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EPIDEMIOLOGY

Psychosocial stress is associated with benign breast disease in young Chinese women: results from Project ELEFANT

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Abstract

Purpose Psychosocial stress, including bereavement and work-related stress, is associated with the risk of breast cancer. However, it is unknown whether it may also be linked with increased risk of benign breast disease (BBD).

Methods Our study leveraged 61,907 women aged 17–55 years old from the Project ELEFANT study. BBD was diagnosed by clinician. Self-reported data on psychosocial stress over a 10-year period was retrospectively collected from questionnaires and categorised by cause (work, social and economic) and severity (none, low and high). Odd ratios (ORs) for the development of BBD were estimated using logistic regression. The model was adjusted for age, BMI, TSH levels, smoking, alcohol consumption, family history, age of menarche, oral contraceptive usage, education and occupation.

Results Within our study, 8% (4,914) of participants were diagnosed with BBD. Work-related stress [OR 1.57, 95% confidence interval (CI) 1.46–1.69] and financial stress (OR 1.34, 95% CI 1.24–1.44) were significantly associated with BBD incidence, with a smaller but still significant association with social stress (OR 1.11, 95% CI 1.01–1.21). The associations remained significant after exclusion of participants with first- and second-degree family history of breast disease. The presence of multiple forms of stress did not synergistically increase risk. The neutrophil–lymphocyte ratio (NLR), a marker of systemic inflammation and prognostic marker for breast cancer, was not associated with BBD.

Conclusions Psychosocial stress, particularly work-related and financial stress, is associated with increased risk of benign breast disease among young Chinese women.

Keywords Benign breast disease · Stress · Psychosocial stress · Neutrophil–lymphocyte ratio

Abbreviations

BBD Benign breast disease
BMI Body Mass Index
NLR Neutrophil–lymphocyte ratio
OR Odds ratio
SD Standard deviation

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Introduction

Benign breast disease (BBD) is a heterogeneous collection of conditions including cysts, duct ectasia, fibroadenoma, hyperplasia and sclerosing adenosis. It is highly prevalent, affecting approximately 30% of women at some point in their lives, with risk factors for its development including age, ethnicity, higher levels of circulating estrogens, premenstrual syndrome, use of oral contraceptives and endometriosis [1–6]. Diet and lifestyle during adolescent years may be particularly important in modifying risk, with physical activity and consumption of fruit and vegetables (and particularly vegetable protein and antioxidant carotenoids) associated with decreased risk of BBD later in life, while alcohol consumption is positively associated with incidence [1, 5, 7–11]. While most studies have reported no or weak associations between smoking and BBD [12, 13], in utero exposure to cigarette smoke is associated with BBD incidence later in life [14]. Furthermore, the risk of BBD is higher among individuals with a family history of breast cancer [15], which may in part be through genetic variants within DNA repair genes *XRCC1* and *ERCC4* [16]. Importantly, in addition to the immediate impact upon the patient's quality of life [17], BBD has been widely reported to be a risk factor for breast cancer, with the level of risk dependent upon the histologic classification of the lesion in conjunction with whether the patient has a family history of breast cancer [15, 18, 19]. Proliferative lesions are associated with higher cancer risk than non-proliferative lesions [20], with atypical hyperplasia conferring the highest relative risk [18, 19, 21].

Psychosocial stress has been implicated in the development of many human diseases through diverse mechanisms such as modulation of immune function, increases in blood pressure, heart rate and blood glucose levels, and the endocrine response to stress [22, 23]. Furthermore, stress is associated with the maintenance of unhealthy lifestyles, such as overeating, drinking and smoking, which are in themselves risk factors for a number of diseases. A large number of epidemiologic studies have reported an association between stressful life events and the development of breast cancer, including the death of a partner or family member [24–27], post-traumatic stress disorder [28], loss and deficit in childhood [29], and work stress [30]. However, the relationship between psychosocial stress and BBD has not been so well elucidated. Childhood deficit and the illness of a close relative in adulthood are both more common among women diagnosed with BBD than those without, but such associations are stronger for breast cancer [29, 31]. In contrast, strong loss in adulthood is only associated with the development of cancer and not BBD [31]. Other studies have reported that recent and severely stressful events are more common among women diagnosed with breast cancer than those with BBD, but without having analysed their frequency in healthy women and thereby being unable to determine an effect upon the risk of BBD [32]. Therefore, psychosocial stress does not appear to equally promote the development of benign and malignant breast diseases, and further work is required to establish how it may be associated with the risk of BBD and BBD-associated malignancies.

