

The Scientific Committee of the Danish Society of Occupational and Environmental Medicine

## Nightshift work and risk of breast cancer and other cancers

A critical review of the epidemiological evidence

Henrik A. Kolstad

Aarhus University Hospital, Department of Occupational Medicine

## FORORD

Det foreliggende referencedokument er nummer 5 af 5 referencedokumenter, som den videnskabelige komite under Dansk Selskab for Arbejds- og Miljømedicin (VK-DASAM) har bistået Arbejdsskadestyrelsen med at få udarbejdet. Referencedokumentet vedrører spørgsmålet om det videnskabelige grundlag for at antage, at natarbejde kan være årsag til kræft, herunder særligt brystkræft. Opgavens indhold har været beskrevet af Arbejdsskadestyrelsen og opslået og finansieret gennem Arbejdsmiljø-forskningsfonden. Graden af evidens for en årsagsmæssig sammenhæng er rubriceret efter en standard, som DASAM's videnskabelige komite har udarbejdet på baggrund af internationale standarder. Den anvendte standard er vist i referencedokumentets Appendix 1.

Referencedokumentet er udarbejdet af overlæge PhD Henrik Kolstad, Arbejdsmedicinsk Klinik, Århus Universitetshospital. Fra VK-DASAM har forskningschef Jørgen H. Olsen, Institut for Epidemiologisk Kræftforskning, Kræftens Bekæmpelse, været projektleder for at sikre at dokumentet er udfærdiget i overensstemmelse med VK-DASAM's standard for referencedokumenter. Opgaven har været uafhængigt bedømt af to særligt sagkyndige reviewere, professor Anders Ahlbom, Institut för Miljömedicin, Karolinska Institutet, Stockholm og programleder Johnni Hansen, Institut for Epidemiologisk Kræftforskning, Kræftens Bekæmpelse. Professor PhD Staffan Skerfving, Yrkes- och Miljömedicinska Kliniken, Lund, overlæge PhD Johan Hviid Andersen, Arbejdsmedicinsk Klinik, Herning, og afdelingslæge PhD Susanne W Svendsen, Arbejdsmedicinsk Klinik, Århus Universitetshospital, har fungeret som kvalitetssikringsforum.

Dokumentet er efterfølgende gennemgået og drøftet på et heldagsmøde i VK-DASAM med deltagelse af forfatteren, de eksterne reviewere og kvalitetssikringsforum, og sluttelig har forfatteren revideret referencedokumentet i forhold til de fremkomne bemærkninger.

København september 2007

Sigurd Mikkelsen

Formand for DASAM's Videnskabelige Komite.

## CONTENTS

FOREWORD .....	5
DANSK RESUME.....	6
ABSTRACT.....	10
BACKGROUND .....	11
The melatonin hypothesis .....	11
Breast cancer .....	11
Risk factors for breast cancer.....	11
Nightshift work .....	13
Exposures of nightshift work .....	13
LITERATURE SEARCH .....	16
RESULTS .....	18
The individual studies .....	18
Contributory evidence.....	27
DISCUSSION .....	30
Overall findings.....	30
Study populations.....	31
Cancer outcome.....	31
Nightshift work .....	31
Confounding .....	33
Selection bias .....	35
Other relevant data.....	35
Previous literature reviews.....	36
CONCLUSION.....	37
REFERENCES.....	38

FIGURE 1 .....	45
TABLE 1 .....	46
TABLE 2 .....	48
TABLE 3 .....	50
Appendix 1 .....	53

## **FOREWORD**

This evidence-based review was undertaken at the request of the National Board of Industrial Injuries to clarify possible causal associations between fixed nightshift work and / or recurring nightshift work and cancer, including in particular breast cancer. The review follows the procedures and guidelines of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine for establishing a reference document on the causal relation between an occupational exposure and a disease outcome. The review focuses on epidemiological studies of nightshift work and special attention is paid to breast cancer since this is the cancer site that has been most thoroughly studied. Other relevant epidemiological and toxicological data are included but in less detail and mainly based on previous reviews.

Århus September 24, 2007

Henrik Kolstad, M.D., Ph.d.

e-mail: [hkols@as.aaa.dk](mailto:hkols@as.aaa.dk)

## DANSK RESUME

### **Natarbejde og risikoen for brystkræft og andre kræftsygdomme**

#### **En kritisk gennemgang af den epidemiologiske dokumentation**

I 1987 blev der fremsat den hypotese, at den stigende forekomst af brystkræft hos kvinder i den industrialiserede verden var resultat af øget brug af elektrisk lys om natten. Man antog at lyset hæmmede døgnhormonet melatonin og derigennem øgede risikoen for brystkræft. Hypotesen blev bl.a. baseret på dyreforsøg, som kunne tyde på at dette var tilfældet. Siden er der udført et væld af dyreforsøg og epidemiologiske undersøgelser af bl.a. natarbejdere for at be- eller afkræfte hypotesen, som snart kom til at bære navnet melatoninhypotesen.

Årligt får 3.500 kvinder diagnosticeret brystkræft i Danmark, og hyppigheden er mere end fordoblet i løbet af 60 år. Man kan forklare 40-50% af brystkræfttilfældene med kendte risikofaktorer og risikoen er tæt knyttet til udsættelse for naturlige og medikamentelle kvindelige kønshormoner.

Tyve procent af den europæiske arbejdsstyrke oplyser, at de har natarbejde mindst en gang per måned. Ti procent har natarbejde mere end 5 nætter per måned, og 0.4 procent oplyser, at de har fast natarbejde.

I denne litteraturgennemgang gennemgås alle epidemiologiske undersøgelser (undersøgelser af mennesker), hvor der er oplysninger om at deltagerne har haft natarbejde eller skifteholdsarbejde, og hvor man har opgjort forekomsten af brystkræft eller andre kræftsygdomme. I alt blev der identificeret 426 artikler og udvalgt 13 artikler, som tilfredsstillede inklusionskriterierne, som alene forholdt sig til undersøgelsesrelevans og ikke kvalitet. Der var 8 undersøgelser af brystkræft, 3 af prostatakraft, 3 af tyktarmskræft og 4 som undersøgte en lang række kræftsygdomme eller det totale antal kræfttilfælde. Rapporten gennemgår hver enkelt undersøgelse, metoderne beskrives, de centrale fund rapporteres, og styrker og svagheder ved undersøgelse diskuterer og endelig opsummeres der på tværs af undersøgelse.

Af de 13 undersøgelser havde seks undersøgt et udsnit af den generelle befolkning, fire undersøgte sygeplejersker og to undersøgte industriarbejdere og en radiooperatører.

Fem ud af otte undersøgelser viste en forøget forekomst af brystkræft blandt kvinder, som havde natarbejde. Tre af disse undersøgelser fandt statistisk signifikant forøget risiko efter mere end 20-30 års natarbejde. Schernhammer og medarbejdere fandt en relativ risiko på 1,36 efter 30 års natarbejde (mere end tre nattevagter per måned, men ikke fast natarbejde) i deres første undersøgelse fra 2001, medens de i en senere undersøgelse fra 2006 fandt en relativ risiko på 1,79 efter mere end 20 års natarbejde. Begge undersøgelser var udført blandt sygeplejersker uden at de to undersøgelses-grupper overlappede hinanden. Lie og medarbejdere rapporterede en odds ratio på 2,21 efter 20 års arbejde som sygeplejerske på sengeafdelinger med natarbejde. Der var ikke konsistente holdepunkter for at natarbejde af kortere varighed var årsagsmæssigt forbundet med brystkræft. De to senest gennemførte undersøgelser af Schwartzbaum og medarbejdere og O'Leary og medarbejdere viste henholdsvis ingen sammenhæng og en omvendt sammenhæng (flere år med natarbejde var forbundet med faldende risiko for brystkræft).

Der var ingen sammenhængende holdepunkter for at natarbejde var forbundet med tyktarmskræft, prostatakræft eller alle kræftsygdomme set under et.

Epidemiologiske undersøgelser er altid behæftet med mangler, og undersøgelsesernes kvalitet er afgørende for hvor stærke konklusioner man kan drage. En væsentlig del af rapporten består derfor af en diskussion af undersøgelsesernes styrker og svagheder.

Kræftdiagnoser er baseret på veletablerede kriterier og de gennemgåede undersøgelser baserede sig kun i begrænset omfang på undersøgelsesdeltagernes egne rapporteringer, og der var ikke holdepunkter for at helbredsoplysningerne har forringet undersøgelsesernes kvalitet.

Derimod var det en væsentlig mangel ved samtlige undersøgelser, at oplysningerne om natarbejde var overfladiske. Der var upræcise oplysninger om hvornår vagterne lå i løbet af aften og nat, og kun få undersøgelser angav vagternes længde. Da man må forvente, at risikoen for kræft er tæt relateret til antal nattevagter, er det afgørende, at der er gode oplysninger om det kumulerede antal nattevagter, men ingen af undersøgelserne opgjorde dette. De fleste af undersøgelserne oplyste på den anden side antal år med natarbejde, et mål som er upræcist, men som siger noget om det samlede antal nattevagter. Der var kun en undersøgelse af fast natarbejde, som undersøgte risikoen

for prostatakræft. Da fast natarbejde er sjældent forekommende, er det denne rapport's vurdering, at de øvrige undersøgelser primært er baseret på undersøgelsesdeltagere med skiftende natarbejde (selv om ikke alle undersøgelser oplyser dette).

Fire af undersøgelseerne var baseret på registerkoblinger og havde ingen oplysninger om natarbejde for de enkelte undersøgelsesdeltagere. I stedet for antog man, at alle ansatte i særlige fag eller brancher, som var kendt for at have mange natarbejdere, havde natarbejde. Dette betød fx at 40-60% af deltagerne i Hansens og Schwartzbaum et als undersøgelser fra 2001 og 2007 reelt ikke havde natarbejde. På den ene side kan dette betyde, at resultaterne fra disse undersøgelser fortyndes, så man undervurderer den virkelige risiko for fx brystkræft. På den anden side kan det også betyde, at resultaterne ikke afspejler følger af natarbejde, men andre forhold som kendetegner de persongrupper, man har undersøgt.

Man har ofte fremhævet at natarbejdere og skifteholdsarbejdere adskiller sig fra dagarbejdere fx mht. livsstil. Flere undersøgelser har således vist, at der er flere rygere blandt skifteholdsarbejdere. Gennemgangen af de 13 undersøgelser, som udgør kernen i denne rapport, gav dog ikke stærke holdepunkter for at konkurrerende faktorer (forplantningsforhold, livsstil etc.) kan forklare de positive resultater, som præsenteres.

Selektiv deltagelse i epidemiologiske undersøgelser kan skabe store fortolkningsproblemer, fx hvis syge personer, som har haft natarbejde, er mere villige til at deltage end syge, som ikke har haft natarbejde. Generelt, var der ikke stærke holdepunkter for selektiv deltagelse i undersøgelserne, selv om dette kan have gjort sig gældende i enkeltundersøgelser. På den anden side blev det bemærket, at flere af undersøgelserne ikke afrapporterede alle resultater, som de havde datagrundlag for at analysere. Hvis afrapporteringen var afhængig af resultaterne, fx ved at man undlod at beskrive negative fund, kan dette have medført skævvridning af resultaterne. Derfor anbefales forfatterne at offentliggøre resultaterne af disse analyser.

