

ORIGINAL ARTICLE

Prolonged job strain and subsequent risk of cancer in women – a longitudinal study, based on the Danish Nurse Cohort

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ABSTRACT

Background: The role of psychological stress in cancer risk is continuously debated. Stress at work is the most common form of stress and previous studies have shown inconsistent results regarding cancer risk. In this longitudinal study, we examined the association between prolonged job strain across six years and subsequent cancer risk.

Methods and materials: We used data from 6571 cancer-free women from the Danish Nurse Cohort aged 45–70 years at inclusion, and self-reported questionnaires on job strain at baseline in 1993 and again in 1999. Prolonged job strain was defined as high job busyness and speed, and low control in both 1993 and 1999. Information on cancer diagnosis was obtained from the Danish Cancer Registry. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for overall cancer as well as subgroups of virus immune-related, hormone-related, digestive and lung cancers according to level of prolonged job strain. The women were followed from 1 January 2000 until cancer diagnosis, emigration, death or 31 December 2013 (mean follow-up 13 years) and models were adjusted for potential confounders. Effect modification was examined according to working nightshifts and full time.

Results: No significant differences in the risk of overall cancer or any of the cancer subgroups were identified in relation to prolonged busyness, speed, influence, or overall job strain. Effect modification by working full time was observed when examining job influence in relation to overall cancer risk, and by working nightshifts when examining job influence in relation to hormone related cancer risk. However, none of the associations were significant in stratified analyses.

Conclusion: We found no evidence of an increased risk of any cancer among women with prolonged job strain. Since a large proportion of cancer patients perceive psychological stress as a possible cause of their cancer disease, it is of importance to communicate these findings to the public.

ARTICLE HISTORY

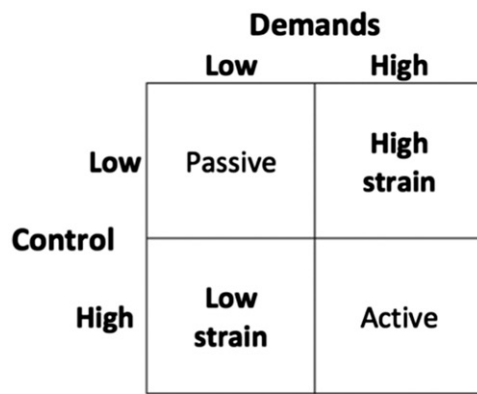
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The role of stress in cancer risk is continuously debated, and many cancer patients attribute their illness to previous experiences of psychological stress [1]. Biological pathways for an association between stress and cancer risk include adverse lifestyle or immune suppressive effects caused by stress-induced corticosteroids reducing destruction of neoplastic cell growth [2]. Previous observational studies of varying quality have investigated the effect of psychological stress on cancer risk with mixed results [3]. However, prospective studies with unbiased exposure information, addressing the risk for recall bias, including adjustment for potentially confounding factors have not been able to establish any association between psychological stress and the risk of cancer [3].

According to The American Institute of Stress, psychological stress at work is the most common type of stress and the prevalence is increasing [4]. Job strain is one of the most frequently used measures of work-related stress, and is defined as high psychological demands, combined with low decision latitude [5]. Demands refer to degree of excessive

workload and the need to work fast. Decision latitude refers to the degree of control, for instance freedom to make own decisions and skill discretion [6]. The interaction between demands and control results in strain when high demands are not buffered by simultaneous high individual control (Figure 1). A total of seven studies, published in nine papers, have examined the association between job strain and subsequent cancer risk. Three were designed as case control studies [7–10] and four as cohort studies [11–15]. Two studies measuring job strain using occupation type observed an increased risk of esophageal and colorectal cancers [8,10], while no associations were found when job strain was self-reported [7,9]. Of the four prospective studies, using 8–13 years of follow-up and adjusting for relevant confounding factors, three found no association between job strain and breast [11,12,14,15], lung, colorectal, prostate, or overall cancer [12], and one observed a significantly increased risk of breast cancer but only in stratified analyses among full-time workers [13]. Only one of the previous studies [12] examined



