A review of the impact of shift work on occupational cancer

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Research review

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ABSTRACT

This report contains a systematic review of the epidemiological and mechanistic evidence from 2005 to 2015 relevant for examining the association between shift work and cancer. The systematic review is supplemented by a review of relevant health and safety practices and policies as well as a compendium of current and ongoing relevant epidemiological work in the field. The systematic review employed standard methodology.

The epidemiological evidence examining the relationship between shift work and breast cancer is now appreciable. Recent studies have better adjusted for potential confounding factors, but many still have imprecise and inconsistent definitions of shift work. Across all the epidemiological evidence examined the overall relative risk is around 1.2 or 1.3. During the write-up of this report a meta-analysis of prospective epidemiological studies was published which provides evidence that the overall relative risk for breast cancer in relation to shift may not be raised at all. The epidemiological evidence for other cancer sites remains relatively sparse and the evidence supporting a causal association remains somewhat limited.

Suppression of night time melatonin production and or obesity remains the most plausible biological mechanism for the association with breast cancer. A number of practices have been implemented, for example shift design, pharmacological interventions etc. to reduce the potential carcinogenic risk of shift work, but have not yet been fully evaluated.

The main recommendations emanating from this review relate to encouraging employers to provide healthy and nutritious food for shift workers as well as the opportunity to exercise and access programmes for smoking cessation and moderating of alcohol consumption. Encouraging employers to facilitate employee participation in national cancer screening programmes is also recommended. Further prospective epidemiological studies with well characterised data on shift working patterns, as well as good data on known and suspecting confounding factors remains warranted.

EXECUTIVE SUMMARY

In 2007, the International Agency for Research on Cancer (IARC) classified shift work that causes disruption to the body's natural circadian rhythm as probably carcinogenic to humans (Group 2A), with the main risk being an increase in the incidence of breast cancer in women working night shifts. This conclusion was based on a review of all the available scientific research, which showed "limited evidence in humans for the carcinogenicity of shift-work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)". The evaluation highlighted the limitations in the available epidemiological evidence, with inconsistencies in the definition of shift or night work used by different researchers.

The proportion of people engaged in shift work in the UK and elsewhere in the EU is around 15%, but this varies between countries (range 6%-30%) and within different industrial sectors, with the occurrence being higher in healthcare, industrial manufacturing, mining, transport, communications, leisure and hospitality sectors. Definitions of night work and night worker differ in different countries. For example, in the UK night work is a period lasting not less than 7 hours, and which includes the period between midnight and 5 am. A night worker is a worker who, as a normal course, works at least 3 hours of his/her daily working time during the night time. Men are more than twice as likely to work shifts compared to women and shift workers are more likely to report that their work has a negative impact on their health.

A number of different routes were taken to identify relevant literature and research. A systematic search was undertaken to identify research publications covering the epidemiology of different cancers associated with shift work. The titles and abstracts of the papers were screened and data were extracted from included papers. Mechanistic papers were further identified through additional searches. To identify any relevant policies, we searched the internet to identify health and safety policies relating to shift work to identify how, if at all, cancer risks were taken into consideration.

In total, 36 scientific papers were identified that examined the epidemiological evidence relating to shift work and cancer and a further 50 were identified that looked at the potential process of causation for specific cancers. A further eight papers examined potential interventions to improve health and wellbeing for those undertaking shift work.

Fifteen reviews and meta-analyses were examined in relation to breast cancer occurrence in women working shifts. Overall the majority of studies showed an increased risk of breast cancer in relation to shift work and an increased risk when shifts had been worked for longer periods. However, many of the studies had limitations because of the lack of clear descriptions of the shift systems used. The review also examined more recent studies of breast cancer from circadian disruption where other risk factors were better controlled. In these studies the association between shift work and breast cancer was still apparent, but the magnitude of the relative risks were reduced from around 1.5 to 1.2, i.e. from 50% higher than expected to 20% higher. A recent study assessed the risk of breast cancer in three prospective cohort studies – The Million Women Study, the EPIC-Oxford Study and the UK Biobank Study that controlled for body mass index and other potential confounding factors, along with a meta-analysis of the available prospective studies. None of the three studies gave a raised relative risk for breast cancer and the meta-analysis suggested that breast cancer risk was not influenced by shift working. Overall we have concluded that the measured relative risk of breast cancer in well-conducted epidemiological studies of female night workers is lower than originally identified and may not be significantly raised. However, because of continuing limitations in the characterisation of shift work, further prospective studies with well-defined shift work data and well controlled for potential confounding factors are still required.

Possible associations between night shift work and prostate cancer, ovarian cancer, colorectal cancer, endometrial cancer and non-Hodgkin's lymphoma were also examined. The evidence for

prostate and ovarian cancer is strongest, but still insufficient to allow any firm conclusions to be made. Further research is necessary to clarify whether there is any risk of night work for these cancers.

When examining the possible mechanisms for an increased breast cancer risk in night workers, the suppression of melatonin from exposure to light at night has been proposed. Melatonin is a hormone produced by the pineal gland in the brain and is associated with control of sleep wake cycles (circadian rhythms). Melatonin production is reduced in humans when they are exposed to light and it is known to have anti-carcinogenic properties. The increased cancer risk could also be due to the known association between obesity and breast cancer since it is known that shift workers may have a poorer diet than day workers and may be more likely to be obese or have other lifestyle factors associated with cancer.

The use of bright white light at night within workspaces was seen as positive in maintaining alertness at night and improving sleepiness levels during the day. However, exposure to bright light during the night causes circadian disruption and further research is required to find out if it is preferable to increase wakefulness at night or minimise circadian disruption using lower intensity (blue) lighting. Reducing exposure to light at the end of shift using dark glasses (weather and light intensity permitting), and using black out blinds at home may improve the quality of sleep after shifts.

Research into shift design over the last 40 years has suggested that forward rotating shift systems (day, evening and night shifts) are preferable as a means of reducing circadian disruption. In addition, ensuring no more than 4 night shifts are worked at a time and that there is adequate recovery rest after shifts as well as adequate rest breaks during the shifts worked has positive impacts. Adopting best practice in design of shift patterns is recommended, although its impact on cancer risk has not been evaluated.

Strategic napping has also been examined as a means of improving alertness. Naps taken before starting a night shift and naps taken during a night shift have been found to reduce sleep deprivation. However, it is not always possible to take naps depending on the impact of sleep inertia (going from sleep to wakefulness) and the requirements of the work. The effect of strategic napping on cancer risk has not been evaluated.

Individuals working shifts are significantly less likely to attend screening for breast or colorectal cancer than day workers, although there is no difference in relation to cervical cancer. Sectoral differences were also identified where those working in manufacturing, transportation and material moving and food preparation, servicing and production were less likely to attend screening appointments. It is recommended that employers should facilitate shift workers to attend screening appointments.

Some practitioners have advocated the use of melatonin as a supplement to attempt to adjust sleep time, although the available research studies did not show an improvement in daytime sleepiness levels and an effective dosage is difficult to calculate. A number of other pharmacological interventions have been evaluated including the use of stimulants to reduce sleepiness. Modafinil, which promotes wakefulness, in a small research study showed improvements in measures of sleepiness and later sleep onset compared to the control group. The use of caffeine has also been examined where having a nap before night shift followed by 300 mg of caffeine (that's around 3 cups of coffee) improved vigilance performance, but day time sleep length was reduced. Using hypnotics to improve daytime sleep have also been examined and tamazepam while improving sleep length initially, after a number of night shifts the effect was reduced. At this time the evidence for the use of pharmacological interventions is limited and they are not recommended as a strategy to reduce cancer risks in shift workers.

Lifestyle factors have also been examined in relation to shift work. Shift workers are more likely than other workers to be overweight or obese, and they are at increased risk of diabetes and cardiovascular disease. It is not properly understood why shift workers gain more weight, although it

may be due to poor diet (lack of opportunities at night for healthier eating options) or it may be a consequence of eating food at the wrong time to allow it to be fully metabolised. While further research into the diet of shift workers is warranted, there is sufficient evidence to recommend that employers should encourage better eating habits amongst shift workers.

While there is some evidence of an exposure-response relationship between the occurrence of breast cancer and the length of time working night shifts, it is probably not sufficiently strong to suggest limiting the length of time that individuals continue to work night shifts.

There are a number of policy and guidance documents available to help manage shift work and the associated health outcomes, and while they generally acknowledge the potential link between shift work and breast cancer there is very little information available on cancer prevention. This probably reflects current lack of knowledge in this area amongst practitioners.

At the current time the scientific evidence of an association between shift work and breast cancer is stronger than in 2007 when IARC carried out their evaluation. However, the magnitude of any risk from working night shifts is most probably less than was originally thought, and may even be zero. Research on the risk of other cancers such as prostate and ovarian cancer is inconclusive.

The main potential mechanism for cancer being associated with night work is the suppression of melatonin production due to exposure to light at night. However, other direct and indirect mechanisms may play a part including the difficulty of night workers maintaining a healthy diet, which may result in obesity and this may be the ultimate cause of the observed breast cancer risk.

Epidemiological evidence on its own can never conclusively prove that an exposure causes a disease; it is the combination of epidemiology, experimental toxicology and mechanistic studies that must be evaluated. Further research may ultimately show that the cancer risk from nightshift workers is not due to night work but to some other factor such as diet or another risk associated with working during the night.

From the research compiled in the report there are a number of practice points that employers should be taken forward in the workplace:

- Develop a workplace policy for night work that informs workers about the potential cancer risks and sets out prudent strategies to minimise the impact of shift working on health;
- Design shift patterns around a fast forward rotating systems that helps prevent circadian disruption and ensure that the number of consecutive night shifts worked are minimised;
- Instigate health promotion initiatives amongst night shift workers to improve their diet and help them maintain a healthy body mass. Provide advice on strategies to improve sleep quality;
- Encourage use of dark glasses on the way home after shift (weather and light levels permitting) to ensure melatonin levels are not reduced. In addition, promote the use blackout blinds in bedrooms to try and improve daytime sleep quality; and
- Encourage night shift workers to attend appropriate health screening appointments.

INTRODUCTION

The International Labour Office (ILO) defines working in shifts as a "method of organisation of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of individual workers".[1] Several types of shift work exist[2] and the following definitions are used in the UK Labour Force Survey:

Shift work definitions

Three-shift working

The day is divided into three working periods: morning, afternoon and night. This type of shift work usually, but not always, involves one or more weeks of mornings, followed by one or more weeks of afternoons, followed by one or more weeks of nights.

