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Job Stress and Breast Cancer Risk

The Nurses' Health Study

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Workers tend to perceive certain features of their jobs as harmful to health and are alert to associations between job stress and health outcomes, but few observational studies have evaluated the role of job stress in carcinogenesis. The authors prospectively assessed the association between job strain, measured by Karasek and Theorell's job content questionnaire in four categories (low strain, active, passive, and high strain), and breast cancer risk among participants in the Nurses' Health Study. A total of 37,562 US female registered nurses were followed for up to 8 years (1992–2000), and 1,030 cases of invasive breast cancer were ascertained during that period. All participants were still in the workforce at baseline and completed the job content questionnaire. Adjusted for age, reproductive history, and other breast cancer risk factors, the multivariate relative risks of breast cancer, in comparison with women who worked in low-strain jobs, were 0.83 (95% confidence interval (CI): 0.69, 0.99) for women in active jobs, 0.87 (95% CI: 0.73, 1.04) for women in high-strain jobs, and 0.90 (95% CI: 0.76, 1.06) for women in passive jobs. Findings from this study indicate that job stress is not related to any increase in breast cancer risk.

breast neoplasms; hormones; occupational exposure; stress; workplace

Abbreviations: CI, confidence interval; RR, relative risk.

Several studies have implicated stressful life events as a risk factor for breast cancer (1–4). However, the association between stress and breast cancer remains unclear, particularly since many of the key studies on this topic have been retrospective (case-control studies) (5). Given that job conditions are a major source of stress in women's lives, we sought to test the association between work stress and breast cancer in a large, ongoing cohort study. The job strain model, pertaining to jobs characterized by a combination of high psychosocial demands and low levels of control, is the leading approach to characterizing work stress. Job strain has been associated with risk of coronary heart disease and hypertension (6–12), but results have not been entirely consistent (7). Furthermore, jobs with low control have been associated with increased mortality from all causes (13).

Acute stress has been reported to be beneficial for tumor inhibition in humans, primarily through enhancement of the immune response (14), whereas chronic stress has been associated with a depressed immune response that may promote cancer (15–17). Therefore, we sought to test the hypothesis that job strain, as a form of chronic stress, may increase the risk of breast cancer. Data from well-conducted observa-

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tional studies evaluating the impact of job strain on breast cancer risk have so far been sparse; the studies have been either retrospective by design or based on few cases, and results have not suggested an important role of job stress in carcinogenesis (18, 19). The only prospective study of this issue—preliminary findings from our own cohort—reported no association between breast cancer risk and job strain (18), but it was limited by the small number of cases ($n = 219$) and the short follow-up period (2 years).

Other evidence suggests that adverse psychological working conditions may affect the overall health (20, 21) and quality of life (22) of workers. Moreover, workers tend to perceive certain features of their jobs as harmful to their health (23). The public is thus highly alert to associations between job stress and health outcomes. Therefore, additional investigations of associations between job stress and health outcomes, particularly cancer, are warranted. We studied the cumulative effects of job strain on breast cancer risk in a large cohort of registered nurses, with repeated measures of job characteristics and 8 years of follow-up.

MATERIALS AND METHODS

Study population

In 1976, 121,700 female registered nurses aged 30–55 years and living in 11 large US states were enrolled in the Nurses' Health Study. Since baseline, they have completed biennial mailed questionnaires that include questions on their health status, medical history, and known or suspected risk factors for cancer (24) and heart disease (25). The factors inquired about include age, age at menarche, parity, age at first birth, weight, height, menopausal status, family history of breast cancer, and personal history of benign breast disease and cancer. Every 2 years, follow-up questionnaires have been sent to cohort members to obtain updated information on potential risk factors and to identify newly diagnosed cases of cancer and other major medical events. Follow-up data are available for over 90 percent of the cohort. In 1980, the questionnaire was expanded to include an assessment of diet (24, 26) and alcohol consumption.