Inspired by Karasek's Demand/Control model (6)

Figure 1. Relationship between demands and control.

other cancers than breast cancer. Also, only one of the previous studies used more than one follow-up measure of the job strain exposure [15]. Studies have shown that job strain may change over time questioning the quality of studies including only one observation of job strain: In one study more than 50% of participants with high job strain at baseline reported no job strain at follow-up four years later [16]. The only previous study including a subanalysis on prolonged job strain found no significant association with the risk for breast cancer [15]. Thus, to disentangle if prolonged job strain may play a role across cancer types, we examined a large cohort of nurses ($N=6571$), including six years of follow-up on the job strain exposure followed by 13 years of follow-up on cancer risk, using access to detailed questionnaire information on the exposure and potential confounders as well as objective information on cancer outcome.

Material and methods

Study population

The Danish Nurse Cohort, which has previously been described in detail [17], was established in 1993, and invited all female Danish nurses above 44 years of age, who were members of the Danish Nurses' Association ($N=23\,170$) to participate in the study [17]. Information on health, socioeconomic status, working conditions, and lifestyle factors were collected by questionnaire at baseline in 1993, with follow-up in 1999 and 2009.

The current study was based on information from women who responded to measures on job strain at baseline in both 1993 and 1999 ($N=15\,322$). We excluded women who had reached the retirement age >65 years in 1999 ($n=6917$), were unemployed in either 1993 or 1999 ($n=821$), had died ($n=4$) or had a cancer diagnoses prior to 1 January 2000 ($n=421$), or had missing values on any of the job-strain exposures ($n=176$) or covariates ($n=412$). A total of 6571 participants were included for analyses.

Exposure to job strain

Three single items measured job strain. Demands was measured by busyness ('How often are you so busy, that

Table 1. Cancer incidence by cancer group and ICD-10^a codes.

Cancer group	Incidence	ICD-10 codes
Overall	855	C00-C80; C88.0-C88.2; C90; DD09.0; D09.1; D30- D33; D35.2-D35.4; D41.1- D41.4; D41.7-D41.9; D42; D43; D44.3-D44.5
Hormone-related	423	C50; C54-C56; C57.0-C57.4; C58
Virus immune-related	57	C22; C44; C46.0; C53; C81-C85; C88.3-C88.9; C91-C96
Digestive (excl. liver)	126	C15-C21; C23-C26; C45.1-45.9; C48
Lung	80	C33; C34; C39

^aInternational Classification of Diseases.

you find it hard to fulfill your tasks?': never, rarely, sometimes, often or almost always) and job speed ('How is the work speed or work load at your job?': too high, somewhat high, suitable, somewhat low or too low). Control was measured by job influence ('How high is your ordinary influence on organizing your daily work?': high, moderate, low or no). For the present study, we chose to dichotomize the job-strain items due to few individuals in the most strained categories: [busyness (low: never or rarely vs. high: often or almost always), speed (low: too low, somewhat low or suitable vs. high: somewhat high or too high), influence (low: no, low or moderate vs. high: high)]. Overall, job strain was estimated combining information from all three items: prolonged high job strain was defined as combined high busyness, high speed, and low influence in both 1993 and 1999.

Cancer diagnosis

In Denmark, all permanent residents are assigned a personal identification number, which is registered in the Danish Civil Registration System (CRS). The register is updated continuously and contains information on vital status including date of emigration and death [18]. The personal identification number provides a key variable enabling linkage of each participant to the Danish Cancer Registry which contains records of all incidents of malignant neoplasms in the Danish population [19]. We obtained information on cancer diagnosis classified according to the International Classification of Diseases, 10th edition (ICD-10) and grouped as overall cancer as well as into four cancer subgroups (Table 1). We excluded other skin cancers than melanoma from the analysis.