Continental shifts

This is a continuous three-shift system that rotates rapidly: for example, three mornings, then two afternoons, then two nights. Usually there is a break between shift changes.

Two-shift system early/late-double day

Normally two shifts of eight hours each: for example, 6 am-2 pm and 2 pm-10 pm. Shifts are usually alternated weekly or over longer intervals.

Split shifts

These are full shifts divided into two distinct parts with a gap of several hours in between. Used in industries where peak demands are met at different times of the day, for example catering, passenger transport and service industries.

Morning shift

If full-time, most commonly 6 am-2 pm. This code is used if the morning shift is the only shift worked or worked part-time during the morning.

Evening shift

If full-time, most commonly 3 pm-12 midnight. Also used for part-time shift 5 pm-9 pm or 6 pm-10 pm. Part-time evening shifts are usually called twilight shifts.

Night shift

If full-time, most commonly 6 pm-6 am, and usually continuing after midnights. This code is used only for permanent night work.

Weekend shift

This code is used for work during Fridays, Saturdays, Sundays (6 am-6 pm), when there is no other work.

Other type of shift work

This code is only used when none of the above apply.

Shift working is most prevalent in health-care, industrial manufacturing, mining, transport, communications, and leisure and hospitality sectors. There is a marked gender difference, with men almost twice as likely to work shifts as women (23% vs 14%). The proportion of people engaged in shift work in the UK has remained consistent over the past decade, with just under 15% engaging in shift work most of the time and a further 3-4% occasionally working shifts.[3] In the UK the two shift system is the most prevalent accounting for 30% of shifts.[2] In the EU 2.6% of the workforce permanently work nights and a further 4.3% occasionally work nights.[*] Shift workers are 1.5 times more likely than other workers to self-report that their work negatively affects their health.[4]

In 2007 a Working Group of the International Agency for Research on Cancer (IARC) classified shift work that involves circadian disruption as probably carcinogenic to humans (Group 2A). The majority of epidemiological studies considered by the IARC Working Group, including two independent studies of nurses, had modestly increased risks of breast cancer in long-term employees compared with those not engaged in shift-work at night. These studies were considered to be limited by potential

[*] 2014 Labour Force Survey, Eurostat

confounding and inconsistent definitions of shift work as well as the high potential for recall bias in retrospective studies relying on participant recall. The incidence of breast cancer was also modestly increased in most studies of female intercontinental flight attendants who experienced jet-lag, although these studies were limited by the potential for selection bias, proxy measures of exposure and potential for uncontrolled confounding.[5]

In their consideration of the experimental evidence, the IARC Working Group noted that several different rodent models had been used to test the effect of circadian rhythm disruption on tumour development. In most of these studies the effect of constant light, dim light at night, and simulated chronic jet-lag was to increase tumour incidence. No effect was seen for pulses of light at night or constant darkness. The Working Group also considered studies investigating the effect of reduced nocturnal melatonin concentrations or removal of the pineal gland and most showed increases in the incidence or growth of tumours.[5]

Exposure to light at night disturbs the circadian rhythm and suppresses melatonin production in rodents and causes deregulation of the circadian genes involved in cancer-related pathways. The clear evidence for carcinogenicity in studies using experimental animals and the limited evidence in humans contributed to the decision of the IARC Working Group.[5]

Because the human evidence was based on a series of epidemiological studies, many of which used imprecise definitions of shift work, that are difficult to compare, the Working Group published a consensus statement on what aspects of shift work should be captured in future epidemiological studies. They recommended that cross-sectional or short-term longitudinal studies of workers engaged in specific work shift schedules according to the degree of their circadian disruption be carried out. They identified that measurement of biomarkers at single time points would be of limited value because of considerable intra-individual variation, although assessment of circadian gene expression might provide novel insight into circadian regulation and may differ by shift schedule and time of day. IARC further recommended that further prospective epidemiological studies are required to clarify the relationship between shift work and cancer.[6]

This document presents a review of the epidemiological and mechanistic evidence from the last 10 years on the carcinogenicity of shift work, although the evidence from animal experiments is not considered. It also documents current and planned research in the area and, assuming the relationship between shift work involving night work and cancer is adverse and causal, presents suggestions for possible management interventions for those responsible for the long-term health of shift workers. This latter objective makes use of current shift work policies and practices of regulators, employers and trades unions.

METHODS

The general approach to the identification of the relevant epidemiological literature was to identify epidemiological reviews and meta-analyses published since 2005, that is, from 2005 onwards. Our search protocol is set out at

Appendix 2. Our aim was to only include individual epidemiological studies that have been published since the latest year considered by the majority of the most recent reviews sourced from the searches. As well as the epidemiological evidence, we also looked for the important mechanistic evidence over the last 10 years. Examination of experimental evidence on animals is outside the scope of this report. In the studies of humans, we also looked for trends in pattern of shift working and the practicality of evidence that might be relevant for policy and practice in potentially reducing the future risk of cancer.

Literature searches

Literature searches of the peer-reviewed literature in English from 2005 to 2015 were undertaken for systematic reviews and meta-analyses, and mechanisms of cancer and shift work. The search strategies employed in September 2015 were respectively:

("shift work" OR shift-work OR shiftwork OR "night work" OR ("work patterns" and (rotat* OR shift))) AND ("breast cancer" OR "prostate cancer" OR "colon cancer" OR "endometrial cancer" OR "bladder cancer" OR "ovarian cancer" OR "gastro-intestinal cancer" OR (hormone-dependent AND cancer) OR cancer OR (womb AND cancer) OR (uterus AND cancer)) AND ("systematic review" OR review OR meta-analysis OR "cohort study" OR case-cohort study" OR "case-control study" OR "intervention study" OR "experimental study")

and

("shift work" OR "shift-work" OR "shiftwork" OR "night work" OR ("work patterns" and (rotat* OR shift))) AND ("breast cancer" OR "prostate cancer" OR "colon cancer" OR "endometrial cancer" OR "bladder cancer" OR "ovarian cancer" OR "gastro-intestinal cancer" OR (hormone-dependent AND cancer) OR cancer OR "colorectal cancer" OR (womb AND cancer) OR (uterus AND cancer)) AND (mechanism OR mechanistic OR pathway OR "phase shift" OR "sleep disruption" OR "sleep disorder" OR "sleep-wake cycle" OR "sleep-wake schedule" OR "lifestyle factors" OR chrono-disruption OR chronodisruption OR "biological night" OR "biological clock*" OR "circadian dis*" OR "circadian rhythm" OR (low* AND "Vitamin D") OR (low* AND melatonin) OR ("light at night"))

The search terms were selected on the basis of relevant terms used in major shift work and cancer studies, and these were added to, and refined, on the advice of subject experts within the project group.

Search terms had been tested by running the searches in Proquest Dialog databases, which included Current Contents, EMBASE, Scisearch, BIOSIS Previews, PsychInfo, and Toxfile, and separately in PubMed, since this database usefully highlights any search terms not found in the searches through the use of Mesh Terms.

The searches for systematic reviews and meta-analyses were undertaken in the Proquest Dialog databases, which include MEDLINE, to ensure as broad a coverage as possible.

Since initial searches in PubMed appeared to identify the relevant mechanistic materials, the mechanistic searches were carried out using this database.

Bibliographic information, including abstracts, was saved in a RefWorks database. Scanning the abstracts in RefWorks identified additional relevant cancers for this study (hormone-dependent e.g. prostate and ovarian, colorectal, and non-Hodgkin's lymphoma). Additional searches were run in PubMed to identify relevant papers, but only a few additional references were found. These were added to the RefWorks database. A supplementary search was carried out in August 2016 which relaxed the restriction on cancer type.

A subsequent search of Google Scholar and PubMed, using the keywords health and safety, cancer, and shift work identified relevant health and safety papers, which were added to the RefWorks database.

Since the latest year in which studies considered within an epidemiological review was primarily 2013, searches were run on cohort and case-control studies from the beginning of 2013, and these new

references were added to RefWorks. Care was taken to ensure that studies were not included as part of a review or meta-analysis and also separately. The search strategy employed to identify major studies that post-date the most recent reviews was:

("shift work" OR "shift-work" OR "shiftwork" OR "night work" OR ("work patterns" and (rotat* OR shift))) AND ("breast cancer" OR "prostate cancer" OR "colon cancer" OR "endometrial cancer" OR "colorectal cancer" OR "bladder cancer" OR "ovarian cancer" OR "gastro-intestinal cancer" OR (hormone-dependent AND cancer) OR cancer OR (womb AND cancer) OR (uterus AND cancer))

Health and Safety Policies

Internet searches were undertaken to identify health and safety policies and guidance on shift work that might be informative in relation to cancer prevention. These included Google searches and searching the web sites of relevant organisations including the Health and Safety Executive, trade unions, and employers. The search terms used in Google were: health and safety, policy/polices, shift work, and cancer.

For all searches, citations in the included papers were searched for additional papers. Where papers were earlier updates of later studies, these were obtained in case they contained relevant methodological material.

Current, ongoing and planned research

In addition to the use of the search strategy we identified current and planned international research in the area using the following two approaches; contacting key researchers and contacting funding bodies. The first approach included contacting key researchers about recent work they have published or current work they are completing on shift work and cancer. These key researchers were identified from the papers found in the literature searches, as those that had written multiple papers in the area. Further experts were identified via conference abstracts. Secondly funding bodies were contacted to identify any research that they had recently, currently or planned to commission or coordinate in the area. The funding bodies contacted were identified through the research team and Google searches. We identified ongoing work during data extraction, through conference papers. The results of all these approaches are documented in Appendix 1.

Selection of studies

After the searches were completed, the titles and abstracts stored in RefWorks were initially screened independently by two reviewers to eliminate papers not relevant to the questions of interest. To complete this, the inclusion criteria were applied (see

Appendix 2). Those titles and abstracts meeting these criteria were carried forward, those not meeting the criteria were excluded and for those where it was unclear if the paper met the criteria, a conservative approach was taken and the paper was carried forward for fuller consideration in the full publication.

