# Night work and breast cancer: a causal relationship?

**Gezondheidsraad** **President**
Health Council of the Netherlands

To the State Secretary for Social Affairs and Employment

Subject: Presentation of advisory report entitled
'Night work and breast cancer: a causal relationship?'
Your reference: A&G/W&B/04 53184
Our reference: U-723/DC/798-D
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Date: June 29, 2006

Dear State Secretary,

I am pleased to present herewith the advisory report entitled 'Night work and breast cancer: a causal relationship?'. In July 2004 your Ministry requested the Health Council to examine the possible relationship between night work and breast cancer. The remit was to review the current level of knowledge and ascertain whether further research is warranted.

The advisory report in which these questions are answered was prepared by the Standing Committee on Health and Environment, which for this purpose acted as an ad hoc committee. External experts have also been consulted. The report was subsequently reviewed by the Standing Committee on Medicine.

The Committee concludes that there is an association between the prolonged performance of night work (i.e. over a period of decades) and increased incidence of breast cancer. However, the currently available data do not warrant the conclusion that breast cancer is actually caused by the night work. Nor is there any evidence as yet for a mechanism that could explain this association. The Committee therefore makes recommendations for further research.

In the Committee's opinion, the research findings do not, at present, justify recommending special measures for women who perform night work for prolonged periods in addition to the current breast-cancer screening programme. If new, scientifically sound research findings were to produce evidence of a causal relationship then one could consider what specific measures need to be taken.

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Finally, the Committee notes that there is evidence to suggest an association between night work and other risks to health. The Committee therefore recommends that the research into the effects of night work should be broadened, and not confined to breast cancer alone.

I have today also sent this advisory report to the Minister of Health, Welfare and Sport, the Minister of Social Affairs and Employment and the State Secretary for Housing, Spatial Planning and the Environment, so that they too can take note of its contents.

Yours sincerely,

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# Night work and breast cancer: a causal relationship?

to:

the State Secretary for Social Affairs and Employment

No. 2006/15E, The Hague, June 29, 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.


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# Contents

# Summary

In its 2002 monitoring report, the Netherlands Centre for Occupational Diseases (NCvB) called attention to the possible relationship between night work and breast cancer in women. It was prompted to do so by the publication in 2001 of three occupational epidemiology studies revealing an association between night work and the occurrence of breast cancer. This in turn led the State Secretary of Social Affairs and Employment to request that the Health Council provide a review of current knowledge on this topic, an opinion on its policy relevance and recommendations for further research.

### Relationship between night work and breast cancer

A systematic review of epidemiological studies on night work and breast cancer was published in 2005, which also included studies of airline flight attendants. That same year also saw the publication of a British assessment of night work and breast cancer. The Committee utilises these studies (among others) in this advisory report.

The epidemiological studies identify an association between the performance of night work and an increased incidence of breast cancer in women. Whether this is a causal relationship is unclear. The two most informative studies, conducted among a large group of female nurses in the United States, point to an increased incidence of breast cancer following long-term exposure to night work. Incidence of breast cancer was approximately one and a half times higher after at

least 20-30 years of night work than among female nurses who did not work at nights. However, the studies display significant limitations with regard to the estimation of exposure to night work. These relate to the definition of night work (i.e. what hours), how night work was quantified (actual number of nights and/or hours within a specific time-frame) and how the night workers have been assigned to the study groups (possible presence of night workers in the control group).

Based on an evaluation of the epidemiological research data, the Committee concludes that a relationship has been found between prolonged periods of night work and higher incidence of breast cancer in women. However, the currently available data do not warrant the conclusion that this is a causal relationship.

### Possible mechanisms

No mechanism has been identified that could explain a possible causal relationship between night work and breast cancer. A chronic disruption of the circadian rhythm could well have an effect on the production of melatonin, a hormone involved in the regulation of the sleep pattern. Disturbed melatonin secretion has been associated with the occurrence of breast cancer, though this has not been proven. Moreover, other factors that display a circadian rhythm (e.g. components of the immune system or genes that control the circadian rhythm) could equally be influenced by night work. Further research is required in this area.

### Further research

The Committee believes that consideration should be given to the association that has been identified in the studies between prolonged periods of night work and increased incidence of breast cancer. This is, in part, justified by the high incidence of breast cancer among women in the Netherlands. Other significant factors to be considered are the anticipated increase in working time (i.e. the need to continue working to a later age), the growing participation of women in the workforce and the attendant increase in night-shift work. The Committee therefore recommends that further research be conducted, which should include both epidemiological studies and research into a possible causal mechanism. Wherever possible, this should draw on existing research at national and international level.

## Policy implications

Women in the Netherlands aged 50 to 75 years have access to regular population screening for breast cancer (once every two years). At present, the research findings do not, in the Committee's opinion, justify recommending special measures for women who perform night work for prolonged periods in addition to the current breast-cancer screening programme. If new, scientifically sound research findings were to produce evidence of a causal relationship then one could consider what specific measures need to be taken.

Chapter 1

# Introduction

## 1.1 Request for advice

In its 2002 monitoring report, the Netherlands Centre for Occupational Diseases (NCvB) called attention to the possible relationship between night work and breast cancer in women.[27] Based on three occupational epidemiology studies from 2001[9,16,39], in which an association is apparent between night shift work and the occurrence of breast carcinoma, the NCvB estimates that one third of the breast cancer cases in women doing shift work (including a night shift component) in the Netherlands are associated with the working of shifts.

The State Secretary of Social Affairs and Employment is now requesting that the Health Council provide a review of current knowledge on this topic, an opinion on its policy relevance and recommendations for further research. The request for advice is included in Annex A. Based on this request, this advisory report answers the following three questions:

1 What does research tell us about the relationship between exposure to night work and the incidence of breast cancer in women who perform night work, and what is known about the underlying mechanism?
2 Do the research results currently warrant the development of new policy?
3 What additional research is to be recommended in order to analyse a possible relationship between night work and breast cancer?

## 1.2 Working procedures

On 10 February 2005 the President of the Health Council of the Netherlands requested a number of members of the Standing Committee on Health and Environment to prepare the advisory report. The Standing Committee is acting as an ad-hoc committee for the purposes of this report. The membership of the Committee can be found in Annex B, which also contains a list of the external experts that the Committee has consulted for this report.

How has the Committee approached this task? It has searched the databases *Pubmed* and *Toxline* for relevant publications in the period 1995-2005. The search terms used are *breast cancer* in combination with one or more of the following words: *shift, night work, melatonin, cortisol, flight attendants, circadian rhythm*. The final literature search was performed in February 2006. In formulating its opinion, the Committee was subsequently influenced in particular by the reports of Shuker and Harrison 2005[41] and Swerdlow 2003[44] and the review articles of Erren 2002[10], Megdal *et al.* 2005[26] and Schernhammer and Schulmeister 2004.[36]

## 1.3 Types of epidemiological research and outcome measures employed

This advisory report discusses results from two forms of epidemiological research: the cohort study and the case-control study.