Ud over kerneundersøgelserne af natarbejde og risiko for kræft gennemgår rapporten anden videnskabelig dokumentation, som kan belyse en eventuel årsagssammenhængen mellem natarbejde og brystkræft og andre kræftsygdomme. Disse undersøgelser fokuserer altovervejende på melatonin hypotesen. Det var ikke ambitionen af beskrive alle disse undersøgelser, men at give en balanceret



oversigt over de vigtigste resultater. Der foreligger flere dyreforsøg, som viser at melatonin kan reducere tumorcellers vækst, og en modsat effekt ses hvis dyrene udsættes for lys om natten. Men disse undersøgelser er udført på natdyr (fx rotter), og det er usikkert i hvilket omfang man kan overføre disse resultater til mennesker (dagdyr). Der er kun udført to relevante undersøgelser af melatoninniveau og risiko for brystkræft, den ene viste, at et lavt melatoninniveau er forbundet med forøget risiko for brystkræft, den anden undersøgelse fandt ikke denne sammenhæng. Flere undersøgelser af blinde har vist nedsat risiko for brystkræft, og man har spekuleret på om dette kunne være fordi de er mindre påvirket af lys og dermed har højere melatoninniveauer, men der er ikke undersøgelser, som viser dette. Undersøgelser af natarbejdere har vist, at de har nedsat melatoninniveau, men der er kun marginale forskelle, hvis man ser på den samlede udskillelse hen over døgnet. Hvis det sidstnævnte mål er det mest relevante, tyder dette ikke på at melatoninhypotesen kan forklare den forøgede forekomst af brystkræft, som ses i flere undersøgelser af natarbejdere. Tidligere oversigtsartikler har lagt vægt på undersøgelser af piloter og stewardesser, fordi disse kan være udsat for jetlag og natarbejde. Ingen af de publicerede undersøgelser havde dog oplysninger om natarbejde, og de blev derfor ikke inkluderet blandt kerneundersøgelserne i denne rapport. Det skal dog bemærkes, at de nyeste undersøgelser ikke fandt forøget risiko for brystkræft blandt flyvepersonale med langdistance flyvning, hvor man vil forvente at jetlag og natarbejde er hyppigst forekommende.

Det konkluderes, at fem ud af otte undersøgelser viser forøget forekomst af brystkræft. Tre af disse undersøgelser viser statistisk signifikant forøget forekomst af brystkræft efter 20-30 års natarbejde. Dette kan tyde på, at mange års natarbejde forøger risikoen for brystkræft. Resultaterne for korterevarende natarbejde er derimod ikke konsistente. Der er flere grunde til at man skal være varsom i fortolkningen af den foreslåede langtidseffekt af natarbejde: Antallet af undersøgelser er lille, alle positive undersøgelser er gennemført blandt sygeplejersker på natarbejde, og risikoforøgelsen er beskednen. Dette gør resultaterne sårbare mht. bias, tilfældighed og confounding, selvom vi ikke har været i stand til at udpege specifikke fejlkilder.

Alt i alt er der begrænset dokumentation for at der er en årsagssammenhæng mellem natarbejde og brystkræft (+).

Der er utilstrækkelig dokumentation for årsagssammenhæng mellem natarbejde og prostatakræft (0), tyktarmskræft (0) og alle kræftformer set under et (0).

## **ABSTRACT**

**Objectives** This paper systematically reviews if nightshift work increases the risk of breast cancer or other cancers.

**Methods** Studies that specifically included information on nightshift or shift work and reported cancer occurrence were focused upon. A systematic search of Medline and Science Citation Index was conducted until May 2007. The quality of each paper was discussed with respect to design, exposure and outcome information, bias, confounding and exposure response assessment.

**Results** Thirteen relevant reports were found and eight reported relative risk for breast cancer, three for colon cancer, two for prostate cancer and four for all cancer. Most studies had crude information about nightshift work, four register linkage studies had no individual exposure information but relied on exposure probabilities assessed on a group-level, and no studies analysed cancer risk by the cumulative number of night shifts (however, most studies did so by number of years of nightshift work). Confounding did not seem to be of major concern. Presentation of results was not always complete and it would have been appreciated if the reasons for leaving some findings out were reported. There were indications of a long-term effect of nightshift work (more than 20-30 years), but the number of positive studies are small, they are all conducted among nurses and risk estimates are only moderately increased. This makes the results sensitive to bias, chance and confounding.

**Conclusion** There is limited evidence for a causal association between nightshift work and breast cancer, while there is insufficient evidence for colon cancer, prostate cancer and overall cancer.

## **BACKGROUND**

### **The melatonin hypothesis**

In 1987 Stevens hypothesized that the rising risk of breast cancer seen in industrialized societies was, at least partly, due to the increased use of electric lighting at night (1). It was suggested that light at night could suppress melatonin output and increase estrogen level and thereby increase the risk of breast cancer. The idea was based on experiments in rodents showing that constant light affected mammary tumorigenesis and epidemiology that breast cancer risk was highest in the most industrialized societies. The melatonin hypothesis stimulated various lines of research, from laboratory studies using animal models to epidemiologic studies of humans exposed to light at night and nightshift work. Recently, the hypothesis has evolved from merely a question of suppression of melatonin output to a question of disruption of the circadian rhythm, interaction with clock genes and light exposures in early life (2).

### **Breast cancer**

The vast majority of invasive breast cancers are of epithelial origin and originate from the mammary ducts (3). Infiltrating duct carcinomas constitute about 80 percent of breast cancers. Less frequent histological types are medullary carcinoma, lobular invasive carcinoma, mucinous carcinoma and tubular carcinoma. Non-intrinsic tumours (e.g. lymphoma) and metastases to the breast are rare.

Annually 3530 women and 22 men are diagnosed with breast cancer in Denmark and 8.9% of women and 0.1 per cent of men are diagnosed before they reach an age of 75 years and the relative five year survival is 77 percent for women and 80 percent for men (4). The age standardized annual breast cancer rate has doubled for women from about 40 in 100,000 in 1945 to 85 in 100,000 in 2000. The rate has been stable during this time period for men.

### **Risk factors for breast cancer**

As much as about 50 percent of all breast cancer cases can be attributed to known risk factors (5).

*Age* For women the risk increases steeply by age until menopause and levels off thereafter. For men the risk increases gradually by increasing age (4).

*Family history* The risk of breast cancer increases with number of first-degree relatives (mother, sisters, daughters) with breast cancer (6). Familial breast cancer accounts for less than 10 percent of breast cancer and mutations in the BRAC1 and BRAC2 genes appear to be responsible for two-thirds to three quarters of these cases (3).

*Endocrine and reproductive factors* Breast cancer risk is associated with prolonged exposure to female sex hormones (7,8). A large number of epidemiological studies have demonstrated that late onset of the menstruation cycle decreases the risk of breast cancer later in life with an odds ratio (OR) of about 0.8 for those 15 year or older at menarche compared with those below 12 years (9). Late natural menopause increases the risk (OR 2.0 for those 55 years or older at menopause compared with those below 45 years) (9). Cancer of the breast occurs more frequent among women who remain nulliparous with estimates of relative risk ranging from 1.2 to 1.7 and the risk decreases by number of children (9). The risk furthermore increases by increasing age at first birth independently of number of children and ORs about 1.6 have been reported for women older than 35 years at first birth compared with women younger than 18 years (9).

*Exogenous hormone replacement therapy and oral contraceptives* Combined oral contraceptives are associated with a 20 percent increased risk of breast cancer among current users that disappears 5-10 years after stopping (10). A 30-60% increased risk of breast cancer is seen in current and recent users of exogenous hormone replacement therapy (11).

*Alcohol, tobacco, diet an adiposity* The risk of breast cancer increases by increasing intake of alcohol in a dose-dependent fashion with a 7.1% increase in the relative risk for each additional 10 g per day intake of alcohol (12). Smoking is, on the other hand, not associated with breast cancer (12). Adiposity and excessive weight gain are risk factors for breast cancer but apparently primarily in postmenopausal women (3,13). A high caloric intake, especially of saturated fats, might be linked to increased breast cancer risk, however, findings for dietary factors are conflicting (3).

*Other risk factors* The risk of breast cancer is also associated with a prior diagnosis of lobular carcinoma in situ, radiation therapy to the chest (14). Breast cancer is found more frequently in women of higher socio-economic status which probably is related to lifestyle factors such as reproductive history, alcohol use and exogenous hormone use (3).

*Environmental exposures.* There is until now limited evidence that chemical occupational or environmental exposures are risk factors of breast cancer (15).

*Male breast cancer.* Little is known about risk factors for breast cancer in men due to the rarity of the disease. However, studies of environmental or other exogenous risk factors conducted among men may have advantages over studies conducted among women because the lack of competing reproductive factors (16).

### **Nightshift work**

According to the International Labour Organisation (ILO) Night Work Convention the term *night work* or *night shift* means all work, which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 a.m. The term *night worker* means an employed person whose work requires performance of a substantial number of hours of night work, which exceeds a specified limit. The competent authority shall fix this limit after consulting the most representative organisations of employers and workers or by collective agreements. None of these definitions are, however, used in any of the studies included in this document.

In a 2000 survey, 3 percent of the Danish work force reported nightshift work (any work between 23 p.m. and 4 a.m. (17). About 20 percent of employees or self-employed workers in the EU countries in 2000 and 2005 reported that they worked at least one night a month (at least 2 hours between 10 p.m. and 5 a.m.) (18). Ten percent worked 1-5 nights and 10 percent more than 5 nights per month. Furthermore, 0.4 percent reported permanent night shifts, while 18 percent worked alternating day and night or evening shifts (19). Night work was most prevalent (>30 percent) in agriculture, hotels and restaurants, transport, communication, and health (18).

### **Exposures of nightshift work**

*Light* In offices and hospitals the illuminance at the cornea is about 100-300 lux during night and daytime work compared with 10,000 lux outdoors during daytime and 0.1-5 lux when at sleep during night and daytime (20). A threshold level of 30 lux of white light for melatonin suppression has been suggested (20).

*Stress* Activation of the HPA-axis has been suggested as a major mediator of illness and disease (e.g. cardiovascular disease) in shift workers, but very little research addresses this issue (21).

*Behavioural factors* A previous review reported that nine out of 11 studies showed 1.07-1.48 times more smokers among shift workers than among day workers, while two studies had shown reduced prevalence ratios (0.56 and 0.96) (22). That review documented no strong indications that alcohol consumption or exercise differ between shift workers and day workers. Only few differences were observed with respect to nutritional intake but frequency and timing of meals may change during shift work and there were some indications that shift workers are heavier than day workers (two out of 10 studies, eight showed no difference).

The distribution of behavioural factors among nightshift and day workers were reported in five of the studies included in this review (23-28). Table 1 gives an overview of this information and shows that nightshift workers more often smoke (on average about 20-30% more smokers), have a higher body mass index (BMI) and less often use hormone replacement therapy than day workers. Nightshift workers also seems to have early menarche more often but no consistent patterns are apparent for other reproductive factors across the five studies. It should, however, be noticed that 3-6 times higher alcohol consumption was reported in trades with at least 60% female employees working at night compared with all female employees (28).

*Sleep deprivation* Nightshift workers often complain about insufficient sleeping because the quality of daytime sleep may be worse than night time sleep (20,29).

*Melatonin in nightshift workers* A large field study of nurses recently demonstrated a decreased urinary 6-sulphatoxy melatonin concentration in mixed shift workers during nightshift workdays compared with days off (intra-individual comparisons) and compared with fixed dayshift workers (inter-individual comparisons) (30). Urinary 6-sulphatoxy melatonin levels were specified for 3-hour intervals during 24-hour periods. Fixed night shift workers showed somewhat lower concentrations than mixed night shift workers during night shift workdays of borderline significance. 24-hours 6-sulphatoxy melatonin output was not reported but showed no significant association with nightshift work (Personal communication, Åse Marie Hansen). Others have shown irregular light-dark cycles in nightshift workers but unaffected total melatonin levels across a 24-

hour day (20). Borugian et al compared 24-hour melatonin levels in rotating shift workers with day workers and found lower levels during night shifts but higher during day shifts or days off (31). Shernhammer et al showed lowered 6-sulfatoxymelatonin levels in the morning urine of 14 nurses participating in the Nurses Health Study that worked at least one nightshift during the previous two weeks when compared with nurses working no night shifts during this period (32).

