



**Institute for Environment  
and Health**

# Shift Work and Breast Cancer

Report of an Expert Meeting  
12 November 2004

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# Executive Summary

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In November 2004, the Health and Safety Executive (HSE), Medical Research Council (MRC) and Department of Health (DH) sponsored an expert meeting, organised by the MRC Institute for Environment and Health (IEH) on research into shift work and breast cancer. The key goal of the meeting was to address the following questions.

- Is there currently a need to undertake further epidemiological studies on shift work and breast cancer, particularly within the UK?
- Should experimental studies be undertaken to investigate possible biological mechanisms for any impact of shift work on breast cancer?
- What is the rationale for recommending either further studies, or that no further action is needed, at this time?

## Conclusions

Shift work is a pattern of working that can be expected to continue and even increase, and it is likely that even more varied and 'abnormal' work patterns will be adopted in the future.

Presently, the evidence for an association between shift work and breast cancer is suggestive, but the relationship is not confirmed. Although a causal relationship is biologically plausible, empirical evidence for this is lacking.

Shift work might impact not only on breast cancer but also on other diseases, such as coronary heart disease. Further research would be required identify the key factors that might be associated with apparent changes in susceptibility to certain diseases among shift workers.

While the biological mechanisms underlying any effect of shift work on disease are not yet elucidated, disruption of circadian rhythms is likely to be important.

## Recommendations

Although there is a need to clarify further whether the association between shift work and breast cancer might be causal, it is recommended, in the first instance, that further research should investigate more holistically the relationship between shift working and susceptibility to major disease. In this context, further investigations should take the form of epidemiological studies focused on exploring possible disease associations *per se*. A review of the literature on shift work and heart disease would be useful. However, it is also recommended that, should additional information on the relationship between breast cancer and shift work become available, it might be appropriate and would be possible to commission, quickly, an investigation or investigations focused specifically on associations with this disease.

The most cost-effective way to provide additional information on the relationships between shift work and disease would be to modify existing, ongoing cohort studies (and in particular the UK Biobank study) by adding specific questions on patterns of shift working, life-time history of shift working and on endpoints that could identify disruptions to the circadian clock.

Although no particular experimental research is recommended *per se*, the development of suitable experimental animal models, to establish the biological basis for the disruption of circadian rhythms

and the impact of any such disruption on disease incidence and progression, would be helpful in the formulation of relevant questionnaires for such cohort studies and in the design of appropriate, more specific studies in humans, should these prove to be needed.

Data on biological mechanisms obtained from experimental studies, together with additional data from ongoing cohort studies, will help confirm whether there is any association between shift work and breast cancer and will help underpin the basis for the design of more specific and selective studies, as required.

These initial recommendations pertain to long-term research activities entailing relatively low marginal costs. If new scientific or clinical information or increased concern about any association between shift work and breast cancer becomes apparent, more costly studies could be undertaken to provide results more rapidly, such as case-control investigations of shift work and breast cancer, nested within existing cohort studies that have collected information prospectively about potential confounding factors.

# 1 Introduction

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Following the issue of a report reviewing epidemiological studies on shift work and breast cancer (Swerdlow, 2003), the Health and Safety Executive (HSE), Medical Research Council (MRC) and Department of Health (DH) undertook to convene an expert meeting to review the need for possible further research in the area and, if necessary, to help define the research agenda. The MRC requested the MRC Institute for Environment and Health (IEH) to organise the meeting on behalf of the co-sponsors.

A meeting of experts in the field was held at MRC Head Office, in London, on 12 November 2004. A list of the participants in the meeting is provided in Annex 1; the agenda for the meeting is given in Annex 2.

Currently, shift work and breast cancer is not a major UK policy concern; however, government departments and agencies wish to keep abreast of any developments in the field that might indicate that a higher degree of concern is warranted. The key goals of the meeting were to advise on the following questions:

- Is there currently a need to undertake further epidemiological studies on shift work and breast cancer, particularly within the UK?
- Should experimental studies be undertaken to investigate possible biological mechanisms for any impact of shift work on breast cancer?
- What is the rationale for recommending either further studies or that no further action is needed, at this time?

Section 2 summarises the key discussions at the meeting. The conclusions and recommendations are summarised in Section 3.

## 2 Discussion

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### 2.1 Epidemiological studies

#### 2.1.1 Evidence for association between shift work and breast cancer

Consideration that there might be an association between shift work and breast cancer was initiated, in part, by early observations on pineal function, ‘light-at-night’ and melatonin secretion (reviewed in Swerdlow, 2003). Pineal hypofunction might promote breast cancer, and one factor that has changed, over a similar period to that in which the incidence of breast cancer has increased, is provision of light-at-night, which could impair pineal secretion of melatonin. The question is essentially whether light-at-night can explain recent increases in breast cancer incidence, and whether this is the factor behind the hypothesised shift-work and cancer connection. As reviewed in the document by Swerdlow (2003), four key epidemiological studies — the Norwegian maritime operators cohort, the US nurses cohort, the Seattle case-control study and the Danish case-control study (Table 2.1) — and some more general observations provide information relevant to an evaluation of the possible link between shift work and breast cancer.

Although the Norwegian maritime radio operators cohort study (see Swerdlow, 2003) was not conducted to investigate shift work *per se*, it is an interesting study because those doing shift work comprised a very similar group to those who were not. Very often the two groups have quite different characteristics. One of the strengths of the study, therefore, is that there are few possible confounders. The information on shift work is not individualised but based on known work patterns for the ships on which the radio operators worked. The cohort was divided into pre-and post-menopausal breast cancer groups; this is intrinsically a sound approach, as different factors may affect the onset of breast cancer in the different age groups.