Covariates

We included information on self-reported covariates measured in 1999 including body mass index (BMI) [underweight (<18.5), vs. normal weight ($18.5-25$) vs. overweight (>25)], smoking (daily, vs. occasional, vs. previous vs. never smoker), alcohol consumption (none vs. 1-7 vs. >7 units per week), physical activity in leisure time [high activity (competitive sports several times per week or exercising >4 hours per week) vs. medium activity (walking, biking or other light activity >4 hours per week) vs. low activity (<4 hours per week)], physical activity at work [primarily sitting vs. primarily standing/walking vs. standing/walking including lifting vs. heavy strenuous work], working nightshifts (day, evening or

rotating shifts vs. night only) and full-time work (≥ 37 hours vs. < 37 hours)]. Age (continuous) was obtained from the personal identification number.

Statistical analyses

Descriptive statistics were conducted on covariates according to level of busyness, speed, influence, and pooled job strain using t-tests on continuous variables presented as mean and standard deviation (SD) and χ^2 -tests on categorical variables presented as frequencies (%).

We used Cox proportional hazard models to estimate whether prolonged high job strain (high overall, high busyness, high speed and low influence, respectively) was associated with cancer risk (overall, virus immune-related cancer, lung cancer or cancer related to hormone or digestive systems, respectively). In a subanalysis, we compared cancer risk in participants with low job strain at both time points to those with increasing, decreasing, or repeatedly high levels of job strain. The risk estimates are presented as hazard ratio (HR) and 95% confidence intervals (CI). We followed the participants from 1 January 2000 until first cancer diagnosis, death, emigration or end of study on 31 December 2013, whichever came first. Age was used as underlying time scale. Adjustment for covariates was based on previous evidence and resulted in three models fitted for each job-strain measure: First crude analyses including age as underlying time scale (data not shown), second with adjustment for confounding from nightshift and full-time work, and third with additional adjustment for the mediating effect from the life-style-related factors smoking, alcohol consumption, BMI, physical activity at work, and leisure time. Continuous covariates were categorized when we expected non-linear associations to cancer risk based on previous evidence. Proportional hazards were examined, and if non-proportional hazards were present, the covariate was included in the model as strata.

Effect modification of working nightshifts and full time versus part time, respectively, was examined for multiplicative interactions by including interaction terms in the models. If a significant effect modification was observed, analyses were stratified. In attrition analyses, we compared the participants in the present study to the women who completed the baseline questionnaire in 1993 but who were excluded from our analyses on each exposure (χ^2) while adjusting for age. Reported *p* values are two-sided. An overall significance level of 0.05 was used. Analyses were performed in R version 3.3.1.

Results

We followed 6571 women until cancer diagnosis ($n=855$), death without a previous cancer diagnosis ($n=92$), emigration ($n=31$) or end of study on 31 December 2013. Mean follow-up time was 13 years (range 1 month–14 years), and median age in 1999 was 55 years (range 51–65). Descriptive analyses showed that women who worked fewer nightshifts and were more physical active in their jobs had higher job

strain (Table 2). Between 1993 and 1999, 26% altered from either high to low or from low to high level of job strain (Table 3). During follow-up 13% of the participants developed cancer.

Cancer risk

No significant difference in risk of overall cancer or any of the cancer subgroups was identified according to prolonged job strain measured as prolonged high busyness and speed, low influence, or total high job strain, respectively (Table 4).

Effect modification according to working full time was observed when examining job influence in relation to overall cancer risk ($p=0.02$). Also, effect modification was observed according to working nightshifts when examining job influence in relation to hormone-related cancer risk ($p=0.03$). However, in stratified analyses associations were non-significant. Among full-time workers, women with prolonged low influence ($n=1117$) compared to high influence ($n=2083$) had an overall cancer risk of HR 0.83 (0.67–1.03). In contrast, among part-time workers the risk was HR 1.17 (0.98–1.42). Among women working nightshifts, persons with prolonged low influence ($n=161$) compared to high influence ($n=216$) had a risk of hormone-related cancer of 1.86 (0.95–3.63). In contrast, among persons without regular nightshifts the risk was HR 0.85 (0.70–1.05). Neither working full time nor working nightshifts modified the associations between busyness, job speed, or overall job strain.

