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Does stress cause cancer?

There's no good evidence of a relation between stressful events and cancer

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In 1893 Snow presented what might be the first statistical summary of the psychological characteristics of patients with breast or uterine cancer.[1] Some 250 women with these cancers were described as having a "general liability to the buffets of ill-fortune." Over 100 years later we still find researchers preoccupied with showing whether stressful life events are related to cancer—as in this week's study by Protheroe et al (p 1027).[2] Many clearly believe that life is more stressful than ever before and that one consequence of this ubiquitous stress is disease, including cancer. Sontag describes this as a metaphorical view of disease as the "outward expression of character."[3] In more practical terms, patients with cancer may believe that their disease results from too much stress and relatives may feel guilty for contributing to the emotional ill health of the patient. Such beliefs may also have a bearing on what people do about seeking and sticking to treatment. It is important therefore to have a clear idea of what the evidence does show.

Two recent literature reviews have concluded that there is no good evidence for any relation between stressful life events and breast cancer,[4,5] and both point out that the typical methods used in studies of the relation are problematic at best. What then should we make of this most recent study? The methods used are fairly well in line with previous research.[2] Women attending breast clinics in west Leeds after discovering a suspicious breast lump but before learning the outcome of biopsy were asked about life stresses in the previous five years. Biopsy outcome then identified those with malignancy (106) and those with benign disease (226). Women with malignancy were no more likely to experience one or more severe life events (adjusted odds ratio 0.91) or severe difficulties (odds ratio 0.86) in the previous five years than those with a benign lump.

While consistent with the recent literature reviews, these findings stand in contrast to an earlier report by Chen et al, in the *BMJ*, using much the same methods, which suggested that women with breast cancer were nearly 12 times more likely to experience severe life events over the same period before diagnosis.[6] Why the discrepancy and what do these findings tell us about the relation between life events and breast cancer?

It is arguable whether the methods used in either of these studies could ever represent an adequate test of the hypothesis of a link between stress and cancer. Retrospective recall of life events in the five years before learning whether a breast lesion is malignant or benign constitutes a relatively weak test of the hypothesis, compared with good prospective studies. In Protheroe et al's study, even this most basic safeguard against recall bias was ignored as 30% of the women with cancer knew their diagnosis by the time they were interviewed.[2]

Two other features of the two studies are worth comment. Both are described as case-control studies but might be better described as cross sectional. In a true case-control study the controls are drawn from the same population as the cases. However, the women with cancer are considerably older—an average of 10.6 years in the study of Protheroe et al and 7 years in that of Chen et al. Many of the other studies using these methods report similar age differences.[5] It is unclear to what extent these studies can control for such large age differences in their analyses. This is important as age relates directly to risk of breast cancer and to experiencing particular life events.[5]

Both studies also use multivariate modelling with many predictors and relatively few outcome events—that is, cancers. A general rule of thumb is that there should be at least 10 outcome events for each predictor entered into the model,[7] so the multivariate analyses in these studies are probably overfitted and the estimates unstable. This is particularly so in the study of Chen et al, where12 predictors were entered into a model based on 41 women with cancer. While adjustment for other factors should lead to more precise estimates of effects, the reverse is true in their analysis, with the unadjusted odds ratio increasing from about 3 to 12 in the adjusted model, with a correspondingly large increase in the confidence interval surrounding the estimate. This suggests that life events are so correlated with one or more of the other variables that it is difficult to disentangle their effect. Similar criticisms apply to Protheroe et al's study, with 19 predictors entered into their model.

It is easy to go on picking holes in the methods of these types of studies—and perhaps unfair. One difficulty is that the hypothesis being tested is so vague. This is not the fault of the authors; the literature has not developed much beyond such vagueness. Any hypothesised relation does not seem to relate to cancer causation (causative factors may well be operating many years before detection) but may have something to do with stress accelerating the development of lesions or otherwise influencing the probability of diagnosis. The hypothesis needs to be stated in some more biologically plausible form to allow a stronger test of the association. Prospective longitudinal designs would be a good place to start.