## LITERATURE SEARCH

Three methods were used in combination to identify the epidemiological literature relevant to nightshift work and cancer risk: First, a computerized search was conducted in PubMed in May 2007. Search terms included night work, night shift, or shift work (text words) or circadian rhythm, work schedule tolerance, circadian disruption and chronobiology disorders (MeSH terms or subheadings) and cancer (text term) or neoplasms and risk, rate, odds ratio, incidence, or mortality (MeSH terms). Then references were extracted from the bibliographies of the articles identified. All abstracts were reviewed and the final set of studies decided upon. We included original epidemiological studies that specifically included information on night or shift work and the risk of cancer. No animal studies were included. Finally, we conducted a search in Science Citation Index based on three core publications (23,28,33).

We identified 426 articles. After reviewing the abstracts, 61 articles were selected for a detailed evaluation. Of these 12 were original epidemiological studies of night or shift workers and cancer risk and thus met the inclusion criteria (23-28,33-38) (Figure 1). We also identified 26 reviews or hypothesis papers (2,15,20,39-61), 6 letters (62-67), 3 editorials (68-70) and 1 news report (71) in addition to 6 papers focusing on flight attendants (72-77) and 7 focusing specifically on melatonin (78-82,82,83). Finally, Anders Ahlbom, who reviewed this document, informed us about a study in press conducted by him, Judith Schwartzbaum, and Maria Feychting that we also included in the review (84).

The 13 selected studies of nightshift workers included seven studies of breast cancer (23,25,26,33,36,37,68), two studies of prostate cancer (27,38), one study of colon and rectum cancer (24), and three studies of all cancer (34,35). Tynes et al reported the risk of colon cancer and all cancer in addition to breast cancer (36) and Schwartzbaum et al reported all major cancer sites including breast, prostate, colon, rectum and all cancer (84). The 2003 study by Schernhammer et al about breast cancer and the later study by Schernhammer about colon cancer were based on the same study population (23,24). The 2006 study by Schernhammer et al about breast cancer (26) was based on a study population that did not overlap that of the authors' 2001 study (23). Table 2 presents main characteristics of the 13 studies and table 3 presents the principal results, cancer site by cancer site.



We did not include epidemiological studies of pilots, flight attendants, physicians, radiologist, military and police employees, fire fighters, police and law enforcement personnel that have been included in previous reviews (48,56), since these studies did not specifically include any information about nightshift work for the study participants. A former review about nightshift work focused on cancer risk in aircrew (53) and we therefore included studies of airline flight attendants and pilots in addition to other relevant toxicological and epidemiological data in the section on contributory evidence. That part of the review was not comprehensive or systematic but the ambition was to include a balanced set of the most relevant studies.

## RESULTS

### The individual studies

#### Breast cancer

**Tynes et al** conducted a register linkage case control study among 2619 women recorded in a national register of certified radio and telegraph operators that mainly had worked in the merchant navy (36). A total of 50 incident breast cancers (ICD-7 [International Classification of Diseases 7<sup>th</sup> version] - code 170) were identified in a national cancer register and 259 age-matched controls were drawn from within the study population. Histories of employment on ships were obtained from a seamen register and a shipping journalist and a researcher with detailed knowledge of the merchant navy classified each ship with respect to shift work (4 categories: 0, 1, 2, 3). It was stated that this classification reflected the frequent presence in the radio room both at night and day. The shift work variable was multiplied with number of years employed within each category (this was however not clearly stated) and this index was used together with duration of employment in the analyses. Analyses were adjusted for a fertility-variable (no children, first child born at age <25, first child born at age ≥25), but only for participants born 1935 or later (this information was available for 6 out of 21 cases above 50 years of age, apparently information was complete for participants below 50 years of age). Data were presented separately for women below 50 years and 50 years and older.

The odds ratio of breast cancer increased by duration of employment (p-value, 0.02) and among operators employed for more than 3.1 year (the highest category) an odds ratio of 5.9 (95%CI 0.7-47.7) was observed compared with operators never undertaking nightshift work among those aged 50 years or more. Similar findings were seen if odds ratio was analysed by the cumulative index. For operators younger than 50 years no excess was seen. Comparable results were seen by duration of employment and for analyses only including working histories before age 30. This study also reported SIR values for the most frequent cancer sites among all radio and telegraph operators using the back ground population as the reference and showed a non-significantly increased risk for all cancer (SIR 1.2, 95%CI 1.0-1.4) and colon cancer (SIR 1.3, 95%CI 0.6-2.6).

*A main strength of this study is the internal comparisons within a population expected to be homogenous with respect to competing risk factors other than shift work. Information on shift work relied on expert assessment of register data and selective recall should not have biased the results. Furthermore, follow-up and breast cancer ascertainment relied on good quality cancer and population registers and selection bias probably was not a problem. A main limitation is the sparse*

*control for potential confounding especially among those 50 years or older for which reproductive history only was available for about one third of the participants. Classification of nightshift work on ship-level is sound if working schedules within individual ships were homogenous for all radio and telegraph operators working on the same ship, but this was not commented on and the expert exposure classification was not validated.*

**Davis et al** conducted a population based case control study of night shift work and breast cancer (33). Case patients were women aged 20-74 and diagnosed with breast cancer (ICD-O [International Classification of Diseases for Oncology] 174.0-174.9) between 1992 and 1995 and identified by the SEER cancer surveillance program. Age and sex matched control subjects were identified by random-digit-dialing. Seventy-eight percent of cases and 75 percent of controls agreed to participate. Through individual interviews a lifetime occupational history was obtained that included any job lasting 6 months or longer. For each job it was asked about the percentage of time worked at day, evening and graveyard shift. Graveyard shift was defined as “beginning work after 7.00 p.m. and leaving work before 9 a.m.”. For the 10 years prior to diagnosis three variables characterized graveyard shift work further: Ever worked graveyard shift, hours per week graveyard shift, and number of years of at least one graveyard shift per week.

The adjusted odds ratio of breast cancer for ever working the graveyard shift during the 10 years prior to diagnosis was 1.6 (95%CI 1.0-2.5). The risk increased by number of hours per week on the graveyard shift (p-value, test for trend 0.03) and by number of years with at least one graveyard shift per week (p-value, test for trend 0.04) within this 10 year period. These analyses were adjusted by parity, family history of breast cancer, oral contraceptive use, and hormone replacement therapy.

*Main strengths of this study are quantified information about nightshift work with respect to intensity (hours/week) and duration (years) and adjustment for the principal potential confounders. Main limitations are a low proportion of subjects with shift work (due to the population based design), the fact that random-digit-dialing may have contributed to selection bias if nightshift-working controls less frequently answered the telephone, and a definition of graveyard shift that may include non-overnight work). It is noticed that no risk estimates were presented for life time work history of graveyard shifts, even if this information was obtained.*

**Schernhammer et al** studied the risk of breast cancer following working rotating night shifts among nurses participating in the US Nurses' Health Study (23). The study enrolled 121,701 female nurses aged 30-55 years in 1988. After exclusions were made for those with incomplete data or a previous cancer, 78,562 comprised the study population that was followed until 1998. The participants in 1988 completed a questionnaire that included questions about nightshift work that was defined as "rotating night shifts with at least three nights per month in addition to days or evenings". The participants reported if they had been diagnosed with breast cancer and the national death index was searched for additional cases and a total of 2441 cases of breast cancer were ascertained between 1988 and 1998. Pathology records were identified for 93 percent.

The risk of breast cancer, adjusted for a comprehensive list of known, potential confounders, increased by years on rotating shifts up to 1988 compared with those who never had such work prior to 1988 (p-value for trend 0.02). Among those with more than 30 years on rotating shifts the adjusted relative risk (RR) was 1.36 (95%CI 1.04-1.78). Comparable results were seen for pre- and postmenopausal women. Risk estimates adjusted by age only were almost identical to those obtained by the full models.

*The main strengths of this study are the extensive confounder control, the prospective design, and the high number of participants working rotating shifts. A major limitation is a classification of nightshift work that does not include fixed nightshift work. If fixed nightshift workers have an increased risk of breast cancer and furthermore classified themselves as non-exposed, this has biased the results towards the null. If, on the other hand, the fixed nightshift workers have no increased risk of breast cancer this could be because they adopt an altered circadian rhythm and melatonin is less strongly suppressed. No increased risk in fixed nightshift workers could also indicate non-consistent findings if cumulative number of nightshifts is the relevant exposure metric. Under all circumstances, we would have appreciated to have results for both rotating and fixed nightshift workers.*

**Hansen** reported breast cancer risk among women employed in manufacture of beverages, land transport services, catering and air transport services in a register linkage nested case control study (28). Breast cancer cases aged 30-54 years (n= 7035) were identified in the national cancer registry. Individually matched controls were obtained from a national population registry. Employment

histories since 1964 were gained in a national pension fund for cases and controls. A survey conducted in 1976 showed the highest prevalence of female workers with nighttime schedules (64%-71%) in these four trades.

The odds ratio for breast cancer among women ever employed for more than 6 months in these trades was 1.5 (95%CI 1.3-1.7) compared with women employed in trades with less than 40 percent female employees working nighttime schedules according to the survey. Trades with 40-60% female nighttime workers were excluded from the analyses. Analyses were adjusted for number of children and age at birth of first and last child and current job title. The 1976 survey showed that the average number of alcoholic drinks consumed was substantially higher (>3 times the median value for all female employees) in the four exposed trades. It was stated that there was a positive trend of breast cancer risk with duration of work at night, but only results for those employed for more than 6 years in the exposed trades were presented (OR 1.7, 95% CI 1.3-1.7). Taking account of time since first employment did not influence the risk estimates substantially.

*The main strengths of this study are the high number of incident cases of breast cancer and information on nightshift work based on routine data and independent of participant reporting. The main limitation is the lack of individual information about nightshift work that was represented by employment in four trades. The analyses thus effectively compared four trades with several other trades (not specified) that may differ with respect to other aspects than nightshift work. This may be well-documented risk factors for breast cancer (e.g. alcohol consumption, body mass index, oral contraceptive use, hormone replacement therapy and age at menarche and menopause) as well as risk factors for breast cancer that still are unknown. A more extensive confounder control could at least partly have taken account of this.*

**Lie et al** studied 537 breast cancer cases and 2143 individually matched controls in a register linkage study within a cohort of 44,853 female nurses registered in a national registry of nurses (37). The registry included nurses who graduated from a nursing school in Norway between 1914 and 1980 and were alive in 1949 or born later. Cases were identified by record linkage with the national cancer registry based on ICD-7 codes. For each case, four controls alive and without breast cancer at the time the cases were diagnosed with breast cancer, were randomly drawn from the cohort and individually matched by year of birth.

Work histories were reconstructed from the registry of nurses. This registry included self-reported information on work place and to some extent ward or department for the period prior to 1968 (the last regular update) and only sporadic data thereafter. Additional data were obtained from censuses from 1960, 1970 and 1980 if the census occupational code was 'nursing'; 'nursing and other care work' or the industry code was 'health work'. All work at infirmaries was defined as night work except for managerial jobs, teaching and work at physiotherapy or outpatient departments. Information on work place was incomplete after 1960 because the censuses did not include information on work place.

ORs were analysed by conditional logistic regression adjusting for age at birth of first child and number of children and total employment time. The adjusted OR of breast cancer increased by years with night work, as defined by the authors, and the risk was two-fold increased if night work had lasted 30 years or more compared with no night work. A test for trend showed a p-value of 0.01. A similar pattern was seen if the last 20 years of employment were disregarded.