In 1982, we assessed self-perceived job stress by asking the nurses how they would rate the amount of stress in their daily life at work (severe, moderate, light, or minimal). In 1992 and 1996, Karasek and Theorell's job content questionnaire (27) was sent to study participants as part of the biennial questionnaire, and 75,453 of the women returned it. We excluded women who did not answer the job content questionnaire in either 1992 or 1996 or who reported breast cancer or any other cancer (other than nonmelanoma skin cancer) before the return of the baseline questionnaire. Thus, a total of 37,562 women remained to form the population for this analysis, and 287,805 person-years of follow-up were accrued from 1992 to 2000.

Ascertainment of job strain

Karasek and Theorell's job content questionnaire is a 27-item instrument that measures both the psychological workload (demand) of a job and the level of control available for managing the workload. The instrument was designed to be self-administered by the subject in 15 minutes with minimal guidance. The job content questionnaire is based on the job demand/control model, which offers two main hypotheses: 1) the combination of high job demands and low job control precipitates psychological and physical strain ("high-strain" jobs) and 2) jobs with both high demands and high control lead to well-being, learning, and personal growth ("active" jobs) (27). The job-demand subscale is the sum of five items inquiring about excessive work, conflicting demands, insufficient time to work, fast pace, and working hard. The job-control scale is the sum of two subscales: skill discretion, as measured by six items (learning new things on the job, potential to develop new skills, having a job requiring skill, task variety, the work's not being repetitious, and having a job requiring creativity), and decision authority, as measured by three items (freedom to make decisions, choice about how to perform work, and having a lot of say in the job). The work-related social support scale is the sum of two subscales: support from coworkers (four items) and support from supervisors (four items). For each item, the respondent can choose from one of four responses ranging from "strongly disagree" to "strongly agree." The psychometric properties and particulars of the job content questionnaire have been reported in detail elsewhere (6, 27, 28).

In the demand/control model, the demand and control subscales are split along the median values of responses to create a 2×2 matrix of job conditions. According to the model, jobs high in demands and low in control ("high-strain" jobs) are the most harmful (27). The remaining three categories of jobs defined by the demand/control matrix are low demands/high control ("low-strain" jobs), high demands/high control ("active" jobs), and low demands/low control ("passive" jobs). In accordance with previous research, we used low-strain jobs as the reference group for comparison with other types of jobs. An extension of the demand/control matrix further posits that jobs characterized by high demands, low control, and low social support at work ("iso-strain" jobs) are associated with poor health outcomes (28). Information on job strain and social support in the Nurses' Health Study was first assessed in 1992 and was updated in 1996.

Documentation of breast cancer diagnoses and deaths

Incident breast cancer was defined as a breast cancer diagnosis made after the return of the questionnaire and before May 2000. Nurses who reported a diagnosis of breast cancer were asked for permission to review their medical records for confirmation. Approximately two thirds of the deaths among cohort members were reported to us by next of kin or the postal system in response to follow-up questionnaires. In addition, we searched the National Death Index to identify deaths among the nonrespondents to each 2-year questionnaire. The computerized National Death Index is a highly sensitive resource for identifying deaths in this cohort (29). Data on mortality were more than 98 percent complete (29, 30). For all deaths possibly attributable to breast cancer, we requested permission from family members to review the medical records. All interviews and reviews of medical

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records were conducted by investigators without knowledge of exposure to job strain. A total of 1,030 incident invasive breast cancers were diagnosed between June 1992 and May 2000, and pathology records were obtained for 94 percent of the women. Although the 1,030 women with breast cancer included 64 whose pathology reports had not yet been obtained, we based our analyses on the total, because the accuracy of self-reporting has been extremely high: 99 percent of pathology reports confirmed the diagnosis (31). In addition, an analysis limited to cases confirmed by pathology reports yielded the same association with job strain.

Statistical analysis

For each eligible participant, person-years of follow-up were counted from questionnaire return to the date of a diagnosis of breast cancer or death or until May 2000, whichever came first. Job strain was categorized into four types of job conditions: high-strain jobs, active jobs, low-strain jobs, and passive jobs. The presence or absence of work-site support was also incorporated into the existing demand/control job-type matrix, replacing the previous four categories with eight.

We cumulatively updated the baseline information on job strain with job strain scores from the 1996 questionnaire in all analyses; thus, job-strain information from the 1992 questionnaire was used to predict outcomes during the period from 1992 to 1996, and the average of the 1992 and 1996 job-strain scores was used to predict outcomes for subsequent cases (i.e., 1996–2000). Cumulative averaging can reduce within-person variation, and it provides a more stable assessment of associations than single measures (21).