To investigate this question, we studied a retrospective record of psychosocial stress and the incidence of BBD among 61,907 young adult women within the Young ELEFANT based in Tianjin, China. Stress was categorised into work-related, social and financial stress. We estimated the risk of BBD according to the form of stress endured and its presence in isolation or in combination with other forms, adjusting for lifestyle and family history of breast disease.

Materials and methods

Study participants

Our study included participants from Project Environmental and LifEstyle FActors iN metabolic health throughout life-course Trajectories (ELEFANT), which comprises three cohorts based upon stage in life: Baby ELEFANT; Young ELEFANT; and Elderly ELEFANT. For this study, we focussed upon women within the Young ELEFANT cohort who were residents in Tianjin, China and aged between 17 and 55 (mean age 29.5; SD 4.5), who were attending clinic for a regular check-up. Basic characteristics, clinical data and questionnaires were collected from the participants at local hospitals during regular check-ups (Table 1). Exclusion criteria for this study included cancer diagnosis, pregnancy and missing values, resulting in a total of 61,907 participants used for analysis.

Psychosocial stress questionnaires

Psychosocial stress was assessed by structured questionnaire to enquire if participants experienced work-related stress, social stress or financial stress. This was performed using shortened versions of the Occupational Stress Indicator (OSI) [33] and the Perceived Stress Scale (PSS-10) [34], both of which have been validated and widely utilised in China and across the world. The PSS-10 is a self-report instrument which measures the perception of stress and ability to cope, such as how unpredictable, uncontrollable and overloaded the individual perceives their life to be. Each of the 10 items is graded on a Likert-type scale ranging from 0 (never) to 4 (very often), and total scores (0–40) calculated. The OSI enables the assessment of occupational

Table 1 Participant characteristics

Variable	($n=61,907$)
Age (years), mean (SD)	29.5 (4.5)
BMI (kg/m^2), mean (SD)	22.6 (4.6)
TSH (mIU/L), mean (SD)	2.4 (8.2)
Menarche age (years), mean (SD)	13.8 (1.4)
First degree relative with BBD or breast cancer, *n* (%)	2139 (3.5%)
Second degree relative with BBD or breast cancer, *n* (%)	733 (1.2%)
Smoker, *n* (%)	825 (1.3%)
Second-hand smoking, *n* (%)	2273 (3.7%)
Drinks alcohol, *n* (%)	4452 (7.2%)
Oral contraceptive usage, *n* (%)	30,328 (49.0%)
Occupation, *n* (%)	
Farmer	32,814 (53.0%)
Manual worker	6445 (10.4%)
Self-employed or service worker	4916 (7.9%)
Office worker or medical professional	13,485 (21.8%)
Housewife/househusband	2464 (4.0%)
Unemployed or other	1783 (2.9%)
Education, *n* (%)	
< 9 years	23,370 (37.6%)
10–15 years	11,782 (19.0%)
>16 years	26,826 (43.3%)
Work-related stress, *n* (%)	
No	47,961 (77.5%)
Low	12,778 (20.6%)
High	1168 (1.9%)
Social stress, *n* (%)	
No	56,780 (91.7%)
Low	5074 (8.2%)
High	53 (0.1%)
Financial stress, *n* (%)	
No	51,989 (84.0%)
Low	9258 (15.0%)
High	660 (1.1%)
Benign breast disease, *n* (%)	
Hyperplasia	4259 (6.9%)
Fibroadenoma	154 (0.2%)
Fibroadenoma with hyperplasia	131 (0.2%)
Other	370 (0.6%)
Total	4914 (7.9%)