*A major strength of this study is the high number of participants. A major limitation is the lack of individual information about nightshift work and partly incomplete data on work histories. The authors stated that almost all nurses employed at infirmaries worked rotating shifts during the first decades of the 20th century but the burden of night work varied between departments and permanent nightshift workers became more common from the middle of the century. If there is a causal association between nightshift work and breast cancer such misclassification of exposure has biased this study towards weaker risk estimates. But nurses working in infirmaries may be characterized by other factors and not necessarily only by nightshift work that may have confounded the results towards erroneously higher risk estimates. It was taken account of some potentially strong confounding factors in the analyses (age at first of first child and number of children) but it is an open question to what extent other known and still unknown risk factors for breast cancer may have contributed to the increased risk seen. It is noticed that age was not adjusted for in analyses by duration of employment and this may have confounded results even if age of first child was included in the models.*

**Schernhammer et al** analysed rotating night shifts and the relative risk of breast cancer in the Nurses' Health Study II that enrolled 115,022 nurses aged 25-42 years in 1989 (26). The population did not overlap that studied by Schernhammer in 2001 (23). Participants filled in questionnaires about night work in 1989, 1991, 1993 and 1997 and retrospectively in 2001 for the time periods 1993-95 and 1997-99. Rotating nightshift work was defined as in the previous report (23). Questions were asked about months working rotating nightshifts in 6 categories (0, 1-4, 5-9, 10-14, 15-19 and  $\geq 20$  months) and permanent night shifts for 6 or more months. In the analyses participants were classified by the lifetime total number of years they worked rotating nightshifts until the date of diagnosis. Other procedures were comparable with the analyses based on the Nurses' Health Study I. Nurses who reported more than 20 years of rotating nightshift work showed an elevated relative risk of breast cancer compared with nurses never working rotating nightshifts (RR 1.79, 95% CI 1.06-3.01) after adjustment for multiple potential confounding factors (but this did not change results substantially from the age-adjusted RR-estimates). There was no increased risk with fewer years working rotating nightshifts.

*The major strengths and limitations of this study parallel those of the previous study conducted by Schernhammer et al from 2001 (23). It is noticed that risk estimates were not presented for working fixed nightshifts even if this information was obtained.*

**O'Leary et al** conducted a population based case control study of breast cancer 1996-97 on Long Island, New York (25). They included 467 cases and 509 controls recruited through a multi-step procedure and participation rates were not easily computable. Cases were newly diagnosed patients with first primary invasive or in situ breast cancer identified by weekly contacts to hospitals, pathology departments and physicians in the study area (85). Occupational histories were obtained for all jobs held for 6 months or longer during the 15 years prior to diagnosis (cases) or reference date (controls). The frequency (days per week, month, and year), duration, and type of shift work were ascertained for each job and the participants were specifically asked about overnight shifts defined as "starting as early as 7.00 p.m. and continuing until the next morning". Among cases 5.3 percent and among controls 9.8 percent had ever worked overnight shifts during the previous 15 years.

The OR for breast cancer, adjusted for age, parity, family history, education, and previous benign breast disease was 0.55 (95%CI 0.32-0.94) for any overnight shift work and 0.64 (95%CI 0.28-1.45) for overnight shift work but no evening shift work. The corresponding crude OR-estimates were 0.53 (95%CI 0.32-0.88) and 0.57 (95%CI 0.26-1.25), respectively. The adjusted ORs decreased by duration of overnight shift work (only periods with > 1 night shift/week were included) and an OR of 0.32 (95%CI 0.12-0.83) was seen for the longest exposure category ( $\geq 8$  years). The OR of breast cancer following evening shift work was 1.21 (95% 0.90-1.64) but according to the melatonin hypothesis evening work should not be a risk factor for breast cancer (1).

*The main strengths of this study are the detailed definition and quantification of nightshift work and the relevant confounder control. The major limitations are the small number of study participants, the low proportion nightshift work and the retrospective reporting. Furthermore, information on nightshift work was only obtained for the last 15 years and an effect of more past exposure may have been overseen. The inverse relationship between nightshift work and breast cancer was unexpected but the authors did not discuss why this could be.*

#### Prostate cancer

Kubo et al studied 14,052 men working between 1988 and 1990 and providing information on work schedule and followed them until 1997 (27). In a self-administered questionnaire, the participants were asked which work schedule they had been engaged in the longest: "Fixed night work or alternate night and day work". Twenty percent reported fixed or alternate night and day work. Incident cases of prostate cancer (ICD-10 C61, n=31) were identified by linkage with several regional cancer registries. Analyses were adjusted for a long list of potential confounders and the reference was daytime work. The study showed relative risks of 2.3 (95% CI 0.6-9.2) for fixed night work and 3.0 (95%CI 1.2-7.7) for alternate night and day work. No analyses by duration of nightshift work were conducted.

*The major strength is the prospective design. Major limitations are the low statistical power since only 3 cases of prostate cancer occurred among workers on fixed night shifts and 7 occurred among workers on rotating night shifts, the vague definition of nightshift work, and the lack of any*



*quantitative data on the extent of nightshift work, and thus no assessment of exposure response relationships.*

**Conlon et al** utilized previously collected population based case control data to assess a possible association between shift work and prostate cancer (38). A total of 760 cases recorded with a cancer registry diagnosis of prostate cancer and 1632 controls reported lifetime work history and for each job lasting one year or more described the usual work time as: “Day time shift, evening/night shift, rotating shift, other”. Participants were classified as ever having worked full-time rotating shifts (excluding those working part-time rotating shifts) and according to duration of this work. Among the controls 44 percent reported ever working fulltime-rotating shifts. Analyses were adjusted for age and family history of prostate cancer. The OR of prostate cancer was 1.19 (95%CI 1.00-1.42) for ever working rotating shifts. There was no trend by years of rotating shifts (p-value, 0.42).

*The major strengths of this study are the high number of cases and quantitative information on duration of rotating shift work. Major limitations are the lack of a definition of rotating shift work and probably this category included a high proportion of men working evening shifts but no night shifts as indicated by the high prevalence working rotating shifts. Furthermore, the exposure contrast when compared with the general population is expected to be small. We noticed that information was obtained for evening/nightshift but no risk estimates were presented.*

#### Colon and rectum cancer

**Schernhammer et al** studied the risk of colon and rectum cancer following rotating nightshifts in the US Nurses’ Health Study (24), and the study population was almost identical with the population of Schernhammer et al’s publication from 2001 (23). Participants with ulcerative colitis, Chron’s disease or familial polyposis syndrome in addition to a previous cancer (except non-melanoma skin cancer) were excluded and the population then comprised 78,586 participants. Information on nightshift work was identical to the information of the 2001-study. Analyses were adjusted for an extensive list of potential confounders and showed that women who worked 1-14 or 15 years or more on rotating nightshifts had relative risks of colon cancer of 0.93 (0.74-1.17) and 1.32 (0.93-1.87). A test for trend showed a p value of 0.20. When rectum was included in the case category a similar pattern was seen but the trend test reached statistical significance (p-value 0.04).

*The main strengths and limitations of this study are identical to those mentioned for the Schernhammer et al 2001 study. It is noticed that risk estimates for other cancers than colorectal cancer were not presented but that this information was obtained for the study population (86).*

All cancer

**Taylor et al** included 4188 male workers employed for at least 10 years in shift work in e.g. coal, bricks, metal and vehicle manufacture industry in a retrospective cohort study 1956 to 1986 (34). Forty-five percent worked 3-shift weekly rotating shifts, 35% 3-shift rapid rotating, and 19% alternate day and night. A total of 722 died during follow up and 219 died from cancer, while 188.8 deaths were expected according to the age and calendar year adjusted national rates, p-value <0.05. This corresponds with an SMR-value of 1.16. Results were also presented for ex-shift workers, who did not fulfil the 10-year night shift work criterion, that SMR-value was 1.12 (29 observed deaths).

*The main strengths of this study are the high number of cancer deaths and the independent pay roll based information on shift work schedule. The main limitations are the limited confounder control (including chemical occupational exposures and smoking) and the lack of any exposure response assessment.*

**Rafnsson et al** conducted a retrospective cohort study of 211 men employed in a fertiliser plant for at least 1 year 1954-85 and followed them until 1985 (35). They all worked 3 shifts according to pay roll information and 34 died during follow up, 10 due to cancer, while 9.01 were expected from the national rates. The mortality decreased by years of shift work.

*The main strengths of this study are the independent information about work schedule and the analysis by duration of shift work. A major limitation is the small number of cancer deaths.*

**Schwartzbaum et al** analysed all major cancer sites in a cohort study of all gainfully employed inhabitants of Sweden ( $\geq 20$  hours/week) included in the 1960 and the 1970 censuses. Three percent of the men and 0.3 percent of the women were classified as shift workers by the authors (69,759 men and 3057 women). Among them 6792 incident cases of cancer were identified in the national cancer registry during the follow up period 1970-1989. The classification of shift workers relied on a job exposure matrix constructed from a survey of living conditions 1977-1981. Shift workers were

defined by occupation-industry combinations recorded in the censuses with at least 40% working rotating shifts with 3 or more possible shifts per week or working any hour between 1.00 am and 4.00 a.m. at least one day per week. The most common exposed occupations were paper and paperboard worker, paper pulp worker, furnace worker, fire fighter, policeman, civilian protective service worker and railway engine worker among men and crane and hoist operator, delivery woman in paper and printing industry and midwife among women. The reference population was occupation-industry combinations with less than 30 percent shift workers.

The risk of all cancers combined, breast, colon, rectum and prostate showed observed values close to the expected. This was also the case when analyses were restricted to workers employed in a job classified as shift worker both in 1960 and 1970 and when only workers of jobs with more than 70% shift workers were classified as exposed. A slightly increased risk of thyroid cancer in men (SIR 1.35, 95% CI 1.02-1.79) was the only positive finding suggested.

*The main strengths of this study are the tabulation of risk estimates for all major cancer sites, the large study population and the independent exposure classification. The main limitation is the lack of individual information about nightshift work that was represented by employment in several occupation-industry combinations with as much as 60% workers not engaged in shift work. This limitation was comparable to that described for the Hansen study (28). Furthermore, the proxy measure for cumulative nightshift work was crude and confounder control was limited.*

### **Contributory evidence**

#### Light at night at home and latitude of residence

Some epidemiological studies have suggested light at night at home to be associated with breast cancer. Davis and colleagues showed an increased risk in women who did not sleep when the nocturnal melatonin peak typically occurs (33) and O'Leary found an increased risk among women who frequently turned on the light at home during sleep hours (25), but both studies relied on self-reported retrospective information about light exposure, and information bias was a likely explanation on the findings. Furthermore, the participants were presented for several other questions about light at night that were unrelated with breast cancer occurrence.

Lower breast cancer incidence has been reported in the arctic region and it has been hypothesized that lower light exposure during wintertime may at least partly be a causal link (69).

#### Pilots and flight attendants

Flight attendants have an increased risk of breast cancer and it has been suggested that this is related with exposure to light at night (53), however, studies published so far have not assessed nightshift work specifically. Pukkala et al. reported an increased incidence of prostate cancer among male airline pilots that increased by number of long haul flights (that is expected to include nightshift work and jet lag), but the risk also increased by increasing cosmic radiation dose and the all-cancer, colon and rectum cancer incidence did not exceed the expected numbers (87). In a large European study of airline cabin attendants, all-cancer, large intestine and rectum cancer mortality was decreased for both sexes compared with the background population (88). Mortality from breast cancer was slightly increased in women but showed no trend by duration of employment. Rafnsson et al. reported increasing risk of breast cancer by length of employment among Icelandic cabin attendants flying long haul international flights in the pre-jet period before, but no trend after jet planes were introduced in 1971 (89). Kojo et al. analysed the risk of breast cancer among Finnish female cabin attendants and showed no evidence that the risk increased by number of long haul flights (72).

#### Cancer risk and melatonin in the visually impaired

The risk of breast cancer and possibly also prostate cancer seems to decrease by increasing degree of visual impairment (90). Blind persons show abnormal melatonin rhythms (91), but the level of melatonin output during a 24 hour period measured by the major melatonin metabolite 6-sulphatoxymelatonin, does not correlate with the level of visual impairment (92,93).

Feychting 1998 may be included here.

#### Melatonin and breast cancer

In a prospective study, urinary concentrations of 6-sulfatoxymelatonin in 24-hour urine samples did not differ between breast cancer patients and control subjects (94), while in an other prospective study the OR of breast cancer declined by increasing levels of 6-sulfatoxymelatonin in morning urine samples (80).