Data extraction

Following the screening of the titles and abstracts the full papers were obtained for the 'included' papers. At this stage the data extraction sheet was developed to include sections on;

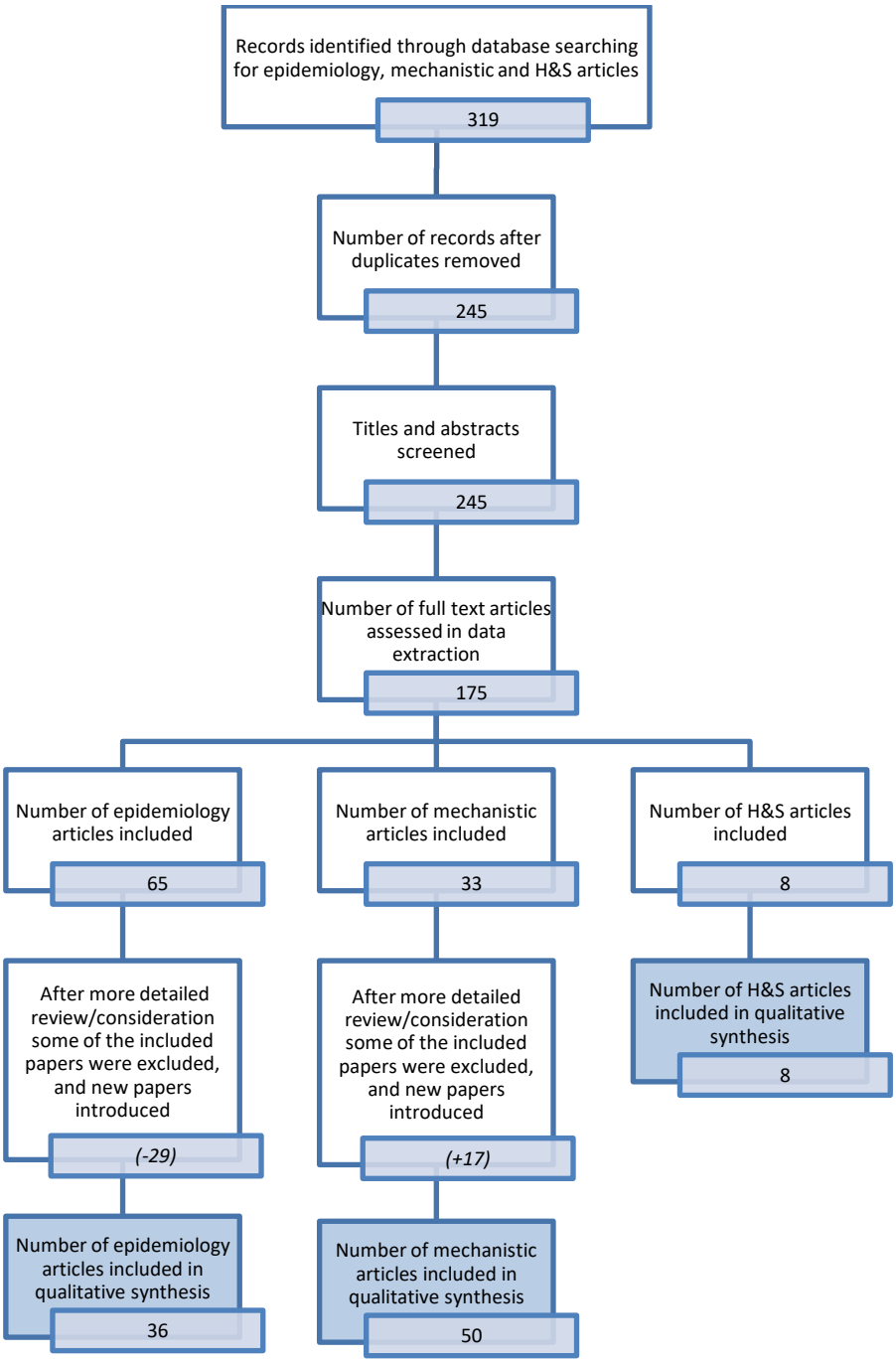
- Screening for relevance
- Research questions being addressed
- Quality Criteria for cohort studies (applied Newcastle-Ottawa scale for cohort studies) and case-control studies (applied Newcastle-Ottawa scale for case-control studies)
- Selection bias
- Confounders
- Withdrawals and drop-outs
- Additional notes and comments

It was understood and agreed in the project team that all types of studies (epidemiology, mechanistic and H&S) would be included in the single data extraction sheet, therefore there was an expectation that not all sections would apply to all papers. The team of five reviewers (from the project team) undertook a pilot of the data extraction sheet with a sample of papers, to firstly test the sheet and secondly to establish if there was consistency in approach and results. From this it was identified where the data extraction sheet needed slight adaptations, which were subsequently made and that there was an overall good level of consistency across results from reviewers.

Five reviewers undertook the data extraction and each publication was reviewed independently by two reviewers. The data extraction initially involved the identification of the relevance of the obtained full papers for inclusion in the review or whether at this stage they should not have their data extracted and be excluded or identified as ongoing work in the area. Where there were inconsistencies in these results between the two reviewers, a third reviewer was consulted.

At this point the epidemiology, mechanistic and health and safety paper methodologies differed slightly in how they progressed due to a more detailed review/consideration during the review process. The included epidemiology papers from the data extraction (from 2013 onwards) were considered along with relevant papers cited within them. Papers that did not provide further data or information to the review were excluded at this point. For the mechanistic papers the included papers from the data extraction process were considered, during a more detailed consideration as the review was being written and as issues arose from the findings, further searches were done to include papers of relevance. As with the review of epidemiological studies, publications that did not provide new knowledge were excluded at this point. The health and safety papers that were included as a result of data extraction were the papers that were included in the review. In Figure 1 a flow diagram of the study selection process has been presented.

Figure 1 Flow diagram of study selection



RESULTS

Epidemiology Studies

In this section, we examine the epidemiological evidence from reviews and meta-analyses that have been published since 2005, supplemented by individual cohort and case-control studies published since the beginning of 2013 and included in the majority of the reviews and the meta-analysis. Reviews and individual studies of breast cancer and cancers other than breast cancer are considered separately.

Breast Cancer Reviews

Fifteen relevant systematic reviews and/or meta-analysis of breast cancer were published between January 2005 and September 2013 (**Table 1**). **Table 2** sets out the component studies included in the primary reviews and meta-analyses. It is interesting to note that despite defining their study inclusion and exclusion criteria in advance, no two papers included the same set of studies. This gives an indication of the difficulties in carrying out reviews in this area of epidemiology. Perhaps the most critical area is whether studies are comparing or combining cancer risk estimates that are attempting to estimate compatible measures of shift work.

Megdal *et al*. (2005) carried out a fixed effect meta-analysis of female cabin crew and of other women who worked night shifts.[7] Night shift work was defined as being a surrogate for exposure to light at night with subsequent melatonin suppression. The meta-Relative Risk (RR) for all studies combined was 1.48 (95% CI: 1.36 to 1.61), with the meta-RR for female cabin crew and other female night shift workers being similarly around 1.5. Although this was a generally well conducted review, the authors were not able to examine exposure-response. They also carried out a meta-regression in the absence of significant heterogeneity despite the suggestion that such explorations of heterogeneity can lead to false-positive results.[8] The authors concluded that shift work including work as a flight attendant increased breast cancer risk by around 50% and that the increased breast cancer risk may be associated with engagement in night work and a related decrease in melatonin production.[7]

Erren *et al.* carried out a meta-analysis of chronodisruption (a relevant disturbance of the circadian organisation of physiology, endocrinology, metabolism and behaviour) and cancer.[9] They identified 19 eligible studies and looked separately at flight personnel and other shift workers in a meta-analysis. They found significant excesses of breast cancer in both groups of workers but cautioned against a causal interpretation because of differing assessments of chronodisruption and the lack of control for confounding in the majority of studies. As for Megdal *et al.*[7], there were limited data available to explore exposure response. Kolstad undertook a critical review of the epidemiological evidence, including only eight relevant studies.[10] Unlike the previous two papers, he examined exposure-response to the extent that it was available. He concluded that there was limited evidence for a causal association between night shift work (as defined in the studies included in his review) and breast cancer.

Viswanathan and Schernhammer examined the results of eight epidemiological studies of night shift work (as defined in the studies included in their review) and breast cancer risk and determined that there was an increased relative risk for breast cancer from night shift work of 40%.[11] They reiterated the earlier increased risk in flight attendants of 44%. They additionally pointed out that there was evidence from two prospective cohort studies of nurses that the risk increased with long duration of rotating night shift work of over 20 years and over 30 years respectively, after controlling for breast cancer risk factors, including age, reproductive history, body mass index, family history of breast cancer, benign breast disease, the use of hormones and smoking status. They described the epidemiological evidence as being “compelling”. Although they stated this, the lower 95% confidence limit was marginally above one. Whether a relative risk of below 2 can be described as compelling evidence of an excess is debatable. The authors concluded that there is increasing support for a potentially important link between disrupted night time production of melatonin and breast cancer risk.

In a secondary review, Costa *et al.* referred to the findings of the IARC working group in which six out of nine studies showed an increased risk of breast cancer in women associated with shift work that involves circadian rhythm disruption.[12] They stated that the epidemiological studies published so far, although dealing with large cohorts and controlling for several personal confounders, had a rather

rough definition of the exposure to shift/night work, which did not allow for proper assessment of the risk associated with circadian disruption. As for some of the earlier reviews, Costa *et al.* did not examine exposure-response and cancer was only one of a number of health outcomes examined. Costa *et al.* concluded that shift work is a risky condition according to the WHO's definition of "health" in relation to many health disorders probably including cancer.

Stevens *et al*. in a review examining circadian impact in relation to shift work in the epidemiology considered by the IARC working group reiterated the findings from the IARC monograph that six out of eight studies found significant and similarly strong associations of shift work with breast cancer risk. Exposure-response data was also considered where available. They concluded that the evidence from humans of shift work involving circadian rhythm disruption may be an important risk factor for breast cancer.[6] This paper's main purpose was to consider circadian impact for defining shift work in epidemiological studies, as an important limitation of the epidemiological evidence to date was the lack of a clear and uniform definition of shift work. They concluded that the important data to be collected related to the shift system, years on a particular non-day shift schedule, cumulative exposure to the shift system over a working life, and shift intensity.

Wang *et al.* carried out a secondary review of the evidence in which the quality of studies was evaluated using the modified Royal College of General Practitioners (RCGP) three-star system and concluded that the evidence that breast cancer was caused by night work was suggestive[13]. Shift work was not explicitly defined by the authors and it seems a little odd that they chose to cite Kolstad's review as providing only limited evidence for a carcinogenic effect of shift work in relation to breast cancer, but not other reviews that were more positive that a causal association existed.

