kept by their parents for 21 days after immunisation.[12] These results need to be interpreted with some caution. Firstly, data were analysed for only 7831 children (65% of the cohort) and, more importantly, specific questions relating to joint symptoms were not asked of the parents. Furthermore, joint symptoms may develop later than 21 days after immunisation.[4 8]

The introduction of universal measles, mumps, and rubella immunisation of young children has implications for child morbidity and public health. Although joint and limb complaints were not uncommon, in most instances morbidity was slight and the episodes self limiting. Coryza, fever, skin rash, swollen glands, and sore eyes were common background events among both immunised and non-immunised children. Many children consulted their doctors, and some were admitted to hospital, mostly for reasons unrelated to the vaccine. Nevertheless, immunisation with measles, mumps, and rubella vaccine carries a risk of first ever episodes of joint symptoms, particularly in children under 5 years and in girls. The most severe cases of arthritis were interestingly seen in older boys. This is of some reassurance given that current policy will result in most children in the United Kingdom being immunised at about 12 months of age.

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Life events and breast cancer prognosis

Jennifer Barraclough, Pamela Pinder, Marie Cruddas, Clive Osmond, Irving Taylor, Michael Perry

University Department of Psychiatry, Royal South Hants Hospital, Southampton SO9 4PE
Jennifer Barraclough, senior research fellow
Pamela Pinder, research assistant

MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO9 4XY
Marie Cruddas, statistician
Clive Osmond, statistician

University Surgical Unit, Royal South Hants Hospital, Southampton SO9 4PE
Irving Taylor professor of surgery

Queen Alexandra Hospital, Portsmouth PO6 3LY
Michael Perry, consultant surgeon

Correspondence to: Dr Jennifer Barraclough, Sir Michael Sobell House, Churchill Hospital, Oxford OX3 7LJ.

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Abstract

Objective—To determine whether psychosocial stress, in the form of adverse life events and social difficulties, depressive illness, or lack of confiding relationships, shortens the postoperative disease free interval in breast cancer patients.

Design—Prospective follow up of a cohort of newly diagnosed breast cancer patients for 42 months after primary surgical treatment, using a life events and social difficulties schedule (LEDS) and assessment of depressive symptomatology (DSM-III).

Setting—Patients recruited from breast clinics in Southampton and Portsmouth were interviewed in their homes.

Patients—204 women (83% of 246 consecutive cases) treated either by mastectomy or wide excision followed by radiotherapy interviewed four, 24, and 42 months after operation.

Main outcome measures—Hazard ratios for relapse of breast cancer in relation to various measures of psychosocial stress. Relapse was defined as local recurrence or distant metastasis, or both, with histological or radiological confirmation and timed from the month when clinical symptoms began.

Results—After adjustment for age and axillary lymph node involvement, the hazard ratio associated with severe life events or social difficulties (excluding "own health" ones), or both, during the year before breast cancer surgery was 0·43 (95% confidence interval 0·20 to 0·93); for those during the follow up period it was 0·88 (0·48 to 1·64). For prolonged major depression before surgery and during the follow up period, hazard ratios were 1·26 (0·49 to 3·26) and 0·85 (0·41 to 1·79) respectively. For absence of a full confidant the figures were 0·93 (0·42 to 2·09) and 0·86 (0·38 to 1·93).

Conclusion—These results give no support to the theory that psychosocial stress contributes to relapse of breast cancer.

Introduction

Whether emotional stress affects the course of cancer is a question of relevance to scientists and clinicians, of concern to patients and their families, and of interest to the general public. Laboratory studies, mostly using animal tumour models, have shown immunological and hormonal pathways through which stress might alter host resistance, but the relevance of these findings to the clinical course of human cancer is not known. One recent review of clinical research in the field concludes: "Most studies that have controlled for the biological contribution have found the magnitude of psychosocial influences to be small."[1]

Despite the lack of evidence, belief in a causal stress-cancer link seems to be widespread, forming a rationale for many modern complementary therapies and media presentations and having implications for clinical practice. If psychosocial factors affect prognosis then cancer treatment programmes should include more psychosocial care. If they do not, patients could be spared the burden of wondering if their own or other people's behaviour is to blame for progression of their disease.

