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 induction 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.

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. 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. 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
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 night-time 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>
<thead>
<tr>
<th>Trade</th>
<th>No. of Women</th>
<th>% Working at Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td>83,896</td>
<td>41</td>
</tr>
<tr>
<td>Furniture manufacture</td>
<td>3,365</td>
<td>50</td>
</tr>
<tr>
<td>Cleaning services</td>
<td>10,889</td>
<td>51</td>
</tr>
<tr>
<td>Water transport services</td>
<td>1,503</td>
<td>59</td>
</tr>
<tr>
<td>Manufacture of beverages</td>
<td>2,942</td>
<td>64</td>
</tr>
<tr>
<td>Land transport services</td>
<td>6,283</td>
<td>69</td>
</tr>
<tr>
<td>Catering</td>
<td>24,511</td>
<td>70</td>
</tr>
<tr>
<td>Air transport services</td>
<td>4,912</td>
<td>71</td>
</tr>
</tbody>
</table>

Source: Hansen, 1978.13

<table>
<thead>
<tr>
<th>Trade</th>
<th>Drinks per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture of beverages</td>
<td>8.8</td>
</tr>
<tr>
<td>Land transport services</td>
<td>4.6</td>
</tr>
<tr>
<td>Catering</td>
<td>6.6</td>
</tr>
<tr>
<td>Air transport services</td>
<td>7.5</td>
</tr>
<tr>
<td>All female employees</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Source: Hansen, 1978.13
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. 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 breast cancer, prior benign breast disease or exposure to reproductive factors. 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, flight attendants, and radio and telegraph operators. In the latter group, a positive trend was found with duration of night work. 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. 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. Melatonin is regulated via the retina by the light/dark cycle and influences the biological regulation of circadian rhythm, sleep, and probably tumor growth. It is synthesized by the pineal gland, predominantly at night, and is immediately secreted into the blood. Exposure to relatively weak light (200–400 lux) during night-time quickly decreases melatonin secretion. Physiological concentrations of melatonin have been shown in vitro to inhibit the growth of human breast cancer cells. Additionally, low serum melatonin concentrations have been reported in women with oestrogen-receptor-positive breast cancer. Impaired pineal secretion of melatonin is also associated with 5-lipoxygenase activity in B-lymphocytes, and increased ovarian oestrogen and pituitary gonadotropin production, 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. 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. An association between chronobiological disturbance and breast cancer, explained by the melatonin hypothesis, is therefore biologically plausible.

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.

<table>
<thead>
<tr>
<th>Trade</th>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime†</td>
<td>5847</td>
<td>5723</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Manufacture of beverages</td>
<td>41</td>
<td>36</td>
<td>1.2</td>
<td>0.7–1.8</td>
</tr>
<tr>
<td>Land transport services</td>
<td>39</td>
<td>37</td>
<td>1.1</td>
<td>0.7–1.7</td>
</tr>
<tr>
<td>Catering</td>
<td>300</td>
<td>201</td>
<td>1.5</td>
<td>1.2–1.7</td>
</tr>
<tr>
<td>Air transport services</td>
<td>54</td>
<td>27</td>
<td>1.9</td>
<td>1.6–3.0</td>
</tr>
<tr>
<td>All night work combined</td>
<td>434</td>
<td>301</td>
<td>1.5</td>
<td>1.3–1.7</td>
</tr>
<tr>
<td>Employments &gt; 6 years</td>
<td>117</td>
<td>63</td>
<td>1.7</td>
<td>1.3–1.7</td>
</tr>
</tbody>
</table>

* 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.

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