Low strain was used as the reference group in all analyses. In subanalyses, we utilized categories based on tertiles of the demand and control scores individually as the main exposure. For each participant, person-months were allocated to categories of years worked under any of the four job conditions according to the 1992 and 1996 data.

Information about breast cancer and established risk factors for breast cancer was updated according to the biennial follow-up questionnaire. Information on alcohol consumption was updated every 4 years, in 1990, 1994, and 1998. The initial analysis was based on incidence rates, with person-months of follow-up used as the denominator. We used relative risk as the measure of association, defined as the incidence rate of breast cancer among women in various categories of job conditions divided by the incidence rate among women with low-strain jobs. Mantel-Haenszel summary relative risks were calculated, adjusting for age in 5-year categories (32). Cox proportional hazards models were used to calculate relative risks with adjustment for age, reproductive history, and other known risk factors for breast cancer. For all of these factors, indicator variables were created for missing values and included in the analyses.

Tests for statistical (multiplicative) interaction were performed with likelihood ratio tests. Pearson's interclass correlation coefficient was used to obtain an estimate of the correlation between the 1992 and 1996 job-demand and job-control scores for assessment of 4-year reproducibility. All statistical tests were two-sided. We used the SAS statistical package for all analyses (33).

RESULTS

In 1992, 20.5 percent of women in the study sample worked in low-strain jobs (n = 7,687), 32.4 percent worked in passive jobs (n = 12,175), 25.8 percent worked in high-strain jobs (n = 9,689), and 21.3 percent worked in active jobs (n = 8,011). Most of the baseline characteristics of women with low-strain jobs were similar to those of women with other types of jobs. However, women with a component of high control in their jobs tended to have a higher educational level than women with little control in their jobs (table 1). Women who did not answer the job content questionnaire in 1992 did not differ substantially from respondents in terms of their risk profile.

Table 2 shows the relation between job type and risk of breast cancer. More demanding jobs were associated with a modest decrease in breast cancer risk: Women with active jobs had a 17 percent lower risk of breast cancer than women with low-strain jobs (multivariate-adjusted relative risk (RR) = 0.83, 95 percent confidence interval (CI): 0.69, 0.99). Among women who worked in high-strain jobs, we observed a nonsignificant 13 percent lower breast cancer risk (RR = 0.87, 95 percent CI: 0.73, 1.04). Incorporation of work-site support into the job strain categories did not substantially modify these associations. Among women who worked part-time, the inverse association between high-strain jobs and breast cancer risk was slightly stronger (RR = 0.75, 95 percent CI: 0.58, 0.97).

Job strain was only weakly associated with lifestyle or dietary variables such as alcohol consumption. However, to rule out the possibility that alcohol consumption could account for the observed relation between job strain and breast cancer, we added this variable, as well as the educational levels of the nurses and (if married) their husbands (as markers of socioeconomic status), to our final Cox regression models. We also adjusted for smoking history, recent weight change, caregiving (any type of caregiving stress and spousal caregiving stress), job insecurity, marital status (single, married, divorced, widowed), region of residence (California, Northeast, Midwest, South), and type of nursing job. However, none of these variables remained in our final model because their addition did not alter our estimates.

Job strain experienced in the past could more strongly predict breast cancer risk than current job strain. Therefore, we analyzed the relation between job stress as assessed in 1992 and the risk of breast cancer from 1998 through 2000, which gave us 273 women with breast cancer. Despite the 6-year latency period, job strain was similarly associated with risk of breast cancer (for active jobs vs. low-strain jobs, multivariate RR = 0.56, 95 percent CI: 0.34, 0.91; for high-strain jobs vs. low-strain jobs, RR = 0.86, 95 percent CI: 0.56, 1.30). These associations were somewhat weaker when we did not adjust for social support at work. Moreover, in 1982, we asked nurses how they would rate the amount of stress in their daily life at work (severe, moderate, light, or minimal). We found no association between this measure of self-perceived job stress, which has not been evaluated for its