In a cohort study, the cases of disease (in this case, breast cancer) that occur in the exposed and non-exposed subcohort are identified and related to the size of this subcohort at time point 0, or to the "person-time at risk" (i.e. the time during which subjects are present in a cohort and are therefore being observed) accrued in the subcohorts.[5]

Case-control studies of breast cancer are based on identified cases of the disease – usually in a dynamic population, where the number of people can change as a result of birth, emigration or immigration – and seek to determine the degree of exposure in those cases. The same procedure is followed with a sample selected from the rest of the same, dynamic, population: the controls.[5]

The measures used to indicate the strength of an association are the relative risk (RR) and the odds ratio (OR). The relative risk (RR) is a measure of the effect of the exposure that is identified in a cohort study and is used in this advisory report to indicate the possible relationship between night work and breast cancer. The

RR is the ratio of the incidence of breast cancer in a group exposed to night work to the breast cancer incidence in a group that is not exposed to night work.[5] Thus the RR is the factor by which the risk of breast cancer increases upon exposure to night work. For example, an RR of 1.36 means that the incidence in the exposed group is 1.36 times greater (or the risk is 36% higher) than in the non-exposed group.

The odds ratio (OR) is a means of comparing not the number of cases of disease but the prevalence of exposure in the patient group with exposure in the control group. It is therefore the outcome of case-control research. An OR is expressed as the ratio between the number of exposed and non-exposed patients on the one hand and the number of exposed and non-exposed controls (i.e. those who are not sick) on the other. When investigating a disease with a low incidence (as a rule of thumb, one that occurs in less than 5% of the study population), an OR usually provides a good approximation of the relative risk.[5] This is why the OR from case-control studies is being used in this advisory report as an alternative to the relative risk that is calculated from cohort research.

Finally there is the standardised incidence ratio (SIR), which is used to measure the effect in those studies of breast cancer incidence in which the general population serves as the control group.

## 1.4 Structure of the advisory report

In chapter 2 the Committee examines the possible association between night work and the incidence of breast cancer in women who perform night work and reviews the current level of knowledge. The possible underlying mechanism is also discussed. This answers the first of the questions posed in this report. In chapter 3 an opinion is given about the policy relevance of the findings and, at the same time, recommendations are made for additional research, thus answering the second and third questions. The concluding chapter recapitulates the conclusions and recommendations.

Chapter 2

# Research findings

What does scientific research tell us about a possible link between night work and breast cancer? This question is answered from two perspectives. Sections 2.1 and 2.2 explore what is known about the incidence of breast cancer and the associated risk factors among women in general and in particular among women who perform night work. Section 2.3 discusses what is known about the underlying mechanism that may explain a possible association.

## 2.1 Breast cancer incidence

There are huge differences in the incidence of breast cancer worldwide. A number of incidence rates are given below by way of illustration (Table 1). In the period from 1993 to 1997, breast cancer incidence among women in the age group 55-64 years ranged from 28 per 100,000 per year in a province in China to 469 per 100,000 per year in a section of the Hawaiian population. In the Netherlands, breast cancer incidence was comparable with that in Denmark, at around 300 women per 100,000 per year. The incidence of breast cancer in Spain, on the other hand, was far lower.

*Table 1* Breast cancer incidence worldwide (women aged 55-64), 1993-1997.[28]

| Cancer registry | Age-standardised incidence[a] |
|---|---|
| US, Hawaii: Hawaiian | 469 |
| Switzerland, Geneva | 350 |
| US, California, San Francisco: white | 377 |
| US, SEER: white | 325 |
| The Netherlands | 294[1] |
| Denmark | 297 |
| Spain, Granada | 131 |
| Japan, Miyagi Prefecture | 88 |
| Thailand, Chiang Mai | 41 |
| China, Qidong | 28 |

[a] Age-standardised incidence per 100,000 per year (world standard population

Breast cancer is the commonest form of cancer in Dutch women aged over 40. The average incidence of breast cancer in the Netherlands across all age groups is currently 120 cases per 100,000 women per year and increases sharply with advancing age. Thus breast cancer incidence among women aged 40-45 is 130 per 100,000 per year, whereas it is around 300 per 100,000 per year in the age group 60-64.[1]

## 2.2 Epidemiological research into an association with night work

It is a known fact that the incidence of breast cancer increases with age. The majority of breast-cancer cases occur after women have been through the menopause. Epidemiological research shows that this is due to genetic, behavioural and environmental factors that can occur during various stages of life[17] (though not all cases of breast cancer are attributable to one or more of these factors).

Known breast-cancer risk factors are: breast cancer in a first-degree relative, mutations in inherited genes (BRCA1 and BCRA2), previous breast malignancies, early age at first menstruation, women without children (or with few children), late age at birth of first child, late age at menopause, use of oral contraception and hormone replacement.[17,48] In addition, it is thought that limited physical activity, overweight and alcohol consumption may play a role in the occurrence of breast cancer.[48]

However, there is also evidence from recent epidemiological research to suggest that night work is correlated with a higher incidence of breast cancer in women[9,16,39], which is also the subject of this advisory report. What is the current state of knowledge on this topic? The results from epidemiological research are

first briefly outlined and then presented in table form. The Committee then discusses the quality of the available research and gives its opinion on the usefulness of the research results in answering the questions posed in this report.

### Review of the research results

Megdal and associates[26] have recently (2005) published a systematic review and meta-analysis of a total of 13 epidemiological studies on night work and breast cancer, including studies among airline flight attendants. Night work is defined in all of these studies as any form of rotating shift work that includes night work. These studies are used in this advisory report.

Some studies (case-control and cohort studies) have calculated the relative risk of breast cancer occurring in women in relation to night work. These studies are summarised in Table 2a. Other epidemiological research has looked at the incidence of breast cancer among airline flight attendants. In these studies a standard incidence ratio (SIR) was calculated, with the national population serving as the comparison group. These studies are shown in Table 2b. An explanation of the different types of research and risks can be found in section 1.3.

A population of 78,562 female, mainly postmenopausal, white nurses was followed up for 10 years in the prospective cohort study by Schernhammer *et al.*[39] The relative risk of breast cancer in women who had been working rotating night shifts (defined as working at least 3 nights per month) for 1-14 years and 15-29 years was 1.08 for both periods (95% confidence intervals (CI) ranged from 0.99 to 1.18 and from 0.90 to 1.30, respectively) when compared with female nurses who had only worked 'day duty' (defined as working otherwise than in rotating shifts with at least 3 nights per month). Female nurses who had spent 30 or more years working night duty were calculated to have a statistically significant relative risk of breast cancer of 1.36 (95% CI 1.04 to 1.78), compared with those who had only worked day duty. The test for trend with the number of years spent working night duty was statistically significantly positive ($p = 0.02$).