## Biological mechanisms

Originally it was hypothesized that light at night could suppress melatonin output and increase estrogen levels and thereby increase the risk of breast cancer but at present it is unclear if light at night or melatonin affect estrogen levels in humans (2). Melatonin has been shown to have a strong oncostatic effect on chemically induced tumors with increased tumoral latency (the time elapsing from the administration of the carcinogen and the appearance of palpable mammary tumors) in rodents and constant light stimulates tumorigenesis in rats, but not in all studies (40,59). In a frequently cited study by Blask et al. constant light increased the growth of a human breast cancer xenograft implanted into a nude rat model (95). Melatonin has also been proposed to act as an antiestrogen, to enhance immune function, and to have antioxidant properties (96). Anderson reported a significant reduction in number of breast tumors in female rats that were exposed to constant light from an age of 26 days (97) that contrasted earlier findings from rats exposed to constant light beginning before birth and Stevens has hypothesized that light exposure in utero may increase the breast cancer risk of the daughters (2).

## **DISCUSSION**

### **Overall findings**

Years of nightshift work was the principal measure of exposure analysed across the studies reviewed, except for the studies authored by Kubo et al and Taylor et al (27,34). Three studies reported significantly increased risk of breast cancer for long-term night shift work beyond 20-30 years (23,26,37). Virtually no effects were seen for shorter durations. The two studies by Hansen et al and Davis et al showed small influence of duration of employment on the risk of breast cancer (28,33), but they defined long-term shift work as durations of 3 or 6 years and more, respectively. However, both reported increased risk of breast cancer in the overall analyses (ever vs. never) of statistical significance. O'Leary et al showed a negative trend by increasing years of night shift work (no statistical testing of the trend was presented) (25). Others reported trend tests by duration of night shift work of statistical significance {Davis, 2001 148 /id} {Schernhammer, 2001 147 /id} {Lie, 2006 41 /id}. However, these tests have to be interpreted with caution since increased risks in single categories may heavily have influenced the p-values. Furthermore, it was not always clear if the tests were based on the original continuous exposure data or the categorical classification (e.g. the midpoint value).

Tynes et al observed increasing risk for breast cancer for those above but not for those below 50 years of age. Schernhammer et al reported comparable risks for premenopausal and postmenopausal nurses (23) and Lie did the same for nurses below 50 years of age and 50 years (37).

Kubo et al and Conlon et al indicated increased risks for prostate cancer for both fixed and rotating nightshifts but the number of cases were few or the effect only marginal (27,38). Schernhammer et al reported increasing risk of colon cancer by duration of rotating night shifts (24) that was supported by a slightly increased SIR-value observed by Tynes et al among all radio and telegraph operators (36), but Schwartzbaum et al observed no increased risk of colon cancer (84). The overall occurrence of all cancer was close to the expected values in the four studies that analysed this outcome (relative risk estimates between 1.0 and 1.2) (34-36,84), and a negative exposure response relationship was indicated in the only study that assessed duration of shift work and does not support a causal effect due to occupational factors (35).

### **Study populations**

Of the 13 studies, six were based on the general population, four studied nurses (three independent populations), two studied industrial workers and one study included radio and telegraph operators. It was noticed that the three studies indicating a long-term effect of night work on breast cancer risk all were conducted among nurses (23) (26,37).

### **Cancer outcome**

Cancer diagnoses relied on cancer register data, weekly reports from diagnosing institutions, medical records and death certificates and are expected to have high specificity in all studies and unrelated with exposure status. The identification of cases in the three studies (two independent study populations) of Schernhammer et al (23,24,26) did, however, rely partly on self reports and may have been affected by night work status, but this is less likely.

### **Nightshift work**

O'Leary defined night shift work most precisely (25). The definition of Davis et al was less specific and did not request that the shift should last overnight. Schernhammer et al, Kubo et al and Conlon et al did not request that the participants considered timing or duration of the night shift work during the day (23,27,38).

O'Leary et al (25) and Davis et al (33) classified the participants as exposed in the principal analyses if they had experienced 1 nightshift per week or more that corresponds well with the 3 days per month criterion applied by Schernhammer et al (23). Given the low prevalence of workers on fixed nightshift among all nightshift workers (0.4 percent vs. 20 percent (18)) all studies mainly analysed the effect of non-fixed (or rotating) nightshift work. One exception is the study by Kubo et al that specifically reported results for fixed nightshift workers (27). The present database thus does not allow any assessment of a possibly different risk profile for fixed nightshifts.

In the population based studies the prevalence of nightshift work was three percent among men and 0.3 percent among women in the study by Schwartzbaum (84), 5% among women in the studies of Davis et al (33) and Hansen (28), and 20% and 44%, respectively, in the studies by Kubo et al (27)

and Conlon et al (38). These differences probably reflect different working conditions across the study populations but also the different definitions of nightshift work.

As expected, the cut off levels used to define increasing levels of nightshift work differed across studies but it was noticed that this also was the case for the three studies authored by Schernhammer et al (23,24,26). It would obviously be of interest to see all results lined up by using the same cut off points.

Information about night shift work was obtained retrospectively in the 3 case control studies and thus reporting may have been influenced by case status, but shift work is easily estimable, and information bias probably has not been a major concern. On the other hand, selective recall might have affected the results for ambient light levels at night in the homes significantly.

In the four register linkage studies, nightshift work was assessed on a group level (ship, industry, type of hospital department occupation-industry combinations) and thus was estimates of the likelihood of night shift work, e.g. an estimated 40 percent of the “exposed “ participants in the study by Hansen were not involved in nightshift work (28). Lie et al and Tynes et al did not assess the degree of misclassification of nightshift work and Tynes et al did not differ between evening and night shifts (36,37). Schwartzbaum et al apparently included an unknown proportion of workers on evening shift in the exposed category of their principal analyses (84). More than 60 percent of the workers of this study classified as exposed were furthermore not engaged in shift work. These studies compared ships, hospital departments, occupations and industries, which are proxy measures of nightshift work that may have low specificity. Such misclassification of exposure is expected to be non-differential with respect to cancer status and thus will bias a true association towards the null. On the other hand, it is likely that such rather broad proxy measures may be proxies for other exposures and not only nightshift work. The Hansen study exemplifies this showing that manufacture of beverages, land transport services, catering and air transport services (proxies for night shift work) also are proxies for alcohol consumption (28). The results of these studies thus may have been confounded in any direction and not necessarily towards the null. On the other hand, these studies are robust with respect to information bias and selection bias due to the complete register data from independent sources.



Nightshift work per se is not expected to be a risk factor for cancer but is a surrogate measure for e.g. light at night or circadian phase shift, or a factor that influences an intermediary risk factor e.g. sleep deprivation, diet or life style that is causally related with cancer. In any case, one will expect that cancer risk increases by the cumulative number of night shifts, regardless of whether this work entails fixed nightshifts or rotating nightshifts. Workers with fixed nightshifts are expected to cumulate a higher number of shifts than rotating nightshift workers and excluding them from the analyses will thus reduce the power to detect a true effect. In line with this reasoning, Kubo et al showed slightly higher risks of prostate cancer in fixed nightshift work than in rotating nightshift work (27). It would therefore be of interest to have data presented for the fixed nightshift workers of the Nurses Health Study II (26) and based on the lifetime working histories of Davis et al's study (33).

It has been argued, on the other hand, that workers on rotating or mixed nightshifts should be at the highest cancer risk because they do not retrain to an altered circadian rhythm (23). However, a large field study of melatonin profile of nightshift workers showed lower melatonin concentrations in fixed nightshift workers than in mixed night shift workers (30). Offshore workers working 2 weeks on 12-hour night shifts adapt to an altered circadian rhythm and show rates of phase shifts of 1-2 hours per day (98). However, we have not been able to identify field studies of melatonin profiles among nurses or others working a limited number of nights per week documenting that mixed or rotating nightshift workers have more irregular circadian phases than day workers or permanent nightshift workers.

Davis et al and O'Leary et al only considered night shift work during the 10-15 years prior to diagnosis (25,33). But since animal data suggest that an effect of night shift work is mediated by suppression of the oncostatic effect of melatonin this should not be a limitation since a long induction or latency period is not expected if the melatonin hypothesis holds true. Furthermore, taking account of time since first exposure did not affect results significantly (28,36,37,37).

### **Confounding**

There is good evidence that nightshift workers included in this review more often smoke, have a higher BMI, and less often take hormone replacement therapy than dayshift workers. Smoking is not a risk factor for breast cancer but may be a proxy for other factors related to lifestyle and socio-

economic status that may be risk factors for breast cancer (12). The inverse relationship between socio-economic status and breast cancer risk does, however, not support this argument (3). A higher prevalence of women with early menarche was indicated among nightshift workers but generally no consistent differences compared with day workers were observed with respect to reproductive factors; however, differences were seen within individual studies that should be accounted for in the adjusted analyses.

The women classified as nightshift workers in the Hansen study consumed up to 6 times more alcohol than all female employees (3.5-6.0 drinks/week vs. 1.1 drink/week) but alcohol can only explain few percent of the observed increased risk of breast cancer (12) and has barely confounded his results significantly.

The three studies that suggested an effect of long-term nightshift work were all conducted among nurses (23,26,37). On the one hand, this may have been a strength, because extraneous risk factors are expected to be less a problem in analyses relying on comparisons within a profession. On the other hand, this may also have been a major limitation since these nightshift nurses may have shared common yet unknown risk factors other than nightshift work and we would have felt much more confident if the results were replicated across different occupations and industries.

Confounder control was limited in the four register studies because routine register data on e.g. body mass index, oral contraceptive use, hormone replacement therapy and age at menarche and menopause were not available (28,36,37,84). This was also the case for the two prostate cancer studies but this reflects the sparse knowledge about the causes of this disease. Several studies did not control for oral contraceptive use or hormonal replacement therapy and Schernhammer et al was the only to adjust for alcohol consumption (23,24,26). Still it has to be emphasized that no strong confounding effect was indicated by the studies of Schernhammer et al and O'Leary who presented crude risk estimates in addition to the adjusted estimates (23,25,26).

One also has to bear in mind, that if alcohol or smoking habits or other cancer risk factors, are influenced by nightshift work (act as intermediary risk factors), adjusting by these factors may blur causal relationships.

### **Selection bias**

Participation rates were generally high in all studies and selective study participation is not expected to have influenced the findings significantly, especially this was the case for the register linkage studies with almost complete data. The Davis et al study may be an exception since they identified controls by random-digit-dialing that may possess specific problems when studying nightshift work, since night working controls may not be reached by telephone as often as day workers (33).

On the other hand, selective reporting of findings within the individual studies may have influenced the overall risk pattern obtained for nightshift work. For instance, Schernhammer et al presented results for colorectal cancer but not for other cancer sites even if they argued in favour of a general effect on tumorigenesis of light at night and this information was collected in the Nurses Health Study (24,86). Furthermore, Schernhammer et al and Conlon et al obtained data on fixed shift work and Davis on lifetime nightshift work but neither present the findings for these exposure measures (26,33,38). Hansen left workers of industries with an estimated 40 - 60 percent nightshift workers out of the analyses (28). Schwartzbaum et al did the same to those with 30 – 40 percent shift workers. If the decisions whether results should be presented or not were made a priori, results should not have been affected. But if the decisions were data driven the overall risk pattern might have been more varied. We are of course aware that numerous decisions have to be made when data are extracted, analysed and presented and much information must be left out in the sake of parsimonious results and clear conclusions but we would have appreciated if these decisions were more thoroughly described and the non-presented results briefly mentioned.

