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No evidence that social stress is associated with breast cancer incidence

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Abstract Women commonly attribute the experience of stress as a contributory cause of breast cancer. The purpose of this study is to investigate the associations between a history of social stress and breast cancer risk. A total of 11,467 women with no prior history of breast cancer, participants in the European Prospective Investigation into Cancer (EPIC)-Norfolk population-based prospective cohort study, completed a comprehensive assessment of lifetime social adversity exposure. Summary measures of social adversity were defined according to difficult circumstances in childhood, stressful life events and longer-term difficulties in adulthood, derived measures representing the subjective ‘impact’ of life events and associated ‘stress adaptive capacity’, and perceived stress over a 10-year period. Incident breast cancers were identified through linkage with cancer registry data. During 102,514 (median 9) person-years of follow-up, 313 incident breast cancers were identified. No associations were observed between any of the summary social adversity measures and subsequent breast

cancer risk, with or without adjustment for age, menopausal status, parity, use of menopausal hormones, age at menarche, age at first birth, family history of breast cancer, physical activity, social class, body mass index, height, and alcohol intake. This study found no evidence that social stress exposure or individual differences in its experience are associated with the development of breast cancer. These findings may aid strategies designed to meet the psychosocial and emotional needs of breast cancer survivors and may be interpreted in a positive way in the context of commonly voiced beliefs that the experience of stress is a contributory cause of their disease.

Keywords Breast neoplasms · Epidemiology · Life events · Prospective studies · Psychological stress

Introduction

Breast cancer is the most common cancer in women, accounting for around 23% of all cancers worldwide, and is the leading cause of death from cancer in women [1]. Surveys of breast cancer survivors, and of those with no history of breast cancer, find that women commonly attribute the experience of stress as a contributory cause of this disease [2–4]. This view is supported by animal model-based psychoneuroimmunological evidence concerning the effects of behavioural stress on tumorigenesis and the biological mechanisms involved [5–7]. In addition, psychological distress factors are known to be associated with established anthropometric, behavioural, and lifestyle factors that may contribute to tumour growth and development [5, 8–10]. A recent comprehensive review and meta-analysis of the relationship between psychosocial factors and cancer incidence (and survival) showed no overall

We are saddened to report that Sheila A. Bingham died on June 15, 2009.

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association between exposure to stressful circumstances and breast cancer [11]. However, women appear unconvinced by studies that find no association between stressful life events (e.g. death of a child) and subsequent breast cancer risk [12], as such studies take no account of individual differences in the subsequent effects of such experiences [13, 14]. We are unaware of any study that has included evaluation of such individual differences in stress adaptive capacity associated with the experience of specific adverse life events and subsequent breast cancer risk. Clarification of this relationship would have the potential to inform attribution of breast cancer aetiology, and to contribute to evidence-based approaches to psycho-oncology practice. Based upon data collected from participants free of breast cancer in the United Kingdom European Prospective Investigation into Cancer (EPIC)-Norfolk population-based prospective cohort study [15], we investigate the associations between a history of social adversity, defined by stressful life event exposure together with individual differences in reported capacity to cope with the consequences of those stressful events, and their subsequent risk of breast cancer over 9 year follow-up, independent of established risk factors.

Methods

Participants and measures

Residents of Norfolk (UK) were recruited during 1993–1997 into the United Kingdom European Prospective Investigation into Cancer (EPIC)-Norfolk study using general practice age–sex registers. The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent [15]. Baseline questionnaire assessment for women included details of menopausal status, number of full-term pregnancies (parity), age at first (live) birth, use of menopausal hormones (HRT), age at menarche, and family history of breast cancer. Social class was defined according to the Registrar General's occupation-based classification scheme. A subsequent health check attendance included assessment of body mass index (BMI), determined according to the Quetelet Index (weight in kilograms divided by height in metres squared). Total consumption of alcohol was derived from responses to a semi-quantitative food frequency questionnaire (FFQ) (see [16] for further details). A validated physical activity index was derived from two questions on past-year work and recreational activities [17]. Incident breast cancers among EPIC-Norfolk participants to December 2006 were identified through linkage with the East Anglian cancer registry. Cancers were coded using the International Classification of

Diseases for Oncology, Second Edition (ICD-O-2), and breast cancer was defined as C50.0 to C50.9.