In a second prospective cohort (NHS II) by Schernhammer *et al.*[38], a different population of 115,022 female, mainly premenopausal, white nurses was followed up over a 12-year period. The experimental conditions were comparable to the earlier Schernhammer study, but this time with a different population. Nurses who had spent at least 20 years working night duty were calculated to have a statistically significant relative risk of 1.79 (95% CI 1.06-3.01) for breast cancer when compared with the group that had worked day duty. It was noted, however,

that the group of nurses performing prolonged periods (more than 20 years) of night work was fairly small (407 women). No increase in the relative risk of breast cancer was calculated for those who had spent less than 20 years working night duty.

The case-control study conducted among Danish working women (7,035 breast cancer patients and 7,035 controls) by Hansen[16] also shows that a prolonged period of night work (defined as the number of years spent in occupations predominantly involving night work) is associated with an increased incidence of breast cancer. The risk of breast cancer was higher (OR 1.5; 95% CI 1.2 to 1.7) after spending six months or longer working night shifts than in the control group of day workers (defined as the number of years spent in occupations predominantly involving day work). Hansen also discovered a higher risk of breast cancer (OR 1.7; 95% CI 1.3 to 2.7*) compared with the control group of predominantly day workers after more than six years of occupational exposure to night work.

In a case-control study conducted by Davis *et al.*[9], 813 women with breast cancer and 793 controls underwent in-person interviews which included questions about night work (defined as working during a shift (eight-hour period) between 7 pm and 9 am) in the 10 years before the patients had been diagnosed. The researchers discovered a relationship between ever having worked at night (defined as at least one night shift per week) and breast cancer (OR 1.6; 95% CI 1.0 to 2.5), with a positive trend for the number of hours of night work per week ($p = 0.03$) or the number of years with at least 1 night shift per week ($p = 0.04$).

Tynes[46] conducted a retrospective cohort study among 2,619 Norwegian women with exposure to electromagnetic fields who had been employed as radio and telegraph operators on sea-going merchant ships (night work included). An increased incidence of breast cancer was discovered in this cohort (SIR 1.5; 95% CI 1.1 to 2.0) after an observation period of 30 years (1961-1991). A case-control study conducted within this cohort (50 breast cancer patients and 4-7 controls per patient) resulted in a statistically insignificant relative breast-cancer risk of 4.3 (OR 4.3; 95% CI 0.7 to 26) for women over 50 years of age in the group with the highest cumulative exposure. The relative risk for women under 50 in the same group was 0.9 (OR 0.9; 95% CI 0.3 to 2.9).

Kliukiene[19] has conducted a follow-up study within the same cohort as Tynes[46], but with a 10 year longer observation period (1961-2001). In this nested case-control study (99 patients and 388 controls) the relative risk for women

* The original publication gives an upper-limit confidence interval of 1.7. However, correspondence with the author indicates that this should be 2.7.

aged 50 and over in the group with the highest cumulative exposure came out lower than in the previous study by Tynes (1996) at 2.37 (95% CI 0.88 to 6.36). In women from the highest cumulative exposure group who were under 50, the relative risk was 1.78 (OR 1.78; 95% CI 0.59 to 5.41) – somewhat higher than in the earlier Tynes study (1996).

In a Norwegian case-control study of 537 female nurses with breast cancer, nested within a cohort of 45,000 Norwegian female nurses, a relative breast-cancer risk of 2.2 (OR 2.21; 95% CI 1.10-4.45) was identified after 30 years of night work (defined as years of employment as a hospital nurse).[23,26]

A number of incidence studies have been conducted among a specific group of night workers, namely female airline flight attendants.[26] The original aim of these studies was to investigate the relationship between increased exposure to cosmic radiation and cancer. However, Megdal's meta-analysis also evaluated these studies with regard to the information that they provided about exposure to any form of night work. The underlying assumption was that the circadian rhythm might be disrupted in flight attendants as a result of exposure to time-zone changes and to night work.[26]

Pukkala (1995)[29] has conducted a retrospective cohort study among 1,577 women who had worked as flight attendants for a Finnish airline company. An increased incidence of breast cancer was identified after an observation period of 26 years (SIR 1.87; 95% CI 1.15-2.23).

A comparable increase in the incidence of breast cancer was discovered in 2001 by Rafnsson[30] in a retrospective cohort study conducted among 1,532 women who had worked as flight attendants for an Icelandic airline company (SIR 1.6; 95% CI 1.0 to 2.4). A lag time of 15 years was applied.

Two other incidence studies among flight attendants of an airline company in the United States produced corresponding values.[33,49]

Three Scandinavian studies among flight attendants also produced increased standardised incidence ratios for breast cancer, but these increases were not statistically significant.[15,24,25]

The meta-analysis by Megdal and associates (2005[26]) assembled all of the studies concerning night work and breast cancer, including those conducted among airline personnel. On this basis they calculated an increase of 48% in the risk of breast cancer among women (1.48; 95% CI 1.36-1.61). The increase in breast-cancer risk for airline flight attendants was 44% (SIR 1.44; 95% CI 1.26-1.65) and for other night workers, 51% (RR 1.51; 95% CI 1.36-1.68). On the whole, the authors consider it unlikely that publication bias – i.e. the possibility

that researchers have only published results that indicate a positive association between night work and breast cancer – has influenced the results.

*Table 2a* Epidemiological research concerning night work and the risk of breast cancer

