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Original Paper

Life Events and the Risk of Breast Cancer: a Case–control Study

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A case–control study was undertaken to investigate the possibility of an association between stressful life events and the development of breast cancer. Ninety-nine breast cancer cases, and 99 controls matched by age and area of residence, completed a life events inventory to measure life change and distress scores over a 2-year and a 10-year period. Study subjects were also interviewed to establish potential breast cancer risk factors; their height and weight were measured; they completed a food frequency questionnaire and provided a fasting blood sample for hormonal assay. After adjusting for potential confounders, women with a 10-year life change score greater than 210 (i.e. the highest quartile) had 4.67 times the risk of developing breast cancer, compared with those in the lowest quartile ($P < 0.05$).

Key words: breast cancer, stress, life events

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INTRODUCTION

THE RELATIONSHIP between the mind and the body is a complex one that has fascinated mankind for centuries. From the earliest days of study into disease, the idea that a person's emotional state can influence the development or outcome of their illness has held a strong appeal. Indeed, we are now aware of a number of physical disorders—such as ulcers, migraines, asthma, eczema and high blood pressure—in which stress obviously plays an important role. Is it possible that breast cancer is similarly affected?

Despite the advances in our understanding of cancer, it can still be an unpredictable disease. Cases are continually reported in which, for no apparent reason, the patient survives well beyond expectations, the cancer lies dormant for some time, the growth rate of the cancer fluctuates noticeably, or the cancer regresses altogether. When such clinical observations cannot be fully explained within the usual frame of reference, it is tempting to look for a more 'metaphysical' reason for these phenomena.

For centuries, the idea that emotional factors contributed to the development of cancer was taken for granted. It was not until the late 19th century that any attempt was made to determine whether this belief had any foundation: Herbert Snow carried out a detailed statistical study of 250 patients at the London Cancer Hospital [1]. He found that in 156 of these, "there had been immediately antecedent trouble, ... often in very poignant form, as in the loss of a near relative". Although he did not compare these with a control group, Snow's study was as comprehensive and methodical as was possible at the time. In fact, despite the increasingly sophisticated approach of contemporary research, studies of the impact of stress upon cancer continue to be flawed by methodological problems; the issue is frustratingly complex.

We have undertaken a study to determine whether women with breast cancer have significantly more stressful life events in the years preceding their diagnosis than matched controls.

PATIENTS AND METHODS

Selection of study participants

Between February 1985 and August 1987, 108 women with breast cancer were identified from pathology records at the Queen Elizabeth II Medical Centre in Perth, Western Australia. Once approval was obtained from their surgeon, the women were sent a letter inviting them to participate in a diet and lifestyle study. Those who did not respond were

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followed up with a second letter and telephone call. Initially, all women agreed to participate. However, 9 were later excluded for the following reasons: one was pregnant, two died before relevant data and specimens could be obtained, five withdrew for personal reasons, and one provided dietary data that were obviously erroneous and could not be rectified.

The 99 breast cancer cases entered into the study were matched by age (5-year intervals) and area of residence (electoral district) with women selected at random from the electoral roll. The invitation letter and follow-up for these controls were the same as for the actual cases. If a control declined to participate, she was replaced by another woman who matched the selection criteria, also from the electoral roll. A matched control was obtained for all cases entered into the study. However, due to incomplete data, only 98 case–control pairs were included in this analysis.

Data collection

All women were interviewed at home by a single interviewer. Cases were seen 3–6 months after their surgical intervention; if they were undergoing chemotherapy, they were not interviewed until 6 weeks after their treatment had finished. Controls were interviewed as soon as possible after the corresponding cases. The interviewer obtained demographic details and information on potential breast cancer risk factors, such as menstrual status, age of menarche, age at menopause, parity, age at birth of first child, use of hormones, family history of breast cancer and others. Height and weight were also recorded, using a standard set of scales.

In addition, the participants were asked to complete a Life Events Inventory as developed by Tennant and Andrews [2]. This comprises a list of 67 life events for which a score has been allocated based upon two different scales: a life change scale, which assesses the extent of life change produced by the event, and a distress scale, which reflects the amount of distress caused by the event. Participants were asked to indicate which events had occurred, and in what year each event took place.

Study subjects were also asked to complete a food frequency questionnaire and a fasting blood sample was taken from which serum levels of various hormones were derived. These data have been published elsewhere [3].