satisfaction and stress by measurement of 40 items regarding stressors and job satisfaction on a 6-point Likert-type scale. The scale ranges from no stressful experience (1) to highly stressful experience (6) for stressors, and from strong disagreement (1) to strong agreement (6) for job satisfaction. We captured the degree of stress from "none", "low" and "high" and dichotomised as yes (high or low) or no (none) for the analysis. Instructions provided to the participants for completion of the questionnaires described work-related stress as including anxiety, depression and workload pressure; for social stress to include personal relations with family, friends or colleagues; and for economic stress to include financial deprivation and maintenance of finances. The questionnaires were built to obtain data on psychosocial stress over the previous 10 years.

Benign breast disease

Project ELEFANT participants attending a pre-pregnancy check-up at local hospitals in the Tianjin area between January 2014 and September 2015 were included in this study. They were examined by clinicians as part of their routine check-up. More than 30 clinics in the Tianjin area participated in the project. The check-ups incorporated physical examination, biochemical analysis of blood and urine specimens, and collection of data on demographics, lifestyle, medical and reproductive histories, medication use, and familial history of disease. Primary screening for BBD was performed by palpation and B-ultrasonography, with individuals identified as having high-risk lesions referred for biopsy and assessment by pathologist.

Statistical analysis

We used multivariable logistic regression models to examine the associations between each of the three forms of stress (work-related, social and financial) and BBD. In each regression model, we adjusted for the following covariates selected a priori: age; body mass index (BMI); thyroid-stimulating hormone (TSH) level in blood; age of menarche; first-degree relative breast disease diagnosis; second-degree relative breast disease diagnosis; smoking status; second-hand smoking status; drinking status; oral contraceptive usage; education; and occupation. Thyroid hormones are known to stimulate proliferation of breast cancer cells by binding to and activating the estrogen receptor [35], and, while studies have reported conflicting results, there is evidence for an association between thyroid disease and breast cancer risk [36, 37]. In our analysis, thyroid-stimulating hormone levels were a strong predictor for BBD (p value for log likelihood test: <0.0004). We therefore adjusted for levels of thyroid-stimulating hormone in our model because it may be an important predictor for the outcome. To assess the sensitivity of the model to the choice of confounders included, we repeated the analyses with no covariate adjustment. To eliminate the potential genetic contributions to BBD, we further evaluated the associations between stress and BBD in two restricted sub-cohorts: (1) women with no first-degree family history of breast disease; and (2) women with no first- or second-degree family history of breast disease. To investigate

Table 2 Associations between psychosocial stress and benign breast disease

Psychological stress	All participants n = 61,907		Without first degree n = 59,768		Without first or second degree n = 59,035	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Work-related stress	1.57 (1.46–1.69)	< 0.0001	1.63 (1.51–1.76)	< 0.0001	1.62 (1.50–1.75)	< 0.0001
Social stress	1.11 (1.01–1.21)	0.0350	1.14 (1.03–1.25)	0.0119	1.14 (1.03–1.26)	0.0104
Financial stress	1.34 (1.24–1.44)	< 0.0001	1.37 (1.27–1.48)	< 0.0001	1.36 (1.26–1.47)	< 0.0001

Analyses were performed across all participants and restricted to those with no first-degree family history of breast cancer and BBD and those without either first- or second-degree family history of such breast disease. The three forms of psychosocial stress were modelled separately, with each adjusted for age, BMI, thyroid-stimulating hormone level in blood, age at menarche, first degree relative with diagnosis of breast cancer or BBD (only for the models for all participants), second-degree relative breast disease diagnosis (only for the models for all participants and those without first-degree family history), smoking status, second-hand smoking status, drinking status, oral contraceptive usage, education and occupation. ORs are presented for individuals self-reporting stress (low or high) in comparison to those reporting none

whether associations between psychosocial stress and BBD may be through systemic inflammation, we computed neutrophil-to-lymphocyte ratio, a widely accepted measure of systemic inflammation and which predicts survival among breast cancer patients [38], and evaluated the association between neutrophil-to-lymphocyte ratio and BBD. To assess the relation between multiple forms of stress, we constructed a categorical variable that takes the eight values corresponding to unique combinations of stress, which ranges from no stress to stress in all three life areas (Table 3 shows these combinations). We estimated the relation between BBD and this categorical variable using no stress as the reference group.