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TABLE 1. Mean age and age-standardized* characteristics of participants according to category of job strain† (*n* = 37,562), Nurses' Health Study, 1992

Subject characteristic	Job strain category			
	Low demand/high control (low strain) (*n* = 7,687)	Low demand/low control (passive) (*n* = 12,175)	High demand/low control (high strain) (*n* = 9,689)	High demand/high control (active) (*n* = 8,011)
Mean age (years)	55.4 (5.9)‡	56.6 (6.2)	54.5 (5.6)	54.0 (5.3)
Menarche before age 12 years (%)	22.9	22.8	23.1	24.1
Nulliparous (%)	5.8	6.0	5.9	6.6
Parity ≥5 (%)	12.0	13.2	12.6	10.3
Age at first birth ≥30 years§ (%)	6.8	7.2	7.1	7.0
First-degree family history of breast cancer (%)	12.1	11.8	12.3	11.9
History of benign breast disease (%)	45.6	45.7	48.2	48.6
Ever use of oral contraceptives (%)	58.3	55.8	56.1	57.7
Postmenopausal in 1992 (%)	76.7	76.8	77.7	76.9
Mean age (years) at menopause	46.8 (8.6)	47.4 (7.9)	46.6 (8.8)	46.4 (8.7)
Age at menopause ≥55 years¶ (%)	4.4	4.5	4.1	5.1
Current postmenopausal hormone use for ≥5 years (%)	18.6	17.1	19.3	18.7
Body mass index# in 1992 ≥25 (%)	48.9	48.1	47.6	46.8
Current smoking (%)	13.5	13.8	15.3	16.2
Mean current alcohol consumption (g/day)	5.2 (9.4)	4.8 (9.2)	4.5 (8.5)	5.2 (9.2)
Mean height (inches)**	64.7 (2.7)	64.4 (3.2)	64.5 (3.2)	64.6 (3.0)
Socioeconomic status (husband's education beyond high school)†† (%)	48.3	43.8	42.4	46.1
Nurse's education higher than a bachelor's degree (%)	20.4	7.4	7.2	20.7
Type of nursing job (%)				
Administrative	13.4	5.5	6.6	21.4
Operating room	1.3	2.1	6.8	3.7
Inpatient	6.5	10.4	23.6	13.0
Outpatient	12.7	11.2	9.8	9.5
Educator	8.1	3.4	2.7	7.0
Other nurse	36.2	47.0	42.1	31.6
Former nurse, currently in nonnursing occupation	21.8	20.4	8.4	13.8

* Data were standardized for age in six categories (45–49, 50–54, 55–59, 60–64, 65–69, and ≥70 years) as of the 2-year period in which participants first entered follow-up.
† Assessed by means of Karasek and Theorell's job content questionnaire (27).
‡ Numbers in parentheses, standard deviation.
§ Among parous women only.
¶ Among postmenopausal women only.
# Weight (kg)/height $(m)^2$.
** 1 inch = 2.54 cm.
†† Among married women only.

psychometric properties, and breast cancer risk (for severe stress vs. minimal stress, RR = 1.04, 95 percent CI: 0.89, 1.21; table 3). We repeated analyses using this question and lagging exposure for up to 12 years, and the results remained unchanged.

We further investigated the possibility that the lower breast cancer risk associated with active and high-strain jobs resulted from detection bias caused by less active mammography screening behavior among these women. When we excluded women whose cancer may have been detected incidentally or only by screening (breast tumors of sizes <2 cm) and restricted the outcome to more advanced lesions, the relative risks for breast cancer were not materially altered (for active jobs vs. low-strain jobs, multivariate RR = 0.77, 95 percent CI: 0.49, 1.21; for high-strain jobs vs. low-strain jobs, RR = 0.81, 95 percent CI: 0.53, 1.23).