Social adversity assessment

During 1996–2000, a total of 11,820 (of 15,810 eligible EPIC-Norfolk) women participants, aged 41–80 years, completed the Health and Life Experiences Questionnaire (HLEQ), an assessment of social and psychosocial circumstances. The comprehensive assessment of social adversity included specific (potentially), traumatic circumstances experienced prior to age 17, the lifetime occurrence of a set of specific, commonly markedly stressful adverse events, and a chart approach designed to enable recording of prolonged periods of personal difficulty (see [18] for full details). Assessment of childhood experience was designed to represent areas commonly included in both questionnaire and interviewer-based assessments of childhood adverse experience (separation from their mother for more than 1 year; hospital stay for two or more weeks; parental divorce; parental unemployment; an experience that was so frightening as to be thought about for years; being sent away from home because of doing something wrong; parental alcohol or drug use, and experience of physical abuse). Assessment of adverse event experience in adulthood was restricted to those incidents considered most likely to be remembered reliably over an extended period. Event selection was based upon those developed for the questionnaire version of the List of Threatening Experiences (LTE-Q) [19]. A total of 16 specific adverse events, and a further undefined event of personal significance, were included in the questionnaire with up to two most recent events recorded and dated. These involved serious illnesses (injuries or assaults) experienced by the participant (or a first-degree relative), relationship events (concerning separation, divorce, termination of pregnancy), work events (retirement, redundancy or being fired), and loss experiences through death (of first-degree relatives). Further questions asked how much each event upset participants at the time, and how much they felt they had got over it now.

Life event exposure was summarised as the total number of moderately or extremely upsetting life events (excluding participants' own illness) experienced during the past 5 years with subcategories of events defined as those involving loss (through deaths of first-degree relatives) and other (non-loss) events [all other events, with the exclusion of events involving participants' illness, non-specific events, and (the relatively low impact) retirement events]. In addition, the questions on event upset and resolution permitted construction of indices of event impact and event adaptation, where a high score represented greater impact of, and slower adaptation to, event experiences, respectively (see [18, 20] for full details). A calendar-based Personal Life Chart was designed to aid recall and

assessment of participants' lifetime experiences of prolonged personal difficulty. This format provided a brief way of representing prolonged periods of personal difficulty. The chart allowed each participant to record the onset and offset times of (up to six) prolonged difficulties in their lives and to briefly describe them. Long-term difficulty exposure was summarised as at least one period of long-term difficulty (experienced either by the participant or close family (spouse/partner, parent, sibling, or child) and excluding difficulties that were solely due to participants' own health problems) reported to have ended within the past 5 years. In addition, the HLEQ included a single question relating to perceived stress, asking "All things considered, how stressful do you believe that your life has been over the past 10 years?" with response choices: not at all stressful, rarely stressful, moderately stressful, markedly stressful, and extremely stressful.

Statistical analysis

Summary measures of social adversity were defined [18, 20–22] as the total number of childhood difficult circumstances reported; the total number of life events experienced during the past 5 years; loss and other (non-loss) events experienced during the past 5 years; the index of impact; the index of adaptation; at least one period of long-term difficulty reported to have ended within the past 5 years; and marked or extreme perceived stress over the past 10 years. The associations between these summary measures of social adversity and incident breast cancer were investigated using Cox proportional hazards regression, implemented in Stata version 8.2 [23]. Results are presented as hazard ratios: A. stratified by age (in 10 year bands) and menopausal status [coded as not post-menopausal (i.e. pre- or peri-menopausal) and as menopause at age <45, 45–49, 50–54, and age \geq 55 years] and B. with further adjustment for parity (0,1,2,3, \geq 4 full-term pregnancies), use of menopausal hormones (HRT: current, former, never), age at menarche (<13, 13, 14, \geq 15 years), age at first (live) birth (nulliparous, age <20, 20–24, 25–29, and \geq 30 years), family history of breast cancer (none versus \geq 1 first-degree relative previously diagnosed with breast cancer), physical activity (inactive, moderately inactive, moderately active, and active), social class (I, II, III non-manual, III manual, IV, and V), BMI (<20, 20–24.99, 25–29.99, \geq 30), height (in cm), and alcohol intake (grams/day) (both included as continuous variables).