All analyses were performed in SAS 9.4.

Results

A total of 61,907 participants were included for analysis in this study. The mean age of the participants was 29.5 (SD ± 4.5); they were healthy weight (BMI = 23, SD ± 4.6), showed a typical average age at menarche (13.8 years old, SD ± 1.4), and 49.0% (30,328) had used oral contraceptive pills at least once. Only 1.3% (825) were current smokers and 3.7% (2,273) were exposed to second-hand smoke. Among the participants, 1.9% (1,168) had experienced high levels of work-related stress, only 0.1% (53) experienced high social stress, and 1.1% (660) reported high financial stress, while 7.1% (4374) recorded experiencing more than one form of stress (high or low) at the time of data collection. There was a first-degree family history of BBD or breast cancer among 3.5% (2,139), and 1.2% (733) reported second-degree family history. A total 7.9% (4,914) of the participants were diagnosed with BBD (Table 1).

Participants who have ever experienced work-related stress had a significantly increased odds of diagnosis with BBD (OR 1.57, 95% CI 1.46–1.69, $p < 0.0001$). Financial stress and social stress were also significantly associated with increased risk of BBD (OR 1.34, 95% CI 1.24–1.44, $p < 0.0001$; OR 1.11, 95% CI 1.01–1.21, $p = 0.04$, respectively) (Table 2). Odds ratios estimated from the crude model were larger and are shown in Supplementary Table 1.

The self-reporting of multiple forms of stress did not synergistically affect the risk of BBD. Young women with financial stress but without social and work-related stress showed the highest BBD risk (OR 2.33, 95% CI 1.90–2.87, $p < 0.0001$). This was higher than observed among those

Table 3 The effect of multiple forms of stress upon risk of benign breast disease

Work-related stress	Social stress	Financial stress	Forms of stress	OR (95% CI)	*p*
−	−	−	0	1 (Ref)	Ref
+	−	−	1	2.11 (1.92–2.32)	< 0.0001
−	+	−	1	1.60 (0.84–3.04)	0.1503
−	−	+	1	2.33 (1.90–2.87)	< 0.0001
+	+	−	2	1.85 (1.44–2.38)	< 0.0001
+	−	+	2	1.93 (1.75–2.12)	< 0.0001
−	+	+	2	1.35 (0.74–2.46)	0.3238
+	+	+	3	1.70 (1.54–1.89)	< 0.0001

The effect of form(s) of stress in isolation or in combination upon the risk of benign breast disease. The model was adjusted for age, BMI, thyroid-stimulating hormone level in blood, age of menarche, first-degree relative breast disease diagnosis, second-degree relative breast disease diagnosis, smoking status, second-hand smoking status, drinking status, oral contraceptive usage, education and occupation

who had both work-related and financial stress (OR 1.93, 95% CI 1.75–2.12, $p < 0.0001$), and those who reported all three forms of stress together (OR 1.70, 95% CI 1.54–1.89, $p < 0.0001$) (Table 3).

The association between experience of psychosocial stress and increased BBD remained after removing women with family history of BBD and breast cancer from the analysis. Young women without first-degree family history of breast disease ($n = 59{,}768$) displayed increased risk of BBD with work-related stress (OR 1.63, 95% CI 1.51–1.76, $p < 0.0001$), social stress (OR 1.14, 95% CI 1.03–1.25, $p < 0.01$) and financial stress (OR 1.37, 95% CI 1.27–1.48, $p < 0.0001$) (Table 2). These associations remained after the further exclusion of young women with second degree of family history of breast disease ($n = 59{,}035$) (Table 2).

To evaluate whether the association between stress and BBD is through increased inflammation, we utilised data on neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation. There was no significant association between BBD and NLR (OR 1.01, 95% CI 0.99–1.02, $p = 0.17$) after adjusting the model for age, BMI, thyroid-stimulating hormone level in blood, age at menarche, first- and second-degree family history, smoking status, second-hand smoking exposure, alcohol consumption, oral contraceptive use, education and occupation (Table 4).

