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Cohort study of cancer risk among male and female shift workers

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Key terms: cancer; cancer risk; cohort study; female; male; melatonin; shift worker

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Cohort study of cancer risk among male and female shift workers

by Judith Schwartzbaum, PhD,[1, 2, 3] Anders Ahlbom, PhD,[2] Maria Feychting, PhD[2]

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Objectives Melatonin, a hormone that inhibits experimentally induced cancers, is suppressed by nighttime exposure to light so that nighttime shift workers may be at an increased risk of cancer. Previous studies of shift workers found an increased risk of breast cancer among women and suggested a possible increased risk of colon cancer among women and prostate cancer. The present study was conducted to see whether these previous findings could be confirmed and whether shift workers are at elevated risk for cancer at additional sites.

Methods Altogether 2 102 126 male and 1 148 661 female workers were identified who worked in both 1960 and 1970. Their jobs were classified according to the percentage of shift workers, and they were followed from 1971 through 1989 or until they were diagnosed with cancer or died. Standardized incidence ratios (SIR) were used to compare the adjusted cancer incidence rates for shift workers with those for nonshift workers.

Results Cancer rates were not elevated for the male shift workers [all sites combined: N=6524 cases among shift workers, SIR 1.02, 95% confidence interval (95% CI) 1.00–1.05; prostate: N=1319, SIR 1.04, 95% CI 0.99–1.10] or for the female shift workers (all sites combined: N=268, SIR 1.00, 95% CI 0.89–1.13; breast: N=70 cases, SIR 0.94, 95% CI 0.74–1.18).

Conclusions No evidence was found for an association between shift work and breast or prostate cancer, or all cancer sites combined among shift workers.

Key terms cancer; melatonin.

It has been hypothesized that nighttime shift work may be associated with an increase in cancer risk. This hypothesis is based on experimental evidence (1, 2) that melatonin, a hormone secreted by the pineal gland, protects against cancer development. This hormone is produced at its highest levels during the night, and its expression may be suppressed by exposure to light. Stevens hypothesized that nightwork, by causing nighttime exposure to light, reduces peak melatonin production and would therefore be expected to increase the risk of breast cancer (3, 4). Recently, periodic diurnal measurements of 6-sulfatoxymelatonin levels (the major urinary metabolite of melatonin) in the urine of 170 nurses who worked day, evening, or night shifts verified the melatonin-reducing effects of fixed nightshift work (5). There are, however, only limited data on humans available regarding the effect of melatonin on cancer development. Two recent cohort studies that measured prediagnostic melatonin levels in women subsequently diagnosed with breast cancer and their controls reported conflicting results (6, 7).

The mechanism for the potential effect of melatonin on cancer risk was initially thought to be its ability to alter estrogen production (8). Therefore, of ten previous studies of nonairline shift workers and cancer (9–17) seven are of female breast cancer (9, 10, 12–14, 16–18), two are of prostate cancer (11, 18), and the last is of female colon cancer (15). In a meta-analysis of 13 studies of female breast cancer among night workers (including airline workers), Megdal et al (19) found an aggregate fixed-effects standardized incidence ratio (SIR) of 1.48 [95% incidence ratio (95% CI 1.36–1.61]. Excluding the seven studies of airline workers (who clearly differ from other shift workers because of their potential exposures to ionizing radiation (20, 21)), the aggregate SIR for the remaining six studies of shift workers was 1.51 (95% CI 1.36–1.68). However, the studies included in this meta-analysis have different definitions of exposure or varying exposure duration, and some findings are of borderline statistical significance. Since this meta-analysis was published, conflicting results from an additional study have been reported showing a decreased risk of breast

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cancer among overnight shift workers [odds ratio (OR) 0.55, 95% CI 0.32–0.94).

In addition to an effect on estrogen production, it has been suggested that melatonin inhibits cancer risk because of its antioxidant properties (22). Therefore, it is possible that, if shift work reduces melatonin production, shift workers may have an elevated risk for cancer at sites in addition to the breast, prostate, and colon. The primary purpose of our present study was to expand research on the association between shift work and cancer by looking at cancer risks at many sites among both male and female night and rotating shift workers in a large occupational cohort.

