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# Are work-related stressors associated with diagnosis of more advanced stages of incident breast cancers?

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**Abstract**
*Objective* To assess the relation between work-related stressors and breast cancer incidence and prognostic characteristics (estrogen receptor status, grade, lymph node status, size, stage) at the time of diagnosis.
*Methods* The 18,932 women included in the Danish Nurse Cohort reported work-related stressors in 1993 and again in 1999 and were followed until the end of 2003 in national registries. Prognostic characteristics were obtained from a clinical database and fewer than 0.1% were lost to follow up.
*Results* During follow-up, 455 women were diagnosed with breast cancer. Neither women with high work pressure (HR = 1.17; 95% CI: 0.79, 1.73) nor women with self-reported low influence on work organization (0.98; 0.69, 1.39) or long working hours (0.93; 0.54, 1.58) were at higher risk of breast cancer than women with no such stressors. Women with high work tempo had a slightly higher risk of breast cancer (1.25; 1.02, 1.54) than women with a suitable work tempo, but there was no dose-response effect. There were no clear differences in the prognostic characteristics of breast tumors diagnosed in women with and without work-related stressors.
*Conclusions* Work-related stressors do not affect breast cancer risk or the prognostic characteristics of incident breast cancers at the time of diagnosis. These results may be a comfort to working women and can hopefully prevent self-blaming among women who develop breast cancer.

**Keywords** Breast neoplasms · Prognosis · Prospective studies · Psychological stress · Workplace

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## Introduction

Breast cancer is a major public health problem [1], and there is a growing interest in how psychological stress may affect the risk of breast cancer [2–6]. A rise in breast cancer incidence in North America and Europe has occurred parallel to the major changes in the labor market, which took place in the aftermath of World War II. More women have been included into the labor force and the pace of work seems to be continuously increasing. Thus, work conditions such as long work hours, concerns about not being able to manage work on time, and low influence on one's job tasks may be major sources of stress in modern women's lives.

Contrary to common beliefs, stress does not seem to increase the risk of breast cancer [2], and some studies have even suggested that it may lower the risk [7, 8]. However, most studies in this area have thus far focused on the potential relation between major life events and risk of breast cancer [2, 9–15], while fewer studies have addressed

the more chronic exposures to stressors at work or in everyday life [8, 16–18]. Only two prospective studies have previously assessed the association between work-related stressors and risk of breast cancer, both of which used data from the Nurses' Health Study with 2 and 8 years of follow-up, respectively [16, 19]. They defined work-related stress (job strain) as the combination of high demands and low control at work and found women with high strain jobs to be at slightly lower risk of breast cancer compared to women with low strain jobs [16].

One may also be concerned that stress could lead to the diagnosis of more advanced stages of breast cancers with poorer prognoses; either because women exposed to stressors discover their breast cancer at a later stage or because they have a more malignant tumor. Further, chronic exposure to stress may also affect synthesis and metabolism of sex steroid hormones, especially estrogens [20]. As estrogen-related factors are known risk factors for breast cancer, stress may affect estrogen receptor (ER) positive and ER negative tumors differently. The present study will include information on estrogen receptor status as well as information on other prognostic factors such as histological grade, axillary lymph node status, and stage of the disease at the time of diagnosis.

We aim to prospectively assess a potential relation between work-related stressors and first-primary breast cancer incidence and prognostic characteristics in a large cohort of Danish nurses followed for 10 years.

## Materials and methods

### Study population

The Danish Nurse Cohort is a longitudinal study initiated in 1993. All 23,170 registered Danish nurses above the age of 44 were invited to participate in the cohort. The nurses received a mailed questionnaire followed by up to two reminders. The 19,898 women who returned the questionnaire constituted a response proportion of 86%. In 1999, a new round of questionnaires was sent out and the cohort was supplemented with all nurses who had turned 45 in the intervening period. The 24,155 women who participated in the second examination represent a response proportion of 76%. The 15,322 women who participated in both examinations as well as the 4,576 women who participated only in the 1993 round and the 8,833 women who participated only in the 1999 round were included into the study, for a total of 28,731 women. The vast majority of participants were Caucasians and all participants gave informed consent. In the analyses, the baseline was postponed 1 year in order to account for some latency time between cause and effect. Women with breast cancer before baseline ($n$ = 761), who were censored before baseline ($n$ = 120), who were not working at baseline ($n$ = 6,514), who lacked information on work-related stressors ($n$ = 783) or other covariates ($n$ = 1,621) were excluded; leaving 18,932 women for the analyses.