| Type of study/ Reference | Study population | Source of exposure information; definition of exposure to night work | Exposure category | Relative risk after adjustment (95% CI[a]) | *p* trend test | Adjustment for[b] | Evaluation by the Committee | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Weakness | Strength |
| Prospective cohort Schernhammer 2001[39] | 78,562 mainly white postmenopausal American female nurses; age 54-60 yrs at start of 10-year observation period (1988-1998) Nurses' Health Study | Two-yearly questionnaire by post; number of years of rotating night shift with at least 3 nights/ month (in addition to evenings and afternoons in that month). Control group without these rotating night shifts | 1) never<br>2) 1-14 yrs<br>3) 15-29 yrs<br>4) ≥30 yrs | 1) RR[a] 1.0<br>2) RR 1.08 (0.99-1.18)<br>3) RR 1.08 (0.90-1.30)<br>4) RR 1.36 (1.04-1.78) only statistically significant for postmenopausal women | 0.02 | L, P, Le, H, Lm, Lmp, F, W, BMI, O, Alc, Lg, GB | Probably permanent night workers in control group.<br>No information about light intensity and frequency of night work.<br>No validation of self-reported duration of night work.<br>No information about specific lifestyle factors and socio-economic status. | Large prospective cohort with homogeneous population, long observation period.<br>Adjusted for known breast-cancer risk factors. |
| Prospective cohort Schernhammer, 2006[38] | 115,022 mainly white premenopausal American female nurses. Age approx. 36 yrs at start of 12-year observation period (1989-2001) Nurses' Health Study II | Two-yearly questionnaire by post; number of years of rotating night shift with at least 3 nights/month (in addition to evenings and afternoons in that month). Control group without these rotating night shifts | 1) never<br>2) 1-9 yrs<br>3) 10-19 yrs<br>4) ≥20 yrs | 1) RR[a] 1.0<br>2) RR 0.98 (0.87-1.10)<br>3) RR 0.91 (0.72-1.16)<br>4) RR 1.79 (1.06-3.01) | 0.65 | L, P, Le, H, Lm, Lmp, F, W, BMI, O, Alc, Lg, GB, R, Fa. | Probably permanent night workers in control group.<br>No information about light intensity and frequency of night work.<br>No validation of self-reported duration of night work.<br>No information about specific lifestyle factors and socio-economic status. | Large prospective cohort with homogeneous population, long observation period.<br>Adjusted for known breast-cancer risk factors. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Patient-control Hansen, 2001[16] | 7,035 Danish working women (aged 30-54 yrs) with breast cancer, (Danish cancer registry), one control per patient, randomly selected from female workforce (pension scheme members) | Individual employment histories; years of employment (min. ½ yr) in occupational groups with mainly night work (>60% of workers do night work). | 5-yr induction time included<br>1) < ½ yr<br>2) > ½ yr<br>3) > 6 yrs (comparable result with 10- and 15-yr induction time) | 1) OR[b] ~1.0<br>2) OR 1.5 (1.3-1.7)<br>3) OR 1.7 (1.3-2.7) | 0.02 | B, L, P, Le, Ll | No individual exposure data for night work.<br>Night workers probably assigned to day-worker group (less than 40% of workers do night work).<br>Limited adjustment for known breast-cancer risk factors. | Large population. Adjustment for social class (B) is also, in part, adjustment for Alc, Lm and Lmp. |
| Patient-control Davis, 2001[9] | 813 women from Seattle area with breast cancer and 793 controls (aged 20-74 yrs) | In-person interview concerning the 10 yrs before diagnosis. Graveyard shift work (working for an 8-hour period between 7 pm and 9 am) | 1) At least 1 graveyard shift<br>2) Each additional hour of shift work per week<br>3) > 5.7 hours per week<br>4) Each extra yr of working > 1 shift/ week | 1) OR 1.6 (1.0-2.5)<br>2) OR 1.1 (1.0-1.1)<br>3) OR 2.3 (1.0-5.3)<br>4) OR 1.1 (1.0-1.3) | 0.04<br>0.03<br>0.04<br>0.04 | P, O, H, F | Exposure only defined as ever having worked between 7 pm and 9 am, and interview relates to a limited period (10 years).<br>Limited adjustment for known breast-cancer risk factors. | Individual night-work data. |
| Historical cohort, Tynes, 1996[46] | 2,619 mainly postmenopausal Norwegian female radio and telegraph operators certified between 1920 and 1980, mainly working at sea; observation period 30 yrs (1961-1991) | Employment report from Norwegian registration of seaman; night work with exposure tot artifical light and radioapparatus. | Not defined | SIR[b] 1.5 (1.1 - 2.0) (comparison group is total Norwegian female population). | | | Study primarily aimed at relationship between electromagnetic radiation and breast cancer. Exposure to night work not well defined. | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ditto with nested patient-control Tynes, 1996[46] | 50 women with breast cancer and 4-7 controls per patient | Three categories of cumulative exposure to night work (light at night and electro-magnetic fields) are based on number of yrs worked at sea and workload (based on type of ship: category 1, 2 or 3). Cumulative exposure category: (none), low, moderate, high. | 'high': age ≥ 50<br>'high': age <50 | OR 4.3 (0.7-26.0)<br>OR 0.9 (0.3-2.9) | 0.01 | Le, P | Scarcely any adjustment for known breast-cancer risk factors.<br>No individual night-work data, but assignment to three ill-defined cumulative exposure categories. Also exposure to time-zone changes. | Potential confounding effect limited by readily comparable groups with and without exposure to night work. |
| Historical cohort with nested patient-control Kliukiene, 2003[19] | Same cohort as Tynes, but longer observation period 40 yrs (1961-2001), 99 women with breast cancer, approx. 400 controls | | Not defined<br>'high': age ≥50<br>'high': age <50 | SIR 1.30 (1.05-1.58) (comparison group is total Norwegian female population).<br>OR 2.37 (0.88-6.36)<br>OR 1.78 (0.59-5.41) | <br>0,03<br>0,03 | Le, P | Ditto | Ditto and longer observation period than Tynes 1996. |
| Nested patient-control Lie, 2006[23] | 537 Norwegian nurses with breast cancer (Norwegian cancer registry) and 4 controls per patient drawn from cohort of all (44,835) Norwegian nurses | Registered nurses: Norwegian health registry; number of years worked as hospital nurse | 1) Never<br>2) >0-14 yrs<br>3) 15-29 yrs<br>4) ≥ 30 yrs | 1)OR 1.0<br>2)OR 0.95 (0.67-1.33)<br>3)OR 1.29 (0.82-2.02)<br>4)OR 2.21 (1.10-4.45) | <br><br><br>0.01 | P | Only adjusted for parity. Exposure to night work not clearly defined.<br>Reconstruction of work history based on registry of nurses and official censuses, assuming that all hospital nurses perform night work. Control group exposed to night work during three-year training. | Large cohort |

[a] CI: confidence interval; SIR: standardised incidence ratio; OR: odds ratio; RR: relative risk or risk ratio.

[b] Abbreviations used: Alcohol consumption (Alc), job/occupation (B), body mass index (BMI); family history of breast cancer (F); physical activity (Fa); height (Lg); benign breast cancer (GB); smoking (R) and reproductive factors: 'other' hormone therapy (H); age (L); age at birth of first child (Le); age at birth of last child (Ll); age at menarche (Lm); age at menopause (Lmp); use of oral contraception (O); number of children, parity (P); change in weight between 18 years and menopause (W).