Study population and methods

Our study is a register-based cohort study covering all members of the Swedish population who were gainfully employed and working at least half time (≥20 hours per week) in 1970 and who were included in both the 1960 and 1970 population censuses. The latter condition allowed us to identify a subgroup employed as shift workers according to both the 1960 and 1970 censuses. Their inclusion in both censuses was required so that we could evaluate the effect of the duration of employment as a shift worker. Altogether 3 250 787 workers were identified, 2 102 126 men and 1 148 661 women. These workers were followed from 1971 through 1989 or to the date of their death, whichever came first. Information about date of death was obtained from the Swedish Cause of Death Register. All of the cases of cancer that occurred within the study base were identified from the nationwide Swedish Cancer Register. Both registers are maintained by the National Board of Health and Welfare. Notification to the Cancer Register is mandatory for all physicians in hospitals and other establishments for medical treatment under public or private administration. Notification is also made by pathologists and cytologists. Approximately 97% of the cases are morphologically verified. Altogether 201 508 cancer cases among men and 99 263 cases among women were identified during the observation period.

Exposure assessment

Information on each cohort member's occupations was obtained from the 1960 and 1970 censuses. The censuses also include information about each worker's industry and socioeconomic status. This occupational information was used as a basis for categorizing participants according to shift work.

Information about work schedules in different occupations within specific industries was obtained from the annual Survey of Living Conditions (ULF) conducted by Statistics Sweden during 1977–1981. Over these years, altogether 55 323 persons were randomly selected from the Swedish population, and 46 438 (84%) participated in personal interviews conducted by specifically trained interviewers. The participants answered questions about their usual occupation and workhours [eg, daytime, evening and night hours, rotating shift work with two possible shifts per day, rotating shift work with three or more possible shifts per day ("three-shift" schedule), or varying timetable]. Working a rotating shift with three or more possible shifts per day usually entails alternating daytime and nighttime workhours. Furthermore, the participants were asked to give information about when they started and ended working each day during the week preceding the interview.

For the purpose of this study, our goal was to identify occupations in which a large proportion of workers had workhours that could affect melatonin levels (ie, who had workhours during the night). Therefore, we defined shift workers as those who reported that their workplace had a rotating schedule with three or more possible shifts per day or had workhours during the night (any hour between 0100 and 0400) at least 1 day during the week preceding the interview. The latter information was included to capture also those who did not follow a "regular" working schedule, but who may have had workhours that included night work. Finally, we calculated the percentage of shift workers in each combination of job title and industry in the Survey of Living Conditions.

Thus the job-exposure matrix that we constructed contained information about the percentage of shift workers in each job title and industry combination and was linked to the census data obtained for each person in the cohort. In our analyses, we classified, as shift workers, people working in job-title and industry combinations with at least 40% shift workers.

We also conducted analyses in which we considered as exposed those working in occupation–industry combinations in which at least 70% of the participants were shift workers. The cancer incidence among the exposed persons was compared with that of people in occupation–industry combinations in which less than 30% stated that they were shift workers. The participants in occupations in which 30% to 39% of the workers were shift workers were excluded from these analyses. We also conducted analyses in which the unexposed group was defined as occupation–industry combinations in which 100% of the participants stated that they worked during the day.

In our primary analyses, the participants were categorized as exposed or unexposed to shift work according to occupation and industry in 1970 and were subsequently followed for cancer occurrence (or death) for

19 years. However, in additional analyses, we also took duration of exposure into consideration when exposure was defined as being a shift worker according to both the 1960 and the 1970 censuses.

Confounding factors

We adjusted for potential confounding by age, socioeconomic status, occupational position (employed manager, other employee, self-employed with employees, self-employed without employees), county of residence, marital status, and urbanization. Marital status and urbanization were not included in the final analyses, as they did not affect the results.

Statistical methods

We measured the association between shift work and cancer occurrence using the standardized incidence ratio (SIR) and assessed random variability with a 95% confidence interval (95% CI) on the assumption of a Poisson distribution. The expected number of cases was calculated on the basis of the number of person-years and national age (in 5-year age categories) and calendar-year specific incidence rates (including persons resident in Sweden at the time of both the 1960 and 1970 censuses who reported gainful employment in 1970 and worked at least half time). The confounding factors described in the previous paragraph were taken into account.