Among women who had answered both the 1992 and the 1996 job content questionnaires (*n* = 27,086), we compared job types assessed 4 years apart to investigate how many nurses reported a change in job strain. The majority of person-time was accrued from job types that did not change between 1992 and 1996. Furthermore, both job-demand

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TABLE 2. Adjusted relative risk of breast cancer according to category of job strain* (*n* = 37,562), Nurses' Health Study, 1992–2000

Job strain category	No. of cases	Person-years of follow-up	Age-adjusted		Multivariate	
			RR†	95% CI†	RR‡	95% CI
Low demand/high control (low strain)§	242	60,455	1.0		1.0	
Low demand/low control (passive)	336	91,172	0.89	0.76, 1.06	0.90	0.76, 1.06
High demand/low control (high strain)	250	72,842	0.87	0.73, 1.04	0.87	0.73, 1.04
High demand/high control (active)	202	63,336	0.83	0.69, 1.01	0.83	0.69, 0.99

* Assessed by means of Karasek and Theorell's job content questionnaire (27).

† RR, relative risk; CI, confidence interval.

‡ Adjusted for age (years), age at menarche (≤12, 13, or ≥14 years), parity (nulliparous or 1, 2, or ≥3), age at first birth (<25, 25–29, or ≥30 years), family history of breast cancer in a sister or mother (yes/no), benign breast disease (yes/no), oral contraceptive use (yes, no, or missing data), current body mass index (weight (kg)/height $(m)^2$: <21, 21–22.9, 23–24.9, 25–28.9, or 29–≥40), quintile of physical activity (metabolic equivalents/week), educational attainment (registered nurse, bachelor's degree, master's degree, or doctoral degree), husband's education beyond high school (yes/no), alcohol consumption (none, <90 g/week, or ≥90 g/week), postmenopausal hormone use (never, past user for <5 years, past user for >5 years, current user for <5 years, or current user for >5 years), menopausal status (yes/no), height (≤150, 151–155, 156–160, 161–165, 166–170, 171–175, 176–180, or >180 cm), and age at menopause (≤43, 44–46, 47–49, 50–52, 53–55, 56–58, or >58 years).

§ Reference category.

scores and job-control scores from 1992 were reasonably well correlated with the scores obtained in 1996 (job demands: Pearson's $r = 0.54$; job control: Pearson's $r = 0.59$). When we restricted our analyses to women who reported no change in job strain between 1992 and 1996 (51.7 percent), associations became slightly stronger (for active jobs vs. low-strain jobs, multivariate RR = 0.77, 95 percent CI: 0.56, 1.07; for high-strain jobs vs. low-strain jobs, RR = 0.76, 95 percent CI: 0.56, 1.04).

We also separately investigated the effects of job demands and job control and found no significant associations (table 4). When we examined the association between job demands and breast cancer stratified by job control, we found no apparent difference (data not shown), and adding an interaction term for demand × control did not significantly improve the fit of the model ($\chi^2 = 1.67$, $p > 0.5$).

DISCUSSION

In this prospective study of job strain and breast cancer risk among women working primarily in nursing, we found little evidence that high strain increased breast cancer risk. In fact, women in high-strain jobs appeared to have a modestly decreased risk of breast cancer in comparison with women in low-strain jobs. We observed a 17 percent lower risk of breast cancer among active women than among low-strain women. The risk reduction was significant, ruling out an adverse effect of job strain on breast cancer risk. Job strain

TABLE 3. Adjusted relative risk of breast cancer according to self-perceived amount of stress at work (*n* = 70,830), Nurses' Health Study, 1982–2000

Self-perceived job stress	No. of cases	Person-years of follow-up	Age-adjusted RR*	95% CI*	Multivariate RR†	95% CI
None‡	384	62,214	1.0		1.0	
Light	705	121,606	0.94	0.82, 1.05	1.01	0.88, 1.16
Moderate	1,939	325,538	0.96	0.86, 1.07	0.99	0.87, 1.12
Severe	515	80,436	1.05	0.92, 1.19	1.04	0.89, 1.21

* RR, relative risk; CI, confidence interval.

† Adjusted for age (years), age at menarche (≤12, 13, or ≥14 years), parity (nulliparous or 1, 2, or ≥3), age at first birth (<25, 25–29, or ≥30 years), family history of breast cancer in a sister or mother (yes/no), benign breast disease (yes/no), oral contraceptive use (yes, no, or missing data), current body mass index (weight (kg)/height $(m)^2$: <21, 21–22.9, 23–24.9, 25–28.9, or 29–≥40), quintile of physical activity (metabolic equivalents/week), postmenopausal hormone use (never, past user for <5 years, past user for >5 years, current user for <5 years, or current user for >5 years), height (≤150, 151–155, 156–160, 161–165, 166–170, 171–175, 176–180, or >180 cm), and age at menopause (≤43, 44–46, 47–49, 50–52, 53–55, 56–58, or >58 years).

