



THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 30

**The association between shift  
working and breast cancer – an  
updated report**

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# **INDUSTRIAL INJURIES ADVISORY COUNCIL**

## **The association between shift working and breast cancer- an updated report**

### **Position Paper 30**

#### **Summary**

1. In 2008 the Danish National Board for Industrial Injuries decided to offer compensation to women who developed breast cancer following a long history of shift working. At the time, the Industrial Injuries Advisory Council (IIAC), which advises the Secretary of State on matters relating to the Industrial Injuries Scheme in the UK, reviewed the case for prescription (Position Paper 25).
2. Little evidence was found that shift work could increase the risk of breast cancer sufficiently to allow attribution to work in the individual applicant on the balance of probabilities, and in these circumstances the Council felt unable to recommend prescription under the Scheme.
3. Since 2009, four further research reports have been published on this topic and two further systematic reviews. This paper summarises the totality of evidence now before the Council.
4. The new evidence covers a Chinese cohort of 73,049 women, including 16,549 women working night shifts for more than 20 years and three case-control studies involving in excess of 2,500 cases of breast cancer. The earlier evidence base included one study involving over three million adults working shifts at least half of the time and several other reports involving thousands of cases of breast cancer. New and older reviews on the topic have covered around 20 research studies.

5. Although a causal association is by no means firmly established, collectively, these now suggest the possibility of a moderately elevated risk of breast cancer associated with prolonged (more than 20 years) of night work. However, there remains insufficient evidence of a magnitude of effect that would support prescription.
  
6. The Council continues to monitor ongoing research in this important area of inquiry.

*This report contains some technical terms which are explained in a concluding glossary.*

## Background

1. In 2009 the Industrial Injuries Advisory Council (IIAC) published a report (Position Paper 25) reviewing the evidence on shift working and two adverse health outcomes, breast cancer and ischemic heart disease. The topic of breast cancer in particular remains of active research interest, and the Council has become aware of new findings published since 2009 on this outcome. This Position Paper summarises briefly the evidence before the Council in 2009 and updates this by incorporating more recent research. It also sets out the Council's view on prescription in light of the enlarged body of evidence.
2. The Council's 2009 paper was stimulated in part by a report of the World Health Organisation's International Agency for Research on Cancer (IARC) (IARC 2008), which had classified shift working as "probably carcinogenic to humans" (Grade 2b); and by the subsequent decision of the Danish National Board for Industrial Injuries to compensate women who developed breast cancer following a history of night working.
3. IARC's expert working group had considered the findings of eight epidemiological studies in humans, concluding that six of these provided evidence of a moderately increased risk in breast cancer in those who had worked shifts for many years. Additionally, the results of several rodent studies suggested to IARC a potential mechanism related to the hormone melatonin, production of which may be disrupted by exposure to light at night.
4. However, the Agency drew attention to certain limitations in the data, notably the possible influence of other confounding factors on the results, the inconsistency across studies in the definition of shift work and the fact that the studies were restricted largely to specific occupations, notably nurses and flight attendants.
5. The Danish National Board had commissioned its own review, which described the human evidence for a causal association between nightshift work and breast cancer as 'limited' and the results as "sensitive to bias, chance and confounding". However, under its rules of operation, the

classification awarded by IARC (probably carcinogenic) was sufficient to cross the threshold for automatic compensation.

6. In its 2009 report, IIAC also considered the findings of a review commissioned by the Health and Safety Executive (HSE) (Swerdlow, 2003), a report of a workshop of experts convened by the Medical Research Council (IEH, 2005), original papers identified by the Council's Research Working Group, and a meta-analysis of 13 studies by Megdal *et al* (2005).
7. The majority of the considered studies showed a slightly increased risk of breast cancer associated with shift working. The dataset included two large well-conducted cohort studies and five case control studies. In the case of one of the cohort studies (Schernhammer, 2001) the increased risk was associated with more than 30 years of night work but no increase in risk was found in a survey of over 3 million adults working shifts for  $\geq 20$  hours/week at two census points a decade apart (Schwartzbaum 2007). In only two relatively small case control studies was a doubling of risk identified within specific subgroups (older women in one study, shift work for more than 30 years in another (Tynes 1996, Lie 2006)). The meta-analysis by Megdal *et al* implied a risk, if truly present, that was increased by less than 50%.
8. As explained in other reports, in the case of diseases which have other common non-occupational causes in the population and in which occupationally-related and non-occupational cases cannot be distinguished from one another reliably on clinical grounds, the Council normally seeks robust evidence that risks are at least doubled in some well-defined circumstances of exposure before recommending prescription. This requirement arises from a legal framework under which an outcome needs to be attributed to work activity on the balance of probabilities, which in turn has a bearing on the magnitude of the risk of disease that must be present. (It should be noted that the requirements for prescription within the Danish system of compensation differ, as the focus is on the demonstration of a possible causal link, with less account taken of the magnitude of the effect.)