Yong and Nasterlack cast doubt on the consistency of the exposure-response data considered by the IARC working group, suggesting that there was a great deal of heterogeneity regarding dose-matrix and dose-response relations. They also criticised the IARC monograph for not defining "circadian disruption". They updated the literature by including an additional six studies, half of which showed some evidence of an increased risk in the highest exposure category. They extracted the definitions of shift work from the individual studies when summarising the epidemiological evidence. They also cast doubt on the ability of the literature in flight attendants to provide supporting evidence for the association due to a large proportion of flights not travelling across time zones. They concluded by stating that an association could not be ruled out between shift work and some cancer types on the basis of the epidemiological evidence, but preferred to conclude that there is no reason to believe in general that shift workers in general face an increased cancer risk.[14]

Dickerman and Liu examined the epidemiological evidence restricted to nurses.[15] They determined that nurses who worked rotating shifts had an increased risk compared with permanent day workers and that studies have reported a dose-response relationship between breast cancer risk and increased years and hours per week of night shift work. However, they also concluded that additional well-designed human studies were required, before definitive conclusions could be drawn about the effects of shift work and exposure to light at night on breast cancer and before interventions can be designed for prevention and mitigation of breast cancer. It is not necessarily correct that the mechanism needs to be elucidated before an intervention can be designed.[15]

A review by Leonardi *et al*. of eight case-control and four cohort studies identified an association between shift work and breast cancer in six out of eight studies and two of the cohort studies showed an association, but the other two examined did not.[16] They pointed out that the two most recent studies showed that night shift work represented a concrete risk of breast cancer because in both studies the main IARC indicators had been developed. They stated that the totality of the literature was still problematic, e.g., risk is too moderate, definition of night shift too rough and uncertain estimation of confounders. They concluded there remained a need to reduce the incidence of cancer by examining cancer risk factors and that one of these might be night shift work, which is increasing in industrialised countries.

A systematic review by Ijaz *et al.* that incorporated a meta-analysis, examined evidence from 16 studies.[17] They searched for studies that had two of the three recommended characteristics for shift work suggested by Stevens *et al*.[6] i.e., shift system, shift direction and shift intensity. Interestingly they state that the complete set of confounders for shift work and breast cancer are presented in a directed acyclic graph, although they only adjusted for age, ethnicity, socio-economic status, number

of children or age at first child and body mass index. Their analysis included a risk of bias assessment in and across the included studies. The authors determined the overall quality of the evidence to be low due principally to the differences in effect estimates by study design and that there was insufficient evidence for a link between night shift work and breast cancer; although they could not rule out a link between the two.

A meta-analysis by Wang *et al.* focussing on exposure-response, which used Drums and Blacks scale to ascertain methodological quality, found significant positive relationships for increased breast cancer risk and cumulative years of working nights, numbers of night shifts, and working more than 3 nights per month.[18] Of the three cohort studies examined, the Nurses' Health Study I and II found an increased risk in the highest duration of work as a nurse, but the study by Pronk *et al.,* concluded that a positive exposure-response relationship is likely to be present for breast cancer.[19]

A meta-analysis of five cohort and 10 case-control studies found an overall relative risk of 1.21, and when short and long term shift workers were examined separately, no evidence of an increased risk in either.[20] Nor did they find evidence of any linear or other exposure-response relationship due to marked between-study variability in exposure measurement.

The most recent and possibly the most detailed meta-analysis examined circadian disruption in general was carried out by He *et al*.[21] As well as shift work (extracted according to the definition in the component studies), and work as a flight attendant, He *et al.* also examined the effects of short sleep duration and light at night. Overall, there was a significantly positive association between circadian disruption and breast cancer risk. This included a positive association for shift work, exposure to light at night and employment as a flight attendant, but not for short sleep duration. A significant dose-response relationship was obtained for shift work from selected case-control studies, but overall it was concluded that although their study demonstrated the circadian rhythm disruption descriptor is associated with an increased breast cancer risk, its existence and nature remained uncertain and that further rigorous prospective studies were required to confirm the relationship.

A recently published review of shift work and breast cancer by Pan *et al.* examined the evidence in 16 epidemiological studies.[22] It found an increased risk of breast cancer in shift workers in most of the studies and an increased risk primarily in women with longer duration of employment. Importantly it pointed out that shift workers are more often obese compared to non-shift workers and so obesity may be a potential mediator of the observed association between shift work and cancer risk. They concluded that the evidence for an association between shift work and increased breast cancer risk was now compelling.[22]

Reviews for cancers other than breast cancer

The studies included here are summarised in **Table 3**. Erren *et al.* conducted a meta-analysis that included consideration of prostate cancer in male flight attendants in studies published up to 2007. Overall a statistically significant elevated relative risk was found and the elevated risk of prostate cancer was consistent with the chronodisruption hypothesis. However, there was insufficient dose-response information and so they concluded that further research was needed to clarify whether chronodisruption or some other exposure(s) to flight attendants or shift workers could explain the findings.[9]

In a critical review of the epidemiological evidence for shift work and other cancers, Kolstad concluded that there was insufficient evidence, based on a lack of increased relative risks, from four studies of an association for prostate cancer or colon cancer.[10]

In a review looking at the epidemiological evidence for endometrial cancer, Viswanathan and Schernhammer showed there was an increased adjusted relative risk in a single prospective study of nurses who worked 20 or more years on rotating night shifts, but also noted that there was no excess observed in leaner women.[11]

In his commentary on the IARC review, Costa mentioned that there were sporadic indications of associations between shift work involving circadian rhythm disruption and other cancers, namely endometrial, prostate, colorectal cancers and non-Hodgkin's lymphoma.[12] In their examination of the epidemiological evidence of shift work and chronic disease, which examined existing reviews, Wang

et al. concluded that there was limited and inconsistent evidence for an association for prostate cancer, based on only three studies.[13] They also concluded that the evidence for colorectal cancer and non-Hodgkin's lymphoma was limited and inconsistent. Stevens *et al.* reported that there is mounting evidence from human studies that shift work involving circadian disruption may be an important risk factor for prostate cancer.[6]

A systematic review of circadian disruption and prostate cancer by Sigurdadottir *et al.* concluded that there was an increased risk of prostate cancer, that the association was plausible, and could be due to pilots having more regular health checks, but more research was needed before definitive conclusions could be drawn.[23]

In their review of the state of evidence, Yong and Nasterlack concluded that, aside from two research studies of prostate cancer, little new evidence had emerged since the IARC review for cancers other than breast cancer.[14]

In their book chapter Pan *et al.* reached similar conclusions, that is, that too few studies have been published to reach meaningful conclusions in relation to cancers other than breast cancer.[22] They also suggested that obesity strongly influences endometrial cancer risk in particular so this should be accounted for in future studies.

In their meta-analysis of night shift work and colorectal cancer, Wang *et al.* found an overall raised risk from all studies combined and case-control studies as well as a significant exposure-response relationship.[24] They concluded that the findings were indicative of an association but that further work was needed to confirm the findings.

From these reviews the epidemiological evidence for an association with shift work for colon/colorectal cancer, endometrial cancer and non-Hodgkin's lymphoma is very limited. The evidence is strongest for prostate cancers, with some reviews finding evidence of a statistically significant excess. However, even in these circumstances the authors of the reviews concluded that more evidence was needed before final conclusions could be drawn.

Recent studies of circadian disruption and breast cancer

The IARC working group suggested that a number of domains of a shift and a shift schedule be captured in future epidemiological studies of cancer including:

- Shift system (start time of shift, number of hours per day, rotating or permanent, speed and direction of a rotating system, regular or irregular);
- Years on a particular non-day shift schedule and cumulative exposure to the shift system over the subject's working life;
- Shift intensity (time off between successive work days on the shift schedule.[6]

The studies included in this section are summarised in **Table 4**. Fritschi *et al.*[25] conducted a retrospective case-control study of a priori biologically-based shift work factors and breast cancer. The cases were women aged between 18 and 80 years who had a first incident invasive breast cancer diagnosis between May 2009 and January 2011 identified based on mandatory reporting of invasive cancer by pathology laboratories and other clinical sites. Cases were excluded if their diagnosis was ductal carcinoma in situ or was not primary breast cancer, they previously had cancer, or their diagnosis was more than 213 days before the cancer registry report, leaving 1,205 incident cases included.

Controls were selected during the same time period using the Western Australia electoral roll, and frequency age-matched to the expected distribution of cases. Potential controls with a previous diagnosis of invasive breast cancer were excluded, leaving 1.789 controls included. Further ineligibility criteria for cases and controls included: incorrect address, deceased, too unwell to participate, inadequate English and not resident in Western Australia. Altogether 58% of the eligible cases and 41% of eligible controls consented to participate.

Data collection was in two stages: a questionnaire followed by a telephone interview. The questionnaire collected information on demographic characteristics, reproductive history, family

history of breast cancer and lifestyle factors including physical activity and sleep. They also completed questions to obtain data on circadian phase measurement, amplitude and stability. Participants also provided information retrospectively on each job they had held for at least 6 months. A follow-up interview was allocated to any job in which the women identified that they worked shifts. Questions included: type of roster, whether they worked for any number of hours between midnight and 5 am (graveyard shift). Specific questions were also asked of flight attendants.

The adjusted odds ratio for ever having worked the graveyard shift was 1.16 (0.97 to 1.38, 381 exposed cases). For duration of exposure to graveyard shifts of less than 10 years, the adjusted odds ratio was 1.25 (1.00 to 1.56, 149), for 10 to 20 years was 1.09 (0.79 to 1.50, 98) and for over 20 years was 1.02 (0.71 to 1.45, 84). The p-value for the trend was 0.04, albeit with the risk decreasing as exposure to shift work increased. The odds ratio for ever having been exposed to light at night was 1.15 (0.96 to 1.38, 335), for phase shift was 1.22 (1.01 to 1.47, 309) and for sleep disruption was 1.21 (0.95 to 1.55, 158). This was a well-conducted study with the exposure assessment having a high probability of capturing shift work and it being objectively assessed and meeting most or all of the domains suggested by IARC. Another strength is the number of variables adjusted for in the analysis. It would have been good if the response rate was better and job data were captured by telephone interview rather than the occupational records. The authors concluded that their study needed to be repeated before determining what advice should be given to women around the world who work at night.