‡ Reference category.

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TABLE 4. Adjusted relative risk of breast cancer according to job demand/control, level of social support at work, or type of nursing job (*n* = 37,562), Nurses' Health Study, 1992–2000

	No. of cases	Multivariate* RR†	95% CI†
Demand/control group			
Level of demand‡			
Low§	365	1.0	
Intermediate	339	0.94	0.81, 1.09
High	326	0.90	0.78, 1.05
p for trend¶		0.19	
Level of control‡			
Low	309	0.96	0.82, 1.13
Intermediate	373	1.00	0.86, 1.16
High§	348	1.0	
p for trend¶		0.64	
Level of social support#			
High§	476	1.0	
Low	263	0.91	0.78, 1.06
Type of nursing job			
Administrative	120	1.11	0.90, 1.36
Operating room	26	0.71	0.48, 1.06
Inpatient	122	0.91	0.75, 1.12
Outpatient	127	1.13	0.92, 1.37
Educator	64	1.21	0.92, 1.58
Other nurse§	418	1.0	
Former nurse, currently in nonnursing occupation	153	0.91	0.76, 1.10

* Adjusted for age (years), age at menarche (≤12, 13, or ≥14 years), parity (nulliparous or 1, 2, or ≥3), age at first birth (<25, 25–29, or ≥30 years), family history of breast cancer in a sister or mother (yes/no), benign breast disease (yes/no), oral contraceptive use (yes, no, or missing data), current body mass index (weight (kg)/height $(m)^2$: <21, 21–22.9, 23–24.9, 25–28.9, or 29–≥40), quintile of physical activity (metabolic equivalents/week), educational attainment (registered nurse, bachelor's degree, master's degree, or doctoral degree), husband's education beyond high school (yes/no), alcohol consumption (none, <90 g/week, or ≥90 g/week), postmenopausal hormone use (never, past user for <5 years, past user for >5 years, current user for <5 years, or current user for >5 years), menopausal status (yes/no), height (≤150, 151–155, 156–160, 161–165, 166–170, 171–175, 176–180, or >180 cm), and age at menopause (≤43, 44–46, 47–49, 50–52, 53–55, 56–58, or >58 years).

† RR, relative risk; CI, confidence interval.

‡ Relative risks were mutually adjusted for demand/control.

§ Reference category.

¶ Wald test for the trend in demand or control scores, treating the scores as a continuous linear term.

Numbers do not add up to 1,030 because of missing information on social support.

was not associated with endogenous hormone levels, which further supports these findings.

Karasek and Theorell's job strain model (27) proposes an interaction between job demand and job control that produces psychological strain. According to the model, demanding jobs, when accompanied by a low level of control, are considered detrimental to health. Previous studies have provided some support for an association between high-strain jobs and cardiovascular disease (6, 7, 27). Few studies, however, have examined an association between job strain and cancer risk. Courtney et al. (19) investigated whether job stress was associated with the risk of colon cancer in a population-based case-control study containing 744 cases of colon cancer and matched controls. Low job control was associated with a modestly increased risk of colon cancer (odds ratio = 1.3, 95 percent CI: 1.0, 1.6), but high job demand was not. Preliminary findings from the Nurses' Health Study, with only 2 years of follow-up and 219 case subjects, reported no association between breast cancer risk and job strain (for high-strain jobs vs. low-strain jobs, RR = 0.78, 95 percent CI: 0.52, 1.16) (18).

Job strain was not related to cancer-related behaviors in our cohort; findings from other prospective studies are in line with our observation (34). However, to rule out the possibility that the lack of association between job strain and breast cancer risk in our data was due to uncontrolled confounding, we adjusted for many potentially confounding factors. None of them, including level of social support at the work site, altered our result. We had no information on current night-shift work and therefore were not able to account for this type of working schedule in our analyses. However, a crude comparison of lifetime years of having worked rotating night shifts (at least three nights per month) up to 1988 and job-strain dimensions as assessed in 1992 revealed no important relation between job strain and night-shift work.