We carried out a prospective interview study to test the main hypothesis that experience of adverse life events shortens the disease free interval following treatment for operable breast cancer. This approach was chosen for three reasons. Firstly, studying the prognosis, as opposed to the onset, of cancer permits the use of a prospective design with more precise timing of variables. Secondly, life events such as bereavement or divorce represent one aspect of "stress" that can be measured with reasonable accuracy. Thirdly, breast cancer is a common disease and attracts

much interest from the psychosocial viewpoint.

Besides life events, our interview schedule covered long term social difficulties, depressed mood, and availability of confiding relationships. Other psychological variables, such as personality and attitude to disease, were outside the scope of the study.

Method

PATIENTS

Women presenting to participating surgeons at the Royal South Hants Hospital, Southampton, or Queen Alexandra Hospital, Portsmouth, between February 1986 and August 1987, who were aged 70 or less and found to have breast cancer without clinical evidence of spread beyond the axilla were identified through monthly checks of surgical records.

Physical details (age; menopausal status; size of tumour; number of axillary nodes affected as determined by histological examination; treatment given) were abstracted from case notes. Initial management comprised either mastectomy (followed by radiotherapy in a few cases) or local excision always followed by radiotherapy. Most node positive postmenopausal women were prescribed tamoxifen postoperatively for variable lengths of time. Adjuvant chemotherapy, which would now be offered to node positive premenopausal women, was not then in use at the centres concerned. The few patients on whom axillary dissection had not been performed were assumed to be node negative since none had nodes palpable clinically. Tumour histology was not graded in a consistent manner, and hormone receptor status was available for a minority of patients only, so these variables could not be used in the analysis.

INTERVIEWS

Having sought permission from her family doctor, we wrote to each patient to request a series of three home interviews. These took place at four, 24, and 42 months after operation. Each interview inquired about the experiences of the previous 18 months, yielding data about the period from one year before breast cancer surgery until three and a half years afterwards. The same person (PP) conducted all interviews.

The Bedford College life events and difficulties schedule (LEDS)[2] was used to assess life events (for example, bereavements) and social difficulties (for example, unemployment). Use of this schedule, in contrast to simpler life event checklists, involves rating each event and difficulty according to the individual circumstances. The section about the subject's own health was left to the end to safeguard as far as possible the interviewer's blindness to the presence of recurrence. Symptoms of major depression were elicited using DSM-III criteria.[3] Each interview lasted between one and three hours.

Interviews were tape recorded and transcribed, and the abstracted material was discussed by the two investigators (JB and PP) trained in using the life events and difficulties schedule. Events and difficulties were rated according to their classification, severity, independence, and timing.

Classification refers to the domain of life concerned — for example, own health, others' health, bereavement, and marital situation. Since events and difficulties affecting patients' health might have a direct biological link with relapse of breast cancer, apart from any effect mediated through emotional stress, "own health" events and difficulties were analysed separately from the other kinds.

Severity was rated on separate six point scales according to short term and long term threat, both "contextual" (objective) and "reported" (subjective). Events rated 1 or 2a on long term contextual threat and difficulties rated 1 or 2 were designated "severe" in accordance with the Bedford College system.

Independence from the patient's own behaviour or state of health was assessed. Events resulting directly from recurrent breast cancer—for example, being hospitalised for pathological fracture of the hip—were not counted. We did include events resulting from the original diagnosis—for example, cancellation of emigration plans.

Timing was determined at interview with reference to written evidence, such as diaries, when available. Dating of own health events was checked against hospital and family doctors' records. Events that followed symptoms of recurrence were not counted.

To avoid losing patients who relapsed and died between one interview and the next, one of us (JB) carried out regular checks of hospital case notes and made inquiries of breast care nursing sisters and family doctors. If a patient had relapsed before her next interview was due we asked to see her earlier, although this meant sacrificing the interviewer's blindness. If the patient had already died we asked to interview her nearest relative.

Relapse of breast cancer was defined as local recurrence or distant metastasis with histological or radiological confirmation and was timed from the month when clinical symptoms or signs began.