### **Other relevant data**

The supportive database in favours of a causal association between light at night and thus nightshift work and breast cancer is large, but still there are numerous conflicts. Animal experiments have documented significant oncostatic effects of melatonin. But it has been emphasized that results based on nocturnal animals should only be generalized to diurnal humans with caution (44). Night shift workers have lowered melatonin levels during nightshifts and may adopt to an altered circadian rhythm during longer periods of nightshift work but the total 24-hour melatonin output is apparently not significantly affected by nightshift work at least among nurses (the profession most extensively studied for breast cancer risk) working mixed and fixed nightshifts. Airline crew are expected to experience jet lag and nightshift work during long haul flights and have increased risk

of breast cancer, and possibly also of prostate cancer. But data based on individual flight histories are sparse and equivocal. Blind persons that may be insensitive to light exposure have decreased risk of breast cancer which is in line with a cumulative effect of light at night (and nightshift work). But this finding is not in line with the circadian disruption hypothesis because many visually impaired have free running cycles and furthermore it is not clear whether blind individuals secrete more melatonin than the sighted. Studies of light at night at home are supportive of a causal effect of nightshift work but vulnerable to information bias and thus have to be interpreted carefully. Finally, only two prospective studies of melatonin level and cancer risk have been conducted and they present conflicting results, and no data are at present available showing such an effect for instable melatonin rhythms.

### **Previous literature reviews**

We identified 26 previous reviews or hypothesis papers about nightshift work, light at night and the risk of cancer. Conclusions generally were in line with that of Megdal, Schernhammer and colleagues: “In summary, this meta-analysis suggests that shift work, including work as a flight attendant, increases the risk of breast cancer by 48%.” (53), Hansen et al: “..there is so far relative consisting evidence that working non-day time may increase the breast cancer risk among females” (48) and Davis et al: “Collectively these findings provide intriguing evidence that suggest working at night, or in occupations characterized by night shift work, may be associated with an increased risk of cancer” (46). Anthony Swerdlow was more careful in his conclusion: “Hence, the possibility that shift work per se increases the risk of breast cancer cannot be dismissed, but on the other hand it remains possible that the apparent associations are due to confounding” (99). None of these reviews included the papers published in 2006 and 2007 by O’Leary et al (25), Kubo et al (27) and Conlon et al (38) and Schwartzbaum et al (84) included in this review.

## **CONCLUSION**

Five out of the eight studies of breast cancer in women indicates increased risks. Three of the positive studies show significantly increased risk following 20-30 years of nightshift work. Hence, there are indications of an effect of long term night shift work on breast cancer risk. Findings for shorter durations of exposure are inconsistent. There are several reasons for caution regarding the suggested long term effect, the number of studies is small, the positive studies were all conducted for the same occupational group, nurses on night shift and the risk estimates are only moderately raised. This makes the results sensitive to bias, chance and confounding, although we have not been able to pinpoint specific sources.

In conclusion, there is limited evidence for a causal association between night shift work and breast cancer (+), while there is insufficient evidence of a causal association for prostate cancer (0), colorectal cancer (0), and overall cancer (0).

Nightshift work is prevalent, the incidence of breast cancer is high and an even slightly increased risk may carry a heavy burden for public health. A wealth of new studies of the physiological and pathophysiological effects of environmental lighting and circadian disruption are expected to provide path breaking new insights (100). Still, further epidemiologic studies of night shift work and risk of breast cancer as well as other health effects are needed. These studies should especially focus on reliable exposure data obtained on an individual level and include a wide range of occupational groups.

## REFERENCES

1. Stevens RG. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol* 1987;125:556-61.
2. Stevens RG. Artificial lighting in the industrialized world: circadian disruption and breast cancer. *Cancer Causes Control* 2006;17:501-7.
3. Margolese RG, Hortobagyi GN, Buchholz TA. Neoplasms of the breast. In: Kufe DW, Pollock RE, Weicheslbaum RR, Bast RC, Gansler TS, Holland JF et al., editors. *Cancer Medicine*. Hamilton: BC Decker Inc., 2003:1879-1970.
4. Clemmesen IH, Nedergaard KH, Storm HH. *Kræft i Danmark*. Copenhagen: Kræftens Bekæmpelse FaDL'S Forlag; 2006.
5. Madigan MP, Ziegler RG, Benichou J et al. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995;87:1681-5.
6. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* 2001;358:1389-99.
7. Sasco AJ, Kaaks R, Little RE. Breast cancer: occurrence, risk factors and hormone metabolism. *Expert Rev Anticancer Ther* 2003;3:546-62.
8. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. *N Engl J Med* 2006;354:270-82.
9. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993;15:36-47.
10. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* 1996;347:1713-27.
11. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* 1997;350:1047-59.
12. Hamajima N, Hirose K, Tajima K et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 2002;87:1234-45.
13. Krebs EE, Taylor BC, Cauley JA et al. Measures of adiposity and risk of breast cancer in older postmenopausal women. *J Am Geriatr Soc* 2006;54:63-9.

14. Breast cancer (female). Dynamed 2007.
15. Coyle YM. The effect of environment on breast cancer risk. *Breast Cancer Res Treat* 2004;84:273-88.
16. Meguerditchian AN, Falardeau M, Martin G. Male breast carcinoma. *Can J Surg* 2002;45:296-302.
17. Tüchsen, F., Bøggild, H., Burr, H., and Villadsen, E. *Arbejdstid, arbejdsmiljø i Danmark 2000*. Copenhagen: National Institute of Occupational Health, 2002.
18. European Foundation for the Improvement of living and Working Conditions. Fourth European Working Conditions Survey. Luxembourg: Office for Official Publications of the European Communities, 2007.
19. European Foundation for the Improvement of living and Working Conditions. Third European survey on working conditions 2000. Luxembourg: Office for Official Publications of the European Communities, 2001.
20. Figueiro MG, Rea MS, Bullough JD. Does architectural lighting contribute to breast cancer? *J Carcinog* 2006;5:20.
21. Knutsson A. Methodological aspects of shift-work research. *Chronobiol Int* 2004;21:1037-47.
22. Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health* 1999;25:85-99.
23. Schernhammer ES, Laden F, Speizer FE et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst* 2001;93:1563-8.
24. Schernhammer ES, Laden F, Speizer FE et al. Night-shift work and risk of colorectal cancer in the nurses' health study. *J Natl Cancer Inst* 2003;95:825-8.
25. O'Leary ES, Schoenfeld ER, Stevens RG et al. Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol* 2006;164:358-66.
26. Schernhammer ES, Kroenke CH, Laden F et al. Night work and risk of breast cancer. *Epidemiology* 2006;17:108-11.
27. Kubo T, Ozasa K, Mikami K et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol* 2006;164:549-55.
28. Hansen J. Increased breast cancer risk among women who work predominantly at night. *Epidemiology* 2001;12:74-7.
29. Ingre M, Akerstedt T. Effect of accumulated night work during the working lifetime, on subjective health and sleep in monozygotic twins. *J Sleep Res* 2004;13:45-8.

30. Marie HA, Helene GA, Hansen J. Diurnal urinary 6-sulfatoxymelatonin levels among healthy Danish nurses during work and leisure time. *Chronobiol Int* 2006;23:1203-15.
31. Borugian MJ, Gallagher RP, Friesen MC et al. Twenty-four-hour light exposure and melatonin levels among shift workers. *J Occup Environ Med* 2005;47:1268-75.
32. Schernhammer ES, Rosner B, Willett WC et al. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev* 2004;13:936-43.
33. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 2001;93:1557-62.
34. Taylor PJ, Pocock SJ. Mortality of shift and day workers 1956-68. *Br J Ind Med* 1972;29:201-7.
35. Rafnsson V, Gunnarsdottir H. Mortality study of fertiliser manufacturers in Iceland. *Br J Ind Med* 1990;47:721-5.
36. Tynes T, Hannevik M, Andersen A et al. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 1996;7:197-204.
37. Lie JA, Roessink J, Kjaerheim K. Breast cancer and night work among Norwegian nurses. *Cancer Causes Control* 2006;17:39-44.
38. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. *Epidemiology* 2007;18:182-3.
39. Anisimov VN. The light-dark regimen and cancer development. *Neuro Endocrinol Lett* 2002;23 Suppl 2:28-36.:28-36.
40. Anisimov VN. The role of pineal gland in breast cancer development. *Crit Rev Oncol Hematol* 2003;46:221-34.
41. Anisimov VN. Light pollution, reproductive function and cancer risk. *Neuro Endocrinol Lett* 2006;27:35-52.
42. Anisimov VN, Vinogradova IA. [Light-dark conditions, melatonin and risk of cancer]. *Vopr Onkol* 2006;52:491-8.
43. Blask DE, Dauchy RT, Sauer LA. Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. *Endocrine* 2005;27:179-88.
44. Bullough JD, Rea MS, Figueiro MG. Of mice and women: light as a circadian stimulus in breast cancer research. *Cancer Causes Control* 2006;17:375-83.
45. Cornelissen G, Halberg F. Chronobiologic response modifiers and breast cancer development: classical background and chronobiologic tasks remaining. *In Vivo* 1992;6:387-402.



46. Davis S, Mirick DK. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. *Cancer Causes Control* 2006;17:539-45.
47. Feychting M, Ahlbom A. [Can light exposure affect the risk of breast cancer? Female flight attendants and shift-workers probably the most vulnerable groups]. *Lakartidningen* 2001;98:4316-8.
48. Hansen J. Risk of breast cancer after night- and shift work: current evidence and ongoing studies in Denmark. *Cancer Causes Control* 2006;17:531-7.
49. Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. *Cancer Causes Control* 2006;17:489-500.
50. Jasser SA, Blask DE, Brainard GC. Light during darkness and cancer: relationships in circadian photoreception and tumor biology. *Cancer Causes Control* 2006;17:515-23.
51. Kenny C. Breast cancer. Night shifts put nurses at risk. *Nurs Times* 2001;97:9.
52. Kheifets LI, Matkin CC. Industrialization, electromagnetic fields, and breast cancer risk. *Environ Health Perspect* 1999;107 Suppl 1:145-54.:145-54.
53. Megdal SP, Kroenke CH, Laden F et al. Night work and breast cancer risk: a systematic review and meta-analysis. *Eur J Cancer* 2005;41:2023-32.
54. Patel D. Shift work, light at night and risk of breast cancer. *Occup Med (Lond)* 2006;56:433.
55. Pauley SM. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypotheses* 2004;63:588-96.
56. Schernhammer E, Schulmeister K. Light at night and cancer risk. *Photochem Photobiol* 2004;79:316-8.
57. Schernhammer ES, Schulmeister K. Melatonin and cancer risk: does light at night compromise physiologic cancer protection by lowering serum melatonin levels? *Br J Cancer* 2004;90:941-3.
58. Stevens RG. Lighting during the day and night: possible impact on risk of breast cancer. *Neuro Endocrinol Lett* 2002;23 Suppl 2:57-60.:57-60.
59. Stevens RG. Circadian disruption and breast cancer: from melatonin to clock genes. *Epidemiology* 2005;16:254-8.
60. Stevens RG, Rea MS. Light in the built environment: potential role of circadian disruption in endocrine disruption and breast cancer. *Cancer Causes Control* 2001;12:279-87.
61. Bonde JP, Andersen JH, Frost P et al. [Health examinations in connection with night work.]. *Ugeskr Laeger* 2007;169:2005-7.
62. Frenzel-Beyme R. The melatonin hypothesis: a matter of method. *Environ Health Perspect* 2002;110:A72-A73.