*Table 2b* Research into the incidence of breast cancer among airline flight attendants[a,b]

| Type of study/ Reference | Study population[a] | Exposure category[b] | Standardised incidence ratio (SIR) (95% CI[c]) | Adjustment for[d] | Evaluation by the Committee | |
|---|---|---|---|---|---|---|
| | | | | | Weakness | Strength |
| Retrospective cohort Pukkala, 1995[29] | 1,577 stewardesses with Finnish airline companies; observation period 26 yrs (1967-1992) | Start of observation period according to number of years of service:<br>1) 15 yrs<br>2) 15-19 yrs<br>3) ≥ 20 yrs | <br>1)SIR 1.87 (1.2-2.2)<br>2)SIR 3.4 (1.5-6.8)<br>3)SIR 2.1 (1.1-4.0) | L | Only adjusted for age. Exposure to night work poorly defined. | |
| Retrospective cohort Rafnsson, 2001[30] | 1,532 stewardesses with Icelandic airline companies; observation period 42 yrs (1955-1997) | 1) Average length of service 8 yrs (1-39 years).<br>2) Observation period started 15 yrs after recruitment<br>3) Recruitment after 1971 (heaviest exposure to cosmic radiation at a young age); at least 1 yr of service followed by 20- yr lag time. | 1) SIR 1.5 (1.0-2.1)<br>2) SIR 1.6 (1.0-2.4)<br>3) SIR 4.1 (1.7-8.5) | P, Le | Scarcely any adjustment for known breast-cancer risk factors. Exposure to night work poorly defined. | |
| Retrospective cohort Reynolds, 2002[33] | 44,021 female members of Association of Flight Attendants in California: 1988-1995 | Total study population | SIR 1.42 (1.09-1.83) | L, L on recruitment, number of yrs of service; international vs internal flight routes. | Only adjusted for age. Exposure to night work poorly defined. | |
| Retrospective cohort Wartenberg, 1998[49] | 287 retired female airline flight attendants of US company | Total study population | SIR 2.00 (1.00-4.30) | L | Only adjusted for age. Also occupational exposure to pesticides in cabin. Exposure to night work poorly defined. | |

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|---|---|---|---|---|---|
| Retrospective cohort Haldorsen, 2001[15] | 3,105 female flight attendants with Norwegian airline company, observation period 1953-1996 | 1) Total study population ≥ 15 yrs of service | 1) SIR 1.1 (0.8-1.5)<br>2) SIR 0.9 (0.3-2.2) | L, P, Le, length of service, length of service before 26 yrs of age. | Limited adjustment for known breast-cancer risk factors. Exposure to night work poorly defined. |
| Retrospective cohort Linnersjõ 2003[24] | 2,324 female female flight attendants with Scandinavian Airline System, observation period 1961-1996 | Total study population | SIR 1.30 (0.85-1.74) | L, number of long-distance flight hours and altitude | Only adjusted for age. Unclear whether adjustment for number of long-distance flight hours and altitude relates to both night work and breast cancer. Exposure to night work poorly defined. |
| Retrospective cohort Lynge 1996[25] | 915 female airline flight attendants in Denmark, observation period 1970-1996 | Total study population | SIR 1.61 (0.90-2.70) | L | Only adjusted for age. Exposure to night work poorly defined. |

[a] The national population was the comparison group in all of these studies into incidence among airline flight attendants. The data are obtained from the airline companies and national cancer registries.

[b] The original aim of these studies was to investigate the effect of cosmic radiation and breast cancer. Megdal has stratified the results of these studies by some form of night work. Megdal makes the assumption that flight attendants on long-distance and international flights are occupationally exposed to disruption of circadian rhythm as a result of time-zone changes and working at night.

[c] CI: confidence interval; SIR: standardised incidence ratio

[d] Abbreviations used: age (L); number of children, parity (P); age at birth of first child (Le); age at birth of last child (Ll).

## Opinion on the usefulness of the results

What is the quality of the studies? How robust are the results of each study and of the studies as a whole in terms of the possibility of there being a causal relationship between night work and an increased incidence of breast cancer? The studies under consideration have been evaluated by Swerdlow[44], Shuker and Harrison[41], Schernhammer and Schulmeister[36], and recently by Megdal *et al.*[26] The Committee makes use of these evaluations, *inter alia*.

There are two well-conducted studies of any significance, namely the two Nurses' Health Studies performed by Schernhammer in the United States.[38,39] These are prospective cohort studies conducted among a large population of female nurses, in which adjustments were made for known breast-cancer risk factors (potential confounders). These studies provide evidence to suggest an increased incidence of breast cancer following long-term exposure to night work (RR 1.36 (95% CI 1.04 to 1.78) after at least 30 years and RR 1.78 (95% CI 1.06-3.01) after at least 20 years). The other studies are retrospective. The limitations apparent in all of the available studies are discussed below.

Exposure to night work varies and is sometimes not clearly defined. Thus Schernhammer[38,39] defines night work as rotating night shifts with at least 3 nights per month, whereas Davis[9] defines night work as working for a period of 8 hours between 7 pm and 9 am. In the studies conducted among radio and telegraph operators at sea, night work is an element of cumulative exposure, with other factors being electromagnetic fields and artificial light.[19,46] In the studies involving airline personnel, night work is quantified by means of a rough estimate of the length of service.[26] Moreover, it is not always clear whether night work alone is meant, or night work in combination with shifts performed at other times. Consequently it is not possible to draw a definitive conclusion with regard to an association between night work and breast cancer.

Furthermore, the amount of night work in the available studies has not been adequately quantified. Studies often only report the duration of a period in which night work was performed, and not the exact frequency (i.e. the actual number of nights and/or hours within a specific time-frame).[9,16,19,38,39,46] Inadequate quantification of night work can lead to an incorrect estimate of the strength of an association between night work and breast cancer.

In some studies it is possible that the exposure may have been incorrectly classified. Misclassification due to the definition of night work may have occurred in the studies by Hansen, Davis, Tynes and Kliukiene.[9,16,19,46] This

might even be the case in the Schernhammer studies, since the definition of night work could possibly have resulted in permanent night workers being assigned to the control group, which ought to consist exclusively of day workers.[38,39] This could lead to a reduction in the difference in breast cancer incidence between nurses who have been exposed to night work and those who have not. Schernhammer, it should be noted, concludes that no substantial misclassification of exposure has occurred in her study.[38]

Besides occupational exposure to night work, there may also be a possibility of occupational exposure to other factors in some studies. The studies conducted by Tynes and Kliukiene among radio and telegraph operators were primarily aimed at identifying a possible association between exposure to electromagnetic radiation and the incidence of breast cancer.[19,46] Exposure to night work was not directly investigated.

The same applies to the incidence studies among airline flight attendants, which were primarily designed to explore increased exposure to cosmic radiation and the incidence of cancer. Moreover, these workers frequently also perform night work and are exposed to circadian rhythm disturbances (time-zone changes).[26] However, a recent nested case-control study (27 patients and 515 controls) by Kojo and Pukkala (2005)[21] among Finnish flight attendants provides no evidence that work-related factors such as cosmic radiation and disruption of the circadian rhythm contribute to the incidence of breast cancer. It does appear that breast-cancer incidence is related to known risk factors (such as familial occurrence of breast cancer). However, the number of patients in this study is relatively small.

The interpretation of the studies is further hampered by the fact that in many studies no adjustment has been made for known breast-cancer risk factors. It is conceivable that a number of risk factors, such as age at first menstruation, number of children, oral contraception, hormone replacement and alcohol consumption, might possibly be related to night work. These factors could then be potential confounders*, and consequently their effect on the incidence of breast cancer would be erroneously attributed to night work.