The US nurses cohort study (see Swerdlow, 2003) is one of the largest female cohort studies anywhere and is a well-conducted study. Adjustment for confounders is well integrated into the analysis. The questionnaire used in the study asks about rotating shift work and not shift work generally; those who undertook shift work but not rotating shift work would, therefore, be counted in the non-shift work category. This would tend to underestimate any risk associated with shift work. Although it is recognised that breast cancer is more common in professional than other social classes, owing, at least in part, to lower and later parity, and that nurses tend to smoke more than other groups, neither of these factors should affect the outcome of this study, as all subjects were female nurses. While an increased risk was found among nurses who had experienced rotating shift work over a period of 30 years or more, it should be recognised that such a work pattern might apply to only quite exceptional groups of workers.

The Seattle case-control study (see Swerdlow, 2003) adjusted, rather inadequately, for only a few confounders. Many questions were included in the study, and it is possible that the reporting could have focused on significant results and not mentioned others. The exposure parameter in the study was for ‘ever-working’ on the ‘graveyard’ shift (defined as 8 hours worked between 1900–0900 hours). Whether or not such exposure was ‘often’ or ‘usual’ might be important to the analysis; however, the number of hours worked per week on the graveyard shift should help address this. This is salient because duration of exposure appears to be very important.

**Table 2.1** Epidemiological studies with data on shift work and breast cancer

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**Norwegian maritime radio operators cohort**

- 2619 women → 50 breast cancers
- nested case-control study, with extent of shift work categorised according to the ship served upon
- meaning of shift work categories unclear
- significant trend in breast cancer risk with increased shift work, only for breast cancer at age  $\geq 50$  ( $p = 0.01$ )
- relative risk for top category *vs* no shift work = 6.1 (1.5–24.2)
- little information on confounders, but the design may minimise their effect

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**US nurses cohort**

- 10 years follow-up of 78 562 US nurses → 2441 breast cancers
- adjusted for numerous confounders
- significant association of breast cancer risk with number of years of rotating shift work ( $p = 0.02$ )
- relative risk for  $\geq 30$  years *cf* never worked rotating night shifts = 1.36 (1.04–1.78)
- significant only in postmenopausal women
- permanent shift work categorised as non-exposed

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**Seattle case-control study**

- 813 cases breast cancer, 793 controls interviewed
- adjustment for 4 confounders, leaving potential for confounding by other variables
- significant risk of breast cancer:
  - if ever-worked graveyard shift in last 10 years RR 1.6 (1.0–2.5)
  - trend with hours per week worked graveyard shift ( $p = 0.03$ )
  - trend with number of years worked graveyard shift

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**Danish case-control study**

- record linkage between national pension scheme (occupation data) and national cancer registry.
  - 7035 breast cancers, at ages 30–54.
  - 4 occupations categorised as night work (no individual assessment) on basis of a previous survey
  - limited adjustment for confounders
  - significant risk of breast cancer for women in night work occupations (OR 1.5 (1.2–1.7))
  - alcohol consumption  $>3 \times$  median in these occupations
- 

As the Danish case-control study (see Swerdlow, 2003) is a record linkage study, one of its weaknesses is that no personal exposure details are available; shift working is determined only through reference to type of occupation. Of the four studies, this is the one that has most information available on pre-menopausal breast cancer. Only four occupations were listed as involving night work, and as some were very particular occupations (e.g. bar staff), night work might not be the key factor. It was found, for example, that those employed in these four occupations drank more than the

rest of the population. All four occupations had a raised risk but overall the study is unconvincing, despite the large numbers

It is possible that there is more opportunity for drinking during night work. The dual impact of caffeine as a stimulant to keep awake at night and alcohol to aid daytime sleeping might be an interesting factor to consider.

Apart from these four epidemiological studies, which provide information on shift work, there are other studies, including some non-occupational studies, that may shed some light on whether light-at-night and melatonin secretion might be factors in the aetiology of breast cancer (also reviewed briefly in Swerdlow, 2003). Relevant studies include:

- airline cabin staff (generally raised breast cancer risk);
- blind women (generally decreased risk for breast cancer among the totally blind);
- reported light-at-night (one study found increased risk if awake 0100–0200, but no increased risk for light-at-night); and
- women living in the Arctic (generally decreased risk for breast cancer).

However, these studies do not adjust well for potential confounders, as outlined below.

- Airline cabin staff not only experience light-at-night but also crossing time zones and high altitude radiation exposure; the lifestyle may also be consistent with low or no parity and there may be increased opportunity for alcohol consumption.
- Blind women may have different lifestyles to sighted women.
- There are clear demographic and genetic differences, such as differences in age at first birth, duration of breast-feeding, age at menarche and menopause, diet and life-style (e.g. Erren & Piekarski, 1999), between women living in the Arctic and populations living further south.

Based on the available studies, each of which has a different measure of what constitutes shift work, it is not possible to conclude with any surety that a causal association between shift work and breast cancer is either proven or implausible. However, if such an association were to be real then the potential impact would be substantial, as both shift work and breast cancer are so prevalent.