Results

After the exclusion of 353 participants with a history of breast cancer either at EPIC-Norfolk baseline assessment or

who were diagnosed with breast cancer between baseline and HLEQ completion, data from a sample of 11,467 women participants were available for analysis. During a total of 102,514 (median 9.1) person-years of follow-up, 313 incident breast cancers were identified. A total of 8,916 difficult circumstances were reported in childhood (mean 0.78 per participant), with the reported prevalence of difficulties ranging from 0.4% (sent away from home) to 21.1% (hospital stay of two weeks or more). A total of 11,474 moderately or extremely upsetting life events were reported in the 5 years preceding assessment (mean 1.00 per participant), of which 3,917 (mean 0.34) were loss events and 5,345 (mean 0.47) were non-loss events. The prevalence of specific life events reported in the 5 years preceding assessment ranged from 0.5% (problems with the police involving a court appearance) to 16.8% (serious illness or injury of close relative). In addition, 2,060 (18.0% of) participants reported at least one period of (non-health related) long-term difficulty in the preceding 5 years, and 1,859 (16.2%) reported that their lives had been markedly or extremely stressful over the past 10 years.

Table 1 shows that no associations were observed between any of the summary measures of social adversity and incident breast cancer, either with or without adjustment for breast cancer risk factors. In addition, there was no evidence of any differences in findings (stratified by age and menopausal-status) according to obesity (based on 43 cancers among obese women, and 228 cancers among those who were not obese), duration of follow-up (based on 178 breast cancers in the first 5 years of follow-up, and 135 cancers during the period 5 years or more after assessment), menopausal status (based on 113 incident breast cancers among pre- or peri-menopausal, and 200 among post-menopausal women), or age (based on 136 breast cancers among participants aged 41–59 and 177 among those aged 60–80).

Discussion

This study found no evidence that the experience of social adversity was associated prospectively with breast cancers identified among 11,467 women during 9 years of follow-up. This lack of association was consistent for summary measures of long-term difficult circumstances (reported as present during childhood), of specific (usually markedly stressful) life events experienced during the 5 years prior to a baseline psychosocial assessment (including by subcategories of adverse event experience), of periods of longer-term difficulties in adulthood, and for measures representing the subjective impact of (and recovery from, or coping following) stressful experiences, and of perceived stress over the preceding 10-year period. In addition, these

Table 1 Mean (and SD) of summary social adversity measures and hazard ratios (95% confidence intervals) for incident breast cancer

	Mean (SD)	A HR (95% CI)	B HR (95% CI)
Difficulties reported in childhood (per difficulty)	0.78 (1.01)	1.02 (0.91–1.14)	1.02 (0.91–1.16)
Life events in past 5 years (per event)	1.00 (1.23)	0.98 (0.89–1.08)	0.99 (0.89–1.11)
Loss events in past 5 years (per event)	0.34 (0.55)	1.08 (0.89–1.31)	1.21 (0.98–1.51)
Non-loss events in past 5 years (per event)	0.47 (0.73)	1.03 (0.87–1.21)	0.97 (0.81–1.17)
Impact index	0.22 (0.89)	0.98 (0.87–1.11)	0.97 (0.84–1.12)
Adaptation index	0.13 (1.03)	0.95 (0.84–1.06)	0.96 (0.84–1.09)
Long-term difficulties in past 5 years (yes/no)	0.18 (0.38)	1.05 (0.78–1.41)	1.16 (0.85–1.60)
Perceived stress over past 10 years (extreme/marked versus moderate/rare/not at all)	0.17 (0.37)	1.09 (0.81–1.46)	1.17 (0.84–1.64)

A. Stratified by age and menopausal status, B. With additional adjustment for parity, use of menopausal hormones (HRT), age at menarche, age at first birth, family history of breast cancer, physical activity, social class, BMI, height, and alcohol intake

findings of no association were consistent according to menopausal status, age, obesity, and duration of follow-up.