9. Breast cancer is such a disease. Worldwide, breast cancer is the commonest type of cancer diagnosed in women and the most common cause of cancer deaths in women. A number of established non-occupational factors have an important influence on risk of breast cancer. In particular, early menarche (early onset of periods), delayed menarche, late menopause, nulliparity (never having been pregnant) or having fewer pregnancies, and later age at first pregnancy, are risk factors for the disease. Oestrogen-containing hormone replacement therapy may confer risks in later life, as may being overweight and consuming more alcohol. Many of these factors share in common a capacity to increase total exposure to oestrogens, which in turn may influence the rate at which breast tissue cells divide and the chance of spawning pre-cancerous cells. These reproductive risk factors are not equally distributed by social class or occupation, requiring that epidemiological analysis of risks, which allows for other factors ('confounders'), is brought to bear, and making the criteria on doubling of risk all the more relevant.
10. On the strength of the evidence reviewed by the Council in 2009 (paragraphs 6 and 7), the normal threshold for prescription was not met and prescription could not be recommended.
11. Since 2009, four further studies of relevance have been published, together with two more systematic reviews.
12. Pronk *et al* (2010) carried out a prospective population-based cohort study in China among 73,049 women recruited between 1996 and 2000. Women with a history of cancer at study entry, those who had never worked, and those with an incomplete work history were excluded. Cancers were verified through home visits and by accessing hospital medical notes. Lifetime occupational histories were collected that included details of jobs held for more than 12 months. Extent of night-shift working was scored for each job on a four-point scale and total lifetime exposure estimated considering the years spent in jobs with various scores. Also, during a follow-up in 2002-2004, participants were asked if they had ever had a job in which they started work after 10pm at least 3 times a month for more than 12 months. Data was

also collected on the average number of night shifts worked per week, the duration of shift work in years and the years of starting and ending shift work. Estimates of cumulative night shift working by this definition were made. During an average follow-up time of 9 years, 717 women were newly diagnosed with invasive breast cancer. In total, 16,549 women worked night-shifts for over 20 years (confounder-adjusted relative risk (RR) 1.0, 95% Confidence Interval (CI) 0.8 to 1.2) and 6,526 worked night-shift for over 30 years (adjusted RR 1.1, 95% CI 0.9 to 1.5). For self-reported night work, working night shifts for over 20 years was reported by 5,056 women (adjusted RR 0.7, 95% CI 0.4 to 1.2) and working night shifts over 30 years was reported by 1,715 women (adjusted RR 0.9, 95% CI 0.4 to 2.0). Thus, no evidence was found that risks were materially increased.

13. Hansen and Lassen (2011) carried out a case-control study of breast cancer, nested within a cohort of 18,551 Danish female military employees born in 1929-1958. Some 218 cases of breast cancer were documented between 1990 and 2003, and compared with 899 age-matched controls from the same cohort. Information on shift work, sun exposure, diurnal preference (whether 'a morning person' or 'an evening person') and other potential confounders was obtained by questionnaire. An adjusted Odds Ratio (OR) of 1.4 (95%CI 0.9 to 2.1) was observed for ever vs. never having worked night shifts. The RR for breast cancer tended to increase with increasing number of years of night shift work ( $p = 0.03$ ) and with total number of shifts ( $p = 0.02$ ). Risks appear to be related to intensity as well as duration; thus risks were doubled after 15 or more years overall, but after  $\geq 6$  years in those working three or more times per week when the comparator was fewer than three times per week irrespective of duration. The most pronounced effect of night shift work on breast cancer risk was observed in women with a morning chronotype preference and intense (more than the median) exposure to night shifts (OR 3.9, 95%CI 1.6 to 9.5).

14. Pesch et al (2010) interviewed 1,143 incident breast cancer cases from regional hospitals in Germany between 2000 and 2004, together with 1,155 population age-matched controls. Data were obtained on known and

suspected risk factors and on occupational history. Women who reported working shifts had a second interview to gather more detailed information. Night work was defined as working the full time period between midnight and 5 am. In all, 56 cases and 57 controls had worked in a night shift for one year or more (OR 0.96, 95%CI 0.71 to 4.22). Night work for 20 years or more was associated with an elevated but not statistically significant risk of breast cancer (OR 2.48, 95%CI 0.62 to 9.99), based on only 12 cases and 5 controls.

15. Villeneuve *et al.* (2011) carried out a population-based case-control study of breast cancer in France that included 1,230 cases aged 25-75 years and 1,315 controls with no prior history of breast cancer, identified by random digit dialing, and matched by age, socioeconomic status and geographical location. Job details were collected at interview for each job held for more than 6 months. Risk of breast cancer was elevated in women employed for more than 10 years as a nurse (OR 1.4, 95% CI 0.9 to 2.1), although no information was collected *per se* on night-shift working as a possible causal factor.
16. A recent review by Costa *et al* (2010) concluded that the epidemiological studies published so far, although dealing with large cohorts and controlling for several confounding factors, defined exposure to shift and/or night work somewhat loosely and in consequence did not allow for proper assessment of risks associated with circadian disruption.
17. Another recent review by Bonde *et al* (2012) summarized the evidence among studies that quantified duration of shift work and reported that there were statistically significant elevations in risk only after about 20 years working night shifts. However the review's authors also pointed out that to provide additional evidence-based recommendation on prevention of diseases related to night shift work, large studies on the impact of various shift schedules and type of light on circadian rhythms need to be conducted in real work environments.
18. A further large study of breast cancer, commissioned by the HSE and based

on the Million Women's Study, was scheduled to report its findings in 2011. The project has been extended, however, in order to include more women with long-term exposure. We understand that a reporting date of 2015 is now in contemplation.