The population attributable risk of an exposure depends on the proportion of the population exposed and the relative risk associated with the exposure. Just over 5% of the adult (15 years or older) female population in Great Britain is exposed to shift work (based on Table 2.2 and population estimates for England, Wales and Scotland). If the relative risk for breast cancer among shift workers were of the order of 1.3, shift working would be responsible for about 1.5% of the 40 000 new breast cancer cases per year in the UK — that is, 600 cases — a substantial number compared with most occupational cancers. Even with a relative risk of 1.1, and exposure of only 1% of the population, shift work would still account for 0.1% of all cases — that is, about 40 new cases per year.

**Table 2.2** Women in employment undertaking shift work, Great Britain, Spring 2002<sup>1,2</sup>

Type of shift pattern	Numbers employed	95% CI of change (+/-)
All <sup>3</sup> women in employment who usually or sometimes do shift work	1 803 947	1589
Three-shift working	221 603	557
Continental shifts	18 209	160
Two-shift system early/late-double day	562 849	888
Sometimes nights sometimes days	169 483	487
Split shifts	90 381	356
Morning shifts	47 543	258
Evening or twilight shifts	121 168	412
Night shifts	154 400	465
Weekend shifts	24 639	186
Other types of shift work	390 872	740

<sup>1</sup> From ONS Labour Force Survey (see Statistics on shift work available [January 2005] at [http://www.eoc.org.uk/cseng/research/statistics\\_on\\_shift\\_work.asp](http://www.eoc.org.uk/cseng/research/statistics_on_shift_work.asp))

<sup>2</sup> Not seasonally adjusted

<sup>3</sup> Includes women who did not specify shift pattern  
CI, confidence interval

## 2.1.2 Potential confounding factors

The impact of a confounding factor will depend on its own relative risk for the effect that is being evaluated, its distribution in the study population, and its association with the factor studied. The more similar the prevalence of the confounder in the exposed and unexposed group, the smaller its confounding effect will be. Thus a confounding factor would have to carry quite a high relative risk itself and also be strongly associated with the exposure under assessment before it could, on its own, explain a relative risk of, for example, 1.5 or more.

The most important potential confounders in studies on shift work and breast cancer are nulliparity, late age at first birth and alcohol consumption; these are especially important as they may also be related to women's working practices. On their own, such factors are unlikely to explain relative risks as high as 1.5, unless they differ very markedly between shift workers and those who do not work shifts. Other less important potential confounding factors include early menarche, late menopause, HRT, ionising radiation, benign breast disease and genetic factors.

Studies can be designed and analysed to take account of known confounders but difficulties arise when a confounder occurs, in part, as a consequence of the risk factor under study. For example, nulliparity could be associated with shift work because nulliparous women might be freer to engage in such work than women with children to care for might be. However, shift work could itself cause nulliparity. Thus if women without children were excluded from a study on shift workers, in an attempt to avoid confounding, the risk associated with shift work might be under-estimated.

Possible selective reporting, especially in the positive studies, causes concern. However, if new good quality studies were to show a relative risk for shift work and breast cancer in excess of 1.5, it would be hard to attribute this solely to confounding. Furthermore, it would be reasonable to expect that any new studies should be able to control well for the confounders now identified and to address the fact that some confounding factors might be more relevant to one type of shift work than another.

## 2.1.3 Weight of evidence for association between shift work and breast cancer

While the available epidemiological evidence gives some suspicion of an association between shift work and breast cancer, the relationship is not confirmed; certainly no causal association has been

established. Without convincing evidence for biological plausibility (see below) or from new data from ongoing studies, or the confirmed feasibility of conducting additional and more informative epidemiological studies, there seems little reason to initiate major new epidemiological studies at this time.

Nonetheless, while the case for a causal association between shift work and breast cancer would certainly be strengthened by the establishment of a relevant biological mechanism, historically, epidemiological associations have often been identified without any knowledge of biological mechanisms, and in this case it is still not clear which mechanism or mechanisms are most likely to be relevant.

#### 2.1.4 Shift work and other diseases

In addition to the possible association between shift work and breast cancer, other pathologies associated with shift work may warrant further consideration.

- Airline staff have been shown to have an increased risk of melanoma (e.g. Rafnsson *et al.*, 2003).
- A report from the US nurses cohort has identified an increased risk of colorectal cancer among shift workers (Schernhammer *et al.*, 2003).
- Some but not all Nordic studies have found an increased risk of heart disease among shift workers (e.g. Tenkanen *et al.*, 1997; Knutsson *et al.*, 1999; Boggild *et al.*, 1999; Bøggild & Knutsson, 2000).
- Adverse health effects associated with rotating shift work, and arising from circadian discoordination, are widely documented (e.g. Knutsson, 2003).

Unlike breast cancer, melanoma and colorectal cancer are not, primarily, hormone related. Little is known about shift work and male hormone-related cancers (e.g. prostate cancer).

While there is some evidence for an association between heart disease and shift work, with a relative risk of 1.6 reported among men and of 3.0 among women aged 45–55 years (Knutsson *et al.*, 1999), it is not clear that the relationship is causal; furthermore, not all studies find such an association (Boggild *et al.*, 1999). The impact of social class as a potential confounder has been debated (Boggild *et al.*, 1999; Knutsson, 2003).

Although confounding factors in the heart disease studies will have been similar to those pertaining to breast cancer studies, it might be useful to review the designs of studies on other health outcomes, to see if anything useful can be carried forward to improve the design of any future studies on shift work and breast cancer.

