratio (95% CI)	P value
History of benign breast disease v no history (n=120)	0.25 (0.13 to 0.50)	0.000
Age (years)	1.12 (1.08 to 1.15)	0.000
Body mass index (kg/m^2)	1.08 (1.01 to 1.14)	0.017
Ever had hormone replacement therapy (n=107)	0.54 (0.29 to 1.0)	0.05
Units alcohol/week v non-drinkers:		
0-4 (n=97)	1.34 (0.61 to 2.96)	0.47
5-9 (n=72)	2.06 (0.84 to 5.05)	0.113
≥10 (n=66)	2.98 (1.26 to 7.06)	0.013
≥1 severe life event (n=212)	0.91 (0.47 to 1.78)	0.79
4 week difficulty (n=134)	0.86 (0.41 to 1.81)	0.69
2 year non-personal health difficulty (n=40)	0.53 (0.12 to 2.31)	0.39
2 year personal health difficulty (n=56)	2.72 (0.68 to 10.9)	0.16

benign disease were history of benign breast lumps and exposure to hormone replacement therapy. Women diagnosed with malignant breast lump were no more likely to have experienced any of the stressors than women diagnosed with benign lumps or normal breasts.

Severe life events

We wondered whether a severe life event or a mood disorder around the time of clinical presentation could affect the presenting behaviour of the control group.[13] If there were high rates of severe life events among the control group this might obscure a relation between breast cancer and severe life events when one existed. We found no evidence of an increase in severe life events among controls before clinical presentation (fig). Because the events and difficulties we have identified are known to be associated with the onset of depressive disorders, we examined depression in the two groups. For those who were unaware of their diagnosis at the time of interview, scores on the Beck depression inventory were the same in both groups (mean 8.6 v 8.5, t = 0.04, df = 281, P = 0.97). Seven (7%) cases and 21 (9%) controls were taking an antidepressant at the time of the interview (χ^2 = 0.67, df = 1, P = 0.411). This suggests that the experience of life events of women before diagnosis had been the same in both groups.

We noted a larger proportion of controls (47%) than cases (14%) who reported a history of benign breast lump requiring tissue diagnosis. Had there been a relation between severe life events and recurring benign breast lumps this might have concealed a relation between severe life events and cancer when one existed. Further analysis showed that experience of one or more severe life events was not significantly associated with a history of benign breast lump (odds ratio 0.73, 95% confidence interval 0.46 to 1.16; P = 0.182).

Forty two of 70 (60%) women who either knew or predicted they had cancer reported one or more severe life events in the study period compared with 132 of 213 (62%) who knew or predicted they had a benign lump (χ^2 = 0.084, df = 1, P = 0.77). The reporting of severe life events decreased over time. The decay in reporting severe events per 100 participants per quarter was 0.207 for cases and 0.208 for controls. The difference was not significant (t = 0.02, P = 0.98). These calculations suggest that attempts by the women to explain their diagnosis by searching for stress—sometimes called effort after meaning[4]—was not an important source of reporting bias.

Discussion

Possible sampling bias

Case-control studies are notoriously susceptible to bias. We have tried to reduce sampling bias by recruiting from all three clinics serving a defined catchment area, and by making an initial contact with participants in the breast clinic so that losses and refusals were kept to a minimum. Even so we cannot be sure that our controls were representative of all women with benign breast disorders. Such women had, for example, the same rates of family history of breast cancer as the cancer group, probably because this increased the chances of an apparently benign lump being biopsied. Alterna-

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Key messages

- Although there is widespread belief that stress can cause cancer, research evidence is contradictory

- Stressful life experiences are common; about two thirds of women with a breast lump experienced at least one severe life event or difficulty in the 5 years before presentation

- Women diagnosed with breast cancer were no more likely to have experienced a severe stressor than women with a benign lesion

- Knowledge or suspicion of the diagnosis did not influence reporting of severe life events

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tively, they may have been referred to the clinic, or biopsied, because of a recent life stress. Our other results do not support the inference of serious bias in selection of cases or controls.

Confounding

The main potential bias comes from age being a confounder—there was a 10 year difference in age between women with benign and malignant disease. We dealt with this by adjusting for age in the multivariate analysis rather than by recruiting a second sample from the general population, because the latter approach introduces other potential biases, due mainly to difficulties in recruitment for research in life events from community samples.

Other biases

To reduce reporting and measurement bias, we used two interviewers and ensured that borderline events and difficulties were rated at consensus meetings, and that equivocal stressors were rated by a third person unaware of the diagnosis. In addition we avoided subgroup reanalysis,[14] restricting our study to the association between onset of breast cancer and the experience of four types of stressor, which were specified before data were collected.

Conclusion

Our data provide no support for the theory that severe life stresses may be concerned with the cause of breast cancer. This finding agrees with the results of a recent meta-analysis of observational studies examining the relation of life events to risk of breast cancer; the authors found evidence of bias in the literature, but larger and better quality studies showed no association between breast cancer and bereavement or other severe life events.[15] We believe that women with breast cancer can be told that life stresses are unlikely to have played an important part in the development of their disease. The issue of stress and breast cancer relapse is unresolved.

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One hundred years ago

A case of tetany due to exposure to the sun

A boy, aged 13, was brought to me by his mother and a friend, complaining of pains in his arms and legs, and inability to move his hands and feet. He was one of a large and healthy family, and had never suffered from any illness until the day before I saw him. He had been sitting in the sun all the preceding afternoon, and on reaching home complained of headache and vomited. He was sent to bed, and woke up about 5 a.m., complaining of pains in his arms and legs, and that he could not move. He was brought to the surgery at 9 a.m., when it was seen that the hands and feet were rigidly contracted in the position met with in tetany, and he was quite unable to move them. His knee-jerks were markedly exaggerated. He was very nervous and frightened, but apart from the conditions of his hands and feet appeared in good health.

There was not, nor had there been, any gastric or intestinal trouble. He was treated with a calomel purgative and 10 gr. doses of ammonium bromide every four hours. The spasm gradually relaxed, but it was five days before he could walk or use his hands properly. The case appeared interesting owing both to the age of the case patient and to the total absence of any cause for the attack that I could discover other than exposure to the sun, a somewhat unusual, or at least undescribed, cause of tetany.

Catford S.E. Herbert Fox, M.B. Lond. (*BMJ* 1899;ii:1474)

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