

Increased Breast Cancer Risk among Women Who Work Predominantly at Night

Johnni Hansen

Irregular working hours, including working at night, have serious psychological and physiological effects. In a nationwide population-based case-control study, we investigated the breast cancer risk among 30- to 54-year-old Danish women who worked predominantly at night. Individual employment histories were reconstructed back to 1964 for each of 7035 women with breast cancer and their individually matched controls from the records of a nationwide pension scheme with compulsory membership. Odds ratios, including 5 years of induc-

tion time and adjusted for socio-economic status, age at the birth of first and last child and number of children, were estimated by conditional logistic regression analysis. The odds ratio for breast cancer among women who worked at night at least half of a year was 1.5 (95% confidence interval, 1.2 to 1.7), and there was a tendency to increasing odds ratio by increasing duration of nighttime employment. (Epidemiology 2001;12:74-77)

Keywords: women, breast neoplasms, alcohol drinking, melatonin, shift work.

Working irregular hours, including night and shift work, has been acknowledged as an occupational health and safety problem since a century ago, as it has serious social, psychological, and physiological effects.¹⁻³ Acute problems such as drowsiness and accidents have been studied most intensively¹; chronic health problems like gastrointestinal and coronary heart diseases are also relatively well described, although the mechanisms are not fully understood.²⁻⁶ It has been suggested that women with irregular working hours are at increased risk for breast cancer,⁷ since work that requires the use of artificial light (in the evening, night, or early morning) leads to suppression of pineal secretion of melatonin, which may induce continuous production of estrogen involved in breast carcinogenesis.⁸

Irregular work schedules have become increasingly more common in most industrialized societies: in 1980, approximately 26% of men and 18% of women in the United States labor force worked variable shift schedules.² About 20% of the female Danish workforce works at night.⁹ We conducted a case-control study to investigate whether women in Denmark who work predominantly at night have an increased risk for breast cancer.

Subjects And Methods

CASES

Altogether 7565 women with confirmed primary breast cancer, born in the period 1935-59 and 30-54 years of age at the time of diagnosis, were identified in the files of the Danish Cancer Registry, which contains information on diagnosis (ICD-7), names, sex, and unique personal identification number.¹⁰ Information on past employment was reconstructed by record linkage with the files of the nationwide pension fund, adherence to which has been compulsory for all wage-earners in Denmark aged 18-66 years since its establishment in 1964. The fund retains computerized information about each job held, including the name and 10-digit personal identification number of the employee, the dates of start and end of employment and the company name and unique company number of the employer.¹¹ This information is kept even after the employees have retired or died. No employment records existed for 530 of the breast cancer patients (7%), who were never part of the workforce (mainly housewives and assisting farmers' wives), leaving 7035 female breast cancer patients who had an employment history.

CONTROLS

One control subject per case was drawn at random from the files of the Central Population Registry, identified by name, sex, and personal identification number, and matched to the cases on year of birth and sex. Controls had to be alive without cancer and to have been an employee (member of the national pension fund) before the date of diagnosis of the corresponding case. The employment histories of the control subjects were retrieved from the files of the pension fund in the

From Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.

Address correspondence to: Johnni Hansen, Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.

Submitted July 12, 1999; final version accepted August 11, 2000.

Copyright © 2001 by Lippincott Williams & Wilkins, Inc.

TABLE 1. Trades in Which at Least 40% of Female Employees Work at Night

Trade	No. of Women	% Working at Night
Hospitals	83,896	41
Furniture manufacture	3,365	50
Cleaning services	10,889	51
Water transport services	1,503	59
Manufacture of beverages	2,942	64
Land transport services	6,283	69
Catering	24,511	70
Air transport services	4,912	71

Source: Hansen, 1978.¹³

same way as for cases. The principles of the entire data linkage process have been described in detail elsewhere.^{11,12}

WORK SCHEDULES

Information on occupational groups in which employees work predominantly at night was obtained from a nationwide interview-based survey on living and working environment conditions in 1976 among 2603 women.¹³ Night work was most prevalent among unskilled, and relatively young female employees. Trades in which at least 40% of the female responders worked at night are listed in Table 1.

Information on the jobs of each case and control subject was converted into a job classification based on an extended version of the International Standard Industrial Classification of all Economic Activities,¹⁴ used to classify all companies in Denmark by the National Bureau of Statistics. The non-historical job title of each study subject was obtained from the Central Person Registry. Women were considered to work predominantly at night if they had been employed for at least half a year in one or more of the trades in which at least 60% of the female responders had nighttime schedules. Women with the job title of secretary were classified as non-exposed. To reduce the misclassification of nighttime work, study subjects employed in trades with between 40% and 59% night-work were omitted from the study (754 cases and 1011 controls). To take account of induction time, the 5, 10, or 15 years before breast cancer was diagnosed were disregarded, with equivalent treatment for each matched control.