Results

Among the men, approximately 1% of the participants worked in occupations in which at least 70% stated that they were shift workers. The corresponding percentage for women was only 0.06% (N=756). About 3% of the men and 0.3% of the women worked in occupations in which at least 40% was shift workers (table 1). Most of the male shift workers (75.1%) were employees in industry or transport, while the female shift workers were either employees in industry or transport (52.1%) or in technical or commercial occupations (47.8%).

The most common shiftwork occupations among the men were paper and paperboard worker, paper pulp worker, furnace worker, firefighter, policeman, civilian protective service worker (in addition to police work), and railway engineer driver. The most common shift work occupations among the women differed from those among the men and were crane and hoist operator (in basic metal industry), delivery women (in paper and paper products manufacturing and printing and publishing industries), and midwife.

During the study period, 201 508 cancer cases occurred among the men and 99 263 among the women. Tables 2 and 3 show standardized incidence ratios for occupations reported in the 1970 census, and the overall pattern indicates no relation between shift work and prostate, colon, or breast cancer or all sites combined. Most of the standardized incidence ratios for the men

Table 1. Descriptive information for the cohort with people included in the Swedish censuses in 1960 and 1970, who were gainfully employed in 1970 and worked at least 20 hours per week.

Characteristic	Total population				Shift workers [a]			
	Men (2 102 126)		Women (1 148 661)		Men (69 759)		Women (3 057)	
	N	%	N	%	N	%	N	%
Age in 1970								
≤19 years	87 380	4.2	73 147	6.4	2 229	3.2	26	0.9
20–29 years	444 806	21.2	293 269	25.5	13 915	20.2	746	24.4
30–39 years	408 597	19.4	201 584	17.6	12 809	18.6	709	23.2
40–49 years	452 433	21.5	266 103	23.2	16 049	23.3	802	26.2
50–59 years	457 158	21.7	232 213	20.2	16 358	23.8	588	19.2
≥60 years	251 752	12.0	82 345	7.2	6 599	9.6	186	6.1
Socioeconomic status								
Self-employed & employees in agriculture or forestry	204 227	9.7	52 979	4.6	–	.	–	.
Self-employed in industry, trade, transport or service production	136 791	6.5	40 492	3.5	2 273	3.3	2	0.0
Self-employed professionals & upper-level executives	67 298	3.2	11 226	1.0	–	.	–	.
Employees in technical, humanistic, office technique & commercial occupations	644 352	30.7	692 207	60.3	17 106	25.2	1 461	47.8
Employees in industry & transport	992 683	47.2	164 674	14.3	48 580	71.5	1 594	52.1
Employees in service occupations	36 799	1.8	185 182	16.1	–	.	–	.
Military	16 593	0.8	–	.	–	.	–	.
Unknown occupation	3 383	0.2	1 901	0.2	–	.	–	.

[a] Shift work was defined as occupations in which at least 40% of the workers either reported that they worked rotating shifts with three possible shifts ("3-shift" schedule) or had workhours during the night at least 1 day preceding the interview week.