Rabstein *et al.*[26] carried out a retrospective population based case-control study in the Greater Region of Bonn in Germany. The study enrolled 1,143 incident breast cancer cases and 1,155 population controls between 2000 and 2004. Response rates for the cases and controls were 88% and 67% respectively. Controls were ascertained from the population registries of the study region and frequency-matched by age. Inclusion criteria were aged $\leq$ 80 years and being of European descent. Incident cases were women with histopathologically confirmed breast cancer diagnosed within 6 months before enrolment. Data on known and suspected risk factors, including a detailed occupational history were obtained by in-person interviews. Information on shift work and hormone replacement therapy was obtained retrospectively by subsequent telephone interview for 957 cases and 892 controls between 2004 and 2007. Shift work was defined as ever having worked in shift or night work for at least one year during the study period. Night work was defined as ever having done shift work and working the full time period between midnight and 5 am. The adjusted odds ratio for ever employed in shift work was 0.98 (0.74 to 1.79, 112 exposed cases) and the equivalent for night shift work was 1.01 (0.68 to 1.50, 55). When split by oestrogen receptor status, these odds ratios were 0.89 (0.65 to 1.22, 77) and 0.98 (0.63 to 1.50, 39) for oestrogen receptor positive women and 1.36 (0.87 to 2.11, 32) and 1.16 (0.62 to 2.18, 14) for oestrogen receptor negative women respectively. Splitting by the number of night shifts worked gave adjusted odds ratios of 0.66 (0.39 to 1.11, 25) for those working <807 nights and 1.78 (0.89 to 3.58, 23) for those working 807 nights or more. Splitting by cumulative number of night shifts with more than 3 nights per month gave odds ratios of 0.80 (0.47 to 1.36, 25) for <1056 nights and 1.66 (0.80 to 3.46, 20) for 1056 nights or more. Examining the data by duration of night shift work in years gave the following odds ratios: >1-<5 years 0.64 (0.34 to 1.24, 15), 5-<10 years 0.93 (0.41 to 2.15, 11), 10-<20 years 0.91 (0.38 to 2.18, 10), $\geq$ 20 years 2.49 (0.87 to 7.18, 12). These latter results were also presented by oestrogen receptor status with the only statistically significant result being for oestrogen receptor negative women with 20 years or more of night shift work when the odds ratio was 4.73 (1.22 to 18.36, 4). This was a well conducted study and is the only study to have recently examined the importance or otherwise of oestrogen receptor status. The data on shift work was not quite as detailed as recommended be collected by the IARC working group. There was however, good control for a number of potentially confounding variables. The authors concluded that their study suggested that long-term night shift work is associated with an increased risk of oestrogen receptor negative breast cancer, and that further studies focussing on breast cancer subtypes are required to discover the putative mechanisms.

Another retrospective population based case-control study, this time by Menegaux *et al.*[27] was conducted in the Côte d'Or and Ille-et-Vilaine departments in France. Eligible cases were women aged 25-75 years, newly diagnosed for breast cancer between 2005 and 2007. All breast cancer cases were confirmed histologically. Of the eligible cases, 1,232 (79%) were included. Controls were selected among general population women free of cancer and resident in the study areas at the time of the cases' diagnoses. Age and socio-economically matched controls were obtained by telephone

dialling on a quota sampling basis. Among the eligible controls, 1,731 (76%) agreed to participate in in-person interviews. A standardised questionnaire was administered to obtain information retrospectively on variables including sociodemographic characteristics, reproduction history, family history and residential and occupational histories. For each job held for at least 6 consecutive months, a description of the work tasks, work places, occupational exposures and work schedules was obtained. Women were asked if they had worked for at least 1 hour between 11 pm and 5 am during all or part of each job. Any night work was characterised with the month and year of beginning and ending, the usual number of nights per week, and the hour when the shift started and ended. Any night work period was categorised as overnight (night shift of 6 consecutive work hours or more spanning 11pm to 5 am), late evening (night shift between 11pm and 3am) or early morning (night shift starting between 3am and 5 am). The adjusted odds ratio for ever worked nights was 1.27 (0.99 to 1.64, 169 exposed cases). For type of night work the odds ratios were 1.25 (0.79 to 1.98, 42) for late evening, 0.90 (0.36 to 2.21, 9) for early morning and 1.35 (1.01 to 1.80, 120) for overnight. Splitting by duration of night work gave an odds ratio of 1.12 (0.78 to 1.60, 66) for < 4.5 years and 1.40 (1.01 to 1.92, 98) for $\geq$ 4.5 years. Splitting by average frequency of night shifts gave odds ratios of 1.43 (1.01 to 2.03, 84) for <3 and 1.14 (0.82 to 1.59, 80) for $\geq$3 nights per week. Splitting duration of night work with overnight shifts gave odds ratios of 1.27 (0.83 to 1.94, 51) for <4.5 years and 1.40 (0.96 to 2.04, 69) for $\geq$4.5 years. Splitting by average frequency of night shifts gave an odds ratio of 1.61 (1.07 to 2.42, 64) for <3 and 1.13 (0.76 to 1.68, 56) for $\geq$3 nights per week. Analyses were also presented that cross-classified duration and frequency of night work and night work with overnight shifts. Neither scenario showed a pattern of increasing risk with increased exposure. This is a well-conducted study. This study, similarly to the previous study, collected data on shift work which were not as detailed as that recommended by the IARC working group, with good control in the analysis for potentially confounding factors. The study would have been further strengthened by the use of a matched case-control design to improve efficiency and to control for unquantifiable factors.[28] The authors concluded that their study supported the hypothesis that night work plays a role in breast cancer, particularly in women who started working at night before their first full-term pregnancy. In the same study population, a paper[29] examining the role of circadian clock gene polymorphisms and with interaction with night work in breast cancer risk gave slightly different risks, with an odds ratio of 1.32 (1.02 to 1.72, 183 exposed cases) for ever having worked nights and 1.42 (1.08 to 1.88, 136) for working nights for 2 years or more compared to working nights for <2 years.

A prospective Swedish cohort study of 4,036 women, for whom it was possible to classify exposure to shift and day work, examined breast cancer incidence in shift workers with and without night work.[30] Women were recruited from different public and private companies in various years between 1992 and 2003. Occupational history of shift work was obtained retrospectively via questionnaire and data on potential confounders was obtained at baseline, start of follow-up. Data on cancer incidence was obtained from the Swedish cancer registry. Analysis via Cox regression was adjusted for number of children and alcohol intake. The hazard ratio for shift without night work versus day work was 1.23 (0.70 to 2.17, 20 exposed cases) and for shift work with night work versus day work was 2.02 (1.03 to 3.95, 14). This is generally a well-conducted study but it isn't clear whether the data collected on shift work met the IARC working group's recommendations, but the analysis controlled well for potential confounding factors. The analysis did not examine exposure-response in any detail. The authors concluded that their findings support previous research reporting an increased breast cancer risk among night shift workers and they could not rule out shift workers without night work also being at increased risk.

A prospective Dutch study in which the study sample comprised women aged 15-64 years from the 14 Dutch Labour Force Surveys from 1996 to 2009 anonymously linked study participants to their hospital admission data, in particular the first hospital admission coded for breast cancer.[31] Coverage for the hospital admission data is thought to be 95% complete. Data in the Labour Force Surveys on shift work were collected via computer assisted personal interviewing. Participants with a paid job for more than 12 hours per week were asked about working at night. Current exposure to work at night was ascertained with the question: "Do you work at night, between midnight and 6 am?" The answers were recorded as "No", "Yes, sometimes", and "Yes, regularly". Additional data collected included country of birth, whether children were resident in the household and educational level. The study included 2,531 cases of breast cancer from hospital admissions data. The hazard ratio for occasional night work was 1.04 (0.85 to 1.27, 102 exposed cases) and for regular night work was 0.87 (0.72 to 1.05). This is a generally well-conducted study, although the data collected on shift work were relatively simple. Exposure-response was examined via job tenure and contractual working hours.

There was good adjustment for potential confounding factors. Although the data on shift work was collected retrospectively it is unlikely to be biased in relation to breast cancer. The authors concluded that their results showed no association of night work with incident breast cancer, and suggested that night work generally does not increase the risk of breast cancer among women in the Dutch working population.

A retrospective population-based case-control study was carried out in 10 Spanish regions.[32] Enrolled in the study were 1,708 incident breast cancer cases diagnosed from 2008 to 2013 and 1,778 population controls. Cases were women aged 20-85 years with a new histologically confirmed diagnosis of breast cancer living in the catchment area of a participating hospital for at least 6 months. Controls were women with no history of breast cancer living in the same catchment area as the cases. The average response rate for cases was 72% and for controls was 52%. Data were collected by face-to-face interviews performed by trained personnel. Lifetime occupational history was assessed retrospectively for all jobs held for at least 1 year. For each job reported, detailed information was collected on job title, main activity or task performed, beginning and end dates, shift type (day, night, rotating), exact time schedules, hours worked and number of night shifts per month. Information on other risk factors was collected including: age, educational level, family socioeconomic level, race, body mass index (BMI), family history of breast cancer, age of menarche (first menstrual cycle), parity, age of first birth, menopausal status, smoking status, oral contraceptive use, history of hormonal replacement therapy and leisure time physical activity. Data on sleep duration and sleep problems was also collected. Diet including alcohol consumption was also collected. Chronotype was assessed through individual follow-up telephone interview. Clinical information was obtained from medical records. In the fully adjusted model, the odds ratio for ever versus never night work was 1.18 (0.97 to 1.43, 270 exposed cases), for permanent nights was 1.19 (0.89 to 1.60, 114) and for rotating nights was 1.17 (0.91 to 1.51, 156). Splitting by cumulative years of night work gave an odds ratio of 1.21 (0.83 to 1.76, 58) for 1-4 years, 1.13 (0.83 to 1.53, 85) for 5-14 years and 1.21 (0.89 to 1.65, 91) for 15 years or more. Splitting by cumulative years of night work for the same categories gave 1.00 (0.59 to 1.66, 34), 1.17 (0.74 to 1.87, 36), and 1.49 (0.88 to 2.53, 27) respectively. For cumulative years of rotating night work for the same categories the odds ratios were: 1.58 (0.94 to 2.66, 26), 0.96 (0.65 to 1.41, 57) and 1.22 (0.82 to 1.81, 54). Splitting by cumulative number of night shifts gave an odds ratio of 1.15 (0.80 to 1.64, 53) for 36-599 nights, 1.20 (0.85 to 1.70, 48) for 600-1799 nights and 1.18 (0.83 to 1.69, 53) for 1800 nights or more. Using the same categories for the number of permanent night shifts gave: 0.96 (0.50 to 1.85, 12), 1.15 (0.65 to 2.04, 11) and 1.48 (0.81 to 2.68, 13). For cumulative number of rotating shifts, the odds ratios were 1.34 (0.77 to 1.67, 12), 1.32 (0.83 to 2.08, 11) and 1.08 (0.66 to 1.79, 15). For morning chronotype ever night work gave an odds ratio of 1.17 (0.83 to 1.65, 76) for neither chronotype 1.17 (0.82 to 1.69, 69) and for evening chronotype 1.27 (0.81 to 2.00, 46). This is a very well-conducted study with data on night work approaching the level of detail recommended by the IARC working group. Exposure-response analysis was reasonably detailed. Occupational histories were not corroborated by employment history data. The authors concluded that having ever performed night shift work was associated with a small increased risk for breast cancer and especially in subgroups of women with particular hormone related characteristics.