STATISTICAL ASPECTS

We hoped to recruit 250 patients within the time available. On the assumption that 30% would experience a severe life event and 30% would develop relapse of breast cancer during the follow up period, the power of the study (that is, the probability of detecting a genuinely increased risk of relapse following a severe life event) for a sample this size was calculated as 29% for a true relative risk of 1·5, rising to 97% for a true relative risk of 3·0.

Fixed variables, including sociodemographic characteristics of the patient, details of the breast cancer and its treatment, and experience of psychosocial stressors (life events, social difficulties, major depression, an absence of confiding relationships) during the year before surgery were recorded at entry to the study. Time dependent variables, including experience of psychosocial stressors and physical symptoms, were recorded for each month of follow up.

Statistical analysis was carried out with the Cox proportional hazards model with allowance for time dependent variables.[4] The fixed covariates were examined first to find those most strongly related to outcome, in order to allow for these when modelling the time dependent ones. To examine the effect of changes in time dependent variables we used a model in which the effect of the occurrence of the appropriate event or difficulty is to multiply the individual's risk of relapse by a constant value, the hazard ratio, which remains constant thereafter. The only exception was confiding relationships, where risks were allowed to return to the former levels when confidants were lost.

Results

RESPONSE RATE

We interviewed 204 (83%) of 246 consecutive patients who fulfilled the selection criteria. The 42 non-participants included 10 whose family doctors did not want us to approach them and 32 who refused of their own accord. Non-participants had less favourable physical prognostic features than those interviewed (table I). We have no systematic information about the psychosocial characteristics of the non-participants.

Of the 204 patients completing the first interview, two declined the second and one declined the third. Eleven of the follow up interviews were conducted

with the next of kin because the patients concerned were terminally ill or had died. The next of kin of two other deceased patients refused an interview.

PHYSICAL OUTCOME

Relapse of breast cancer was confirmed in 47 (23%) of the 204 patients. Twenty six of these had died by the end of the follow up period. One other patient died from a stroke classed as not related to cancer.

LIFE EVENTS AND SOCIAL DIFFICULTIES

We recorded 1995 events (range 0-45 per patient) and 924 difficulties (range 0-12 per patient). Events and difficulties were often linked—for example, the woman who learnt her husband had lung cancer and nursed him till he died several months later would have two events (husband's cancer diagnosis and husband's death) and two difficulties (husband's health and bereavement—husband), all rated "severe" on the life events and difficulties schedule. Apart from the illnesses and deaths of close relatives, other examples of severe events or difficulties not stemming from own health are divorce, the family home burning down, and caring single handed for a demented mother. During the follow up period 103 patients (51%) reported one or more such experiences. Severe own health events or difficulties—for example, myocardial infarction or renal failure—affected 21 patients (10%).

CORRELATES OF BREAST CANCER RECURRENCE

Axillary node involvement was the variable most strongly associated with relapse; younger age and larger tumour showed more modest associations with poor prognosis (table II). Before the contribution of psychosocial stressors was analysed, adjustment was made for age and axillary node involvement. Tumour size was not included in the model because it added no

contribution after the first two factors had been entered.

We present the contribution of psychosocial stress under the following headings: severe events and difficulties not stemming from own health, major depression of over three months' duration, and lack of a full confidant (tables III and IV). None of these stressors, whether in the year before surgery or during the follow up period, were associated with a substantially increased risk of relapse of breast cancer. On the contrary, most of them had weak inverse associations with relapse.

The psychosocial data were also analysed in other ways: separating events and difficulties, separating broad categories of stress (others' health, bereavement, marital, interpersonal, practical), including all events and difficulties rather than just severe ones, separating pleasant events such as marriage or the birth of a grandchild, and omitting the 14 patients of doubtful axillary node status. None of these analyses produced substantially different results.

The absence of any statistical association between psychosocial stress and relapse is in keeping with our clinical observations that all thirteen patients who experienced the death of a husband, child, or grandchild during the period of the study remained well, whereas many patients who relapsed had described quiet contented lives.

In contrast to the psychosocial stressors, severe own health events and difficulties were associated with increased risk of relapse (tables III and IV); interpretation of this finding is discussed below.

Discussion

SAMPLE SIZE AND DURATION OF FOLLOW UP

The importance of the main biological variables already known to predict a poor prognosis in breast cancer—namely, axillary node involvement and large primary tumour[5]—was clearly confirmed in our study. If psychosocial stress was a risk factor of comparable magnitude we should have shown this too. A larger sample would have been required to ensure that a more modest effect was not missed.