Table 2. Standardized incidence ratios for shift workers [a] in the 1970 census, by cancer diagnosis—2 102 126 men followed from 1971 through 1989. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Diagnosis [b]	Expected (N)	Observed (N)	SIR [c]	95% CI
Lip (140)	61.5	63	1.02	0.80–1.31
Tongue (141)	21.5	15	0.70	0.39–1.15
Salivary glands (142)	18.8	22	1.17	0.77–1.78
Mouth, other & nonspecific (144)	22.9	20	0.87	0.53–1.35
Esophagus (150)	77.4	60	0.78	0.60–1.00
Stomach (151)	387.6	406	1.05	0.95–1.15
Small intestine (152)	36.3	34	0.94	0.67–1.31
Colon (153)	435.9	449	1.03	0.94–1.13
Rectum (154)	321.0	326	1.02	0.91–1.13
Liver (155)	152.7	158	1.03	0.89–1.21
Pancreas (157)	233.3	235	1.01	0.89–1.14
Larynx (161)	79.3	79	1.00	0.80–1.24
Lung & trachea (162)	744.7	706	0.95	0.88–1.02
Prostate (177)	1267.2	1319	1.04	0.99–1.10
Testis (178)	43.4	39	0.90	0.66–1.23
Kidney (180)	297.9	330	1.11	0.99–1.23
Urinary organs (181)	466.0	494	1.06	0.97–1.16
Malignant melanoma (190)	192.8	189	0.98	0.85–1.13
Skin (191)	197.5	224	1.13	1.00–1.29
Nervous system (193)	211.8	218	1.03	0.90–1.18
Thyroid gland (194)	36.2	49	1.35	1.02–1.79
Endocrine glands (195)	86.5	90	1.04	0.85–1.28
Connective tissue, muscle (197)	47.1	46	0.98	0.73–1.30
Other & unspecified (199)	182.8	216	1.18	1.03–1.35
Non-Hodgkins lymphoma (200)	200.5	203	1.01	0.88–1.16
Hodgkins disease (201)	43.3	44	1.02	0.76–1.36
Multiple myeloma (203)	100.0	111	1.11	0.92–1.34
Lymphatic leukemia (204)	101.0	95	0.94	0.77–1.15
Myeloid leukemia (205)	62.2	58	0.93	0.72–1.21
All cancer sites combined	6371.4	6524	1.02	1.00–1.05

[a] Shift work was defined as occupations in which at least 40% of the workers either reported that they worked rotating shifts with three possible shifts ("3-shift" schedule) or had workhours during the night at least 1 day preceding the interview week. Occupations in which <30% of the workers stated a 3-shift schedule or workhours during the night were regarded as unexposed.

[b] The code of International Classification of Diseases, 7th revision, is shown in parentheses. Only diagnoses with at least 20 observed or expected cases have been presented.

[c] Adjusted for age, socioeconomic status, occupational position, and county of residence.

Table 3. Standardized incidence ratios for shift workers [a] in the 1970 census, by cancer diagnosis—1 148 661 women followed from 1971 through 1989. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Diagnosis [b]	Expected (N)	Observed (N)	SIR [c]	95% CI
Stomach (151)	7.39	9	1.22	0.56–2.31
Colon (153)	17.07	16	0.94	0.54–1.52
Rectum (154)	8.77	4	0.46	0.12–1.17
Liver (155)	6.85	8	1.17	0.50–2.30
Pancreas (157)	7.33	8	1.09	0.47–2.15
Lung & trachea (162)	12.43	14	1.13	0.62–1.89
Breast (170)	74.73	70	0.94	0.74–1.18
Cervix uteri (171)	12.96	18	1.39	0.82–2.19
Corpus uteri (172)	16.76	17	1.01	0.59–1.62
Ovary (175)	18.69	15	0.80	0.45–1.32
Kidney (180)	7.41	7	0.94	0.38–1.95
Urinary organs (181)	5.91	9	1.52	0.70–2.89
Malignant melanoma (190)	8.36	11	1.32	0.66–2.35
Skin (191)	3.79	6	1.58	0.58–3.44
Nervous system (193)	9.78	9	0.92	0.42–1.75
Endocrine glands (195)	7.07	2	0.28	0.03–1.02
Other & unspecified (199)	7.78	9	1.16	0.53–2.20
Non-Hodgkins lymphoma (200)	5.99	4	0.67	0.18–1.71
All cancer sites combined	267.1	268	1.00	0.89–1.13

[a] Shift work was defined as occupations in which at least 40% of the workers either reported that they worked rotating shifts with three possible shifts ("3-shift" schedule) or had workhours during the night at least 1 day preceding the interview week. Occupations in which <30% of the workers stated a 3-shift schedule or workhours during the night were regarded as unexposed.

[b] The code of International Classification of Diseases, 7th revision, is shown in parentheses. Only diagnoses with at least 5 observed or expected cases are presented.

[c] Adjusted for age, socioeconomic status, occupational position, and county of residence.

were close to the null, while those for the women represented a range with decreasing sample sizes being associated with larger and also smaller standardized incidence ratios. Possibly reflecting an increased risk of thyroid cancer is the slightly elevated standardized incidence ratio for thyroid cancer among the men (SIR 1.35, 95% CI 1.02–1.79). [The numbers of observed or expected cases of thyroid cancer among the women were not sufficient, that is, at least five in either category, for the results for this tumor to be included for the women (table 3)].