INFORMATION ON CHILDREN

We obtained the birth date of every child of the study subjects from the Central Population Registry, which records information on children of anyone born since 1934. We calculated from these dates the mother's age at the time her first and last child were born.

INFORMATION ON ALCOHOL CONSUMPTION

Drinking alcoholic beverages may be a cause of breast cancer.¹⁵ Individual information on alcohol drinking pattern was not available for the study subjects, but the survey from which the night-work trades were identified

also provided information on number of alcoholic drinks consumed per week, where one drink was defined as one beer, one glass of wine or one small glass of hard liquor. The weekly alcohol consumption of women employed in selected trades and in all trades combined is shown in Table 2.

SOCIOECONOMIC STATUS

The socioeconomic status of each woman was based on the job title, categorized into one of five groups according to the definitions developed by the Danish Institute of Social Sciences.¹⁶ The highest status (1) includes corporate managers and academics; group (2) includes proprietors and managers of small businesses and teachers; group (2) includes technicians and nurses; group (3) includes skilled workers; group (5) includes unskilled workers.

STATISTICAL ANALYSIS

To adjust for socioeconomic status and reproductive factors (number of children, age at birth of first and last child), we estimated odds ratios (ORs) and 95% confidence intervals (CIs) by conditional logistic regression analysis using the statistical package EPICURE.¹⁷

Results

Table 3 shows the adjusted ORs for breast cancer among women who had worked for at least half a year in trades with predominantly (>60%) night work in comparison with women employed in all other trades with less than 40% night work. In the selected trades, the OR for breast cancer was in the range from 1.1 to 1.9. For all night-work combined, the OR was 1.5 (95% CI = 1.3–1.7). The OR for women who had worked for less than half a year in the selected trades was close to unity. We found a positive trend with increasing duration of work at night. Thus, the risk of breast cancer among women with over 6 years of employment in trades with predominantly night work is 1.7 times that of daytime workers. When the 5-year induction time was ignored, the OR decreased marginally. We found little change in relative risk with longer induction times.

Discussion

In this nationwide study in Denmark, we found a 1.5-fold increase in risk for primary breast cancer among

TABLE 2. Alcohol Consumption in Trades in Which at Least 60% of the Female Employees Work at Night

Trade	Drinks per Week	
	Mean	Median
Manufacture of beverages	8.8	6.0
Land transport services	4.6	6.0
Catering	6.6	6.0
Air transport services	7.5	3.5
All female employees	3.5	1.1

Source: Hansen, 1978.¹³

TABLE 3. Odds Ratios for Breast Cancer among Women Employed for at Least Half a Year in Trades with Predominantly Night Work (5 Years Induction Time Included)

Trade	Cases	Controls	OR*	95% CI
Daytime†	5847	5723	1	
Manufacture of beverages	41	36	1.2	0.7–1.8
Land transport services	39	37	1.1	0.7–1.7
Catering	300	201	1.5	1.2–1.7
Air transport services	54	27	1.9	1.6–3.0
All night work combined	434	301	1.5	1.3–1.7
Employments > 6 years	117	63	1.7	1.3–1.7

* Odds ratio adjusted for age, social class, age at birth of first child, age at birth of last child, and number of children.

† Reference category.

women who had worked for least half a year in any trade with predominantly night work. Further, the relative risk tended to increase with increasing duration of night work.

Little is known about the causes of breast cancer or about the steady increase in incidence.¹⁸ Known risk factors, such as reproductive history, family history of breast cancer, prior benign breast disease, and exposure to ionizing radiation and less well-established factors such as alcohol drinking together explain only 20–40% of all breast cancers.^{19,20}

In our study, we adjusted for reproductive events; furthermore, there is no reason to believe that a family history of breast cancer, prior benign breast disease or exposure to ionizing radiation is more prevalent among women who work at night than among the general population of employed women. Regular alcohol consumption may partly contribute to the observed increase in risk, as the rate of alcohol drinking was higher in the selected trades with over 60% night work than among female employees in general (Table 2). Greater alcohol consumption among night-time workers than in the general population has been reported in other studies.² On the other hand, most of the women in the trades we investigated are of lower social classes, in which there is usually a lower relative risk for breast cancer.²¹ Some occupational pollutants are potentially carcinogenic to the female breast, *eg* chlorinated hydrocarbon pesticides, organic solvents, polychlorinated biphenyls, and certain endocrine disrupting chemicals,^{21–23} but such exposures are uncommon in the selected trades.²⁴ Adjustment of the estimated ORs for social class may have partly controlled for alcohol consumption and other potential confounders such as diet, age at menarche, and menopause.²⁵ Therefore, alcohol consumption and confounding by other factors is unlikely to explain the observed increase in breast cancer risk. Further, information bias is unlikely in this study, since employment histories and reproductive and socioeconomic factors were assessed independently and before the cancer diagnosis. Possible misclassification of women in the selected trades, classifying those who worked during the day as instead working at night, would dilute an increased relative risk.