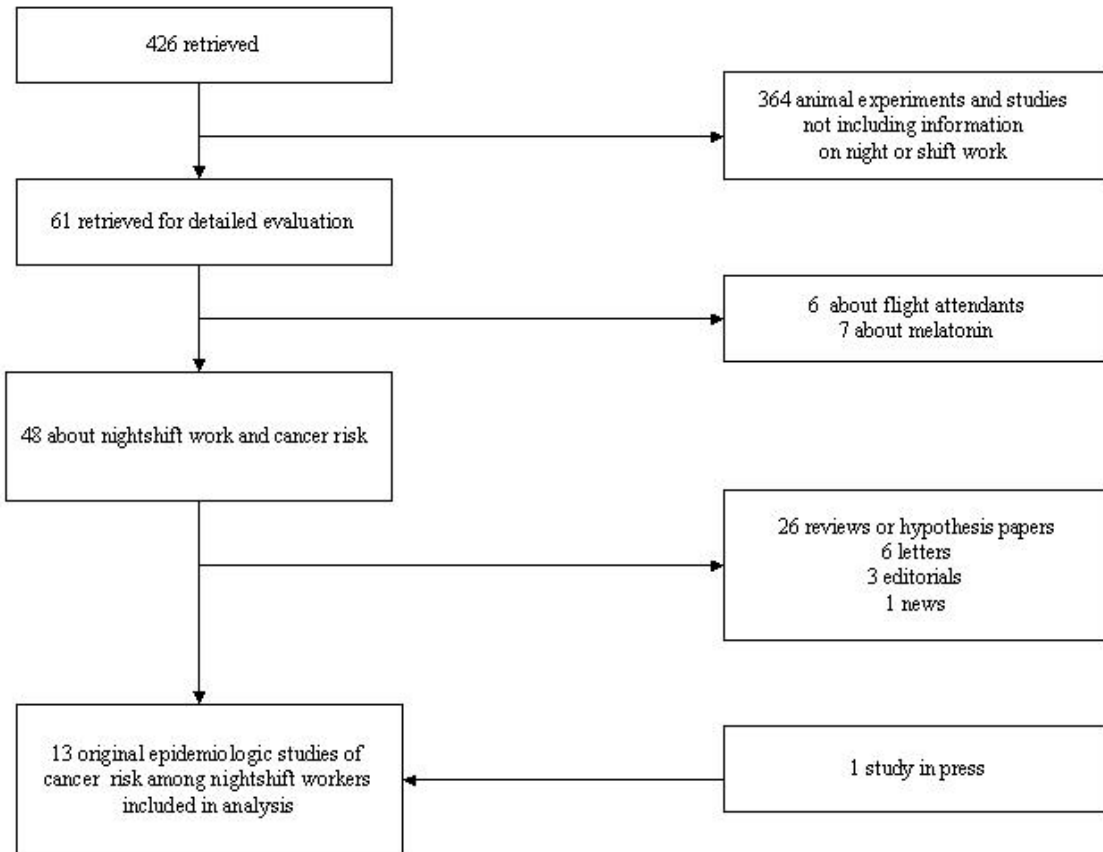
63. Hrushesky WJ, Blask DE. Re: Melatonin and breast cancer: a prospective study. *J Natl Cancer Inst* 2004;96:888-9.
64. Kerenyi N. Re: Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 2002;94:531-2.
65. Porock D, Gentry J. Re: Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 2002;94:530-1.
66. Spiegel D, Sephton S. Re: Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 2002;94:530-3.
67. Tarone RE. Circadian disruption and breast cancer. *Epidemiology* 2005;16:710-1.
68. Hansen J. Light at night, shiftwork, and breast cancer risk. *J Natl Cancer Inst* 2001;93:1513-5.
69. Poole C. The darkness at the end of the tunnel: summary and evaluation of an international symposium on light, endocrine systems and cancer. *Neuro Endocrinol Lett* 2002;23 Suppl 2:71-8.:71-8.
70. Roenneberg T, Lucas RJ. Light, endocrine systems, and cancer--a view from circadian biologists. *Neuro Endocrinol Lett* 2002;23 Suppl 2:82-3.:82-3.
71. Night shifts and colorectal cancer risk. *Mayo Clin Health Lett* 2005;23:4.
72. Kojo K, Pukkala E, Auvinen A. Breast cancer risk among Finnish cabin attendants: a nested case-control study. *Occup Environ Med* 2005;62:488-93.
73. Rafnsson V, Hrafnkelsson J, Tulinius H. Incidence of cancer among commercial airline pilots. *Occup Environ Med* 2000;57:175-9.
74. Rafnsson V, Tulinius H, Jonasson JG et al. Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes Control* 2001;12:95-101.
75. Gurwitz D. Flight attendants, breast cancer, and melatonin. *Lancet* 1998;352:1389-90.
76. Mawson AR. Breast cancer in female flight attendants. *Lancet* 1998;352:626.
77. Radon K, Aberl S, Nowak D et al. Incidence of cancer among commercial airline pilots. *Occup Environ Med* 2000;57:843.
78. Cook MR, Graham C, Kavet R et al. Morning urinary assessment of nocturnal melatonin secretion in older women. *J Pineal Res* 2000;28:41-7.
79. Davis S, Kaune WT, Mirick DK et al. Residential magnetic fields, light-at-night, and nocturnal urinary 6-sulfatoxymelatonin concentration in women. *Am J Epidemiol* 2001;154:591-600.

80. Schernhammer ES, Hankinson SE. Urinary melatonin levels and breast cancer risk. *J Natl Cancer Inst* 2005;97:1084-7.
81. Schernhammer ES, Kroenke CH, Dowsett M et al. Urinary 6-sulfatoxymelatonin levels and their correlations with lifestyle factors and steroid hormone levels. *J Pineal Res* 2006;40:116-24.
82. Stevens RG, Schernhammer E. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev* 2005;14:551.
83. Zhu Y, Zheng T, Stevens RG et al. Does "clock" matter in prostate cancer? *Cancer Epidemiol Biomarkers Prev* 2006;15:3-5.
84. Schwartzbaum, J., Ahlbom, A., Feychting, M. A cohort study of cancer risk among male and female shift workers. *Scand J.Work.Environ.Health* . 2007.
85. Gammon MD, Neugut AI, Santella RM et al. The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res Treat* 2002;74:235-54.
86. Colditz GA. The nurses' health study: a cohort of US women followed since 1976. *J Am Med Womens Assoc* 1995;50:40-4.
87. Pukkala E, Aspholm R, Auvinen A et al. Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. *BMJ* 2002;325:567.
88. Zeeb H, Blettner M, Langner I et al. Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. *Am J Epidemiol* 2003;158:35-46.
89. Rafnsson V, Sulem P, Tulinius H et al. Breast cancer risk in airline cabin attendants: a nested case-control study in Iceland. *Occup Environ Med* 2003;60:807-9.
90. Pukkala E, Ojamo M, Rudanko SL et al. Does incidence of breast cancer and prostate cancer decrease with increasing degree of visual impairment. *Cancer Causes Control* 2006;17:573-6.
91. Sack RL, Lewy AJ, Blood ML et al. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. *J Clin Endocrinol Metab* 1992;75:127-34.
92. Lockley SW, Skene DJ, Arendt J et al. Relationship between melatonin rhythms and visual loss in the blind. *J Clin Endocrinol Metab* 1997;82:3763-70.
93. Klerman EB, Zeitzer JM, Duffy JF et al. Absence of an increase in the duration of the circadian melatonin secretory episode in totally blind human subjects. *J Clin Endocrinol Metab* 2001;86:3166-70.

94. Travis RC, Allen DS, Fentiman IS et al. Melatonin and breast cancer: a prospective study. *J Natl Cancer Inst* 2004;96:475-82.
95. Blask DE, Brainard GC, Dauchy RT et al. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res* 2005;65:11174-84.
96. Sanchez-Barcelo EJ, Cos S, Fernandez R et al. Melatonin and mammary cancer: a short review. *Endocr Relat Cancer* 2003;10:153-9.
97. Anderson LE, Morris JE, Sasser LB et al. Effect of constant light on DMBA mammary tumorigenesis in rats. *Cancer Lett* 2000;148:121-6.
98. Barnes RG, Deacon SJ, Forbes MJ et al. Adaptation of the 6-sulphatoxymelatonin rhythm in shiftworkers on offshore oil installations during a 2-week 12-h night shift. *Neurosci Lett* 1998;241:9-12.
99. Swerdlow, A. Shift work and breast cancer; a critical review of the epidemiological evidence. Norwich: Health and Safety Executive, 2003.
100. Stevens RG, Blask DE, Brainard GC et al. Meeting report: the role of environmental lighting and circadian disruption in cancer and other diseases. *Environ Health Perspect* 2007;115:1357-62.

**FIGURE 1**

Flow chart: Nightshift work and risk of cancer



**TABLE 1**

Characteristics of nightshift workers relative to day workers. Results of 5 epidemiologic studies 2001-2007

Characteristic	Prevalence or magnitude of characteristic among night shift workers relative to day workers by study <sup>a</sup>				
	Schernhammer et al 2001 and 2003 (23,24)	O'Leary et al 2006 (25)	Schernhammer et al 2006 (26)	Kubo et al 2006 (27)	Hansen 2001 (28)
Sex	F	F	F	M	F
Age	↑	↓	↑	.	.
Early menarche	↑ (Age at menarche <12 yr: 26.3% vs. 21.8%)	.	↑ (Age at menarche < 14 yr: 86% vs. 83%)	.	.
Nulliparous	0	↓	.	.	.
Post menopausal	↑	↓	↑	.	.
Young at first birth	↓	.	↑	.	.
BMI	↑ (BMI>25 kg/m <sup>2</sup> : 42.7% vs. 40.1%)	.	↑ (BMI, kg/m <sup>2</sup> :28.9 vs. 25.4)	↑ (BMI >23.9 kg/m <sup>2</sup> : 34.4% vs. 30.8%)	.
Family history	0	↓	0	↑	.
Benign breast disease	↓	↑	↑	.	.
Oral contraceptive	↓	↑	0	.	.
Hormone replacement therapy	↓ (Current HRT ≥yr: 9.1% vs. 10.9%)	↓ (Ever HRT: 24.0% vs. 34.4%)	.	.	.
Physical activity	.	.	.	↓	.
Alcohol	↓	↑	↓	0	↑
Smoking	↑ (Current or former smoker: 24.6% vs. 17.4%)	.	↑ (Current smokers: 14% vs. 10%)	↑ (Current or former smoker: 78.2% vs. 76.5%)	.
Socio-economic status	↓	0	.	.	.
Indoor work	.	.	.	↑	.

## Table 1 footnotes

a If consistency across studies detailed results are presented in parenthesis.

F female

M male

↑ Characteristic more prevalent or more pronounced in night shift workers than in daytime workers

↓ Characteristic less prevalent or more pronounced in nightshift workers than in daytime workers