In tables 4 and 5, the definition of exposure has been changed to include only workers who reported working in occupations in which at least 40% of the employees reported shift work in both the 1960 and 1970 censuses. Again, the overall results were null, with the exception that the standardized incidence ratio for thyroid cancer among the men continued to be slightly elevated (SIR 1.35, 95% CI 0.92–1.98).

To evaluate the degree of sensitivity of our findings to changes in the definition of shift work, we performed an analysis in which we changed the definition of shift work to include only job categories in which at least 40% of those surveyed reported working both night and day during the week preceding the interview (ie, we did not consider as exposed rotating shift workers who did not report working during the night or those working only at night). The results of the analyses using this redefinition (not shown) were almost the same as they are in tables 2 and 3. For the men only, we next restricted the study to occupations characterized by at least 70% of the workers who said they worked rotating or night shifts (as opposed to at least 40% as in tables 2–5). To control for potential unmeasured confounding, this analysis was restricted to employees within industry

Table 4. Standardized incidence ratios for persons working shift work[a] in both 1960 and 1970, by cancer diagnosis—2 102 126 men followed from 1971 through 1989. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Diagnosis[b]	Expected (N)	Observed (N)	SIR[c]	95% CI
Lip (140)	34.48	33	0.96	0.68–1.35
Tongue (141)	12.44	11	0.88	0.44–1.58
Salivary glands (142)	10.27	13	1.27	0.67–2.16
Mouth, other & unspecific (144)	13.92	14	1.01	0.55–1.69
Esophagus (150)	46.49	25	0.54	0.37–0.79
Stomach (151)	224.05	233	1.04	0.91–1.18
Small intestine (152)	21.16	22	1.04	0.68–1.58
Colon (153)	261.10	266	1.02	0.90–1.15
Rectum (154)	192.42	197	1.02	0.89–1.18
Liver (155)	90.44	91	1.01	0.82–1.24
Pancreas (157)	138.53	147	1.06	0.90–1.25
Larynx (161)	48.65	50	1.03	0.78–1.36
Lung & trachea (162)	441.18	397	0.90	0.82–0.99
Prostate (177)	761.51	780	1.02	0.95–1.10
Testis (178)	14.63	9	0.61	0.28–1.17
Kidney (180)	177.65	203	1.14	1.00–1.31
Urinary organs (181)	282.03	300	1.06	0.95–1.19
Malignant melanoma (190)	110.59	116	1.05	0.87–1.26
Skin (191)	120.64	145	1.20	1.02–1.41
Nervous system (193)	115.38	101	0.88	0.72–1.06
Thyroid gland (194)	19.21	26	1.35	0.92–1.98
Endocrine glands (195)	48.03	48	1.00	0.75–1.33
Connective tissue, muscle (197)	27.03	30	1.11	0.78–1.59
Other & unspecified (199)	107.49	136	1.27	1.07–1.50
Non-Hodgkins lymphoma (200)	116.95	109	0.93	0.77–1.12
Hodgkins disease (201)	20.75	15	0.72	0.40–1.19
Multiple myeloma (203)	59.93	65	1.08	0.85–1.38
Lymphatic leukemia (204)	59.41	63	1.06	0.83–1.36
Myeloid leukemia (205)	33.87	31	0.92	0.64–1.30
All cancer sites combined	3751.33	3799	1.01	0.98–1.05

[a] Shift work was defined as occupations in which at least 40% of the workers either reported that they worked rotating shifts with at least three possible shifts ("3-shift" schedule) or had workhours during the night at least 1 day preceding the interview week. Occupations in which <30% of the workers stated that they worked a three-shift schedule or during the night were regarded as unexposed.

[b] The code of International Classification of Diseases, 7th revision, is shown in parentheses.

[c] Adjusted for age, socioeconomic status, occupational position, and county of residence.

and transportation, as most of the shift workers were found in these occupational categories. The results (not shown) were similar to those in table 2, except that a smaller sample size produced broader confidence intervals. The standardized incidence ratio for thyroid cancer was still elevated (SIR 1.73, 95% CI 1.05–2.67). In the last supplemental analysis, the comparison group was restricted to occupations that had no rotating shift or night workers. Again, the results (not shown) were null overall and, in that sense, comparable with those in table 2. However, the standardized incidence ratio for thyroid cancer (SIR 1.08, 95% CI 0.82–1.43) was no longer elevated.