In many epidemiological studies (an exception being the Nurses' Health Studies by Schernhammer[38,39]) it is not possible to make adequate adjustment for potential breast-cancer risk factors, since there is usually a lack of data.[9,16,19,26,29,30,46] Schernhammer notes that she has not sought in her studies to ascertain whether nurses who regularly perform night work differ in terms of

* Confounders are factors (known or unknown) that have been associated both with night work (the exposure) and with breast cancer (the effect).

socio-economic status or lifestyle-associated risk factors from nurses who do not undertake night work. If these factors were to influence the incidence of breast cancer, this might lead to potential confounding, for which no adjustment has been made.[38,39]

Adjustment has been made in some of the airline studies for such factors as altitude, long-distance flight hours and flight routes (international/internal).[26] It is unclear, however, whether these factors are potential confounders.

Interpretation problems are also encountered in meta-analyses. Megdal and associates have assembled all of the studies conducted among night workers, including the airline studies. Their calculations reveal a 48% increase in the risk of breast cancer in women (1.48; 95% CI 1.36-1.61).[26] The authors did not, however, take account of the fact that the frequency of exposure to night work was usually poorly defined in the evaluated studies. In a few studies there was an association with the duration of the period in which night work was performed.

Can publication bias – i.e. the possibility that researchers have only published results that indicate a positive association between night work and breast cancer – also prove problematic? Megdal and associates consider it unlikely that the results have been influenced by publication bias.[26] According to them, this would surely be reflected in an association between the size of the studies and the degree of relative risk and there is no firm evidence of this. Publication bias cannot, however, be ruled out entirely.

## Conclusion

The epidemiological studies conducted to date reveal an association between the performance of night work and an increase in breast-cancer incidence. The two most robust studies indicate an increased incidence of breast cancer after long-term exposure (i.e. over a period of decades) to night work.

However the available body of research also has significant limitations in terms of the definition and quantification of night work, possible misclassification of exposure and frequently inadequate control over potential confounders.

These deficiencies in the studies also limit the robustness of the results. Although there is manifestly an association, current knowledge does not support the conclusion that prolonged night work is the *cause* of the increase in incidence. This needs to be investigated more closely, not only through epidemiological research but also by looking for possible explanatory mechanisms.

## 2.3 Possible mechanisms

Animal experiments have afforded insights into possible explanatory mechanisms for an association between night work and breast cancer. A recent British report reviews various potential mechanisms, citing melatonin, circadian rhythms, circadian clock genes and components of the immune system.[41] Possible mechanisms are also described in a recent article by Stevens[43] entitled 'Circadian disruption and breast cancer: from melatonin to clock genes'. Given the complexity of the mechanisms involved, the Committee has confined itself in this advisory report to undertaking a global literature search. A summary of the principal findings can be found below.

### Melatonin

One of the possible mechanisms whereby night work might increase the incidence of breast cancer in women is derived from the hypothesis advanced by Stevens.[42] This author suggested in 1987 that night-time exposure to light disrupts the secretion of the hormone melatonin, which could possibly give rise to an increased risk of breast cancer in women. Melatonin is a hormone that is mainly produced at night in the pineal gland in the brain and regulates the sleep-wake cycle.

Experimental research from the 1980s and 1990s does, indeed, provide some evidence for a relationship between melatonin and the suppression of tumours. Melatonin has consistently been shown to have oncostatic activity in *in vivo* models with chemically induced mammary tumours in rats. The oncostatic action of melatonin has also been demonstrated *in vitro* in MCF-7 human breast cancer cells. A review of these studies was published by Sanchez-Barcelo in 2003.[35] Furthermore, experimental animal models show that light (24 hours of light per day) inhibits melatonin secretion and increases the growth of transplantable murine liver tumours and human breast cancer xenografts (human breast tumours implanted in experimental animals), when compared with exposure to an alternating cycle of 12 hours of light and 12 hours of darkness.[3,4,8] In the recent xenograft study conducted by Blask (2005[2]), breast cancer xenografts perfused with blood from female volunteers who had been exposed to daylight (and whose blood was therefore melatonin-deficient) exhibited high proliferative activity, whereas perfusion with blood from female volunteers who had been exposed to darkness (and therefore had melatonin-rich blood) suppressed proliferative activity.

There is, however, only indirect evidence for a possible role of melatonin in human breast cancer. According to Erren[10], the melatonin hypothesis can be tested by studying populations with varying exposures to light. In his publication he therefore examines studies of female night workers, blind humans and residents of the Arctic. Despite differences in methodology, potential confounders and definitions of exposure, he ascertains that the results of these studies are in accordance with the melatonin hypothesis. Female night workers do, indeed, exhibit a higher incidence of breast cancer, while incidence is lower among blind people and Arctic residents.

This conflicts with the outcome of a recent prospective nested case-control study by Travis (2004[45]), however, which measured melatonin levels in 127 breast cancer patients and 254 controls. No association was identified in this study between reduced melatonin levels and an increased incidence of breast cancer. The significance of the study is limited, however, by the fact that it only measures total melatonin production over 24 hours, in the form of the main metabolite of melatonin in urine, and consequently no data have been obtained with regard to the level and timing of the nocturnal melatonin peak. Nor is there any information about night work or exposure to light at night.[18]

Schernhammer, on the other hand, reports lower melatonin concentrations (via the metabolite) in the morning urine of breast cancer patients compared with controls. A shortcoming of this study, however, is the fact that changes in the timing of the melatonin rhythm might influence the relationship between melatonin in the morning urine and total melatonin production .[37] As in the Travis study, there are no data on the timing and level of the melatonin peak.

### Circadian rhythms

Our knowledge of the circadian system and its molecular genetics has expanded in recent decades. This has shed further light on possible explanatory mechanisms for an association between night work and breast cancer.

The biological clock (also known as the circadian pacemaker), which is located in the suprachiasmatic nucleus, generates and coordinates circadian rhythms. Although light is the primary stimulus regulating circadian rhythms, the rhythm will stay approximately on a 24-hour cycle even in the total absence of daylight (as in the Arctic region), providing other factors that impact on the circadian clock are maintained (e.g. by regular sleep patterns).

There are other factors apart from melatonin secretion that display a circadian rhythm. These might therefore also be influenced by night work. These factors include alertness, body temperature[31], components of the immune system (NK [natural killer] cells and T [thymus-derived] cells) and endocrine and neuroendocrine factors (such as cortisol, prolactin and growth hormone).

Sleep is also under the control of the circadian clock. It is noted in the literature that many night workers have two hours less sleep, on average, than the general population. This reduced period of sleep is, in part, associated with alterations in glucose metabolism and immune function.[41]

### Immune system

Night work may possibly also disrupt components of the immune system, steroid hormones and a number of neurotransmitters in the suprachiasmatic nucleus that are influenced by light.[6,22,34,50] It is possible that the activity of natural killer cells is more strongly associated with physical exertion than with night-time sleep.

