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## Self reported stress and risk of breast cancer: prospective cohort study

Naja Rod Nielsen, Zuo-Feng Zhang, Tage S Kristensen, Bo Netterstrøm, Peter Schnohr, Morten Grønbæk

### Abstract

**Objective** To assess the relation between self reported intensity and frequency of stress and first time incidence of primary breast cancer.

**Design** Prospective cohort study with 18 years of follow-up.

**Setting** Copenhagen City heart study, Denmark.

**Participants** The 6689 women participating in the Copenhagen City heart study were asked about their perceived level of stress at baseline in 1981-3. These women were followed until 1999 in the Danish nationwide cancer registry, with <0.1% loss to follow-up.

**Main outcome measure** First time incidence of primary breast cancer.

**Results** During follow-up 251 women were diagnosed with breast cancer. After adjustment for confounders, women with high levels of stress had a hazard ratio of 0.60 (95% confidence interval 0.37 to 0.97) for breast cancer compared with women with low levels of stress. Furthermore, for each increase in stress level on a six point stress scale an 8% lower risk of primary breast cancer was found (hazard ratio 0.92, 0.85 to 0.99). This association seemed to be stable over time and was particularly pronounced in women receiving hormone therapy.

**Conclusion** High endogenous concentrations of oestrogen are a known risk factor for breast cancer, and impairment of oestrogen synthesis induced by chronic stress may explain a lower incidence of breast cancer in women with high stress. Impairment of normal body function should not, however, be considered a healthy response, and the cumulative health consequences of stress may be disadvantageous.

### Introduction

Breast cancer is a hormone dependent disease with a clear positive relation to high endogenous concentra-

tions of oestrogen.<sup>1</sup> The risk of breast cancer associated with the acute stress of major life events has been assessed in several studies,<sup>2-5</sup> but less attention has been given to the effect of perceived daily stress.<sup>6-8</sup> Prolonged low key stress of everyday life results in a persistent activation of stress hormones, which may impair oestrogen synthesis,<sup>9</sup> and may thereby be related to a lower risk of breast cancer. Everyday stress may also indirectly affect the risk of breast cancer through changes in health related behaviour. This study explores the impact of everyday stress on the long term risk of first time incidence of primary breast cancer among 6689 women prospectively followed up for 18 years.

### Methods

**Study population**—The Copenhagen City heart study is a longitudinal study initiated in 1976. An age stratified random sample of 19 698 Danish men and women were invited to participate. In 1981-3, 7018 women from the study were examined, and baseline measures of stress were taken. We excluded women with breast cancer before baseline or lacking information on stress or other covariates, leaving 6689 women. Twenty six women were lost to follow-up. A detailed description of the Copenhagen City heart study has previously been published.<sup>10</sup>

**Everyday stress**—The study participants were asked about their level of stress in terms of intensity and frequency. The measure was questionnaire based, and stress was exemplified as the sensation of tension, nervousness, impatience, anxiety, or sleeplessness. We categorised stress scores into low, medium, and high.

**Covariates**—We controlled for the following potential confounders: current oral contraceptive use, hormone therapy, menopause at baseline, body mass

National Institute of Public Health, Øster Farimagsgade 5A, DK-1399 Copenhagen K, Denmark

Naja Rod Nielsen  
student and research assistant

Morten Grønbæk  
professor

Department of Epidemiology, UCLA School of Public Health, Los Angeles, CA, USA  
Zuo-Feng Zhang  
professor

National Institute of Occupational Health, Copenhagen  
Tage S Kristensen  
professor

Clinic of Occupational Medicine, Hillerød Hospital, Hillerød, Denmark

Bo Netterstrøm  
research director

Copenhagen City Heart Study, Epidemiological Research Unit, Bispebjerg University Hospital, Copenhagen  
Peter Schnohr  
consultant

Correspondence to: N R Nielsen  
nrn@niph.dk

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index, number of children, physical activity, alcohol consumption, and education.

**Follow-up**—We followed participants from the date of examination until the first diagnosis of primary breast cancer, death, emigration, or the end of follow-up in 1999. The maximum follow-up time was 16–18 years. We identified primary breast cancer events through the Danish national cancer registry, which contains data on all cancer diagnoses in Denmark, using each participant's unique civil registry number. We followed vital status in the central death registry.