A prospective Swedish cohort study examined incidence of breast cancer in members of the Swedish Twin registry.[33] Twins born in Sweden before 1959 aged 41-60 years at the time of the study were included. Participants underwent a computer-assisted telephone interview between 1998 and 2003. The response rate was 74%. Cancer data were obtained by linkage to the Swedish Cancer Registry. The exposed group was those who had worked for 1-45 years in response to the question: “For how many years have you had working hours that meant you worked nights at least now and then.” This group was compared with a group that had not worked nights. Additional data used as covariates were: educational level, tobacco use, alcohol use, physical activity, BMI, having children, coffee use, previous cancer, menopause, and use of hormones including oral contraceptives. The hazard ratio for working nights for between 1 and 45 years was 0.94 (0.73 to 1.22, 109 exposed cases). Splitting this into different categories yielded hazard ratios of 0.92 (0.65 to 1.29, 57) for 1-5 years, 0.79 (0.45 to 1.37, 16) for 6-10 years, 0.77 (0.43 to 1.38, 18) for 11-20 years and 1.68 (0.98 to 2.88, 18) for 21-45 years. This is a well-conducted study, although the data on night shift work falls below the levels recommended by the IARC working group. There was good control for potentially confounding variables. Work history data was available from national records but not details of shift work within jobs. Exposure-response was examined for duration of employment. The authors concluded that

night work is associated with an increased risk of breast cancer in women, but only after relatively long-term exposure.

Li *et al.* conducted a prospective case-cohort study of breast cancer among a cohort of 267,400 women textile workers in Shanghai, China.[34] Women were followed for breast cancer to 2000 by frequent review of factory medical reports submitted by each factory clinician to a cancer and death registry maintained by the Station for the Prevention and Treatment of Cancer. This was supplemented by manual reviews of records from the Shanghai Cancer Registry and a computerised matching with the Registry. All incident cancer cases were reviewed by pathology reports or histological review of tissue slides. A total of 1,763 breast cancer cases were identified and verified. A total of 4,836 controls from two previous case-control studies supplemented by additional controls were used to produce a set of controls with a similar age distribution as the cases. Excluded were 54 cases and 46 controls due to missing data. Job history information was collected from review of factory personnel records, interviews of factory supervisors and in-depth interviews with women or their relatives. For each job, dates of employment, workshop and job tasks were recorded. Each factory had its own history of shift work that was mandated by government policy. These had changed over time, but fairly uniformly across factories within the same sector. Thus data on shift work were collected by major manufacturing processes. No jobs involved exclusively night work and so night work was only considered as part of a rotating shift pattern. Hazard ratios for breast cancer were examined by number of years on rotating shifts with a 20-year lag. The risks were 1.03 (0.89 to 1.20, 516 exposed cases) for >0-12.8 years, 0.90 (0.74 to 1.10, 180) for >12.8-19.9 years, 0.90 (0.74 to 1.10, 179) for >19.9-27.7 years and 0.88 (0.68 to 1.14, 109) for > 27.7 years. The decreasing trend with increasing duration of exposure was statistically significant ($p = 0.035$). For a 10-year lag and 0-year lag, a similar pattern was observed, but they were not significant at the 5% level of significance. A similar pattern was observed for cumulative number of shifts involving night work. Splitting the data into women aged less than 50 and 50 or older showed no trend for the under 50 year olds and a more pronounced decreasing trend with increased duration of employment in those aged 50 or older. This was a very well-conducted study in which shift work data were corroborated with factory records, although the overall data were not as detailed as preferred by the IARC working group. There was good control for potentially confounding factors and a detailed exposure-response analysis. The authors concluded that this study provided no evidence to support the hypothesis that shift work increases breast cancer risk.

An update to the prospective cohort study of 121,701 US female registered nurses aged 30-55 years at enrolment in 1976 looked at mortality.[35] Information on rotating shifts was collected once in 1988 as part of a questionnaire. Participants were asked the total number of years during which they worked rotating night shifts at least 3 nights per month in addition to days or evenings in that month, and so the question didn't distinguish between permanent and rotating night shifts. Compared to the reference of never worked night shifts, the hazard ratio, adjusted for age, alcohol consumption, physical exercise, multivitamin use, menopausal status, postmenopausal hormone use, physical examination in the past 2 years, healthy eating score, smoking, body mass index and husband's education, for 1-5 years was 1.07 (0.90 to 1.26, 293 exposed cases), for 6-14 years was 0.99 (0.76 to 1.27, 79) and for 15 years or more was 0.99 (0.74 to 1.33, 55) the p-value for trend was 0.83. This was a well-conducted study with good detail on shift work albeit below the level of detail suggested by the IARC working group and not corroborated by occupational records. There was good control for potential confounders and examination of exposure-response for night shift work duration. In view of these results, the authors made no reference to breast cancer in their overall conclusions.

When the association between shift work and breast cancer first came to our attention in the early 2000s and in the following decade or do, studies were being conducted that did not have detailed information on shift work and did not control sufficiently for suspected confounding factors. Studies carried out recently, exemplified by those included in this review, have examined shift work in more detail, although many still fall short of the levels recommended by the IARC working group and have usually controlled for large numbers of confounders. Thus, as is typical in occupational epidemiology, the original relative risk appears to have been reduced from around 1.5 to 1.2. This elevation could still be due to uncontrolled confounding, but that now seems less likely than when IARC conducted their review. The epidemiological evidence for a causal association for shift work and breast cancer is stronger now than it has ever been, albeit with the likely level of relative risk much lower than originally observed.

HSE-funded study

During the finalisation of this report, following external peer-review, we became aware that the HSE-funded study of night shift work had been published.[36] The study included 522,246 participants from the Million Women Study[†], 22,559 from the EPIC-Oxford Study[‡] and 251,045 participants from the UK Biobank study[§]; all of which were prospective cohort studies. The paper also contained a meta-analysis of published prospective studies. The response rate for the Million Women Study and the EPIC-Oxford study on questions relating to shift work was over 97%. Analyses were adjusted for economic status, age at menarche, parity and age at first birth, body mass index, alcohol intake, smoking, strenuous physical activity, family history of breast cancer, living with a partner, use of oral contraceptives, and menopausal hormone therapy. In the Million Women Study, there were 4,809 incident breast cancers and subgroups were defined by selected characteristics including diurnal preference, sleep pattern, adiposity, alcohol use, and history of working as a nurse for 10 years or more. The multivariably adjusted relative risk for ever worked night was 1.00 (0.92 to 1.08, 673 ever exposed) and for <10 years of night shift work was 0.93 (0.83 to 1.03, 400), 10-19 years 1.14 (0.96 to 1.35, 140) and 20 years or more 1.00 (0.81 to 1.23, 89) and no significant trend with duration of nigh work (p = 0.68) was found. In EPIC-Oxford, 181 incident breast cancer cases were diagnosed. Compared with women who had never worked night shifts, the multivariably adjusted relative risk was 1.07 (0.71 to 1.62, 28). The multivariably adjusted relative risk in UK-Biobank was 0.78 (0.61 to 1.00, 67).

The meta-analysis identified prospective studies to 2015 and identified 10 prospective studies. The meta-relative risk was 0.99 (0.95 to 1.03). The authors suggested that use of prospective studies was important because it avoided moderate biases that can result from retrospective methodology. The authors' final conclusion was that night shift work, including long-term night shift work has little or no effect on breast cancer incidence.

This publication alters our conclusions in relation to shift work and breast cancer insofar as although the overall evidence (i.e. from prospective and retrospective studies combined) suggests a small increase in relative risk of not more than around 1.2, this may be due to residual confounding and/or exposure misclassification in retrospective studies. We are more inclined to concur with Travis *et al.'s* views that conclusions should therefore be based primarily on results of the prospective studies as they are less prone to bias; and from that viewpoint, we tend to concur also with their conclusion that "night shift work, including long-term night shift work has little or no effect on breast cancer incidence".

Recent studies of circadian disruption and cancers other than breast cancer

A summary of the studies included in this section is contained in **Table 5**. A registry based retrospective case-control study of ovarian cancer was conducted in Washington State in the USA.[37,38] From 2002 to 2005, women aged 35 to 74 years were included and from 2006 to 2009 women aged 35-69 years were included. Cases were identified through a population-based cancer registry, part of the SEER programme of the US National Cancer Institute. Controls were obtained by random digit dialling and were apportioned into age, calendar time and county strata. Job history and other exposure data were obtained by interview for 74% of cases and 78% of controls. For the primary analysis two shift work variables were created: ever/never work any nightshift and cumulative nightshift work-years. Additional factors adjusted for were: duration of hormonal contraceptive use, number of full-term pregnancies and BMI at age 30. Chronotype was additionally examined. Ever working night shifts was associated with a relative risk of 1.24 (1.04 to 1.49, 293 exposed cases) for invasive epithelial tumours and 1.48 (1.15 to 1.90, 126) for borderline epithelial tumours. When examining cumulative nightshift work-years, there were no indications of a trend with either tumour type. In additional analysis risk of invasive and borderline tumours among women who reported ever working a job with less than half of the work days as nights and who reported working a job with all nights were not materially different from the earlier analyses. A greater proportion of evening chronotypes had ever engaged in night shift work compared with morning chronotypes. This is a well-conducted study although the data on shift work is self-reported and not corroborated with occupational records and was not up to the level suggested by the IARC working group. The study

[†] The Million Women Study http://www.millionwomenstudy.org/introduction/ Accessed October 2016

[‡] EPIC-Oxford Study http://www.epic-oxford.org/home/3/second-follow-up Accessed October 2016

[§] UK Biobank https://www.ukbiobank.ac.uk/ Accessed October 2016

design was not matched, but there was good examination of exposure-response and adjustment for potential confounding factors. The authors concluded that they had found evidence suggesting an association between shift work and ovarian cancer.