Cortisol levels are lower at night and higher during the day. They begin to rise just before waking, but also, for example, in athletes prior to physical exertion. Such changes in cortisol levels are not gradual, but occur in pulses of approximately 2 hours' duration. A shorter period of sleep could potentially disrupt the organisation of these cortisol pulses[41]. Cortisol levels are also influenced by stress.

The secretion of glucocorticoids (such as cortisol) reduces the immune response. If night workers overcome the physiological effects of their circadian clock by adapting their glucocorticoid secretion, their immune system could be suppressed. There is, however, no research to show that this actually occurs.[41]

### Circadian clock genes

The Reppert study[32] shows that light directly influences the expression of so-called clock genes, which control the circadian rhythm. In recent animal studies, disruption of the functioning of clock genes (mutant *Period2*) in mice is associated with accelerated development of malignant tumours and impaired DNA damage response.[11,14] In other experiments with animals, implanted tumours have been found to grow more rapidly if the suprachiasmatic nucleus is "switched off". In this case, a disrupted light cycle results in an increase in spontaneous tumours.[13] Circadian clock genes are therefore possibly also involved in

other biological processes such as cell proliferation, regulation of the cell cycle and apoptosis (a form of cell death).[12,13]

A recent molecular epidemiological study performed by Zhu in 2005[51] reveals an association between a polymorphism in the *Period3* circadian clock gene, which is associated with delayed sleep-phase syndrome*, and breast cancer (OR 1.7; 95% CI 1.0-3.0) in premenopausal women. In this study, the frequency of a mutant of the *Period3* clock gene was found to be increased in blood samples from breast cancer patients participating in a case-control study with around 400 patients and 400 controls.

Based on this finding, a relationship between a disruption of the circadian rhythm and increased susceptibility to tumour development might be biologically plausible. Whether this effect is, in fact, responsible for the association that has been discovered between night work and breast cancer remains unclear.

Night work is also associated in the literature with other effects on health. Van Amelsvoort (2004)[47], for example, describes a study among Dutch shift workers on rotating night shift who were discovered to have more risk factors for cardiovascular diseases than day workers. Scandinavian researchers also report an increased risk of cardiovascular disease among shift workers.[20] Furthermore, there is evidence from the Nurses' Health Study (2003)[40] to suggest that rotating night shifts that include night work might, over a prolonged period, increase the incidence of colorectal cancer.

## Conclusion

The Committee notes that no mechanism has been identified that can explain a possible causal relationship between night work and breast cancer. However, current knowledge of the circadian system and its molecular genetics plainly shows that research into such a mechanism needs to include the circadian rhythm, and possibly also genes that control the circadian clock.

Furthermore, the Committee points out that there is evidence to suggest an association between night work and other risks to health.[10,40,47] Further research could be conducted into a possible relationship between the circadian rhythm and tumour development in general, in which case one would also need to look at

* Delayed sleep-phase syndrome is a chronic sleep disorder in which the patient's biological clock is not in sync with the morning-rise evening-sleep pattern of the majority of adults and adolescents. This problem is probably attributable to a genetic defect that causes the onset of melatonin production to occur several hours later in these patients.

other types of tumours and at effects in men. The possible relationship between exposure to night work and disruption of the circadian rhythm can then be explored.

Chapter 3

# Policy implications and further research

In chapter 2 the Committee reviewed the current level of knowledge concerning the relationship between night work and breast cancer and identified possible explanatory mechanisms for this association. Section 3.1 addresses the question of whether the research results currently warrant the development of new policy, while section 3.2 focuses on what additional research is to be recommended.

## 3.1 Policy implications

The Committee believes that consideration should be given to the association that has been identified in the studies between long-term exposure to night work and the increased incidence of breast cancer. This is all the more important in view of the high incidence of breast cancer among women in the Netherlands. Other significant factors to be considered are the anticipated increase in working time (i.e. the need to continue working to a later age) and the growing participation of women in the workforce and in jobs that include night work*. The Committee therefore primarily recommends that further research should be encouraged both into epidemiological aspects and into a possible explanatory

* Between 2000 and 2005, an average of 335,000 women were engaged in night work in the Netherlands (105,000 women 'sometimes' and 230,000 'regularly')[7]. In the Netherlands, 'night work' is understood to mean work performed between 12 midnight and 6 am. The meaning of 'sometimes' or 'regularly' is not defined in the available data. Furthermore, no records are kept of the duration of night work in the Netherlands.

mechanism. Opportunities to draw on existing research at national and international level should be considered (see also section 3.2).

Pending the emergence of new, scientifically sound research findings, should special recommendations be made for women who have performed night work for prolonged periods? Women in the Netherlands aged 50 to 75 years have access to regular population screening for breast cancer (once every two years). At present, the research findings do not, in the Committee's opinion, justify recommending special measures for women who perform night work for prolonged periods in addition to the current breast-cancer screening programme. If new, scientifically sound research findings were to produce evidence of a causal relationship then one could consider what specific measures need to be taken.

Since there is also evidence to suggest an association between night work and other risks to health, the Committee believes that the research into the effects of night work should not be confined to the occurrence of breast cancer.

## 3.2 Further research

There is consensus in the international literature that further research should focus on epidemiological studies into an association between breast cancer and night work and research into a possible explanatory mechanism. The Committee has considered the potential avenues of research and has several suggestions to make.

### Epidemiological research

Further research could be conducted along the lines of the proposals of Swerdlow[44] and Erren[10], who envisage several large, high-quality, prospective cohort studies aimed at identifying a direct association between night work and breast cancer. These would resemble the Schernhammer Nurses' Health Studies[38,39], but with detailed information about night work (including a definition, duration and frequency, and individual exposure to light) and a closer examination of potential confounders.

Because it often takes 20 years or more before sufficient breast-cancer cases have been found on which to base conclusions in prospective cohort research, and because a large study population is required, the Committee endorses the suggestion made by Swerdlow[44] that data on night work should, if possible, be collected as part of other ongoing cohort studies. These ongoing cohort studies

should satisfy the condition that the necessary parameters for an association between night work and breast cancer must be in place.

Another possibility is to conduct a case-control study among specific occupational groups that perform night work, documenting information about the exposure to night work and potential confounders. This requires a long observation period (in this case, retrospective) and a large number of female subjects.

### Drawing on existing cohort studies in the Netherlands

A number of large cohort studies have been conducted at various institutes in the Netherlands, examples being the Dutch cohort study on the relationship between diet and cancer (NCLS), breast cancer studies performed by the Julius Center for Health Sciences and Dutch population screening for breast cancer. One could investigate whether these studies can provide relevant information about the association between night work and breast cancer, or whether this requires additional new research.

### Drawing on research abroad

It may be possible to draw on existing cohorts in this area at European level. A recent British report concerning shift work and breast cancer mentions various possibilities for modifying existing cohorts in England.[41] In this case it would be preferable to draw on research that explores other night work-related health effects in addition to breast cancer.