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Already some indications exist from prospective studies that there is no relation between stressful events and cancer. The results of a large scale study in the United Kingdom provide little evidence for an association between bereavement in men or women and later cancer.[8] Other research has investigated the long term outcome for prisoners during the second world war and the Korean war.[9] These men clearly suffered extremes of physical and mental hardship, and though they showed excess mortality due to accidental injury, suicide, and cirrhosis of the liver—suggesting continuing psychological distress—there was no excess mortality due to cancer. A second longitudinal study of Japanese men living in Hawaii showed no relation between stressful life situations and later cancer.[10]

Recriminations over real or imagined life stress may be counterproductive for individuals with cancer and their families. They should be reassured that the available scientific evidence does not support any direct role for stressful life events leading to a diagnosis of cancer.

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Only a minor part of cerebral palsy cases begin in labour

But still room for controversial childbirth issues in court

Cerebral palsy develops in 2-3 out of 1000 live births during the first years of life. Its association with complications during childbirth has led to much controversy—and much litigation. This issue of the *BMJ* contains an international consensus statement on what is known about the causal relation between acute intrapartum events and cerebral palsy (p 1054).[1] The statement has been produced by an international task force representing a wide range of sciences, clinical specialties, and professional associations. The document is based on a thorough multidisciplinary literature review with the intention of benefiting research into the causation and prevention of cerebral palsy and helping those who counsel in this field or who offer expert opinion in court.

The common assumption is that perinatal asphyxia is the usual cause of cerebral palsy in term babies.[2] A few years ago a consensus statement from the Australian and New Zealand perinatal societies concluded, "There is no evidence that current obstetric practices can reduce the risk of cerebral palsy. The origins of many cases of cerebral palsy are likely to be antenatal."[3] Important Australian studies have shown that intrapartum hypoxia alone accounts for only a small proportion of cases of newborn encephalopathy and later cerebral palsy.[4 5] A realistic estimate may be that around 10% of cases of cerebral palsy stem from adverse intrapartum events.[2] The consensus statement published in this issue underlines this new insight into the origin of cerebral palsy. It points to events before labour or the newborn period as the main cause of cerebral palsy. This message is important because of the common opinion among the public, and also among some physicians, that cerebral palsy stems from intrapartum events.

The report presents three essential criteria that have to be met for a case of cerebral palsy to be causally linked to an acute intrapartum hypoxic event. The cerebral palsy should be of the spastic quadriplegic or dyskinetic type. There should be early onset of severe or moderate neonatal encephalopathy in a baby born at 34 weeks or later. And there should be evidence of metabolic acidosis in intrapartum fetal, umbilical arterial cord, or very early neonatal blood samples (pH <7.00 and base deficit ≥ 12 nmol/l). These are strict criteria. In particular, providing evidence of metabolic acidosis will create difficulties as pH and base deficit measurements will not be available at smaller hospitals and certainly not at home deliveries.

In addition to these essential criteria, the report presents five other criteria that together suggest an intrapartum timing but which by themselves are non-specific. Some of these criteria—for example "early imaging evidence of acute cerebral abnormality," can be ascertained only when the delivery takes place at a technically advanced hospital. This means that meeting the criteria to define an acute intrapartum hypoxic event and thereby assume a causal relation with cerebral palsy will depend on the place of delivery. Unexpected adverse events in smaller hospitals or outside hospital will have to be judged based mainly on clinical observations as before. Nevertheless, the criteria and the accompanying comments in the consensus document represent important support for expert opinions in court, although some of the controversial issues will still persist.[6]

Research on the causation of cerebral palsy needs to focus more on antenatal events. Evaluation of the condition of the fetus in utero is likely to be greatly facilitated by new technology.[2] There is also a need for

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