An analysis of lung cancer in a prospective cohort of 78,612 women with no previous report of cancer from a cohort of 121,701 US female nurses aged between 30 and 55 years at enrolment in 1976 was carried out. Follow up was from 1988 to 2008. Night shift work duration was reported on a 1988 questionnaire.[39] Cases of lung cancer were self-reported and subsequently confirmed from medical records or from death certificates. Night shift work was characterised as at least 3 nights per month in addition to days or evenings in that month. Analysis was via Cox regression and adjusted for smoking status, age started smoking, amount smoked, time since quitted smoking, fruit/vegetable intake, body mass index, use of oral contraceptives or postmenopausal hormones and menopausal status. Compared to never working rotating night shifts, the lung cancer hazard ratio for 1-5 years was 1.03 (0.91 to 1.16, 572 exposed cases), for 6-14 years working rotating night shifts was 0.96 (0.81 to 1.14, 177) and for 15 years or more was 1.28 (1.07 to 1.53, 164). The p-value for trend was 0.03. This was a well-conducted study although shift work was self-reported it was done in the absence of knowledge of health outcomes, albeit without corroboration of occupational records. Shift work data was below the level recommended by the IARC working group. The analysis adjusted for potential confounding factors and exposure-response analysis was undertaken via Cox Regression. The authors concluded that although the finding could be accounted for by residual confounding by smoking, it could also provide evidence of circadian disruption as a "second hit" in the aetiology of smoking-related lung tumours.

Lin *et al*, carried out a prospective cohort mortality study of shift work and pancreatic cancer in Japanese men.[40] The cohort analysed in the study, was based on the Japanese Collaborative Cohort Study (JACC). It began in 1900 enrolling 110,585 people (46,395 men, 61,190 women) from 45 areas throughout Japan. Participants were aged 40 to 70 at baseline. A self-administered questionnaire was completed at baseline that included questions on demographic characteristics, family history of cancer, medical history, occupation and lifestyle factors. Pre-coded options were made available to facilitate responses. Follow-up continued until 2009. The present analysis was restricted to men who were aged 40 to 65 and who reported working full time or part time at baseline. After excluding men with missing data on occupation and those with a history of cancer, 22,224 men were included in the analysis. Shift work data was collected based on the question: "Which form of work schedule have you engaged in for your longest occupation?" Men were asked to indicate the most frequent schedule that they had undertaken among three work schedules: fixed daytime work, fixed night time work, or rotating shift work. Information was collected on other covariates including age, height, weight, medical history, family history of cancer, smoking status, alcohol consumption, job type, physical activity at work, whether workplace was indoors or outdoors, level of perceived stress, educational level and marriage status. Relative risks were estimated using Cox proportional hazards modelling and were adjusted for potential confounding factors. Using daytime work at the baseline, the relative risk for fixed night time work was 0.61 (0.22 to 1.60,5) and for rotating night work was 0.83 (0.43 to 1.60, 11). The authors acknowledged that their assessment of shift work was crude, lacking information on duration. They concluded that their study did not provide evidence that shift work increases the risk of pancreatic cancer mortality.

A Spanish retrospective population-based case-control study examined the risk of prostate cancer in cases aged 27 to 85 years.[41] All cases had a new histologically confirmed diagnosis from 2008 to 2012 and lived in the catchment area of each hospital for at least 6 months prior to diagnosis. Control subjects were men free of prostate cancer history living in the same catchment area as the cases. Controls were selected randomly from the rosters of General Practitioners and the primary health centres and were frequency-matched to cases by age and study area. In total 74% of cases and 54% of controls completed a face-to-face interview leaving 1,095 cases and 1,388 controls. Lifetime occupational history was assessed for all jobs held for more than a year. Detailed questions were used to ascertain information on shift work for each job, including type of shift work, beginning and ending year, time schedules, hours worked per day, job title and workers activity. Information was also collected on other potential risk factors such as age, educational level, family socioeconomic level, race, BMI, family history of prostate cancer, smoking status, leisure time physical activity and diet. A follow-up telephone interview was conducted to collect missing information on jobs with rotating night shift work and chronotype. Night shift work was defined as a working schedule that involved working partly or entirely between midnight and 6 am at least 3 times per week. The

adjusted odds ratio for ever worked nights versus never worked nights was 1.14 (0.94 to 1.37, 362 exposed cases). For permanent night work this was 1.10 (0.85 to 1.43, 156) and for rotating night work was 1.16 (0.92 to 1.46, 206). Splitting ever night work into cumulative duration in years resulted in odds ratios of 1.10 (0.83 to 1.45, 128) for 10 years or less, 0.94 (0.69 to 1.27, 92) for 11-27 years and 1.38 (1.05 to 1.81, 138) 28 years or more. Looking in terms of number of night shifts gave the following: 1.03 (0.75 to 1.42, 85) for less than 1153 nights, 1.09 (0.78 to 1.52, 71) for 1154 to 2856 nights and 1.30 (0.97 to 1.74, 100) for 2857 nights or more. In relation to chronotype, the odds ratios for ever working nights were 1.14 (0.87 to 1.51, 152) for morning chronotypes, 1.02 (0.72 to 1.44, 90) for neither chronotype and 1.50 (0.85 to 2.66, 49) for evening chronotypes. This is a well-conducted study albeit relying on self-reported shift work, the level of which is below that recommended by the IARC working group. Unconditional logistic regression was used for the analysis in which exposure-response was examined with good adjustment for potential confounding factors. The authors concluded that the overall risk was higher among subjects with evening chronotype, but also increased in morning chronotypes after long-term night work and that they found an association between night shift work and prostate cancer, particularly for tumours with worse prognosis.

Carter *et al.* published an analysis of circadian disruption and ovarian cancer in 161,004 women from the American Cancer Society CPS-II prospective cohort mortality study.[42] Women were excluded if they reported any of the following at baseline: prevalent cancer other than non-melanoma skin cancer, history of ovarian surgeries or hysterectomies, missing menopausal status or artificially-induced menopause, missing data on shift work or were unemployed. The participants were asked: "Do you work rotating shifts?" and "What time of day do you start working?" Rotating schedule workers were those who self-identified as so. All other workers were considered to work fixed schedules: daytime (start between 6 am and 10 am), afternoon/evening (2pm to 4pm) and night (9pm to midnight). Data were also collected on average sleep duration and frequency of insomnia. Statistical modelling adjusted for race, family history of breast or ovarian cancer, age at menarche, menopausal status, age at menopause, age at first birth, parity, duration of oral contraceptive use, postmenopausal oestrogen use, and previous tubal ligation. Included were 1,289 deaths from ovarian cancer. Compared to fixed daytime work, a rotating schedule was associated with an elevated risk of fatal ovarian cancer: relative risk 1.27 (1.03 to 1.56, 101 exposed cases) and fixed night shifts had a relative risk of 1.12 (0.67 to 1.87, 15). No significant associations were observed for sleep duration or insomnia. This was a well-conducted study with self-reported shift work, analysis of exposure-response and analysis that included adjustment for potential confounding factors. The authors concluded that the associated required further examination in other studies.

Gapstur *et al.* conducted a study of work schedule, sleep duration, insomnia and risk of fatal prostate cancer[43] using the same CPS-II study as Carter *et al.*[42] Men were excluded from the analysis if: they reported a history of cancer other than non-melanoma skin cancer, reported no current occupation, didn't answer the shift work question; or didn't state when they started work. A total of 305,057 men were included in the analysis. The statistical analysis adjusted for age, race, education, BMI, smoking history, family history of prostate cancer, and frequent or painful urination. The relative risk for rotating shifts versus fixed day shift was 1.08 (0.95 to 1.22, 268), for fixed afternoon/evening shift was 1.27 (0.97 to 1.65, 55) and for fixed night shift compared to fixed day was 0.72 (0.44 to 1.18, 16). This too was a well-conducted study with the same reasons as the paragraph above, with the additional limitation of only dealing with fatal cancers. Thus the authors concluded that work schedule was not associated with risk of fatal prostate cancer.

Carreón *et al.* conducted a retrospective cohort study of 1,874 workers at a chemical plant employed at some time during 1946 to 2006 who were exposed to vinyl chloride, carbon disulphide and/or o-toluidine.[44] Follow-up was from 1960 to 2007. The plant operated 24 hours a day and a large proportion of workers were in a forward rotating shift work schedule. It is assumed that jobs could be separated into shift or day schedule, but this is not explicitly stated. Mortality from non-Hodgkin's lymphoma was examined in relation to shift work. The standardised mortality ratios for duration of shift work were 2.59 (0.53 to 7.56, 3 cases) for zero duration of exposure, 2.22 (0.46 to 6.48, 3) for worked shifts for less than 1 year and 2.37 (0.77 to 5.52, 5) for worked shifts for 1 year or more. The standardised rate ratios with never worked shift as the baseline were 0.41 (0.08 to 2.08) for less than 1 year working shifts and 0.61 (0.14 to 2.61) worked 1 year or more. The p-value for trend was 0.93. Although a well-conducted study, the data on shift work seemed a little vague and not at the level of detail suggested by the IARC working group and the number of cases involved was relatively small.

Duration of working shifts was examined, but there was limited adjustment for potential confounding factors. The authors concluded that non-Hodgkin's lymphoma risk was not increased in this cohort.

Hammer *et al.* examined the risk of prostate cancer in a retrospective cohort of industrial workers.[45] The cohort consisted of 27,828 male production workers residing in the German federal state of Rhineland-Palatinate who worked for at least 1 year between 1995 and 2005 in a chemical company. Data on shift work and potential confounders such as age, occupational task, and duration of employment were obtained from personnel files. Work schedule was known for all employees. New cases of prostate cancer diagnosed in 2000-2009 were obtained from the state cancer registry. There were 146 new cases of prostate cancer in 12,609 rotating shift workers and 191 in 15,219 daytime workers. Follow-up for mortality was over 90%. The shift workers did not have an elevated hazard ratio for prostate cancer in comparison with daytime workers RR = 0.93 (0.73 to 1.18, 337 cases). Both groups of workers had a higher incidence of prostate cancer than the general population: SIR = 1.44 (1.22 to 1.70, 146) for daytime workers and 1.51 (1.30 to 1.74, 191) for shift workers. This is a well-conducted study with objective data on shift work, albeit at a level below that recommended by the IARC working group. Exposure-response was examined in relation to duration of employment and there was limited ability to adjust for potential confounding factors. The authors concluded that the incidence of prostate cancer did not differ between shift workers and daytime workers, but that further follow-up of the relatively young cohort was required.