Statistical analysis

Life change and distress scores were totalled for the 2-year and 10-year period prior to each participant's interview. As the resulting total scores did not appear to be normally distributed, a log transformation was applied. This normalisation process allowed us to use parametric methods to examine mean differences in scores between matched pairs. Paired *t*-tests were then computed, to determine if total scores between matched pairs (in each score category) were significantly different than zero. As differences in log-transformed values do not have much relevance to the reader, and as means obtained from data which are not normally distributed may not have much significance, geometric means for the case and control groups were calculated to give some indication of the magnitude of the score difference between the two groups. Statistical analyses were performed with the aid of the SAS statistical package.

For relative risk computations, conditional logistic regression was performed (using the SAS PHREG procedure), after classifying life change and distress scores into four levels, each level approximating a score quartile, but representing an even increment. Level 1, the lowest score level, was considered as the baseline against which relative risks of other levels were derived. Risk ratios and 95% confidence intervals were obtained both with and without adjustment for known confounders (including interactions). Furthermore, deviances and degrees of freedom for models with factored scores were compared with corresponding models using unfactored variables to determine if the tendency for the relative risk to increase as the score range increased was significant (i.e. trend test).

RESULTS

Comparison of life event scores

Our analysis of mean differences between life event scores of matched pairs indicates that in our sample, total scores were, on average, higher for breast cancer cases than for the matching controls. This applied to totals accumulated over both the 2-year and 10-year periods preceding each participant's interview, and to both the distress scale and the life change scale. However, mean differences were only significantly different than zero in the case of 10-year life change scores (matched *t*-test *P*-value using log-transformed scores = 0.018). For this score category, cases averaged a score 33.8 points higher than their matched counterpart, compared with 21.0 for the 10-year distress score, 14.3 for the 2-year life change score, and 10.8 for the 2-year distress score.

Geometric means (and corresponding 95% intervals) for the distress and life change scores of cases and controls were also examined, for both the 2-year and 10-year period preceding the participants' interviews (Table 1). All mean scores were consistently higher for cases than for controls. However, overlaps in the 95% confidence intervals for corresponding scores suggest that these results are not statistically significant.

Table 1. Geometric means and 95% confidence intervals (CI) for the 2-year and 10-year distress and life change scores of breast cancer cases and community controls

		Cases	Controls
	Score scale	Mean (95% CI)	Mean (95% CI)
Distress	2 years	33.9 (25.7, 44.6)	27.6 (20.7, 36.9)
	10 years	130.0 (112.6, 150.2)	109.9 (94.3, 128.1)
Life change	2 years	39.7 (30.5, 51.6)	29.8 (22.5, 39.6)
	10 years	158.3 (138.8, 180.5)	126.0 (109.2, 145.4)

Table 2. Breast cancer risk ratios (RR) and 95% confidence intervals (CI) before adjustment for potential confounders, comparing groups with increasing distress and life change scores for the 2-year and 10-year period prior to participant interview

Score period	Score range	Distress scale RR (95% CI)	Life change scale RR (95% CI)
2 years	0–25	1.00	1.00
	26–50	0.60 (0.27, 1.34)	0.89 (0.39, 2.01)
	51–75	0.71 (0.31, 1.62)	1.63 (0.65, 4.09)
	>75	1.42 (0.68, 2.97)	1.46 (0.74, 2.88)
10 years	0–70	1.00	1.00
	71–140	1.30 (0.60, 2.84)	1.85 (0.76, 4.48)
	141–210	1.48 (0.64, 3.42)	1.38 (0.54, 3.50)
	>210	2.24 (0.92, 5.44)	3.35 (1.25, 8.95)*

*$P < 0.02$.

Relative risk analysis

Results of the univariate conditional logistic regression analysis performed to assess breast cancer risk ratios for different levels of distress and life change scores are shown in Table 2. Results are presented for both the 2-year and 10-year period prior to the participants' interviews. As previously mentioned, ranges for each score level were derived from the distribution of score totals for each life event scale and period; the four levels for each period approximate score quartiles (for both the distress scale and life change scale), but ranges have been rounded off to represent an even increment of 25 and 70, for the 2-year and 10-year levels.

Results for the 2-year period (Table 2) were inconclusive, although there was some suggestion that women who experienced the greatest degree of distress and life change may be at slightly higher risk of developing breast cancer than women who have experienced little or no distress or life change. Women with 2-year distress or life change score greater than 75 (i.e. the highest score level) appear to be approximately 1.4–1.5 times more likely to develop breast cancer than those with corresponding scores in the range 0–25 (i.e. baseline level). None of these results were statistically significant. However, trend tests support the theory that increases in these 2-year scores may be associated with increases in relative risk of breast cancer.