### Work-related stressors

The study participants were asked about *pressure of work* using the question "How often are you so busy, that you find it hard to finish all your work tasks?" and the response categories were: never/almost never, occasionally, often, and almost always. *Tempo of work* was based on the question "How is the work pace at your work?" and the response categories were: too low, suitable, too high, and much too high. *Influence* was based on the question "To what degree are you able to influence the organization of your daily work?" with the following response categories: high, medium, low, and none. The participants were also asked about *work hours* and these were categorized into: less than 30 h/week, 31–37 h/week, 38–44 h/week, 45 or more h/week. A standard working week in Denmark is 37 h. All measures were self-reported.

### Covariates

The following minimum sufficient set of potential confounders was identified according to the methods of causal diagrams developed by Greenland, Pearl, and Robins [21]: Age (continuous), age at menarche (≤12, 13, 14, ≥15), parity (nulliparous, 1, 2, ≥3 or more), age at first birth (<25, 25–29, ≥30 years), family history of breast cancer (yes/no), oral contraceptive use (current, former, never user), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m$^2$), physical activity in leisure time (none or very little activity, ≥4 h/week of light activity, ≥4 h/week of high level activity, competition level activity several times per week), physical activity at work (sedentary, mostly standing and walking, standing and walking with some heavy lifting, strenuous work), work shifts (mostly day, day and night, mostly night), alcohol consumption (0, 1–7, 8–14, >14 drinks/week), postmenopausal hormone use (never, past user for <5 years, past user for ≥5 years, current user for <5 years, current user for ≥5 years), age at menopause (pre-menopausal, <44, 44–46, 47–49, 50–52, 53–55, ≥56 years), and height (continuous). All variables were measured at baseline and were updated during follow-up for women who participated in both examinations.

### Follow-up

Participants were followed from the date of inclusion into the study until the date of first diagnosis of breast cancer ($n$ = 455), death ($n$ = 558), emigration ($n$ = 123), or end of follow-up on 31 December, 2003 ($n$ = 17,796). Thus, less than 0.1% was lost to follow-up due to emigration out of Denmark. The follow-up time was taken as time from date of the first examination for women who participated in both waves of the study and from date of participation in the second wave of the study for women who only participated in the 1999-wave of the study. Using the civil registry number, which is unique to every Danish citizen, breast cancer events were identified through linkage to the Danish National Cancer Registry, which contains data on all cancer diagnoses in Denmark since 1942. The cancer diagnoses in the registry are classified according to the International Classification of Disease, 7th revision. The following ICD7-codes were used to identify primary invasive breast cancer cases: 170.0–170.5, 470.0–470.5, and 870.0–870.2. Information on prognostic factors and histopathological details at the time of diagnosis was obtained from linkage to the Danish Breast Cancer Group Corporation register (DBCG), which is a clinical database on all breast cancer operations in Denmark since 1977. The vital status of the study population was followed in the Central Death Registry.

### Statistical methods

Data was analyzed by means of Cox regression models with age as the time variable using SAS/STAT software version 8.2 (SAS Institute, Cary, NC). All work-related stressors met the assumption of proportional hazards. Initially, we estimated the age-adjusted hazard ratio of primary breast cancer associated with each of the four work-related stressors (high pressure of work, tempo of work, influence, and hours of work) separately. Subsequently, multivariate Cox regression models were fitted to adjust for potential confounding from other covariates. We stratified the analyses on menopausal status because some risk factors for breast cancer have different effects in pre- and postmenopausal women. We also stratified the analyses on current hormone use as well as assessed if the combination of having night shifts with either high pressure of work, high tempo of work, or low influence were associated with risk of breast cancer.

Data on prognostic characteristics were available from the DBCG. During the study period, histological grade was performed only on invasive ductal carcinomas, thus the analyses on prognostic characteristics were restricted to these carcinomas. The following prognostic characteristics were addressed in the analyses: estrogen receptor (ER) (positive, negative); histological grade (grade 1, grade 2–3) depending on tubulus formation, number of mitosis and degree of nuclear pleomorphism; axillary lymph node status (positive, negative); tumor size (diagonal of tumor $\leq$2 cm or >2 cm); and stage according to TNM (stage 1, stage 2–4), where T describes the size of the tumor and whether it has invaded nearby tissue, N describes any lymph node that is involved, and M describes metastasis. The Nottingham Prognostic Index (NPI) was calculated as (tumor size (cm) $\times$ 0.2) + histological grade 1–3 + lymph nodes 1–3 (1 = negative, 2 = 1–3 positive lymph nodes, 3 = more than 3 positive lymph nodes) [22]. The index was categorized into good prognosis (score <3.4), moderate prognosis (score 3.4–5.4), and poor prognosis (score >5.4). The prognostic characteristics of breast cancer at the time of diagnosis were dichotomized and treated as single end-points in the analyses. Women with histologies other than invasive ductal carcinoma and women with missing information on the prognostic factor in question were censored at the time of breast cancer diagnosis. A competing risk framework using the Wald test was applied to test if the failure rates of favorable and nonfavorable breast cancers differed statistically among women exposed to the same work-related stressor. For example, we tested if the association between high pressure at work and ER positive tumors was statistically different from the association between high pressure at work and ER negative tumors.