Table 5. Standardized incidence ratios for persons working shift work[a] in both 1960 and 1970, by cancer diagnosis—1 148 661 women followed from 1971 through 1989. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Diagnosis[b]	Expected (N)	Observed (N)	SIR[c]	95% CI
Stomach (151)	3.07	5	1.63	0.53–3.80
Colon (153)	7.11	3	0.42	0.09–1.23
Liver (155)	2.78	4	1.44	0.39–3.69
Pancreas (157)	3.23	4	1.24	0.34–3.18
Lung & trachea (162)	4.69	6	1.28	0.47–2.79
Breast (170)	28.91	28	0.97	0.67–1.40
Cervix uteri (171)	3.50	5	1.43	0.46–3.34
Corpus uteri (172)	7.11	8	1.13	0.49–2.22
Ovary (175)	7.08	8	1.13	0.49–2.23
Kidney (180)	3.41	1	0.29	0.01–1.63
Urinary organs (181)	2.63	3	1.14	0.24–3.33
Malignant melanoma (190)	2.60	5	1.92	0.62–4.49
Skin (191)	1.80	3	1.67	0.34–4.88
Nervous system (193)	3.37	6	1.78	0.65–3.88
Endocrine glands (195)	2.34	1	0.43	0.01–2.39
Other & unspecified (199)	2.94	3	1.02	0.21–2.99
Non-Hodgkins lymphoma (200)	2.18	2	0.92	0.11–3.32
All cancer sites combined	103.00	103	1.00	0.82–1.21

[a] Shift work was defined as occupations in which at least 40% of the workers either reported that they worked rotating shifts with at least three possible shifts ("3-shift" schedule) or had workhours during the night at least 1 day preceding the interview week. Occupations in which <30% of the workers reported a 3-shift schedule or workhours during the night were regarded as unexposed.

[b] The code of International Classification of Diseases, 7th revision, is shown in parentheses.

[c] Adjusted for age, socioeconomic status, occupational position, and county of residence.

Discussion

In a large retrospective occupational cohort study with 19 years of follow-up, we found no evidence for an association between shift work and cancer incidence rates at any site or all sites combined, with the possible exception of thyroid cancer. Our findings are not consistent with those from two recently published studies showing an increased risk of prostate cancer among rotating shift workers (11, 18), nor do they support results from six previous studies (9, 10, 12, 14, 16, 17) suggesting an increased risk of breast cancer among female shift workers, nor are they consistent with findings from a study that reported an elevated rate of colorectal cancer among female shift workers (15).

Although our findings were negative overall, there was some evidence for a weak association between shift work and thyroid cancer among the men. However, we found no additional evidence of a role for melatonin in cancer development among shift workers, and our findings were based on only 49 cases of thyroid cancer among the men so that the elevation of the standardized incidence ratio for thyroid cancer may merely have been a result of sampling variation.

With the exception of two studies on prostate cancer (11, 18), previous studies of cancer among male shift workers have been restricted to airline personnel (23). A Nordic study that included 10 051 male pilots (24) found increased risks for both melanoma (OR 2.3, 95% CI 1.7–3.0) and nonmelanoma skin cancer (OR 2.1, 95% CI 1.7–2.8) among pilots, as well as an increased risk for prostate cancer among those who had been employed for at least 20 years (OR 1.7, 95% CI 0.4–5.1). These findings were confirmed in a recent meta-analysis that included both military and civilian pilots (25). Among female flight attendants, seven studies found elevated risks of breast cancer, and six studies reported a higher than expected malignant melanoma risk (20, 26). Airline personnel, however, differ from other shift workers both with respect to their occupational exposures to cosmic radiation (21) and their greater opportunity for recreational solar exposure. It is therefore difficult to know which factors are responsible for the observed excess cancer risks in this group of workers (20).