Our results are at variance with the only other prospective cohort study to evaluate the association between stressful life events and subsequent breast cancer risk [24]. This study, of 10,808 women in Finland, based upon 180 cancer cases identified during 15 years of follow-up, concluded that life events were associated with an increased risk of breast cancer—findings that were interpreted as suggesting a role for life events in breast cancer aetiology through hormonal or other mechanisms [24]. However, our finding of no association, based upon increased breast cancer endpoint availability, is in agreement with other studies of specific life events (e.g. death of a child [12]), and with those of a recent meta-analysis that concluded no overall association between stressful experience and breast cancer risk [11].

However, others have argued that studies should take account of individual differences in the subsequent effects of stressful experiences [13] and women continue to be concerned that stress is an important contributor to breast cancer risk [14]. The current study included additional measures of variations in reported ‘impact’ and ‘stress adaptive capacity’, calculated based on responses to questions concerning over 100,000 individual stressful life events reported (in both male and female EPIC-Norfolk participants) [18], and of perceived stress. The derived index of stress adaptive capacity, in particular, has been shown to be a marker of future health risks among EPIC-Norfolk participants, with associations shown for all-cause mortality [20] and incident stroke [21]. However, these measures of individual differences in stress experiences were not associated with breast cancer risk in these data.

The main strengths of the current study are the prospective follow-up, its size (with over 300 incident breast

cancer endpoints), and the range of social adversity measures considered. These measures included difficulties experienced in childhood and occurrences of specific stressful life events in adulthood, alongside more subjective measures of the impact of, and recovery following, these experiences, and of longer-term difficulties and overall perceptions of stress over a 10 year period. However, despite the comprehensive assessments of social adversity (see [18] for full details), the pragmatic approach required to assess these experiences in a study of this size may act as a barrier to detecting the perhaps subtle associations that may be present in the general population. In addition, while the current study is to our knowledge the largest such investigation to date, it may be that much larger samples (and longer follow-up) are required to have a realistic chance of detecting associations in a general population setting.

In England, breast cancer is diagnosed in over 30,000 women each year, has a 5-year relative survival of 69.8% (with more than 64.0% of women predicted to survive to the 20th anniversary of their diagnosis), and while associated with over 10,000 deaths annually, approximately 550,000 women are breast cancer survivors [25–28]. In consequence, based upon current evidence, perhaps 40–60% of these survivors believe that stress had caused or precipitated their breast cancer [2, 4]. Of course, causal attributions are post hoc interpretations by patients of the cause of their illnesses, influenced by their strongly held beliefs and attitudes, and in consequence can impact on clinical management, adherence to advised care programmes, and adaptation to clinical prognosis [29, 30]. The results of this research, in conjunction with findings from previous studies, reduce the likelihood that adverse life events exposures are an important contributory cause of breast cancer. We are unaware of any other study that has evaluated reported individual differences in the experience

of specific adverse life events and the subsequent risk of breast cancer. Our findings of no association, following consideration of variations in reported ‘impact’ and ‘stress adaptive capacity’, may therefore be interpreted in a positive way, as for the first time they directly address the commonly voiced beliefs of breast cancer survivors concerning their attribution that the experience of stress is a contributory cause of their disease [2–4, 14]. These results may contribute therefore to an evidence-based approach to (psycho-) oncology practice, through potentially increasing understanding of meaning-focused coping processes, that may lead to improved adjustment to a cancer diagnosis, and could aid strategies designed to meet the psychosocial and emotional needs of breast cancer survivors [31, 32].

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