Discussion

In this study, we analysed self-reported psychosocial stress data to evaluate its association with BBD in 61,907 young adult women in China. We report that work-related stress is strongly associated with BBD in any combination with other forms of stress, while financial stress is the strongest risk factor when only one form of stress was self-reported. Interestingly, there was no synergistic effect of having multiple forms of stress. Furthermore, the association between psychosocial stress and BBD is independent of family history of breast cancer or BBD. Our study suggests that reduction of stress in young adult women may be beneficial in reducing the prevalence of BBD.

Table 4 Association between neutrophil-to-lymphocyte ratio and benign breast disease

	OR (95% CI)	*p*
Crude model	0.98 (0.94–1.02)	0.2887
Adjusted model	1.01 (0.99–1.02)	0.1739

Model adjusted for age, BMI, thyroid-stimulating hormone level in blood, age of menarche, first-degree relative breast disease diagnosis, second-degree relative breast disease diagnosis, smoking status, second-hand smoking status, drinking status, oral contraceptive usage, education and occupation. ORs are presented for an increase of 1.0 in the NLR

There is a substantial body of evidence to suggest that psychosocial stress is associated with an increased risk of breast cancer [24–27, 30, 39–41]. In particular, bereavement has been frequently been reported to be associated with breast cancer risk [24–27], although no association was reported for bereavement in early life with cancer risk in a prospective study of more than 100,000 women [42]. Most large cohort studies have reported moderate effects (OR < 2.00) for the death of a family member or spouse [25, 27] and for job strain [30], although contrasting findings have been reported by two highly powered studies, a meta-analysis and a publication from the Nurses' Health Study, which identified no association between work stress and breast cancer risk [43, 44]. These contradictory findings may in part be due to critical differences in study design and the inherent difficulty in studying the effects of stress due to the heterogeneity of its type, severity and duration. However, to date there have been far fewer studies of psychosocial stress in relation to the development of BBD, a known risk factor for breast cancer. A small prospective case–control study of 115 women related to the Kuopio Breast Cancer Study has reported that losses, deficit and loss of health in childhood were more common among women diagnosed with BBD than in those without [29], and that the illness of a close relative in adulthood was also more commonly present [31]. Interestingly, however, associations between stressful life events and risk were near universally stronger (or only observed) for cancer in comparison to BBD. This is supported by the findings of Chen et al. [32] that recent and stressful life events in the preceding five years were more common among 41 women recently diagnosed with breast cancer than 78 diagnosed with BBD. To the best of our knowledge, our study is by far the largest and most powerful to examine the association between psychosocial stress and BBD risk. While the Kuopio Breast Cancer Study did not identify an association between stress in adulthood and the risk of BBD [31], our study has revealed strong associations between work-related and financial stress and the development of BBD. These novel observations support findings elsewhere of increased risk of breast cancer among individuals with high work stress [30] and may help to bring insight into the mechanisms underlying this association. However, while BBD is known to be a risk factor for the development of breast cancer, most studies examining the effect of stress upon cancer risk have not specifically evaluated the development of breast cancer among individuals previously diagnosed with BBD [45], and therefore further work is required to establish how stress-associated BBD may be implicated in the development of malignancies.

Our findings may suggest that the association between stress and BBD may not be through systemic inflammation,

as no association was observed between NLR and BBD incidence. An alternative mechanism may be through the action of cortisol. Stress induces activation of the hypothalamic-pituitary-adrenocortical (HPA) axis via increased production of glucocorticoids, which in turn leads to increased production of cortisol. Indeed, the most reliable laboratory-based evaluation of stress is the measurement of cortisol levels in blood or saliva [46]. Cortisol is required for normal mammary gland development during puberty and lobuloalveolar development during pregnancy [47], but it is also known to downregulate expression of the *BRCA1* gene [48] and to induce the activity of aromatase [49]. Psychosocial stress may therefore serve to promote breast carcinogenesis by promoting the production of estrogen that stimulates the growth of many breast tumours and by inhibiting the repair of DNA damage.