## Results

A total of 455 women developed breast cancer during 136,758 person-years of follow-up. The mean length of follow-up was 7.2 years. Histological information was complete for 427 cancers of which 344 (81%) were invasive ductal carcinomas, 51 (12%) were invasive lobular carcinomas, and the remaining 32 (7%) were a combination of other histologies, such as mucinous, medullary, papillary, and tubular carcinomas. The prognostic characteristics of the invasive ductal carcinomas are shown in Table 1. Associations between known risk factors for breast cancer, such as parity, hormone use, age at menopause and others were established in an expected manner (data not shown).

### Work-related stressors and incidence of breast cancer

Women who experienced high pressure of work did not have higher risk of breast cancer compared to women with low work pressure (Table 2). Women who reported either too low (HR = 1.46, 95% CI: 0.68, 3.12) or too high (HR = 1.25, 95% CI: 1.02, 1.54) tempo of work seemed to

**Table 1** Prognostic characteristics of invasive breast ductal carcinomas ($n$ = 344)

| Prognostic factor | Categories | *N* (%) |
|---|---|---|
| Estrogen receptor status | Estrogen receptor positive | 256 (77) |
| | Estrogen receptor negative | 77 (23) |
| | Missing | 11 |
| Histological grade | Grade 1 | 122 (36) |
| | Grade 2–3 | 214 (64) |
| | Missing | 8 |
| Lymph node status | Node negative | 193 (56) |
| | Node positive | 151 (44) |
| | Missing | 0 |
| Tumor size | ≤2 cm | 230 (68) |
| | >2 cm | 110 (32) |
| | Missing | 4 |
| Stage (TNM) | Stage 1 | 152 (45) |
| | Stage 2–4 | 188 (55) |
| | Missing | 4 |
| Nottingham Prognostic Index (NPI)[a] | Good prognosis | 153 (46) |
| | Moderate prognosis | 133 (40) |
| | Poor prognosis | 46 (14) |
| | Missing | 12 |

[a] The Nottingham Prognostic Index (NPI) was calculated as (tumor size (cm) × 0.2) + histological grade 1–3 + lymph nodes 1–3 (1 = negative, 2 = 1–3 positive lymph nodes, 3 = more than 3 positive lymph nodes)

have a slightly higher risk of breast cancer than women who felt that the tempo of their work was suitable. Neither women with low influence on their job nor women who worked more than 30 h a week seemed to be at a higher or lower risk of breast cancer compared to women with high influence on their work or women who worked less than 30 h a week. The associations were similar in pre- and postmenopausal women as well as in hormone and non-hormone users. Also, the combination of work-related stressors with working night shifts did not increase the risk of breast cancer (data not shown).

### Work-related stressors and prognostic characteristics of breast cancers

Women who experienced high pressure of work appeared to be more likely to be diagnosed with a tumor with good expected prognosis based on the Nottingham Prognostic Index (1.73; 0.91, 3.29) than women not exposed to such stress (Table 3). At the same time, these women seemed to be slightly less likely to be diagnosed with a tumor of moderate to poor prognosis (0.81; 0.41, 1.58). Women who experienced too low or much too high tempo of work seemed to be more likely to be diagnosed with a tumor with an expected good prognosis based on the NPI compared to women with suitable work tempo. There were no clear associations between influence and any of the prognostic characteristics. Women who worked more than 45 h a week appeared to be a little less likely to develop a tumor with expected good prognosis based on the NPI (0.53; 0.16, 1.75). None of these differences or any of the analyses with each of the individual prognostic factors (data not shown) was statistically significant in competing risk analyses. The analyses may have been limited due to the low number of breast cancers in each prognostic category.

## Discussion

In this prospective cohort study, which includes all Danish nurses above the age of 44 years, we found no clear associations between work-related stressors and incidence of breast cancer. This is in agreement with the results from the Nurses' Health Study where there was no evidence of an increased risk of breast cancer among women exposed to work-related stressors [16]. As previously mentioned, they even reported a slightly lower risk of breast cancer among women with high job strain. This lower risk of breast cancer was not retrieved in the present study.