## 2.2 Exposure: Definition of shift work

Shift work describes patterns of working that can be expected to continue, and even increase, and it is likely that even more varied and ‘abnormal’ work patterns will be adopted in the future. Currently about 1.8 million women are thought to undertake shift work in Great Britain (see Table 2.2).

The same types of shift work have not been evaluated in the different studies, and not all patterns of shift work necessarily include working at night. Rotating shift work will generally include night-time working; other patterns may not. Past studies were not necessarily undertaken to investigate the effects of shift work. Future studies will require much better characterisation of shift work, night work and light exposure during work, as well as sleep deprivation. The length of time someone has undertaken shift work might be an important factor, rather than simply whether he or she has ever

worked shifts. If it is night-time working rather than shift work *per se* that is important, studies investigating rotating shift work are likely to underestimate any risk.

Other potentially important aspects include lifestyle factors and their association with shift working, for example different amounts and timing of alcohol and caffeine consumption, which could also be linked to 'stress' (see below).

Should a biologically plausible mechanism for a causal association between shift work and breast cancer be identified, it might help to determine which kinds of shift work are most important, as it is currently often difficult in epidemiological studies to establish the nature of 'rotating shifts' and 'night work', both in terms of exposure and the effects of exposure. Improved understanding of biological mechanisms (whether these be related to light exposure effects, sleep deprivation, stress or other factors) will help determine which might be the best exposure metrics to use in future studies.

## 2.3 Possible mechanisms and biological plausibility

Until now, considerations have focused on the melatonin/breast cancer hypothesis (see below); however, if a clear association between shift work and breast cancer is established, it will not necessarily be linked to such a mechanism.

Stress in the workplace has been associated with ill-health (e.g. as investigated in the Whitehall study; e.g. UCL, 2004); however, it is not thought that job stress is implicated as an aetiological factor for breast cancer (Schernhammer *et al.*, 2004a).

A key factor in the impact of shift work on health might be sleep deprivation.

### 2.3.1 Melatonin and breast cancer

Currently it is uncertain whether there is any link between melatonin and cancer. It has been shown that prolonged shift work is associated with changed oestrogen levels; it is possible that elevation of blood levels of oestrogen (a risk factor for breast cancer) is mediated by a decrease in melatonin. *In vitro*, some but not all studies indicate that melatonin does have antiproliferative effects at physiological levels (Bartsch & Bartsch, 1997; Blask *et al.*, 2002). Early studies demonstrated that subcutaneous injections of melatonin inhibited the development of dimethylbenz(a)anthracene-induced mammary tumours in rats, and that pinealectomy had the opposite effect (Danforth *et al.*, 1983). However, any anticancer effect of melatonin *in vivo*, in humans remains to be clarified.

It has been suggested that the reduced risk of breast cancer among blind women may arise from the lack of light suppression of melatonin. However, existing data indicate no difference in the timing, duration or amplitude of the melatonin peak between blind and sighted individuals (Lockley *et al.*, 1997; Lockley *et al.*, 2000; Klerman *et al.*, 2001).

The study of melatonin requires cohorts with urine samples. Three studies on the relationship between pre-diagnosis urinary melatonin levels and breast cancer — Guernsey UK, Nurses Health II USA, ORDET Italy — are known to be completed or ongoing, and two further studies — DOM The Netherlands, EPIC-Norfolk UK — have banks of urine samples, which could be used to address the melatonin hypothesis. A nested case-control study in Guernsey (127 breast cancer cases) found no evidence that melatonin levels were strongly associated with the risk for breast cancer (Travis *et al.*, 2004). However, melatonin levels did increase with parity and, as breast cancer risk decreases with parity, the trend is at least consistent with the melatonin hypothesis. A pooled analysis of the three available studies should be possible, as all are members of a collaborative group.<sup>1</sup>

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<sup>1</sup> Cancer Research UK: Endogenous Hormones and Breast Cancer Collaborative Group, available [November 2004] at <http://sci.cancerresearchuk.org/research/ceu/research/endogenous-breastcancer/>

There is some discussion as to the best timing for sampling of urine for melatonin analysis (via the urinary metabolite, 6-sulphatoxymelatonin). First morning void, 24-hour samples and overnight samples have been used; however, sequential samples, at least 3–4 hourly for 48 hours, are ideal for assessing both the amplitude and the timing of production, as melatonin normally peaks during the night. An overnight sample may miss the peak level (depending on timing of the sample). Existing studies have shown that one sample of urine collected first thing in the morning is sufficient to give a representative measure by which to rank women according to melatonin level (Travis *et al.*, 2003); however, inter-individual differences in levels are substantial, melatonin levels decrease with age (in most studies) and the timing of the melatonin peak changes with age. Schernhammer *et al.* (2004b) found an inverse association between night shift work in the period prior to urine collection and urinary melatonin levels. It is worth noting that, as the metabolite is measured in urine, the numerous potential confounders include, for example, modification of melatonin metabolism by medication.

The basic melatonin hypothesis is that light-at-night suppresses melatonin production; melatonin may have oncostatic activity, thus increased risk of cancer may be due to light suppression of melatonin. There is a question about whether the nature (e.g. wavelength) of light is important. While the effect of parity on increasing melatonin levels (see above) and reducing breast cancer levels could be a potential confounder, information on parity is well recorded in studies on breast cancer and therefore appropriate allowance is possible in statistical analysis.