A possible source of our failure to observe an association between shift work and breast cancer among women, if such an association exists, may have been that our assignment of exposure was based on aggregate rather than individual categories. Although we used each person's reported occupation in the 1960 and 1970 census, we defined exposure according to the proportion of people in each job category reporting shift work in large national surveys (N=46 438) that were nevertheless independent of the present cohort. This method of measuring exposure may lead to exposure misclassification as, for example, when a worker in a job category with a low proportion of shift workers, and, therefore, classified as unexposed, actually does shift work. However, when we reduced the degree of potential misclassification among the men by defining exposure as working in occupations in which at least 70% reported shift work, we observed similar null results. Furthermore, when we restricted the unexposed group to only occupations that had no rotating shift or night workers, our findings continued to be negative.

In addition, misclassification may be less than first perceived when exposure is defined as occupations with at least 40% shift workers. This definition does not mean that specificity is only 60% but rather, because only a small percentage of occupations was defined as exposed, most of the workers were correctly classified as unexposed.

One previous study of shift work used an exposure assessment method that was similar to ours. Hansen (10) (table 6) conducted a record linkage case–control study in Denmark in which the individual employment histories of 7035 women with breast cancer and their individually matched controls were obtained from a nationwide pension register. The women were classified as exposed if they had been working in occupations in which at least 60% of the female respondents to a national survey had reported nighttime schedules. Using this aggregate definition of exposure, Hansen found an increased risk of breast cancer for women who worked at night (OR 1.5, 95% CI 1.2–1.7).

Although not an ecologic study, Lie et al (12) (table 6) imputed nightshift work in their case–control study of 537 breast cancer cases and 2143 controls nested in a cohort of Norwegian nurses. To do so, they assumed that nurses who had reported working in infirmaries, except for those with nonclinical job titles, worked at

Table 6. Results and summary of previous studies on the association between shift work and breast cancer among women. (95% CI = 95% confidence interval)

Study (length of exposure)	Effect measure	95% CI	Cases (N)
Tynes et al, 1996 (17) (50 years and older)			
Radio and telegraph operators			
None	1.0		3
Low	3.2	0.6–17.3	6
High	4.3	0.7–26.0	12
Hansen, 2001 (10)			
Primarily airline transport service workers and catering personnel in exposed category			
Daytime	1.0		5847
Ever worked at least 6 months on night shift	1.5	1.2–1.7	434
>6 years	1.7	1.3–1.7	117
Davis et al, 2001 (9)			
Exposed occupations not described			
Never worked graveyard shift	1.0		713
Ever worked graveyard shift during 10 years preceding diagnosis	1.6	1.0–2.5	54
<3 years	1.4	0.6–3.2	15
3–10 years	1.6	0.8–3.2	19
Schernhammer et al, 2001 (16)			
Nurses			
Never shift work	1.0		925
1–14 years rotating or night shift	1.08	0.99–1.18	1324
15–29 years	1.08	0.90–1.30	134
≥30 years	1.36	1.04–1.78	58
Schernhammer et al, 2006 (14)			
Nurses			
Never shift work	1.0		441
1–9 years rotating or night shift	0.98	0.87–1.10	816
10–19 years	0.91	0.72–1.16	80
≥20 years	1.79	1.06–3.01	15
Lie et al, 2006 (12)			
Nurses			
No nightwork	1.0		50
1–14 years of nightwork	0.95	0.67–1.33	362
15–29 years of nightwork	1.29	0.82–2.02	101
≥30 years of nightwork	2.21	1.10–4.45	24
O'Leary et al, 2006 (13) (night shift)			
Exposed occupations not described			
Never shift work	1.0		313
Ever overnight shift work	0.55	0.32–0.94	26
<8 years	0.74	0.32–1.68	11
≥8 years	0.32	0.12–0.83	6

night. Using this estimation method, they found that nurses who worked nights for 30 years or more had higher risks of breast cancer than did nurses who did not work at night after doing so in graduate school (OR 2.22, 95% CI 1.10–4.45) .

Our inability to find an association between shift work and breast cancer may also have been due to our lack of control of risk factors for breast cancer other than marital status and socioeconomic status. Yet we did restrict our study to only economically active people working at least 20 hours per week, and this procedure should have limited any bias caused by the healthy worker effect and, to some degree, also effects caused by parity because housewives were not included in the study. All previous studies of shift work and breast cancer were able to adjust for risk factors for breast cancer to varying degrees. However, none of the studies that reported both crude and adjusted odds ratios (12–17) found a meaningful change in their effect estimates after adjustment, so perhaps known risk factors for breast cancer are not confounders in the present context.