The histological classification of the lesion is known to be associated with variance in cancer risk, with atypical hyperplasia associated with a near fourfold increase in risk, while for proliferative lesions without atypia the increase is under twofold [18]. Prevention of BBD and management of patients following its diagnosis thereby potentially offers an effective strategy to reduce the incidence of breast cancer. However, it should be noted that the presence of BBD impacts upon the patient's quality of life in itself, such as mastalgia. Furthermore, diagnosis of BBD is associated with increased prevalence of anxiety and depression [50]. Therefore, prevention of BBD would bring significant patient benefit both related to and irrespective of reducing future cancer incidence. Our findings suggest that reduction of stress could be an effective means to do this.

Our study has a number of strengths. To our knowledge, ours is the first to examine psychosocial stress with benign breast disease among young Chinese women. The importance of work-related, social and financial stress is often under-estimated in Chinese communities for cultural reasons, and our findings help to highlight the importance of stress as a contributing factor to female health problems. A notable strength of our study is that we have utilised a new, large-scale cohort of 61,907 young female participants that significantly exceeds the size of many cohorts previously used to investigate stress and breast cancer risk [47]. The study was also focussed upon a key time window in the development of BBD when stress levels are likely to be most relevant, as it has previously been demonstrated that the associations of bereavement [42] and alcohol consumption [51] with breast cancer and BBD risk, respectively, are stronger in young adult women. Furthermore, in our analyses we have been able to account for a large number of factors known to be independently associated with the risk of developing BBD, including BMI, age, smoking status, alcohol consumption and family history. We were also able to account for alterations in hormone levels by adjusting the analyses by menarche age and use of the oral contraceptive, the need for which is demonstrated by the reported increased risk of BBD in postmenopausal women receiving hormone replacement therapy [52]. Together, this has enabled a more robust assessment of the influence of stress on BBD risk. As BBD is an important predictor for breast cancer, our study may help to identify key risk factors and plausible biological pathways useful for primary breast cancer prevention. However, our study does also contain several limitations. An inherent problem in the investigation of the effects of stress is the heterogeneity in its forms, duration and severity. Our study has therefore utilised data on self-reported stress levels from questionnaires that enabled participants to delineate between financial, work and social stress, and to categorise these as none, low or high. A small proportion of participants (< 2%) self-reported having high levels of any form of psychosocial stress, which may underestimate its true prevalence in the cohort. While the use of molecular markers, such as cortisol levels, could have provided a more accurate estimate of stress levels at the point of examination, our approach has enabled us to capture stress over a 10-year period. However, the questionnaire data used in this study did not facilitate the evaluation of the effects of the timing and duration of stress. Furthermore, as data on psychosocial stress and history of BBD were collected during a single clinical visit, we cannot fully disentangle the temporal relationship between the two, although we expect our measurements to capture individuals with long-term/chronic stress. Future prospective studies with long-term follow-up are required to elucidate this temporal relationship. We were also unable to examine the association of psychosocial stress with specific forms of BBD due to insufficient numbers of cases of each. Finally, our study did not have data on the income of the individuals. As low socio-economic status may be independently associated with risk of BBD, and as financial stress may be suffered by those across the socio-economic spectrum but more prevalent among those of lower status, we cannot exclude the possibility that our analysis of financial stress was confounded by the effects of poverty.

In conclusion, we report that stress is associated with the risk of benign breast disease in young adults. The form and combination of stresses displayed differential effects on BBD risk, but did not display a synergistic effect. Our findings suggest that stress management may offer an effective means to reduce BBD incidence and, thereby, potentially breast cancer incidence. Further work is required to elucidate how the duration, intensity and timing of stress may be influential, and to investigate the mechanisms by which psychosocial stress promotes the development of breast disease.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflicts of interest.

Ethical approval All procedures and study protocols were approved by the ethical committee of Tianjin Medical University and were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent All the participants within the study provided written informed consent.

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