### 2.3.2 Circadian rhythms

Without any time cues, the circadian rhythm period in humans is generally slightly in excess of 24 hours. Normally the periodicity of the circadian clock can be made to vary very little (e.g. 23–24½ hours, in experimental rodents). However, in genetically manipulated rodents it can vary (Reppert & Weaver, 2002), for example, from 20 hours, in *tau* mutant hamsters, to 28 hours, in *Clock* mutant mice.

The central circadian pacemaker in the suprachiasmatic nucleus (SCN) generates and coordinates circadian rhythms. Light is the primary time cue for the organisation of circadian and seasonal rhythms. However, if other factors that impact on the circadian clock are maintained, such as scheduled sleep patterns, even in the total absence of bright light (e.g. Antarctic conditions), the rhythm will stay, more or less, on a 24-hour cycle. Light-at-night has numerous effects, not just melatonin suppression, and thus the whole circadian system should be considered, not only melatonin levels.

Sleep is under the control of the circadian clock, and most shift workers have, on average, two hours less sleep than the general population. Amongst other things, sleep deprivation is associated with alterations in glucose metabolism and in immune function.

The circadian clock (see Fu & Lee, 2003) influences metabolism, cell proliferation, apoptosis, responses to genotoxic stress and ageing. Circadian rhythms are under the control of clock genes and mutations in some clock genes have been shown to be associated with cancer prone phenotypes (Fu *et al.*, 2002). A length polymorphism in the clock gene *hper3* has recently been found to be associated with an increased risk of breast cancer among premenopausal women (Zhu *et al.*, 2005). Ablation of the SCN is associated with decreased survival time in tumour-bearing rodents (Filipski *et al.*, 2002).

The majority of shift workers rarely adapt their internal clocks. Among the few exceptions are workers on offshore oilrigs (working 1800-0600 hours; Barnes *et al.*, 1998), probably because lifestyle factors in such a situation have little impact relative to the impact of light-at-night. Even in this situation, different patterns of shift work lead to different degrees of adaptation.

Normally, melatonin levels peak at night, corresponding also to the period of lowest body temperature, highest blood fat, lowest point of subjective alertness and poorest reaction times. In the absence of adaptation, shift workers will simply work counter to these natural rhythms. When workers

on rapidly rotating shifts exhibit little shift in the timing of the melatonin peak, the amplitude of the peak may be decreased (although this has not been observed in all of the few existing studies; e.g. Touitou & Motohashi, 1990; Costa & Ghirlanda, 1994; Schernhammer *et al.*, 2004b), probably owing to light suppression.

In the absence of light perception, the circadian rhythm runs to its natural rhythm, slightly in excess of 24 hours. However, in a small number of people who cannot see light, melatonin levels can be suppressed by light, suggesting that other light sensor systems are operating (see Fu & Lee, 2003). Nonetheless, the human circadian clock is relatively insensitive to light. The more intense the light the stronger is the driver controlling the circadian clock. The fact that sunlight is much brighter than most indoor lighting conditions explains, in part, why most shift workers do not adapt their circadian clock.

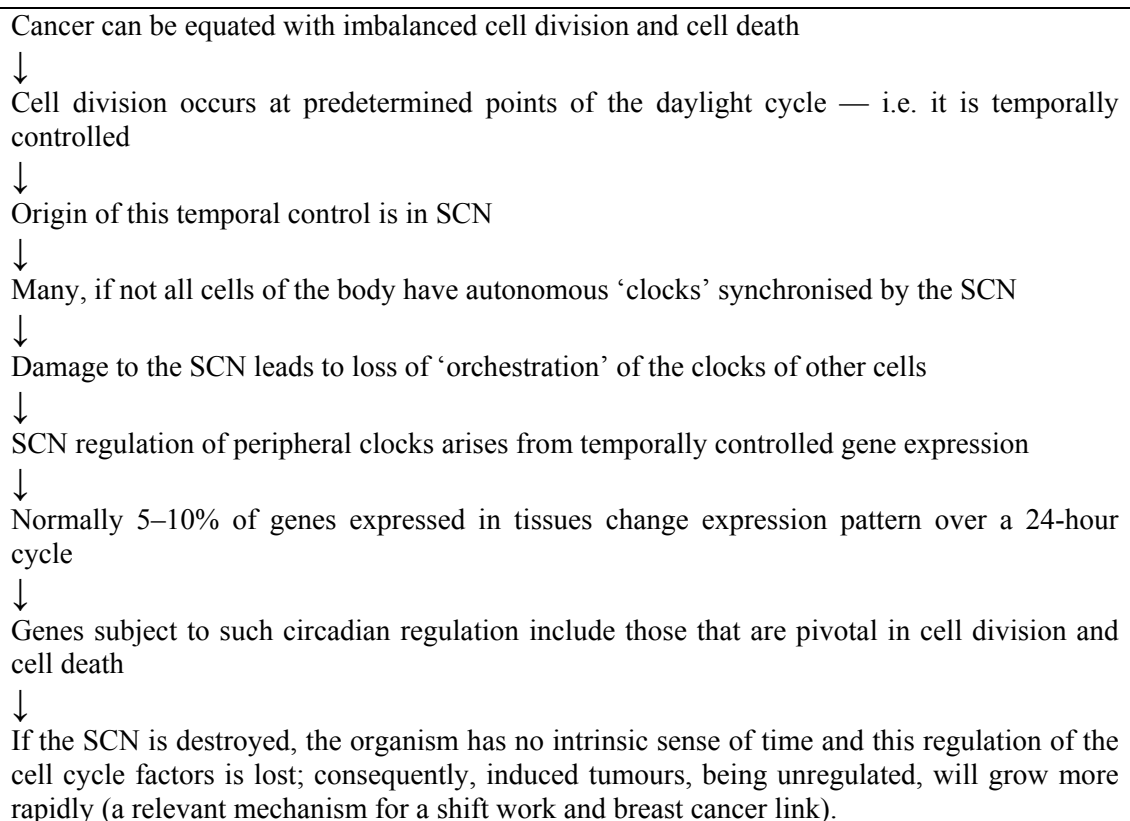
### 2.3.3 Clock genes: Biological plausibility for impact of circadian rhythms on tumour progression