Another reason that our findings for breast cancer among women may differ from those of previous studies is that we focused on different occupations and defined shift work and time of exposure differently. Results of previous studies of female shift workers and breast cancer risk are shown in table 6. Although all of the studies in this table evaluated the risk for breast cancer among shift workers, the occupations examined are diverse and may have subjected the workers to different risks. For example, most of the shift workers in our study were found in industry or transportation; nurses were not defined as shift workers because most Swedish nurses work either a two-shift (with no nighttime hours) schedule or during the day. A small proportion of nurses work only nighttime hours. Three previous studies were restricted to nurses, and one consisted of a high proportion of airline workers. These different occupations may produce associations that result from exposures specific to shift work in that occupation. For example, exposure to cosmic radiation may be greater during long international flights for which nightshift work is required than it is during short domestic flights for which it is not (20). In addition, times of exposure relative to cancer diagnosis differ in previous studies. For example, Davis et al (9) found that working the graveyard shift led to increased breast cancer risk less than 3 years later (OR 1.4, 95% CI 0.6–3.2), while Schernhammer et al (14) found an increased risk of breast cancer only among nurses working at least 20 years on rotating shifts [hazard ratio (HR) 1.79, 95% CI 1.06–3.01]. However, in an earlier study (16), Schernhammer et al found that nurses required at least 30 years of shift work to have an elevated risk of breast cancer (HR 1.36, 95% CI 1.04–1.78). Small numbers of cases are also a problem in some of these studies. For example, although not shown in table 6, a study of rotating shift work and prostate cancer was based on only seven prostate cancer cases among rotating shift workers (HR 3.0, 95% CI 1.2–7.7), producing an unrealistically high upper confidence limit and the related concern that the result may be a false positive finding (27, 28) . In summary, results from previous studies of shift workers, although apparently consistent, are based on heterogeneous populations and different definitions of shift work and may also reflect sampling variation. These inconsistencies and problems may account for our failure to confirm results from previous studies.

Our negative results, however, should be considered in the context of extensive animal evidence suggesting a cancer-inhibiting role of melatonin and its reduction by nocturnal exposure to light. For example, Blask et al (1) injected rats bearing human breast cancer xenografts with blood from 12 human females collected during the day, 2 hours of darkness at night, and following 90 minutes of nighttime exposure to bright light. While melatonin-rich blood collected after exposure to darkness at night inhibited tumor growth, melatonin-deficient blood collected during the day or after nighttime light exposure did not. In contrast, a recent survey of melatonin levels in rotating shift workers by Borugian et al (29) called into question the hypothesis that they have consistently low levels of melatonin. In a study of 24-hour melatonin levels of saliva from 5 office workers and 17 nurses, they found that these workers had lower than normal melatonin levels during sleep but higher than normal levels on arising and during work. As these authors wrote, it is unclear whether rotating shift workers produce less melatonin or produce melatonin at different times and what the biological implications of variations in times of melatonin production are. Therefore, biological evidence of a causal mechanism does not, in itself, provide evidence for the presence of that mechanism in shift workers.

It is important to note that the rationale for a possible association between shift work and increased cancer risk is not restricted to the melatonin hypothesis. There are additional potential physiological effects of shift-work-related disturbances of the circadian system that may increase cancer risk (30) . For example, shift work is associated with metabolic syndrome and increased oxidative stress, and both of these conditions have been shown to be related to increased cancer risk.

Currently, we do not have sufficient evidence to determine whether our null results correctly describe the absence of associations between shift work and cancer in men and women. Although there may be specific problems with each previous study, the collective picture they provide is too consistent to be dismissed by the present ecologic study together with a single conflicting case–control study (13). Nor can we completely dismiss

the biological evidence for a potential association. Therefore, we cannot now draw definitive conclusions either about the association between shift work and cancer or its putative mechanism, the relation between melatonin production and cancer. Studies of shift workers currently being conducted (31) may provide clearer evidence either for or against both the association and the mechanism.

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