For the 10-year period, univariate results suggest an increased risk of breast cancer with increasing levels of distress and life change. Women with 10-year distress scores greater than 210 (i.e. the highest score level) appear to be 2.24 times more likely to develop breast cancer than those with scores less than or equal to 70 (i.e. baseline level). Although the results were not statistically significant, a trend was apparent (and supported by a trend test) such that increasing score levels yielded correspondingly higher breat cancer risk ratios. Similarly, our results suggest that women with 10-year change scores greater than 210 have 3.35 times the risk of breast cancer compared with women at the baseline level. Although a trend was not readily apparent for the life change scale, the results were significant for the highest score level ($P < 0.05$). Furthermore, a trend test did not reject the possibility of increased breast cancer risks for increasing 10-year life change score levels.

Adjusting for potential confounders (taking into consideration age at menarche, nulliparity, breast cancer history, exercise, body weight, body mass index and smoking, as well as alcohol, caffeine, energy, fat, retinol, betacarotene, vitamin B1 and vitamin C consumption), risk ratios were calculated for increasing score levels on the life change scale (Table 3). Women whose 10-year life change scores were at the highest level (i.e. greater than 210) were 4.67 times more likely to develop breast cancer than women at the baseline level. A trend test provided further support for this apparent increase in breast cancer risk for increasing 10-year life change scores.

Table 3. Breast cancer risk ratios (RR) and 95% confidence intervals (CI) after adjustment for potential confounders, comparing groups with increasing life change scores for the 10-year period prior to participant interviews

10-year score range	Life change scale RR (95% CI)
0–70	1.00
71–140	1.96 (0.63, 6.15)
141–210	2.83 (0.79, 10.13)
>210	4.67 (1.33, 16.41)*

*$P < 0.05$.

DISCUSSION

It is difficult to establish the exact extent to which stress, rather than some other factor or combination of factors, is responsible for changes observed in the development of breast cancer. As such, we tried to keep our approach as straightforward as possible, and did not attempt to correlate personality profiles. Our assumption was that regardless of personality type, stressful life events have to be assimilated, and that this requires adaptation and effort; everyone, consciously or otherwise, experiences distress over unwelcome, unpleasant events. Arguing about the degree of adaptive effort required on the part of each individual, or the precise amount of distress, is not necessarily useful. It may even be irrelevant, since there is nothing to suggest that a more acute reaction to stress produces a correspondingly exaggerated endocrine or immune response.

Our results showed that on average, women with breast cancer scored more highly for life change and for distress, over both a 2-year and a 10-year period. The most interesting findings related to the 10-year period. There was a noticeably higher incidence of breast cancer among women with the highest distress scores over 10 years. Similarly, with life change scores over a 10-year period, women with the highest scores were almost five times more likely to develop breast cancer than women in the lowest score quartile, after adjusting for potential confounders. The latter results reached statistical significance.

The fact that we have found significant associations over a 10-year rather than a 2-year period lends support to the observations that breast cancer evolves slowly over a period of several years and that any stress-induced hormonal influence is likely to be gradual and sustained rather than instantaneous [4–6].

Sir James Paget, in his 1870 classic, *Surgical Pathology*, wrote: "The cases are so frequent in which deep anxiety, deferred hope and disappointment are quickly followed by the growth and increase of cancer, that we can hardly doubt that mental depression is a weighty additive to the other influences favouring the development of the cancerous condition" [7]. We are still making similar statements, despite the general failure of research to prove the hypothesis.

The very persistence of the idea may be due to the fact that it is so hard to prove or disprove. Numerous studies have produced results in support of the theory but the factors involved are so densely interwoven that these results are always open to question [8–17]. Similarly, there are reasonable hypotheses to explain the biological processes by which stress could affect cancer growth; but until the connection can be proved, such explanations remain purely speculative.

The problem intrigues and exasperates us precisely because at its core lie two riddles that science has yet to solve: the mystery of what causes disease, and the mystery of the interaction between mind and body. Although we might intuitively feel there must be some connection between emotional strain and physical disorders such as cancer, we are unable to establish this beyond doubt. The question will continue to haunt us until we have an answer, which, given the complexity of the problem, may yet be a long way off.

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