We were concerned that employees with health problems might have shifted into jobs with lower strain because of their health problems, which would have led to underestimation of the effects of job strain on health. However, the associations changed little when we restricted our analyses to women who reported no changes in exposure between 1992 and 1996.

Our finding of a modest inverse association between high strain and breast cancer risk warrants consideration of at least two different scenarios in breast cancer tumorigenesis. Firstly, chronic stress, particularly when combined with low control (i.e., high strain), is hypothesized to result in detrimental changes to the neuroendocrine and immune systems (17, 35). According to Hans Selye's stress theory (36), there are two distinct forms of stress: distress, or "negative" stress, and eustress, or "positive" stress. Stressful events (i.e., distress) increase levels of stress hormones such as cortisol and the catecholamines. Animal models further suggest that chronic stress up-regulates endogenous estrogen levels (37–39). High levels of endogenous estrogen, on the other hand, are strongly associated with increased breast cancer risk among postmenopausal women (40). Therefore, the observed lower risk of breast cancer among nurses with high job demands in our study may suggest that estrogen levels are not important in this association. Further studies, particularly studies of stress hormones and the immune system, are needed to explore these mechanisms. Secondly, however, the immune system may only be indirectly involved in breast

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tumorigenesis, if at all: Breast cancer is a primarily hormone-related tumor (41), and there are strong associations between circulating levels of sex hormones and breast cancer risk (40). Thus, despite the lack of an association between job strain and breast cancer risk, we cannot rule out a possible effect of job strain on other, more immunogenic cancers.

It has been suggested that the relation between job stress and health depends on a person's position in the social hierarchy (42). The inverse association we found between active work (high demands/high control) and breast cancer risk may have reflected the somewhat higher socioeconomic position of nurses in those jobs. However, our multivariate-adjusted analyses controlled for socioeconomic position (educational attainment, spouse's educational attainment, and type of nursing).

Shortcomings of our study that potentially could explain the lack of a positive association between job strain and breast cancer risk must also be considered. Because virtually all of the participants in our cohort were registered nurses, it is possible that there was insufficient heterogeneity among the four categories of strain. However, because we were able to detect a significant inverse association in our data, it seems unlikely that the occupational uniformity of our cohort limited our ability to assess associations between job strain and breast cancer risk. Our assessment of job strain was based on self-reporting, a method in which the assessment of job conditions may itself be contaminated by worker characteristics, such as personality, negative affectivity, and workers' attitudes toward their jobs. Our inability to control for these factors could have led to a bias in our results; however, current evidence does not suggest an important role of psychosocial factors in breast cancer etiology (43). Investigators in previous studies reported a lack of interaction between job demands and job control in their analyses (44, 45). We too were unable to show a joint effect of job demands and job control on breast cancer risk. Moreover, our job stress categories may not have been the best measure of work stress in this cohort, since there continues to be debate in the psychological work-stress community about the ideal operationalization of the demand × control model: Numerous authors have noted the problems of the median split approach (46) and have recommended the quotient index approach (47). However, others have suggested that there is potential for misclassification when even 20 percent cutpoints are used to establish the high-risk group (48), which, in addition, would have made it impossible to assess active work in our study. Thus, how to best measure work stress remains to be determined. This question is particularly relevant for women, since they are more likely than men to be exposed to concurrent stress in the home environment (49). Except for stress induced by caregiving, we had limited data on stress incurred at home. In considering the effects of job stress on women's health, it is important to consider the interaction between work stress and home stress (caused by additional responsibilities in the home, such as caregiving, household chores, and child-rearing). Neglecting the effects of concurrent stresses in the home environment may result in considerable misclassification of the overall stress burden for working women. On the other hand, a recent prospective study based in the Nurses' Health Study found no association between caregiving stress and risk of incident breast cancer (50). Furthermore, controlling for caregiving stress in our multivariate models did not change our findings.

To our knowledge, this study is the largest prospective study to have explored the effects of workplace stress on breast cancer risk. Our findings do not support an increase in risk due to job strain. However, future studies should examine these relations for other cancers that are more susceptible to immune influences than breast cancer.

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