In a subanalysis comparing participants with low job strain at both time points to participants with increasing [HR 0.90 (0.73–1.11)], decreasing [HR 1.22 (1.01–1.48)] or prolonged high job strain [HR 0.84 (0.66–1.07)], we observed an increased risk of overall cancer in women who initially had high job strain but attained low job strain at follow-up, compared to women who reported no job strain at both time points.

Attrition analyses showed that the 6571 participants compared to the 13 327 non-participants did not differ in level of busyness ($p=0.45$), speed ($p=0.56$), job influence ($p=0.06$) or total job strain ($p=0.80$) in age-adjusted analyses.

Discussion

In this prospective cohort study of female nurses, prolonged high job strain was not associated with an increased risk of overall or specific cancer. Our findings are in line with the findings from the two largest previous studies that also showed no associations between job strain and cancer [12,15]. Thus, our results do not confirm the general belief many patients hold of a carcinogenic effect of psychological stress. Rather, we found that those decreasing their stress level over the six-year period seemed to have an increased cancer risk compared to those with persistent low stress. This latter finding may though be a chance finding related to multiple testing. Another possible explanation for the finding might be that nurses make changes in their work life influencing their job-related stress. It is, for example possible that

Table 2. Baseline 1999 characteristics according to prolonged job strain.

	Busyness						Speed						Influence						Job strain					
	Low-low			High-high			Low-low			High-high			Low-low			High-high			Low-low			High-high		
	N	(%)		N	(%)	P	N	(%)		N	(%)	P	N	(%)		N	(%)		N	(%)		N	(%)	P
N	4927			1644			3781			2790			2804			3767			5878			693		
Age 1999, mean (SD)	55.9	(3.4)		55.4	(3.1)		55.8	(3.4)		55.6	(3.2)		55.9	(3.4)		55.6	(3.3)		55.8	(3.3)		55.5	(3.2)	
Night shifts ^a	354	(7.2)		23	(1.4)		328	(8.7)		49	(1.8)		161	(5.7)		216	(5.7)		364	(6.2)		13	(1.9)	
Full-time work ^b	2211	(44.9)		989	(60.2)		1642	(43.4)		1558	(55.8)		1117	(39.8)		2083	(55.3)		2874	(48.9)		326	(47.0)	
BMI 1999																								
-BMI 18.5–25	3126	(63.4)		979	(59.5)		2383	(63.0)		1722	(61.7)		1818	(64.8)		2287	(60.7)		3682	(62.6)		423	(61.0)	
-BMI <18.5	61	(1.2)		21	(1.3)		48	(1.3)		34	(1.2)		37	(1.3)		45	(1.2)		69	(1.2)		13	(1.9)	
-BMI >25	1740	(35.3)		644	(39.2)		1350	(35.7)		1034	(37.1)		949	(33.8)		1435	(38.1)		2127	(36.2)		257	(37.1)	
Physical activity																								
-exercising >4 hours/week	3471	(70.4)		1121	(68.2)		2654	(70.2)		1938	(69.5)		1987	(70.9)		2605	(69.2)		4119	(70.1)		473	(68.3)	
-medium activity	1229	(24.9)		424	(25.8)		952	(25.2)		701	(25.1)		697	(24.9)		956	(25.4)		1468	(25.0)		185	(26.7)	
-low activity	227	(4.6)		99	(6.0)		175	(4.6)		151	(5.4)		120	(4.3)		206	(5.5)		291	(5.0)		35	(5.1)	
Activity at work																								
-sitting	1100	(22.3)		498	(30.3)		874	(23.1)		724	(25.9)		315	(11.2)		1283	(34.1)		1485	(25.3)		113	(16.3)	
-standing/walking	1888	(38.3)		461	(28.0)		1486	(39.3)		863	(30.9)		1032	(36.8)		1317	(35.0)		2158	(36.7)		191	(27.6)	
-walking/lifting	1805	(36.6)		582	(35.4)		1337	(35.4)		1050	(37.6)		1312	(46.8)		1075	(28.5)		2069	(35.2)		318	(45.9)	
-heavy	134	(2.7)		103	(6.3)		84	(2.2)		153	(5.5)		145	(5.2)		92	(2.4)		166	(2.8)		71	(10.2)	
Alcohol																								
1–7 units per week	1990	(40.0)		696	(42.3)		1503	(39.8)		1183	(42.4)		1187	(42.3)		1499	(39.8)		2279	(40.5)		307	(44.3)	
>7 units per week	2450	(49.7)		792	(48.2)		1907	(50.4)		1335	(47.8)		1325	(47.3)		1917	(50.9)		2930	(49.8)		312	(45.0)	
-none	487	(9.9)		156	(9.5)		371	(9.8)		272	(9.7)		292	(10.4)		351	(9.3)		569	(9.7)		74	(10.7)	
Smoking																								
-never	1914	(38.8)		659	(40.1)		1480	(39.1)		1093	(39.2)		1098	(39.2)		1475	(39.2)		2301	(39.1)		272	(39.2)	
-daily	1144	(23.2)		385	(23.4)		866	(22.9)		663	(23.8)		676	(24.1)		853	(22.6)		1357	(23.1)		172	(24.8)	
-occasional	275	(5.6)		72	(4.4)		202	(5.3)		145	(5.2)		135	(4.8)		212	(5.6)		313	(5.3)		34	(4.9)	
-previous	1594	(32.4)		528	(32.1)		1233	(32.6)		889	(31.9)		895	(31.9)		1227	(32.6)		1907	(32.4)		215	(31.0)	