A mechanism for the possible link between circadian dysfunction and cancer initiation and progression is outlined in Figure 2.1. Based on such considerations, the hypothesis that dis-regulation of the circadian rhythm might lead to increased susceptibility to cancer initiation and progression in humans is biologically plausible. It is known, for example, that tumour implants grow faster if the SCN is destroyed, and a disrupted light cycle results in increased spontaneous tumours in experimental animals (Fu & Lee, 2003). Tumour cells are susceptible to circadian rhythms and the immune system (linked with tumour suppression) also shows circadian cycles (see below).

Topics for experimental studies that might contribute to a better understanding of biological mechanisms leading to cancer include:

- the effect of reversing day and night patterns in experimental animals; and
- the impact of different patterns of light exposure on cancer incidence and progression.

**Figure 2.1** Circadian dysfunction and tumour progression



A recently published study demonstrated that implanted tumours grew more rapidly in mice exposed to shifting patterns of light exposure (such that they could never establish a routine;) than in mice on a standard light exposure pattern or kept in total light or total darkness (Filipski *et al.*, 2004). Other studies have demonstrated that mice that have been genetically manipulated so that they no longer have circadian control are more susceptible to spontaneous and induced tumours (Fu *et al.*, 2002).

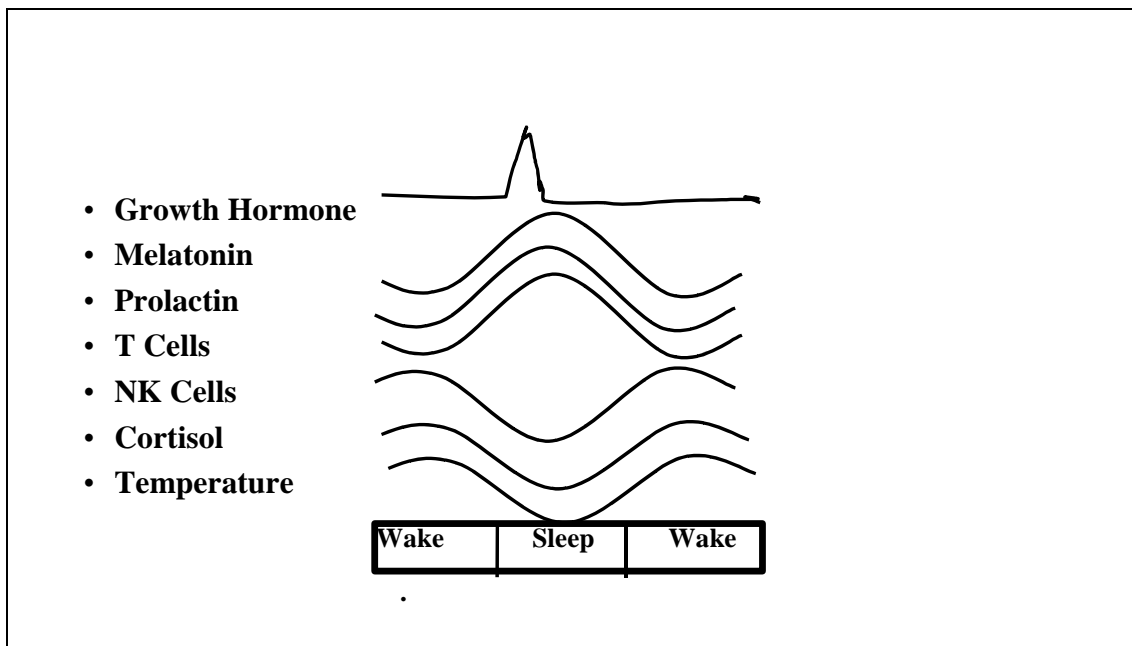
Microarray studies have shown that the circadian clock controls 5–10% of genes. When the SCN is removed in mice, such rhythmic expression is lost (Akhtar *et al.*, 2002).<sup>2</sup> Gene expression in implanted tumours is also rhythmic and synchronised with the circadian periodicity of the host (Filipski *et al.*, 2004).

### 2.3.4 Immune system

Figure 2.2, which illustrates circadian neuroendocrine, immune and temperature rhythms, shows the effects of waking and sleeping on NK and T cells. It is possible that NK and T cell activity might be associated with exercise rather than simply night-time sleeping; NK activity can also be shown to decline in prone subjects.

As can also be seen in Figure 2.2, cortisol levels dip at night and peak during the day. Cortisol levels are anticipatory, in that they start to rise before waking and also, for example, start to rise in athletes before exercise. In practice, cortisol levels do not vary in a smooth curve but in pulses of approximately 2 hours duration. Sleep deprivation would be expected to disrupt the organisation of cortisol pulses. Cortisol levels are also impacted by stress.