Descriptive studies of women with various kinds of night work have relatively consistently shown up to threefold increases in relative risk for breast cancer; such

groups include nurses,^{26–29} flight attendants,^{30–33} and radio and telegraph operators.⁷ In the latter group, a positive trend was found with duration of shift work.⁷ These studies were conducted for purposes other than studying an association of carcinogenicity with night work, however, and most did not include adjustment for major confounders such as reproductive events.

Studies in experimental animals have shown that uninterrupted ocular exposure to visible light increases the risk of mammary cancer.^{34,35} The biological mechanism for this effect is assumed to be suppression of normal nocturnal melatonin production in the pineal gland due to exposure to light during the night. The result is decreased blood melatonin levels.³⁶ Melatonin is regulated via the retina by the light/dark cycle and influences the biological regulation of circadian rhythm, sleep, and probably tumor growth.³⁶ It is synthesized by the pineal gland, predominantly at night, and is immediately secreted into the blood. Exposure to relatively weak light (*ie* about 200–400 lux) during night-time quickly decreases melatonin secretion.^{37,38} Physiological concentrations of melatonin have been shown *in vitro* to inhibit the growth of human breast cancer cells.³⁹ Additionally, low serum melatonin concentrations have been reported in women with oestrogen-receptor-positive breast cancer.³⁶ Impaired pineal secretion of melatonin is also associated with 5-lipoxygenase activity in B-lymphocytes, and increased ovarian oestrogen and pituitary gonadotropin production,⁴⁰ which are associated with increased breast cancer risk. The mechanisms involved in the apparent protective effects of melatonin against tumors are thought to include a direct antiproliferative effect, an enhanced immune response and scavenging of free radicals.^{36,41} Totally blind women, who do not detect light through the eyes and consequently do not have inhibition of melatonin secretion, have an approximately 50% lower relative risk of breast cancer than other women.^{42–44} An association between chronobiological disturbance and breast cancer, explained by the melatonin hypothesis, is therefore biologically plausible.³⁶

Our finding that women who work predominantly at night have an increased relative risk for breast cancer, after adjustment for confounders such as reproductive factors and social class, is in agreement with reports from small cohort studies, in which, however, no adjustment was made for major confounders.^{7,26–33}

Acknowledgment

We thank Erik Jørgen Hansen, National Institute of Social Sciences and Danish Data Archives, for providing data from the national survey on living and working environment conditions.

References

1. Härmä M. New times are here - are we ready? *Scand J Work Environ Health* 1998;24:3–6.
2. Gordon NP, Cleary PD, Parker CE, Czeisler CA. The prevalence and health impact of shiftwork. *Am J Public Health* 1986;76:1225–1228.
3. Spurgeon A, Harrington JM, Cooper CL. Health and safety problems associated with long working hours. A review of the current position. *Occup Environ Med* 1997;54:367–375.