There has been concerns that stress may affect the prognosis of breast cancer [23, 24], though the evidence is inconsistent [25–27]. This study found no clear differences in the prognostic characteristics of incident breast cancers among women exposed to high and low levels of work-related stressors. Further, in the present study we did not find any clear differences in the associations between work-related stressors and ER positive or ER negative breast cancers, which may indicate that plasma-levels of estrogens are not highly affected by work-related stress. This is also in accordance to the results from Nurses' Health Study in which they reported no association between job strain and levels of endogenous sex steroid hormones.

### Strengths and weaknesses

The Danish Nurse Cohort is a large prospective cohort study with updated information on work-related stressors and other covariates. Linkage to nationwide registries ensured nearly complete follow-up and linkage to the DBCG clinical database made it possible to characterize incident breast cancers according to a range of prognostic factors. Detailed information on important risk factors for breast cancer allowed for sound adjustment for confounding.

**Table 2** Incidence, hazard ratio (HR), and 95% confidence interval (CI) for first primary breast cancer associated with work-related stressors among 18,932 women who participated in the Danish Nurse Cohort

| | No. | No. of cases | Incidence per 100,000 years | Age-adjusted HR (95% CI) | Multi-adjusted[a] HR (95% CI) |
|---|---|---|---|---|---|
| High pressure of work | | | | | |
| Never or almost never | 3,294 | 86 | 354 | 1 (reference) | 1 (reference) |
| Occasionally | 8,218 | 196 | 330 | 0.95 (0.74–1.23) | 0.99 (0.76–1.28) |
| Often | 5,919 | 133 | 313 | 0.93 (0.71–1.22) | 0.97 (0.73–1.29) |
| Almost always | 1,501 | 40 | 373 | 1.11 (0.76–1.61) | 1.17 (0.79–1.73) |
| *P*-value | | | | 0.78 | 0.78 |
| Tempo of work | | | | | |
| Too low | 216 | 7 | 469 | 1.62 (0.76–3.45) | 1.46 (0.68–3.12) |
| Suitable | 7,633 | 167 | 304 | 1 (reference) | 1 (reference) |
| Too high | 8,580 | 222 | 357 | 1.20 (0.98–1.47) | 1.25 (1.02–1.54) |
| Much too high | 2,503 | 59 | 325 | 1.12 (0.83–1.51) | 1.21 (0.89–1.64) |
| *P*-value | | | | 0.24 | 0.17 |
| Influence on work | | | | | |
| High | 7,802 | 197 | 349 | 1 (reference) | 1 (reference) |
| Medium | 9,089 | 206 | 312 | 0.87 (0.71–1.05) | 0.87 (0.71–1.07) |
| Low | 1,746 | 43 | 348 | 0.98 (0.71–1.36) | 0.98 (0.69–1.39) |
| None | 295 | 9 | 424 | 1.17 (0.60–2.28) | 1.15 (0.58–2.27) |
| *P*-value | | | | 0.45 | 0.52 |
| Hours of work | | | | | |
| ≤30 h/week | 6,775 | 167 | 336 | 1 (reference) | 1 (reference) |
| 31–37 h/week | 10,269 | 250 | 339 | 1.05 (0.86–1.28) | 1.07 (0.85–1.34) |
| 38–44 h/week | 1,119 | 22 | 272 | 0.87 (0.56–1.35) | 0.83 (0.52–1.31) |
| ≥45 h/week | 769 | 16 | 296 | 0.96 (0.57–1.60) | 0.93 (0.54–1.58) |
| *P*-value | | | | 0.82 | 0.65 |

[a] Adjusted for age, age at menarche, parity, age at first birth, family history of breast cancer, oral contraceptive use, body mass index, physical activity in leisure time, physical activity at work, work shifts, alcohol consumption, postmenopausal hormone use, age at menopause, height

The Danish Nurse Cohort is a highly selected cohort in that it only includes nurses. Most of the nurses worked in very similar jobs, which reduced possible confounding from socio-economic factors. However, this may also have resulted in a lack of sufficient exposure heterogeneity. The nurses included in this study were actually relatively well distributed in all of the different exposure categories. The problem is that we cannot distinguish the objective job conditions from the person's perception of the work situation [28]. For example, say that all nurses had identical work conditions, then the results from this study would apply only to the risk of breast cancer associated with appraisal of the work situation. However, the nurses included in this study had different jobs with somewhat different exposures and we can therefore not distinguish the effect of the actual work situation and the perception of the work situation. Both dimensions may be equally important, but a distinction would have made it easier to target a possible preventive strategy. Thus, the results of this study cannot necessarily be generalized to work-related stressors experienced in other professions, and we cannot exclude that more extreme exposure to work-related stressors may be associated with breast cancer risk.