**Statistical methods**—We used regression models to analyse data with age as the time scale. We used trend analyses to assess dose-response relations between stress and breast cancer. To estimate the effect of prolonged follow-up, we assessed the association in the first and last nine years of follow-up. We ran subgroup analyses to assess potential effect modification.

## Results

**Baseline characteristics**—At baseline mean age was 57 years and 10% of women reported high levels of stress. Some baseline factors varied across women with different baseline stress levels (see [bmj.com](http://bmj.com)). During follow-up, 251 cases of primary breast cancer occurred. A higher percentage of women in the high stress ( $n=261$ , 39.3%) than in the medium stress ( $n=972$ , 30.4%) or low stress group ( $n=991$ , 35.1%) died during follow-up.

**Stress intensity, stress frequency, and risk of breast cancer**—Seven per cent of women reported high stress intensity, and 10% reported high stress frequency. The adjusted hazard ratio of primary breast cancer seemed to be inversely associated with both stress intensity (test for trend,  $P=0.02$ ) and stress frequency (test for trend,  $P=0.06$ ) (table 1).

**Stress score and risk of breast cancer**—After adjustment for potential confounders, an 8% reduction (hazard ratio 0.92, 95% confidence interval 0.85 to 0.99) in risk of primary breast cancer occurred for each increase in stress level on a six point stress scale (table 2). Higher stress was inversely associated with incidence of primary breast cancer (test for trend,  $P=0.02$ ), and high stress was associated with a hazard ratio of 0.60 (0.37 to 0.97) for breast cancer compared with low stress.

**Subgroup analyses**—One hundred and fourteen first time primary breast cancers occurred in the first nine years of follow-up, and 137 in the last nine years. The relative effects of stress on incidence of breast cancer were similar in the two periods of follow-up. Sixteen per cent ( $n=1045$ ) of the women were receiving hormone therapy at baseline, and the effect of stress on risk of breast cancer seemed to be mainly confined to these women. Among women receiving hormone therapy, the hazard ratio for primary breast cancer was 0.83 (0.72 to 0.97) for each increase in stress level on the six point stress scale. No effect modification occurred in subgroups of menopausal status, physical activity, alcohol consumption, oral contraceptive use, education, and number of children.

**Table 1** Incidence and hazard ratio of primary breast cancer associated with intensity and frequency of stress among 6689 Danish women participating in the second examination of the Copenhagen City heart study in 1981–3

	No of breast cancers	Incidence per 100 000 person years	Age adjusted hazard ratio (95% CI)	Multi-adjusted* hazard ratio (95% CI)
<b>Stress intensity</b>				
None ( $n=2214$ )	96	292	1 (reference)	1 (reference)
Light ( $n=2608$ )	97	243	0.89 (0.67 to 1.18)	0.85 (0.64 to 1.13)
Moderate ( $n=1384$ )	44	210	0.74 (0.52 to 1.05)	0.68 (0.47 to 0.98)
High ( $n=483$ )	14	203	0.65 (0.37 to 1.13)	0.61 (0.35 to 1.07)
P value for trend			0.04	0.02
<b>Stress frequency</b>				
Never ( $n=2854$ )	119	282	1 (reference)	1 (reference)
Monthly ( $n=1994$ )	71	228	0.90 (0.67 to 1.20)	0.85 (0.64 to 1.15)
Weekly ( $n=1168$ )	40	227	0.83 (0.58 to 1.19)	0.78 (0.55 to 1.13)
Daily ( $n=673$ )	21	213	0.70 (0.44 to 1.11)	0.67 (0.42 to 1.07)
P value for trend			0.09	0.06

\*Adjusted for age, current oral contraceptive use, other hormone therapy, menopausal status, number of children, body mass index, alcohol consumption, physical activity in leisure time, and education.

## Discussion

Among 6689 women followed up for an average of 18 years, higher self reported everyday stress was associated with lower risk of breast cancer. Our results contrast with those of a Finnish cohort study, which found no association between stress of daily activities and breast cancer, and a Swedish study in which severe mental stress was associated with a higher incidence of breast cancer.<sup>6,8</sup> Some of the discrepancy may be explained by the different measures of stress applied and the fact that the Finnish and Swedish studies included all incident cases of breast cancer, whereas we confined our analyses to first time incidence of primary breast cancer. A greater risk of breast cancer associated with stressful life events is not necessarily in contrast with a lower risk of breast cancer associated with daily stress.