4. Olsen O, Kristensen TS. Impact of work environment on cardiovascular diseases in Denmark. *J Epidemiol Community Health* 1991;45:4-10.
5. Kristensen TS. Cardiovascular diseases and the work environment. A critical review of the epidemiologic literature on nonchemical factors. *Scand J Work Environ Health* 1989;15:165-179.
6. Tuchsén F, Jeppesen HJ, Bach E. Employment status, non-daytime work and gastric ulcer in men. *Int J Epidemiol* 1994;23:365-370.
7. Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 1996;7:197-204.
8. Kerenyi NA, Pandula E, Feuer GM. Oncostatic effects of the pineal gland. *Drug Metabol Drug Interact* 1990;8:313-319.
9. Ørthede E, Nord-Larsen M, Burr H, Nielsen J. Lønmodtagernes arbejdsmiljø 1990 - bind 2. Kortlægning af påvirkninger, arbejdsprocesser og helbred. AMF-forskningsrapporter. København, Arbejdsmiljøfondet, 1992.
10. National Board of Health. Cancer incidence in Denmark 1994. Copenhagen 1998;1-96.
11. Olsen JH, Jensen OM. Occupation and risk of cancer in Denmark. An analysis of 93810 cancer cases, 1970-79. *Scand J Work Environ Health* 1987;13(suppl 1):1-91.
12. Hansen J, Raaschou-Nielsen O, Olsen JH. Increased lung cancer risk among different types of professional drivers in Denmark. *Occup Environ Med* 1998;55:115-118.
13. Hansen EJ. The distribution of living conditions. Main results from the welfare survey. Part I. Theory, method, and summary. Copenhagen, Teknisk Forlag, 1978.
14. Danmarks Statistik. Danmarks Statistik Erhvervsgrupperingskode, DSE 77. København, Danmarks Statistik, 1989.
15. Smith-Warner SA, Spiegelman D, Shiao-Shyuan Y, van den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, Speizer FE, Willett WC, Wolk A, Hunter DJ. Alcohol and breast cancer in women. *JAMA* 1998;279:535-540.
16. Hansen EJ. Socialgrupper i Danmark. Copenhagen, The Institute of Danish Social Science, 1984.
17. Preston DL, Lubin JH, Pierce DA, McConney ME. *Epicure*. Seattle, HiroSoft International Corporation, 1996.
18. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995;87:1681-1685.
19. Kelsey JL. Breast cancer epidemiology. Summary and future directions. *Epidemiol Rev* 1993;15:256-263.
20. Oksbjerg S, Møllekjær L, Johansen C. [Incidence and mortality of breast cancer among women in Denmark 1943-1992]. *Incidence og mortalitet af brystkræft hos kvinder i Danmark 1943-1992*. *Ugeskr Læger* 1997;159:7134-7140.
21. Welp E, Weiderpass E, Boffetta P, Vainio H, Vasama NK, Petralia S, Partanen TJ. Environmental factors for breast cancer. *Scand J Work Environ Health* 1998;24:3-7.
22. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environ Health Perspect* 1993;101:378-384.
23. Hansen J. Breast cancer risk among relatively young women employed in solvent using industries. *Am J Ind Med* 1999;36:43-47.
24. Hansen J. Industriel anvendelse af udvalgte kemiske stoffer og risiko for kræft, 1970-1984. Delrapport I. Kortlægning af 198 potentielt kræft-fremkaldende stoffers forekomst i Danmark. København, Arbejdsmiljøinstituttet, 1992.
25. Henderson BE, Pike MC, Bernstein L, Ross RK. Breast cancer; in Schottenfeld D, Fraumeni JF, Jr., eds. *Cancer epidemiology and prevention*. New York, Oxford University Press, 1996;1022-1039.
26. Rix BA, Lyng E. Cancer incidence in Danish health care workers. *Scand J Soc Med* 1996;24:114-120.
27. Gunnarsdottir H, Rafnsson V. Cancer incidence among Icelandic nurses. *J Occup Environ Med* 1995;37:307-312.
28. Sankila R, Karjalainen S, Laara E, Pukkala E, Teppo L. Cancer risk among health care personnel in Finland, 1971-1980. *Scand J Work Environ Health* 1990;16:252-257.
29. Lyng E, Thygesen L. Occupational cancer in Denmark. Cancer incidence in the 1970 census population. *Scand J Work Environ Health* 1990;16(suppl 2):1-35.
30. Pukkala E, Auvinen A, Wahlberg G. Incidence of cancer among Finnish airline cabin attendants, 1967-92. *BMJ* 1995;311:649-652.
31. Lyng E. Risk of breast cancer is also increased among Danish female airline cabin attendants (Letter; Comment). *BMJ* 1996;312:253.
32. Gurwitz D. Flight attendants, breast cancer, and melatonin (Letter). *Lancet* 1998;352:1389-1390.
33. Wartenberg D, Stapleton CP. Risk of breast cancer is also increased among retired US female airline cabin attendants (Letter). *BMJ* 1998;316:1902.
34. Shah PN, Mhatre MC, Kothari LS. Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res* 1984;44:3403-3407.
35. Mhatre MC, Shah PN, Juneja HS. Effect of varying photoperiods on mammary morphology, DNA synthesis, and hormone profile in female rats. *J Natl Cancer Inst* 1984;72:1411-1416.
36. Brzezinski A. Melatonin in humans. *N Engl J Med* 1997;336:186-195.
37. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980;210:1267-1269.
38. McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Quantal melatonin suppression by exposure to low intensity light in man. *Life Sci* 1989;45:327-332.
39. Blask DE, Wilson ST, Zalatan F. Physiological melatonin inhibition of human breast cancer cell growth in vitro. Evidence for a glutathione-mediated pathway. *Cancer Res* 1997;57:1909-1914.
40. Gammon MD, John EM. Recent etiologic hypotheses concerning breast cancer. *Epidemiol Rev* 1993;15:163-168.
41. Baldwin WS, Barrett JC. Melatonin. Receptor-mediated events that may affect breast and other steroid hormone-dependent cancers. *Mol Carcinog* 1998;21:149-155.
42. Feychting M, Österlund B, Ahlbom A. Reduced cancer incidence among the blind. *Epidemiology* 1998;9:490-494.
43. Coleman MP, Reiter RJ. Breast cancer, blindness and melatonin. *Eur J Cancer* 1992;28:501-503.
44. Hahn RA. Profound bilateral blindness and the incidence of breast cancer. *Epidemiology* 1991;2:208-210.