### Research into the underlying mechanism

The Committee also recommends that consideration should be given to research into a possible explanatory mechanism for the association between night work and breast cancer. At first, this will have to focus on animal experiments so that a systematic investigation of the circadian system can be included. In addition, research needs to be conducted in humans into the way in which exposure to night work influences circadian factors. Furthermore, one could investigate a possible relationship between the circadian rhythm and tumour development in general, in which case one would also need to look at other types of tumours and at the effects in men. The possible relationship between exposure to night work and disruption of the circadian rhythm can also be explored.

## Conclusion

The Committee believes that consideration should be given to the association that has been identified in the studies between long-term exposure to night work and the increased incidence of breast cancer. It therefore recommends that further research be conducted, which should include both epidemiological studies and research into a possible explanatory mechanism. Wherever possible, this should draw on existing research at national and international level.

Chapter 4

# Conclusions and recommendations

## Conclusion concerning an association between night work and breast cancer

The Committee concludes that there is an association between the prolonged performance of night work (i.e. over a period of decades) and breast cancer in women. However, the studies conducted to date have significant limitations in terms of the definition and quantification of night work and possible misclassification of exposure. The available data are therefore insufficient to warrant the conclusion that a causal relationship does exist.

There is no known mechanism that can explain the concurrence of prolonged night work and breast cancer. The Committee believes that it would be prudent to include the circadian rhythm and possibly also the genes that control the circadian rhythm in research into a possible explanatory mechanism.

## Conclusion concerning further research

The Committee believes that consideration should be given to the association between long-term exposure to night work and the increased incidence of breast cancer. This is all the more important in view of the high incidence of breast cancer among women in the Netherlands. Other significant factors to be considered

are the anticipated increase in working time (i.e. the need to continue working to a later age) and the growing participation of women in the workforce and in jobs that include night work. The Committee therefore recommends that further research should be conducted both into epidemiological aspects and into a possible explanatory mechanism. Wherever possible, this should draw on existing research at national and international level.

### Conclusion concerning policy implications

Women in the Netherlands aged 50 to 75 years have access to regular population screening for breast cancer (once every two years). At present, the research findings do not justify recommending special measures for women who perform night work for prolonged periods in addition to the current screening programme. If new, scientifically sound research findings were to produce evidence of a causal relationship then one could consider what specific measures need to be taken.

The Committee recommends a broadening of the focus to include the impact of night work on health in general. Since epidemiological and animal studies have produced evidence for a possible association between night work and other risks to health (such as other tumours and cardiovascular diseases), it believes that research into the effects of night work ought not to be confined to breast cancer alone.

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A Request for advice

B The committee

# Annexes

Annex **A**

# Request for advice

On 30 July 2004 (A&G/W&B/04 53184) the President of the Health Council received the following letter from Mr R Feringa, Director of the Occupational Safety and Health Department at the Ministry of Social Affairs and Employment.

Dear Mr Knottnerus,

The NCvB called attention to the relationship between breast cancer and night shift work in its Monitoring Report on Occupational Diseases in 2002. It was prompted to do so by the publication in 2001 of three occupational epidemiology studies revealing an association between night work and the occurrence of breast carcinoma. Studies were also published in which an increased incidence of this and other forms of cancer was identified among flight attendants.

Melatonin is cited as a possible explanation for the occurrence of breast carcinoma, while a disturbance of cortisol metabolism is regarded as another possibility. The NCvB estimates that one third of the cases of breast cancer in the Netherlands are associated with the performance of shift work.*

I would request that you provide an opinion on the relevance of the relationship between night shift work and breast cancer and the underlying mechanism. If this is not possible on the basis of the exist-

* The report is misquoted here. The correct quotation is: "The NCvB estimates that one third of the cases of breast cancer in women who perform shift work in the Netherlands are associated with the performance of shift work."

ing literature, kindly recommend research that can clarify this issue. I would like to receive your response by 1 March 2005 at the latest.

Yours sincerely,

Director, Occupational Safety and Health Department

Annex **B**

# The committee

The membership of the Committee that drew up the advisory report was as follows:

- Professor JA Knottnerus, *chairman*
  President of the Health Council, The Hague
- Dr WRF Notten, v*ice-chairman*
  TNO Built Environment and Geosciences, Delft
- Professor A Bast
  Professor of Human Toxicology, University of Maastricht
- Dr CJM van den Bogaard, *adviser*
  Inspectorate, Ministry of Housing, Spatial Planning and the Environment, The Hague
- Dr JSM Boleij
  Director, Board for the Authorization of Pesticides (CTB), Wageningen
- Dr CA Bouwman, *adviser*
  Health Council, The Hague
- Professor B Brunekreef
  Professor of Environmental and Occupational Health; University of Utrecht
- Professor MHW Frings-Dresen
  Professor of Work-Related Disorders; Academic Medical Centre, Amsterdam
- Dr HS Hiemstra, *adviser*
  Ministry of Social Affairs and Employment, The Hague

- Dr AEM de Hollander
  Senior researcher, programme manager; National Institute of Public Health and the Environment, Bilthoven
- Professor D Kromhout
  Vice-President of the Health Council, The Hague
- Dr RM Meertens
  Health educationalist; University of Maastricht
- Dr HME Miedema
  Head of Environment and Health; TNO Built Environment and Geosciences, Delft
- Professor GJ Mulder
  Emeritus Professor of Toxicology, Leiden
- Professor WF Passchier
  Professor of Risk Analysis; University of Maastricht
- Professor W Seinen
  Professor of Toxicology, University of Utrecht
- Drs JA Verspoor, *adviser*
  Ministry of Housing, Spatial Planning and the Environment, The Hague
- Professor M de Visser
  Vice-President of the Health Council, The Hague
- A Wijbenga
  Executive director of the Health Council, The Hague
- Dr JH van Wijnen
  Medical officer in environmental health, Amsterdam
- Professor FA de Wolff
  Professor of Clinical and Forensic Toxicology; Leiden University Medical Centre
- Dr PW van Vliet, *scientific secretary*
  Health Council, The Hague

The text of the advisory report was prepared by TMM Coenen, *scientific secretary* of the Health Council, The Hague, in conjunction with Professor MHW Frings-Dresen, Professor W Seinen and Dr JH van Wijnen.

The following experts were consulted:
- Dr ir LGPM van Amelsvoort, epidemiologist, University of Maastricht
- Professor J Arendt, emeritus endocrinologist, University of Surrey, UK
- Professor DGM Beersma, chronobiologist, Zoological Laboratory, University of Groningen, Haren

- Professor D Heederik, epidemiologist, IRAS, Utrecht
- Dr TM Pal, occupational physician, Netherlands Centre for Occupational Diseases, Amsterdam
- Dr MA Rookus, epidemiologist, Netherlands Cancer Institute, Amsterdam
- Professor T Smid, epidemiologist and occupational hygienist, VU University Medical Center and KLM Health Services, Schiphol.

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## The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.