We used four questions regarding pressure, tempo, influence, and hours of work to measure work-related stressors. These exposure measures may not be as comprehensive as a measure of work-related stressors based on theoretical models like the control-demand model [29] or the effort-reward model [30]. Although our questions on work-related stressors were less inclusive than the ones included in more advanced models, they still covered the major dimensions of the control-demand model. Further, we found very similar results as the ones reported for breast cancer incidence in the Nurseś Health Study in which they used the demand-control model [16]. This provides some confidence that our results on prognostic characteristics of incident breast cancers are not seriously distorted by exposure misclassification. There are many more work stressors than the ones measured in the present study, and some of them, like role conflicts, role clarity, quality of leadership, emotional demands, may have been more relevant to nursing. These stressors were unfortunately not measured in the present study.

This study included information on work-related stressors, which only accounts for a fraction of the individual stress burden. In addition to work-related stressors,

**Table 3** Hazard ratio[a] (HR), and 95% confidence interval (CI) for first primary breast ductal carcinoma according to the Nottingham Prognostic Index associated with work-related stressors

| | Good prognosis | | Moderate/poor prognosis | |
|---|---|---|---|---|
| | *n* | HR | *n* | HR |
| High pressure of work | | | | |
| Never or almost never | 25 | 1 (reference) | 35 | 1 (reference) |
| Occasionally | 64 | 1.11 (0.69–1.78) | 80 | 0.94 (0.62–1.40) |
| Often | 47 | 1.18 (0.71–1.96) | 52 | 0.85 (0.55–1.34) |
| Almost always | 17 | 1.73 (0.91–3.29) | 12 | 0.81 (0.41–1.58) |
| *P*-value for differences | 0.41 | | | |
| Tempo of work | | | | |
| Too low | 4 | 2.56 (0.92–7.16) | 2 | 1.20 (0.29–4.95) |
| Suitable | 55 | 1 (reference) | 64 | 1 (reference) |
| Too high | 72 | 1.19 (0.83–1.71) | 93 | 1.31 (0.94–1.81) |
| Much too high | 22 | 1.33 (0.80–2.22) | 20 | 1.03 (0.61–1.72) |
| *P*-value for differences | 0.63 | | | |
| Influence on work | | | | |
| High | 62 | 1 (reference) | 79 | 1 (reference) |
| Medium | 74 | 1.07 (0.75–1.53) | 78 | 0.78 (0.56–1.07) |
| Low | 15 | 1.18 (0.66–2.14) | 18 | 0.97 (0.57–1.65) |
| None | 2 | 0.94 (0.23–3.89) | 4 | 1.24 (0.45–3.45) |
| *P*-value for differences | 0.56 | | | |
| Hours of work | | | | |
| ≤30 h/week | 54 | 1 (reference) | 71 | 1 (reference) |
| 31–37 h/week | 85 | 1.13 (0.77–1.66) | 91 | 0.90 (0.63–1.28) |
| 38–44 h/week | 11 | 1.24 (0.62–2.47) | 8 | 0.73 (0.34–1.56) |
| ≥45 h/week | 3 | 0.53 (0.16–1.75) | 9 | 1.29 (0.62–2.69) |
| *P*-value for differences | 0.28 | | | |

[a] Adjusted for age, age at menarche, parity, age at first birth, family history of breast cancer, oral contraceptive use, body mass index, physical activity in leisure time, physical activity at work, work shifts, alcohol consumption, postmenopausal hormone use, age at menopause, height

one may be exposed to stress at home or to acute stress from major life events. We cannot reject that the combined burden of stress at work and at home may affect breast cancer risk or prognosis. Previous studies on perceived stress from care giving or from everyday life have suggested that the perceived level of stress may actually be associated with lower risk of breast cancer [7, 8].

## Conclusion

We found no support for the concern that women who experience high levels of work-related stressors are at a higher risk of being diagnosed with a prognostic unfavorable breast cancer.

The fact that work-related stressors seem to affect neither breast cancer risk nor the prognostic characteristics of incident breast cancers at the time of diagnosis may be a comfort to working women and can hopefully prevent self-blaming among women who develop breast cancer. Future studies should examine the effect of work-related stressors on the risk of breast cancer in professions with more exposure to heterogeneity.

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