Our follow up period was relatively short in terms of the clinical course of breast cancer. Patients were assigned to the "relapse" category only if they had histological or radiological confirmation of recurrent disease, and other patients presumably had occult recurrences that would have been confirmed with longer follow up. If life events contribute to relapse only after a latent period of some years we might have failed to detect the link, but the finding that severe non-health events or difficulties in the year before diagnosis were associated with such a low relapse rate 42 months later weighs against this possibility.

VALIDITY OF LIFE EVENT DATA

We used a comprehensive and well established measure of life events and a prospective design that enabled most interviews to be conducted with both parties blind to the outcome of the breast cancer; nearly all our patients were cooperative; and the drop out rate was under 2%. However, the validity of all life event interviews depends on the memory and emotional set of the subjects. "Effort after meaning" might have encouraged overreporting of stress in a few interviews carried out after diagnosis of relapse, but relapsed patients reported fewer life events than did the rest. Information obtained from nearest relatives rather than patients themselves might have been incomplete, but probably in respect of minor events and difficulties rather than severe ones, and only a tiny proportion of data was gathered in this way.

TABLE I—*Comparison of breast cancer patients participating and not participating in study*

Variable	Interviewed (n=204)	Not interviewed (n=42)	95% Confidence interval for difference*	p Value
Mean (SD) age	54·3 (11·1)	51·2 (9·0)	−0·6 to 6·7	0·09
Mean (SD) tumour diameter (cm)	2·7 (1·3)	2·9 (1·4)	−0·7 to 0·2	0·30
No (%) with axillary lymph node(s) containing tumour	79 (39)	21 (50)	−28 to 5	0·18
No (%) still menstruating	60 (29)	17 (40)	−27 to 5	0·18
No (%) who had mastectomy	120 (59)	26 (62)	−19 to 13	0·71
No (%) who had radiotherapy	111 (54)	27 (64)	−26 to 6	0·23
No (%) who died before 42 month follow up	28 (14)	10 (24)	−24 to 4	0·15

*Difference between means for continuous variables and percentages for categorical variables.

TABLE II—*Hazard ratios for relapse of breast cancer associated with biological and sociodemographic fixed variables (considered independently)*

Variable	No of patients	Hazard ratio	95% Confidence interval	p Value
Age Group:				
<45	42	1·0		
45-55	62	0·93	0·44 to 1·95	0·85
>55	100	0·58	0·28 to 1·21	0·15
Still menstruating*:				
No	102	1·0		
Yes	60	1·54	0·82 to 2·89	0·18
Axillary nodes containing tumour:				
None	125	1·0		
One or more	79	4·50	2·41 to 8·42	<0·001
Tumour diameter:				
1-4 cm	178	1·0		
>4 cm	16	2·23	1·00 to 4·99	0·05
Mastectomy:				
No	84	1·0		
Yes	120	1·58	0·85 to 2·91	0·15
Legal marital status:				
Single	17	1·0		
Married	148	1·41	0·43 to 4·57	0·57
Divorced or separated	16	1·36	0·30 to 6·07	0·69
Widowed	23	0·94	0·21 to 4·21	0·94
Non-manual occupation:				
No	114	1·0		
Yes	89	0·77	0·43 to 1·38	0·38

* 42 Patients had had hysterectomy.

TABLE III—*Hazard ratios for relapse of breast cancer associated with life events, social difficulties, major depression, and lack of confidants reported in the 12 months before surgery considered independently as fixed variables*

	No of patients	Hazard ratio*	95% Confidence interval	p Value
Severe event or difficulty with own physical health	8	1·92	0·45 to 8·09	0·38
Any severe event or difficulty other than own physical health	54	0·43	0·20 to 0·93	0·03
Major depression lasting at least 3 months	16	1·26	0·49 to 3·26	0·63
Some period without a full confidant	36	0·93	0·42 to 2·09	0·87

*Given for those who experienced the stressor relative to those who did not. Adjustment was made for age in three groups and the number of nodes in two groups.