**Figure 2.2** Harmonious circadian neuroendocrine, immune and temperature rhythms



Glucocorticoid secretion dampens the immune response. As night shift workers overcome the physiological effects of their circadian clock by changing glucocorticoid secretion, it might be expected that they would be immune suppressed; however, no study has demonstrated such an effect.

<sup>2</sup> The working group was made aware of recent, as yet unpublished studies, which indicate that such genes can be resynchronised by corticosteroid.

## 2.5 Forward look

While a link between dis-regulation of the circadian rhythm and increased susceptibility to cancer initiation and progression in humans might be biologically plausible (see above), questions about the specificity of any effect, such as a link between shift work and breast cancer, remain.

Before considering any new studies, a review of ongoing, existing cohort studies, worldwide, to see if they might be expected to yield any data of relevance to an assessment of the impact of shift work on major diseases, would be useful.

### 2.5.1 Exposure

Improved measures of exposure to patterns of shift work and light-at-night might be applied to epidemiological studies and questionnaires. This might include more precise data gathering on the types and duration of shift working, type and intensity of light exposure, changes in sleep pattern, and variables associated with circadian rhythm. Some work still needs to be undertaken to identify parameters that would be most useful for measuring such variations in exposure and effect. The Actiwatch® is a good system for measuring peoples' personal light exposure and activity, and can measure how much they sleep. While current costs would be prohibitive for use in large-scale epidemiology studies, it would be possible to measure representative personal light exposure for short periods of time, during specific activities. However, it should be noted that more sophisticated measures of exposure may result in more complex results and increased likelihood of chance associations.

### 2.5.2 Epidemiological and experimental studies

As well as improved exposure measures, any future new epidemiological studies specifically on shift work and breast cancer should also include better control for confounding. Given concerns about diseases other than breast cancer, design and analysis of future studies on shift work could also usefully incorporate consideration of other major diseases.

Investigation of the underpinning disruption of circadian rhythm should be an important element of future studies. It might be helpful to investigate biological markers of circadian rhythms among people on much less well-controlled shift patterns than those of oilrig workers, for example, and compare these with patterns in the general population. Studies in experimental animals (preferably diurnal animals with a basic physiology that models that of humans) are needed to confirm what effects changes in circadian rhythms have on health. The authors of the recently published study on the association between period3 genotype and breast cancer risk suggest that circadian genes might be a novel panel of potential biomarkers for breast cancer (Zhu *et al.*, 2005).

Sleep disorders in epidemiological studies can be assessed by questionnaires, such as the 'Sleep Assessment Questionnaire' used in a recent US study (Unger *et al.*, 2004).

In considering what type of epidemiological studies might be most useful, it should be noted that case-control studies are limited by potentially biased recruitment and recall of exposures, although the latter is likely to be less of a problem for people recalling whether or not they ever worked shifts than for people recalling past exposures to chemicals in the workplace. A weakness of record linkage studies is the difficulty in getting adequate information on exposure and potential confounders. Prospective cohort studies are the most informative, but a large general population study would be needed to investigate shift work and breast cancer, as only about 5% of women undertake shift work and even fewer work night shifts (see Table 2.2). It would be necessary to take account of all possible confounders.

The most immediately practical solution might be to use the UK Biobank study (250 000 women). Recruitment is expected to start at the end of 2005 and, as questionnaires are still being developed, questions on shift work could be added. However, this will require a long-term commitment and it

would be some time before useful results on shift work and breast cancer were likely to become available.

Another possible approach would be to identify other existing cohorts with data on shift work (e.g. the Breakthrough Generations study (100 000 women))<sup>3</sup> or to identify cohort studies (e.g. Million Women Study<sup>4</sup>, EPIC-Oxford (44 000 women)<sup>5</sup>, UK Women's Health Study (30 000 women Maconochie *et al.*, 2004), EPIC-Norfolk (12 000 women)<sup>6</sup> to which additional questions on shift work could be added at the next follow-up. Alternatively a specific occupational shift work study could be initiated, which would not need to be so large.

In comparison with standard case-control studies, there may be fewer problems with biased recruitment and better information on confounders when case-control investigations are nested within cohort studies that have collected information prospectively on known risk factors for breast cancer. Although the marginal cost of such an approach would be greater than for the other two approaches described above, results would be obtained more rapidly and the approach might be worth considering should new data strengthen the argument for biological plausibility. The Million Women Study already includes a nested case-control study, though there is no investigation of shift work. If a nested case-control study on shift work and breast cancer were to be added, it might be better to select new cases, for additional information, rather than to go back to the cases already used.

Alternatively, and most resource intensive, a new prospective study of shift workers could be considered. For example, it might be possible to assemble a cohort of middle-aged women (and perhaps men also), in the UK, with a high rate of shift work and a comparison cohort with a low rate of shift work, following up for cancers, heart disease and other health impacts. Among women, nurses are one group with a relatively high prevalence of shift work but no long-term cohort studies of UK nurses are known to be currently in progress.

### 2.5.3 Patterns of shift work

It would also be helpful to consider whether advice could be given on the best patterns of shift work to adopt in order to minimise the risk of adverse health impacts. In general, based on psychological perceptions of well being, patterns that shift the circadian clock forward are less disruptive than those that shift it backwards (Knauth, 1993; Hakola & Harma, 2001). However, this may not be true for everyone; people with a preference for evening working/activity will adapt better to a delaying pattern than those with no such preference. Chronotyping, to determine peoples' capacity to cope with shift work, might be informative (e.g. genotyping for extreme 'eveningness' or extreme 'morningness').