^aVersus day, evening or rotating shifts; ^bVersus part-time work.

nurses who are especially vulnerable to job strain will change job when experiencing high job strain, while nurses who are more resistant to the influence of job strain are more likely to persist in a high-strained job. Thus, nurses who report prolonged high strain over time may include especially job-strain resistant individuals. This paradox makes it difficult to measure the truly effect of prolonged job strain.

We observed a significant interaction between job influence and working nightshifts versus other shifts on the association with cancer risk, suggesting a potential higher cancer risk following job strain in women working nightshifts but not in women in other shifts. However, this association did not reach significance in stratified analyses. A biological interaction due to hormonal changes caused by working nights cannot be ruled out but may be a potential mechanism behind the finding of a significant interaction with nightshifts. Also, we cannot exclude that the significant interaction was a chance finding.

The present study has several strengths. First, the available repeated measures of job strain, which has only been investigated in one previous study. The prolonged job strain measure reduces the risk of misclassification that may be seen in studies with one measure only of job strain, hence, may reduce the risk of underestimating an effect of job strain. High-strained women may, due to the high pressure, leave their jobs to attend less strained jobs. Such women will be categorized as high-strained despite the elimination of job strain following the job rotation.

We used almost complete, registry-based and validated information on vital status and all cancer diagnosis [19]

minimizing loss to follow-up and increasing the validity of the study results. Also the information was obtained independent of the study hypothesis for administrative purposes. In the Danish Nurse Study high participation rates of 86% and 81% reduces the risk of non-response bias, where non-responders might differ from the responders on job-strain level. Furthermore, with 13 years of follow-up, the slow progressing development of cancer diseases is taken into account. We also took into account a number of important potential confounders and mediating factors. Still, our use of self-reported lifestyle information could imply misclassification due to underestimation of unhealthy lifestyle patterns such as smoking, underestimation of weight and exaggeration of physical activity [20–22]. Also, measuring job strain with three individual items rather than the total of 15 items included in the demand control [6] scale might have led to some misclassification and may have attenuated some of our estimates.