### **Summary and conclusions**

19. Taken together the data now suggest the possibility of a moderately elevated risk of breast cancer associated with prolonged (more than 20 years) of night work. However, not all of the research supports this conclusion. Also, although some improvements have been made with the passage of time, the evidence base is limited by the methodological difficulties identified in the IARC monograph and in later reviews, associated with inconsistency in the definition of shift work and in factors associated with circadian rhythm disruption and incomplete adjustment for other important non-occupational risk factors.
20. Importantly, although new evidence has emerged since IIAC's last Position Paper in 2009, there is still relative uncertainty regarding patterns of exposure sufficient to meet the required threshold from the Scheme's perspective of a doubling of risk.
21. IIAC remains, therefore, of the view that a sound case for prescription cannot be made on the basis of currently available evidence. However, the Council recognises the importance of the topic and undertakes to keep the growing evidence base under continuing review.

### **Prevention**

22. HSE does not presently regard the evidence about shift work and cancer as such that employers should be asked to do more to protect the health of their shift workers than is already required by the Working Time Regulations 1998 and HSG 256.
23. The principal established risk from shift work is fatigue, which can contribute

to human error, accidents and injuries. To help employers comply with their legal duties, HSE has produced guidance on assessing and managing the health and safety risks of shift work and fatigue. Managing shift work: Health and Safety Guidance HSG 256 includes background information on the health and safety risks associated with shift work and fatigue, UK legal duties and practical guidance on how to reduce the risks. A short summary of the guidance, including the good practice guidelines, is available on the HSE website at <http://www.hse.gov.uk/humanfactors/shiftwork/index.htm> .

### **Diversity and equality**

24. IIAC is aware of issues of equality and diversity and seeks to promote as part of its values. The Council has resolved to seek to avoid unjustified discrimination on equality grounds, including age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender and sexual orientation. During the course of the review of shift work and breast cancer, no diversity and equality issues became apparent.

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## Appendix: A glossary of terms used in this report

### Types of study

**Case-control study:** A study which compares people who have a given disease (cases) with people who do not (controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an *Odds Ratio*, a form of *Relative Risk*.

**Cohort study:** A study which follows those with an exposure of interest (usually over a period of years), and compares their incidence of disease or mortality with a second group, who are unexposed or exposed at a lower level. Is the incidence rate higher in the exposed workers than the unexposed/less exposed group? Sometimes the cohort is followed forwards in time ('prospective' cohort study), but sometimes the experience of the cohort is reconstructed from historic records ('retrospective' or 'historic' cohort study). The ratio of risk in the exposed relative to the unexposed can be expressed in various ways, such as a *Relative Risk*.

**Nested case-control study:** A form of case-control study in which the cases and controls all come from within a well-defined cohort. Controls are selected from subjects that are at risk at the time that a new case arises - in effect, a cohort study in which only some of the non-cases are sampled (for various legitimate reasons – e.g. lowering the costs of special investigations).

### Measures of association

**Statistical significance and P values:** Statistical significance refers to the probability that a difference as large as that observed, or more extreme still, could have arisen simply by chance. The smaller the probability, the less likely it is that the difference can be explained by chance alone, rather than being a real difference. By convention, when this probability is less than 5% ( $p < 0.05$ ) a difference is described as being "statistically significant" Significance tests only describe association. Statistically significant associations are not necessarily causal and can arise due to bias or confounding (see below).



**Relative Risk (RR):** A measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicates a positive association between exposure and disease.* (This may be causal, or have other explanations, such as bias, chance or confounding.)

**Odds Ratio (OR):** A measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure in those without disease, expressed as a ratio. For rare exposures, odds and risks are numerically very similar, so the OR can be thought of as a Relative Risk. *A value greater than 1.0 indicates a positive association between exposure and disease.* (This may be causal, or have other explanations, such as bias, chance or confounding.)

#### Other epidemiological terms used in this paper

**Confidence Interval (CI):** The Relative Risk reported in a study is only an *estimate* of the true value in the underlying population; a different sample may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95% CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). *Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values.*

**Confounding:** Arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease that occurs to a different extent in the groups being compared.

*For example, smoking is a cause of lung cancer and tends to be more common in blue-collar jobs. An apparent association between work in the job and lung cancer could arise because of differences in smoking habit, rather than a noxious work agent. Studies often try to mitigate the effects of ('control for') confounding in various*

ways such as: restriction (e.g. only studying smokers); matching (analyzing groups with similar smoking habits); stratification (considering the findings separately for smokers and non-smokers); and mathematical modelling (statistical adjustment).

**Bias:** A tendency to produce an estimate of effect that is systematically different from the truth (either too high or too low)

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