0 No substantial difference between nightshift and daytime workers

. No data

HRT hormone replacement therapy

**TABLE 2****Main characteristics of 13 epidemiological studies of nightshift work and risk of cancer, 1972-2007**

Study, year and location by cancer site	Design, study population, study period and no. of participants (participation rate)	Source of exposure information	Measure of exposure (prevalence in study base). Exposure period	Outcome (diagnostic criteria). Source. Latency/induction period	Covariates controlled for	Exposure response assessment
Breast cancer Tynes et al. 1996, Norway (36)	Nested case control register linkage study within cohort of telegraph operators 1961-1991, 50 breast cancer cases, 259 age matched controls, 140 all cancers (98%).	Journalist and researcher classified ships according to extent of shift work.	Four categories (0-3) reflecting presence in radio room at day and night (83-90%). Total work history since certification.	Breast cancer (ICD-7, 170). National cancer registry. Separate analyses for exposures prior to age 30 and risk before or after age 50.	Duration of employment and age at first birth (3 levels) for women born $\geq 1935$	Duration (years) and shift-work category x duration. Test for trend of continuous term.
Davis et al. 2001, USA (33)	Population based case control study 1992-95, 767 cases (78%) and 743 controls (75%).	Questionnaire at diagnosis/reference date.	Graveyard shift: Beginning after 7 p.m. ending before 9 a.m. (3-5%). Ten years prior to diagnosis/reference date. Information on graveyard shifts during total work history was obtained but no risk estimates reported.	Breast cancer (ICD-O 174.0-174.9). Regional cancer registry. No analyses by latency.	Age, parity, family history, oral contraceptives, and hormone replacement therapy.	Hours/week and duration (years). Test for trend of continuous term.
Schernhamm et al 2001, USA (23)	Prospective cohort of nurses, 1988-1998, 78,562, 2441 cases (82%).	Questionnaire at baseline (1988).	Rotating night shifts: At least 3 nights/month, in addition to days or evenings in that month (60%). Total work history prior to baseline.	Breast cancer (criteria n. r.). Self-reports confirmed by medical records or national death index, pathology reports for 93%. No analyses by latency.	Age, age at menarche, parity, age at first birth, weight change, BMI, family history, benign breast disease, oral contraceptives, alcohol, calendar year, age at menopause, hormone replacement therapy, menopausal status and height.	Duration on rotating night shifts (years): Never, 1-14, 15-29, $\geq 30$ . Test for trend of continuous term.
Hansen 2001, Denmark (28)	Population based register linkage nested case control study, study period not reported, 6281 cases (93%) and individually matched 6024 controls (participation rate n. r.).	Records of national pension fund.	Job exposure matrix classified 4 trades with at least 60% employees working predominantly at night (5%). Total work history since 1964.	Breast cancer (ICD-7, code not specified). National cancer registry. 5-year latency period.	Number of children, age at birth of first and last child and current job title.	No. >6 years of employment reported separately.
Lie et al 2005, Norway (37)	Register linkage case control study of nurses, 1960-82, 537 cases, 2143 controls matched by year of birth, participation rate n. r.	National registry of nurses and national censuses.	Work at infirmaries, except managerial, teaching, physiotherapy work or work in outpatient departments (90%). Total work history.	Breast cancer (ICD-7, code n. r.). National cancer registry. 20-year latency period.	Age at birth of first child, number of children, and total employment time.	Duration (years) of work at infirmaries.
Schernhammer et al. 2006, USA (26)	Prospective cohort of nurses, 1989-2001, 115,022, 1352 cases (99.5%).	Questionnaire at baseline (1989) and in 1991, 1993, 1997 and 2001.	Rotating night shifts: At least 3 nights/month, in addition to days or evenings in that month (68%). Total work history prior to diagnosis. Information on permanent nightshifts were obtained but not reported.	Breast cancer (criteria n. r.). Self-reports confirmed by medical records or national death index, pathology reports for 98%. No analyses by latency.	Age, age at menarche, menopausal status, age at menopause, age at first birth and parity, BMI, alcohol consumption, oral contraceptives, hormone replacement therapy, smoking, benign breast disease, family history, and physical activity.	Duration (years) of rotating night shifts: Never, 1-9, 10-19, $\geq 20$ .
O'Leary et al 2006, USA (25)	Population based case control study, 1996-97, 487 cases (?%) and 509 controls (?%).	Interview at diagnosis /reference date.	Overnight shifts: Starting after 7.00 p.m. and continuing to the following morning (10%). 15 years prior to diagnosis/reference date.	Breast cancer, newly diagnosed first primary, in situ or invasive. No analyses by latency.	Age, parity, family history, education, and benign breast disease	Duration (years) of overnight shift work.



Table 2 continued

Prostate cancer						
Kubo et al 2006, Japan (27)	Prospective population based cohort study, 1988-97, 14,052, 31 cases (83%).	Questionnaire at baseline.	The longest held work-schedule: Fixed night work (7%) and alternate night and day work (13%).	Incident cases of prostate cancer (ICD-10, C61). Regional cancer registries.	Age, study area, family history, BMI, smoking, alcohol, job type, physical activity, stress, education, and marriage status.	No.
Conlon et al 2007, Canada (38)	Population based case control study, 1995-98, 760 cases, 1632 age matched controls, (response rate n.r.).	Questionnaire filled in retrospectively.	Full time rotating shifts (44%). Total work history. Information on part time rotating shifts and evening/night shifts were obtained but no risk estimates reported.	Incident cases of prostate cancer (criteria n. r.). Cancer registry. Four-level latency analysis.	Age and family history.	Duration (years) of full-time rotating shifts.
Colon and rectum cancer						
Schernhammer et al 2003 (24)	Prospective cohort of nurses, 1988-98, 78,586, 347 colon cancer cases and 103 rectum cancer cases (82%).	Questionnaire at baseline (1988).	Rotating night shifts: At least 3 nights/month, in addition to days or evenings in that month (60%). Total work history prior to baseline.	Incident cases of colon and rectum cancer (criteria n. r.). Self-reported cases confirmed by medical records or national death index.	Age, smoking, BMI, physical activity, aspirin use, screening endoscopy, diet, alcohol, caloric intake, hormonal replacement therapy, and height.	Duration (years) of rotating night shifts: Never, 1-14, ≥15. Test for trend of continuous term.
All cancer						
Taylor et al 1972, UK (34)	Retrospective cohort of industrial workers with >10 years of employment, 1956-68, 4188, 248 cases (0.25%).	Pay rolls	Tree shift weekly rotating, 3-shift rapid rotating, alternate day and night (99%).	All cancer mortality (ICD-7). Death certificates.	Age and calendar year.	No.
Rafnsson et al 1990, Iceland (35)	Retrospective cohort of workers at fertiliser plant, 1954-85 (211, 10 cases).	Pay rolls	3 shifts. Total work history in plant.	All cancer mortality (ICD-7). National bureau of statistics	Age and calendar year.	Duration (years).
Schwartzbaum et al, 2007, Sweden (84)	Population based register linkage cohort study 1971-89 of gainfully employed (≥20 hours/week) in 1960 and 1970, 69,759 men and 3057 women, 6,792 cancer cases (participation rate n.r.)	Population censuses in 1960 and 1970.	Job exposure matrix classified job-title and industry combinations with at least 40% working rotating shifts (3 or more shifts per day) or working any hour 1.00 am-4.00 am at least once a week (3% of men and 0.3% of women). 1960-70.	Incident cases of major cancer sites (classification and criteria n. r.). National cancer registry. No analyses by latency.	Age, socio-economic status, occupational position, county of residence, marital status, urbanization.	Shift work in 1960 and 1970 as proxy for duration of shift work (<10 years).

n. r., not reported

ICD-O, International Classification of Diseases for Oncology

ICD-7, International classification of Diseases, 7<sup>th</sup> edition.

**TABLE 3**

Nightshift work and relative risk of cancer, overall results and results by duration of night shift work, findings of 13 epidemiologic studies, 1972-2007

Cancer site Study, year and country, Subpopulations	Overall RR (95% CI) a No. of cases Definition of exposure	Duration of night shift work					Test for trend, p-value
		Reference RR (95% CI) a No. of cases Definition of duration	Short duration RR (95% CI) a No. of cases Definition of duration	Medium duration RR (95% CI) a No. of cases Definition of duration	Long duration I RR (95% CI) a No. of cases Definition of duration	Long duration II RR (95% CI) a No. of cases Definition of duration	
<b>Breast cancer</b>							
Tynes et al 1996, Norway (36)							
<50 years of age:	-	1.0 3	0.9 (0.2-3.7) 13	0.8 (0.2-3.6) 13	-	-	0.80
≥50 years of age:	-	1.0 1	1.9 (0.2-17.9) 5	5.9 (0.7-47.7) 15	-	-	0.02
		0 year	1-3.1	3.2-14.6 years			
Davis et al 2001, USA (33)	1.6 (1.0-2.5) 54	1.0 733	1.4 (0.6-3.2) 15	1.6 (0.8-3.2) 19	-	-	0.04
	Ever nightshift	< 1 nightshift/week	1-3 years	≥3 years			
Schernhammer et al 2001, USA (23)	-	1.0 925	1.08 (0.99-1.18) 1324	1.08 (0.90-1.30) 134	1.36, 1.04-1.78 58	-	0.02
		Never	1-14 years	15-29 years	≥30 years		
Hansen 2001, Denmark (28)	1.5 (1.3-1.7) 434	1.0 5847	-	1.7 (1.3-1.7) 63	-	-	-
	≥½ year in selected occupations	Day time work		>6 years			
Lie et al 2005, Norway (37)	-	1.0 50	0.95 (0.67-1.33) 362	1.29 (0.82-2.02) 101	2.21 (1.10-4.45) 24	-	0.01
		0 year	1-14 years	15-29 years	≥30 years		
Schernhammer et al 2006, USA (26)	-	1.0 441	0.98 (0.87-1.10) 816	0.91 (0.72-1.16) 80	1.79 (1.06-3.01) 15	-	0.65
		Never	1-9 years	10-19 years	≥20 years		
O'Leary et al 2006, USA (25)	0.55 (0.32—0.94) 26	1.0 469	0.74 (0.32-1.68) 11	0.32 (0.12-0.83) 6	-	-	-
	Ever nightshift	<1 nightshift/week	1-8 years	≥8 years			
Schwartzbaum et al 2007, Sweden (84)	0.94 (0.74-1.18) 70	1.0 n.r.	-	0.97 (0.67-1.40) 28	-	-	-
	≥20 hours/week in selected occupations	<30% shift workers in occupation		>10 years			

Table 3 continued

Cancer site Study, year and country, Subpopulations	Overall RR (95% CI) a No. of cases Definition of exposure	Duration of night shift work					Test for trend, p-value
		Reference	Short duration	Medium duration	Long duration I	Long duration II	
		RR (95% CI) a No. of cases Definition of duration	RR (95% CI) a No. of cases Definition of duration	RR (95% CI) a No. of cases Definition of duration	RR (95% CI) a No. of cases Definition of duration	RR (95% CI) a No. of cases Definition of duration	
Prostate cancer							
Kubo et al 2006, Japan (27)							
Fixed night shift:	2.3 (0.6-9.2) 3	-	-	-	-	-	-
Rotating shifts:	3.0 (1.2-7.7) 7	-	-	-	-	-	-
Longest form of work							
Conlon et al. 2007, Canada (38)	1.19 (1.00-1.42) 369 Ever ≥1 year nightshift	1 391 Never	1.44 (1.10-1.87) 115 1-6 years	1.14 (0.86-1.52) 87 7-21 years	0.93 (0.70-1.23) 81 22-33	1.30 (0.97-1.74) 86 ≥34 years	0.42
Schwartzbaum et al 2007, Sweden (84)	1.04 (0.99-1.10) 1319 ≥20 hours/week in selected occupations	1 n.r. <30% shift workers in occupation	-	1.02 (0.95-1.10) 780 >10 years	-	-	-
Colon cancer							
Tynes et al, 1996, Norway (36)							
	1.3 (0.6-2.6) 9 Ever radio or telegraph operator						
Schernhammer et al 2003, USA (24)	-	1 137 Never	0.93 (0.74-1.17) 169 1-14 years	1.32 (0.93-1.87) 41 ≥15 years	-	-	0.20
Schwartzbaum et al 2007 (84)	1.03 (0.94-1.13) 449 ≥20 hours/week in selected occupations	1 n.r. <30% shift workers in occupation	-	1.02 (0.90-1.15) 266 >10 years	-	-	-

Table 3 continued

All cancer							
Taylor et al, 1972, UK (34)							
	1.16 (p<0.05)	-	-	-	-	-	-
	219						
	≥10 years of shift work	-	-	-	-	-	-
Rafnsson et al, 1990, Iceland (35)							
	1.40	-	4.12	2.02	1.71	0.59	-
	14		4	2	5	3	
	≥1 year shift work		≤1 year	2-5 years	6-15 years	≥16 years	
Tynes et al, 1996, Norway (36)d}							
	1.2 (1.0-1.4)	-	-	-	-	-	-
	Ever radio or telegraph operator						
Schwartzbaum et al 2007, Sweden (84)							
	1.02 (1.00-1.05)	1	-	1.01 (0.98-1.05)	-	-	-
	6524	n.r.		3799			
	≥20 hours/week in selected occupations	<30% shift workers in occupation		>10 years			

a Relative risk, odds ratio, standardized mortality ratio or standardized incidence ratio and 95% confidence interval or p-value.

## Appendix 1

### Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome. Criteria of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine

The following categories are used.

+++	strong evidence of a causal association
++	moderate evidence of a causal association
+	limited evidence of a causal association
0	insufficient evidence of a causal association
-	evidence suggesting lack of a causal association

#### Description of categories:

Strong evidence of a causal association (+++):

A causal relationship is *very likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with *reasonable* confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):

A causal relationship is *likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+):

A causal relationship is *possible*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):

Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

#### Comments:

The classification does not include a category for which a causal relation is considered as established beyond any doubt.

The key criterion is the epidemiological evidence.

The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of a causal association.