The generalizability of our study is limited to women, and previous studies have shown that effect of job strain may differ between men and women, potentially due to differences in sex hormones [14]. Generalizability might also be limited as our participants were all nurses, who have been shown to smoke less, eat healthier, consume more alcohol and exercise more than other females belonging to the same socioeconomic group [23]. Nevertheless, a previous study found no differences between the nurses and other females from the same socioeconomic group in self-reported health or diseases including cancer [23].

In conclusion, when applying repeated measures of job strain, valid information on cancer diagnosis, adjustment for relevant confounders, and low loss to follow-up, we found no support for the general belief that prolonged job strain may increase cancer risk. Our results may bring relief to cancer patients who potentially blame themselves for their cancer diagnosis if they have endured psychological stress at their work.

Table 3. Job-strain levels in 1993 and 1999.

Job-strain level	N
Low-low	4155
Low-high	925
High-low	798
High-high	692

Table 4. Hazard ratios (HR) and confidence intervals (CI) for cancer according to prolonged job strain (high vs. low) in 6571 women.

	Overall cancer			Hormone-related cancer			Virus immune-related cancer			Digestive cancer			Lung cancer		
	N ^a	HR	(CI)	N ^a	HR	(CI)	N ^a	HR	(CI)	N ^a	HR	(CI)	N ^a	HR	(CI)
High job strain ^b	77	0.84	(0.7–1.1)	36	0.80	(0.6–1.1)	6	0.99	(0.4–2.3)	10	0.72	(0.4–1.4)	10	1.23	(0.6–2.4)
Low job strain	778	1.0		387	1.0		51	1.0		116	1.0		70	1.0	
Low influence ^b	369	1.01	(0.9–1.2)	171	0.91	(0.8–1.1)	26	1.09	(0.6–1.9)	62	1.26	(0.9–1.8)	30	0.83	(0.5–1.3)
High influence	486	1.0		252	1.0		31	1.0		64	1.0		50	1.0	
High speed ^b	364	1.03	(0.9–1.2)	179	1.02	(0.8–1.3)	22	0.88	(0.5–1.5)	53	1.01	(0.7–1.5)	38	1.20	(0.8–1.9)
Low speed	491	1.0		244	1.0		35	1.0		73	1.0		42	1.0	
High busyness ^b	211	1.01	(0.9–1.2)	110	1.09	(0.9–1.4)	15	1.12	(0.6–2.1)	31	1.03	(0.7–1.6)	18	0.85	(0.5–1.5)
Low busyness	644	1.0		313	1.0		43	1.0		95	1.0		62	1.0	
High job strain ^c	77	0.84	(0.7–1.1)	36	0.82	(0.6–1.2)	6	1.08	(0.5–2.5)	10	0.66	(0.3–1.3)	10	1.05	(0.5–2.1)
Low job strain	778	1.0		387	1.0		51	1.0		116	1.0		70	1.0	
Low influence ^c	369	1.02	(0.9–1.2)	171	0.94	(0.8–1.2)	26	1.09	(0.6–1.9)	62	1.23	(0.9–1.8)	30	0.81	(0.5–1.3)
High influence	486	1.0		252	1.0		31	1.0		64	1.0		50	1.0	
High speed ^c	364	1.03	(0.9–1.2)	179	1.04	(0.9–1.3)	22	0.92	(0.5–1.6)	53	0.97	(0.6–1.5)	38	1.14	(0.7–1.8)
Low speed	491	1.0		244	1.0		35	1.0		73	1.0		42	1.0	
High busyness ^c	211	1.02	(0.9–1.2)	110	1.10	(0.9–1.4)	15	1.21	(0.7–2.2)	31	0.98	(0.7–1.5)	18	0.78	(0.5–1.3)
Low busyness	644	1.0		313	1.0		43	1.0		95	1.0		62	1.0	

^aNumber of cancer cases; ^bAdjusted for age, nightshifts and full-time work; ^cAdditional adjusted for smoking, alcohol, BMI and physical activity at work and leisure time.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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