### 2.5.4 Other remarks

It is possible that there are other questions to be asked in relation to the health impacts of shift work — for example, increased accidents at night (Smith *et al.*, 1994). It is possible that lessons can be learned from HSE's experience and studies on human factor issues. There are potentially a large number of (other) problems associated with shift work, relating to health, performance and social relationships. It was recommended, in particular, that a review of the literature on shift work and heart disease should be conducted.

Overall, it is considered plausible that circadian rhythms could be the primary mediator of any link between shift work and cancer, because they can affect key factors including cell cycles, stress and melatonin levels, all of which have been postulated to impact on cancer risk.

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<sup>3</sup> *Breakthrough Generations: The UK Study of the Causes of Breast Cancer*, available [February 2005] at <http://www.breakthroughgenerations.org.uk/>

<sup>4</sup> *The Million Women Study*, available [February 2005] at <http://www.millionwomenstudy.org.uk/>

<sup>5</sup> *EPIC-Oxford: Lifestyle Characteristics and Nutrient Intakes in a Cohort of 33 883 Meat-eaters and 31 546 Non Meat-eaters in the UK*, available [February 2005] at <http://sci.cancerresearchuk.org/research/ceu/publications/abstracts/2003-9808463-6-259-269.html>

<sup>6</sup> About EPIC Norfolk, available [February 2005] at <http://www.srl.cam.ac.uk/epic/about/>

# 3 Conclusions and Recommendations

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## 3.1 Conclusions

Shift work is a pattern of working that can be expected to continue, if not increase, and it is likely that even more varied and 'abnormal' work patterns will be adopted in the future.

Presently, the evidence for an association between shift work and breast cancer is suggestive, but the relationship is not confirmed. Although a causal relationship is biologically plausible, empirical evidence for this is lacking.

Shift work might impact not only on breast cancer but also on other diseases, such as coronary heart disease. Further research would be required to identify the key factors that might be associated with apparent changes in susceptibility to certain diseases among shift workers.

While the biological mechanisms underlying any effect of shift work on disease are not known, disruption of circadian rhythms is likely to be important.

## 3.2 Recommendations

Although there is a need to clarify further whether the association between shift work and breast cancer might be causal, it is recommended, in the first instance, that further research should investigate more holistically the relationship between shift working and susceptibility to major disease. In this context, further investigations should take the form of epidemiological studies focused on exploring possible disease associations *per se*. A review of the literature on shift work and heart disease would be useful. However, it is also recommended that, should significant additional information on the relationship between breast cancer and shift work become available, it might be appropriate and would be possible to commission quickly an investigation or investigations focused specifically on associations with this disease. It would first, however, be necessary to check what studies were currently being conducted worldwide.

The most cost-effective way to provide additional information on relationships between shift work and disease would be to modify existing, ongoing cohort studies (and in particular the UK Biobank study) by adding specific questions on patterns of shift working, life-time history of shift working and on endpoints that could identify disruptions to the circadian clock.

Any new studies must distinguish clearly between fixed and rotating shift patterns, and should include a sleep questionnaire and determine light exposure.

Although no particular experimental research is recommended *per se*, the development of suitable experimental animal models, to establish the biological basis for the disruption of circadian rhythms and the impact of any such disruption on disease incidence and progression, would be helpful in the formulation of relevant questionnaires for such cohort studies and in the design of appropriate, more specific studies in humans, should these prove to be needed.

Data on biological mechanisms obtained from experimental studies, together with additional data from ongoing cohort studies, will help confirm whether there is any association between shift work and breast cancer and will help underpin the basis for the design of more specific and selective studies, as required.

These initial recommendations pertain to long-term research activities entailing relatively low marginal costs. If new scientific or clinical information or increased concern about any association between shift work and breast cancer becomes apparent, more costly studies could be undertaken to provide results more rapidly, such as case-control investigations of shift work and breast cancer, nested within existing cohort studies that have collected information prospectively about potential confounding factors.

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# Annex 1 Meeting Participants

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Professor Valerie Beral <sup>7</sup>	Cancer Epidemiology Unit, Cancer Research UK, Oxford
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Professor Anthony Swerdlow	Institute of Cancer Research, Belmont
Dr Matthew Wakelin	MRC Head Office, London

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<sup>7</sup> Unable to attend meeting

# Annex 2 Meeting Agenda

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12 November MRC Head Office, 20 Park Crescent, London

1000–1600

*Chair – Professor Ian Kimber*

**1000-1015**            *Welcome and Introduction*  
Matthew Wakelin and Ian Kimber

**1015–1115**            *Epidemiology of shift work and breast cancer*  
Introduced by Professor Anthony Swerdlow

- Summary of HSE-commissioned review and conclusions

**1115–1145**            *Potential confounding factors*  
Introduced by Professor David Coggon

**1145–1245**            *Forward look at possible epidemiological studies*  
Introduced by Professors Valerie Beral & Tim Key

- Assessing the level of attributable population risk
- Feasibility and length of studies
- Cohorts that could be developed
- Existing cohorts that could be used

**1330-1500**            *Potential biological mechanisms*  
Introduced by Professors Josephine Arendt & Stafford Lightman

- Circadian rhythms
- Clock genes
- HPA / endocrinology
- Immune system

**1500-1600**            *Conclusions and Recommendations*

- Where are we now? What can be said today about the risk?
- Are any actions needed now? Are there grounds for any preventive action?
- Recommendations for further work
- Mechanistic studies
- Epidemiological studies
- Other