TABLE IV—*Hazard ratios for relapse of breast cancer associated with life events, social difficulties, major depression, and lack of confidants following surgery, considered as independent time dependent variables*

Variable	No of patients	Hazard ratio*	95% Confidence interval	p Value
Severe event or difficulty with own physical health	21	3·06	1·29 to 7·31	0·01
Any severe event or difficulty other than own physical health	103	0·88	0·48 to 1·64	0·70
Major depression lasting at least 3 months	45	0·85	0·41 to 1·79	0·67
Some period without a full confidant	48	0·86	0·38 to 1·93	0·72

*Given for those who experienced the stressor relative to those who did not. Adjustment was made for age in three groups and the number of nodes in two groups.

INDEPENDENCE OF LIFE EVENTS FROM INCIPIENT RELAPSE

Clear cut presentation of relapse is sometimes preceded by vague unrecognised prodromal symptoms. Tiredness due to anaemia, or behavioural change due to cerebral metastases, might alter the patient's experience of life events. A subtle decline in the patient's health is hardly likely to be the chief cause of her husband leaving home or her daughter becoming pregnant, yet it might be a contributing factor. Even an apparently independent event like the death of a sick father might be brought forward in time because the patient had become less able to look after him.

Since patients who relapsed reported no excess of life events, this effect was probably not important and it is more relevant to consider the opposite possibility, that the presence of occult relapse prevented the occurrence of life events which would otherwise have taken place. Events that depend on patients' own initiative—for example, moving house or changing job—might well have been less common for those in failing health. This phenomenon is unlikely to explain our results because it would not apply for most of the severe events such as bereavements.

The influence of occult recurrence on the patient's experience of life events can only be guessed at. Restricting the analysis to events rated independent of the patients would have avoided the issue, but at the expense of ignoring major stressors such as divorce that, while not independent, are clearly relevant to the inquiry.

OWN HEALTH EVENTS AND DIFFICULTIES

Severe own health events and difficulties were associated with increased risk of relapse. That patients in poor general health should be more vulnerable to progression of their breast cancer makes intuitive sense. This finding might be spurious, however, because in some cases it was impossible to tell whether symptoms resulted from recurrent breast cancer or from unrelated pathology. For example, one patient had back pain of long standing; x ray examination confirmed osteoporosis but could neither confirm nor exclude bony metastases; some months later she developed visceral metastatic disease.

The finding of a strong association between severe own health problems and subsequent relapse, whether or not it is valid, underlines the importance of analysing own health stressors separately from those of a purely emotional kind.

COMPARISON WITH OTHER STUDIES

Ramirez et al carried out a retrospective inquiry on stress and relapse of breast cancer.[6] They administered the life events and difficulties schedule to 50 recently relapsed breast cancer patients and to 50 control patients matched on physical characteristics and date of original presentation but still in remission. Relapsed patients reported significantly more severe life events and difficulties since surgery than did controls, the relative risk of relapse associated with severe life events being 5·67. Ramirez et al achieved a 100% response rate; ours was only 83%, which may have introduced some sampling bias, but we had the advantages of a larger total number of subjects and a prospective design. In the Ramirez study neither patient nor interviewer could be blind to diagnosis which the authors acknowledged as a possible source of bias. Even taking these methodological differences into account, the large discrepancy between Ramirez et al's results and our own is surprising, and further work may be required to resolve the issue.

As regards our subsidiary finding that prolonged major depression was not associated with an adverse prognosis, this is consistent with the report by Dean and Surtees, who found in a prospective interview study that depression and anxiety at the time of mastectomy were associated with reduced risk of relapse.[7]

CONCLUSIONS

Our prospective interview study of 204 women presenting with operable breast cancer yielded no evidence that psychosocial adversity, as measured by severe life events and social difficulties; prolonged major depression; or lack of confiding relationships are conducive to relapse over a follow up period of three and a half years. These findings cannot be regarded as definitive in view of various methodological limitations, but if emotional stress had a major influence on the prognosis of breast cancer this study should have succeeded in detecting it.

Most severe life events and social difficulties are not preventable. Psychosocial intervention, however skilled, can soften their adverse impact to only a limited degree. Women with a history of breast cancer who fear that unavoidable emotional traumas like bereavement may cause them to relapse should therefore find consolation in our results.

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