### Strengths and weaknesses

The prospective design of the Copenhagen City heart study ensured temporality between stress and incidence of breast cancer. The cohort is a large random sample of the general population of Copenhagen. Linkage of civil registry numbers to nationwide population based registers enabled identification of virtually all cases of breast cancer and nearly complete long term follow-up. However, information on several important risk factors for breast cancer, such as family history of breast cancer, age at menarche, and age at first full time pregnancy, was not obtained (see [bmj.com](http://bmj.com)).

**Table 2** Incidence and hazard ratio of primary breast cancer associated with stress score among 6689 Danish women participating in the Copenhagen City heart study in 1981–3

	No of breast cancers	Incidence per 100 000 person years	Age adjusted hazard ratio (95% CI)	Multi-adjusted* hazard ratio (95% CI)
Continuous			0.93 (0.87 to 1.00)	0.92 (0.85 to 0.99)
Categorised:				
Low stress ( $n=2823$ )	120	285	1 (reference)	1 (reference)
Medium stress ( $n=3201$ )	112	229	0.84 (0.65 to 1.09)	0.80 (0.62 to 1.04)
High stress ( $n=665$ )	19	194	0.63 (0.39 to 1.02)	0.60 (0.37 to 0.97)
P value for trend			0.04	0.02

\*Adjusted for age, current oral contraceptive use, other hormone therapy, menopausal status, number of children, body mass index, alcohol consumption, physical activity in leisure time, and education.

Mammographic screening for women aged 50-69 years was introduced in Copenhagen in 1991.<sup>11 12</sup> Screening took place only in women aged 50-69 years and in the last nine years of our study. The effect estimates were similar in the first and last nine years of follow-up, suggesting that screening is unlikely to have influenced our data.

How stress is defined and measured remains a point of debate. So far the literature has focused on verifiable external stressors with less emphasis on how they are experienced by the individual. The same external stressor may result in different levels of stress in different people. A measure of self-reported stress therefore provides a better measure of the actual level of stress experienced by the individual.

More women in the high stress group (39.3%) than in the medium stress (30.4%) and low stress (35.1%) groups died during follow-up. Although this indicates no systematic difference, it may raise concern about how censoring has influenced the results. Competing causes of death, such as cardiovascular disease, could be associated with risk of breast cancer within strata owing to common risk factors. However, some common risk factors, such as socioeconomic status, have opposing effects on the two diseases, so on average we would expect the bias to level out. Thus, although our results may have been influenced by bias from non-independent censoring, we find it unlikely that this could fully explain them.

#### Possible causal pathways between perceived stress and breast cancer

The physiological effects of acute stressors are in most cases reversible. Problems arise when the stress response becomes chronic and results in permanent disturbances in allostasis. The hypothalamic-pituitary-gonadal axis regulates synthesis and release of oestrogens in a normally functioning female reproductive system. Stress can affect the signals of this axis by activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Studies in mammals have found that activation of the hypothalamic-pituitary-adrenal axis decreases oestrogen synthesis, but data in humans are sparse.<sup>9 13-16</sup> However, in a recent study that used care giving as an indicator of chronic stress, lower concentrations of bioavailable oestradiol were found among female care givers than among non-care givers.<sup>7</sup> Stress induced suppression of oestrogen secretion could therefore explain a reduced risk of breast cancer.

Some women may be more sensitive to hormonal disturbances and more likely to receive hormone therapy to lessen their symptoms. Hormone sensitive women are more likely to be susceptible to stress induced changes in oestrogen synthesis, which could explain why stress mainly seems to be associated with lower risk of breast cancer among women receiving hormone therapy.

#### Conclusions

It is biologically plausible that the lower risk of breast cancer associated with stress observed in this long term prospective cohort study could be due to stress induced imbalances in normal concentrations of oestrogens. However, stress induced disturbances in allostasis cannot be considered a healthy response, and

#### What is already known on this topic

A potential relation between stress and risk of breast cancer has been examined in studies with different designs and conflicting results

The risk of breast cancer associated with the acute stress of major life events has been assessed in several studies, but less attention has been given to the effect of perceived daily stress

#### What this study adds

Higher levels of everyday stress are associated with lower incidence of primary breast cancer in a dose-response manner among middle aged women

Women who receive hormone replacement therapy seem to be most susceptible to this effect

Stress induced disturbances cannot be considered a healthy response, and the cumulative health consequences of stress may be disadvantageous

prolonged stress may have harmful effects on a range of other diseases, especially cardiovascular diseases.

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