A retrospective case-cohort study of night shift work and lung cancer risk in female textile workers was carried out in Shanghai, China.[46] The cohort consisted of 267,400 workers and the case-cohort analysis contained 1,559 lung cancer cases and 3,199 women randomly selected from the parent cohort as non-cases. Cancer incidence in the parent cohort from 1989 to 1998 was identified through the local cancer and death registry. Cancer incidence from 1999 to 2006 was obtained from the Shanghai cancer registry and lung cancer diagnosis confirmed by medical record review. Shift work policies were available for all factories and although they changed over time, they did so uniformly across all 526 factories. Historical shift work profile was obtained for the vast majority of factories. There were no jobs that were exclusively night jobs. The most common shift cycle consisted of two consecutive days (6 am to 2 pm) and then two consecutive evenings (2pm to 10pm). The analysis adjusted for age, smoking status, parity and cumulative endotoxin exposure. Hazard ratios were calculated for zero, 10 and 20 year lags. The relative risks for the 10-year lag for cumulative years of rotating night shifts were 0.76 (0.63 to 0.93, 280 exposed cases) for >0 to $\leq$17.1 years, 0.90 (0.73 to 1.10, 260) for 17.1 to $\leq$24.9 years, 0.95 (0.77 to 1.18, 244) for 24.9 to $\leq$30.6 years and 0.82 0.66 to 1.03, 253) for >30.6 years. There was no significant trend in the hazard ratios (p = 0.277). This is a well-conducted study with shift work data obtained from occupational records, but not as detailed as recommended by the IARC working group. Exposure-response was examined in relation to cumulative years and numbers of night shifts worked, but there was limited adjustment for potentially confounding factors. The authors concluded that rotating night time shift work appears to be associated with a relatively reduced lung cancer risk although the magnitude of the effect was modest and not statistically significant.

An update to the prospective cohort study of 121,701 US female registered nurses aged 30-55 at enrolment in 1976 looked at mortality.[35] Information on rotating shifts was collected once in 1988 as part of a questionnaire. Participants were asked the total number of years during which they worked rotating night shifts at least 3 nights/month in addition to days or evenings in that month, and so the question didn't distinguish between permanent and rotating night shifts. Aside from breast cancer, results adjusted for the same factors mentioned in the breast cancer section, were also presented for lung, ovarian, pancreatic, and colorectal cancers, as well as for non-Hodgkin's lymphoma. None of the findings showed any evidence of an excess risk or trend with duration of exposure apart from lung cancer for which the p-value for trend was 0.05 due to the hazard ratio in the 15 years or more category being 1.25 (1.04 to 1.51, 150 exposed cases). This was a well-conducted study with shift work data based on self-reports only, albeit in advance of outcome data. It is at a level that recommended by the IARC working group. Exposure-response was examined by Cox regression with good adjustment for potential confounding factors. The authors concluded that those working 15 years or more of (rotating) night shift have a modest increase in lung cancer mortality.

A prospective population-based cohort study of biliary tract cancer in Japanese men examined the association between working rotating shifts and the risk of death.[47] Of the 46,395 men included in the Japanese Collaborative Cohort Study, 22,224 were included in the analysis. The men were aged 40

to 65 years at baseline (1988-1990) and followed up to the end of 2009. Information on shift work was collected on the basis of the question "Which form of work schedule have out engaged in for your longest occupation?" Men were asked to indicate the most regular schedule they had undertaken among three work schedules: daytime work, permanent night time work or rotating shift work (which may or may not involve night work). Cox regression was used to estimate hazard ratios adjusted for age, body mass index, history of cholelithiasis (presence of gallstones in the bile duct). History of diabetes, alcohol consumption, cigarette smoking, sleep time, and perceived stress. Compared to daytime work the hazard ratio for biliary tract cancer for permanent night time work was 0.86 (0.31 to 2.36, 4 deaths) and for rotating shift work was 1.50 (0.83 to 2.77, 12). For extrahepatic bile duct cancer the hazard ratio for night time work was 1.19 (0.43 to 3.31, 4) and for rotating shift work was 1.93 (1.00 to 3.72, 11). This was a fairly well-conducted study in which shift work was self-reported from a choice of one shift work category. There was good adjustment for potential confounding variables although exposure-response analyses were limited by the quality of the shift work data and there were relatively few cases. The authors concluded that there may be an increased risk of death from extrahepatic bile duct cancer in the cohort.

Whilst these recent studies provide a little additional evidence for an association for prostate cancer and for ovarian cancer, overall the epidemiological evidence for an association between shift work and cancer other than breast cancer is somewhat limited.

Mechanistic studies

Assuming the association is causal, to enable reliable interventions to reduce the cancer risk from working at night it may be helpful to understand something of the disease causation mechanisms. Should an association between night shift work and breast cancer be established, it would be unrealistic to ban women from working at night but it may be acceptable to advise on modifying other established environmental or lifestyle breast cancer risk factors to reduce risk. In this section we summarise the key causal mechanisms that have been hypothesised and evaluate the evidence to support each.

The IARC Working Group Source[2] highlighted two mechanisms that may be involved in causing cancer: first, that exposure to light at night suppresses the production of the hormone melatonin and, secondly, that epigenetic changes in the genes that control circadian rhythm may promote cancer risk, for example inactivation of circadian PERIOD genes.[5] The Working Group further cited the association between sleep deprivation and the suppression of natural killer (NK) cells, which have been shown to have the ability to kill tumour cells.[48]

Fritishi[49] discuss other possible mechanisms for causation of breast cancer from shift work: phase disruption, sleep disturbance, reduced synthesis of vitamin D because of lower exposure to sunlight for nightshift workers and lifestyle factors such as poor diet. It is plausible that all of these putative mechanisms may be associated with each other and so while the biological process involved may be different it could be difficult, in practice, to disentangle them in an epidemiological study.

Melatonin, which is produced in the pineal gland acting via the suprachiasmatic nucleus, varies rhythmically throughout the day, regulating the expression of clock genes and promoting the onset of sleep. Autonomous circadian clocks, also controlled by the suprachiasmatic nucleus, are also present in cells in peripheral tissues.[50] Exposure to light during the 'biological night' supresses the production of melatonin and it has been hypothesised that this may increase the risk of breast cancer. Animal experiments have fairly consistently shown that melatonin can inhibit the growth of mammary tumours.[51,52] Blask[53] was the first to clearly demonstrate in an animal model with human breast cancer xenografts that increasing intensities of light during each normal dark period produced a dose-related suppression of nocturnal melatonin levels in the blood and a stimulation of tumour growth. It was originally argued that in women, lower circulating melatonin levels might cause or be associated with higher oestrogen concentrations[49], but it is clear that the mode of action would likely have to be more complex and, for example, Langley *et al.*[54] found no association between melatonin and sex hormone levels in a population of nurses working rotating shifts.

Melatonin is known to inhibit the proliferation of human breast cancer cells.[55] More recently, melatonin has been shown to induce programmed cell death (apoptosis) in a wide range of different tumours, including breast cancer.[56] It has an antioxidant effect that frustrates tumour initiation.[57] However, a

decrease in melatonin levels also affects the endocrine producing cells in the gonadotropic axis resulting in increased circulating oestrogen concentrations, which over a lifetime is a risk factor for breast cancer.[57] Support for a role of melatonin in carcinogenesis is provided from studies showing the tumour promoting effects of removing the pineal gland in experimental animals.[58] Hill *et al.*[59] argues that the available data provides the 'strongest understanding and support for the mechanisms underpinning the epidemiological demonstration of elevated breast cancer in night shift workers'.

The scientific evidence is mixed as to whether circulating melatonin is reduced in night shift workers. The main urinary metabolite of melatonin is 6-sulfatoxymelatonin (aMT6s) and it has been shown to be decreased in night shift workers during the night compared to dayshift workers and to remain decreased on days when nightshift workers slept at night.[60] Bhatti *et al.*[38] also found decreased aMT6s concentrations in night shift workers, but noted that the difference between day and night shift workers was smaller amongst workers of Asian origin compared to white race workers. For nurses working on a rotating shift schedule there was a similar pattern of melatonin production regardless of whether working days or nights.[61] In addition, in this study illuminance was only weakly associated with reduced urinary melatonin levels (range <1 to 20 lux). The authors suggest that the rapidly rotating shift pattern investigated (two 12-hour days, two 12-hour nights, 5 days off) or exposure to low light levels while working at night may not importantly disrupt melatonin synthesis.

Basler *et al.*[62] carried out a meta-analysis of five prospective case-control studies of breast cancer where there were measurements of a urinary metabolite of melatonin. Overall there was a statistically significant reduced risk of breast cancer amongst the women in the highest quartile of exposure compared to those in the lowest quartile, with a 2-year time lag between the measurement of melatonin and the cancer diagnosis. However, in a large cohort of US nurses[63] a nested case-control study involving 600 breast cancer cases and 786 matched controls was used to investigate the association between aMT6s and cancer risk. Most of the cases were premenopausal cancers. Melatonin metabolite concentrations were not significantly associated with total breast cancer risk, and further investigation of the time between sample collection and diagnosis showed no effect on the risk estimates. Other epidemiological studies where melatonin had been measured have produced mixed results in terms of association with breast cancer risk.[63]

Further supportive evidence of the possible role of melatonin is provide by Pukkala *et al.*[64] who investigated the risk of cancer with visual impairment, and showed that breast cancer risk in women decreased with the degree of visual impairment, with blind women having about two-thirds the risk of women with good sight. There was a similar although less consistent trend in risk for prostate cancer in men. Flynn Evans *et al.*[65] found a significantly lower prevalence of breast cancer in blind women with light perception than in blind women who could not perceive light (odds ratio 0.43; 95% confidence interval, 0.21–0.85). The increased risk of breast cancer amongst female flight attendants has been seen as supportive of a causal role of chronodisruption, but this group have several other risk factors for breast cancer, e.g. higher nulliparity, alcohol consumption, taller size, that could explain at least part of this observed risk.[66] Also, a recent study of US flight attendants found no association with flight-related circadian-disruption exposures and this study concluded that the risk excess appeared to be largely explained by differences in parity and age at the birth of the woman's first child.[67]

Erren and Reiter[68] highlight that individual tendency to be awake or asleep is determined by both generic (a polymorphism in the PER3 gene appears to be associated with those who have preference for being awake in the evenings) and environmental factors such as age, sex, use of stimulants such as caffeine, use of electronic screens during the evening, and outdoor electric lighting.[69] Personal factors are often used to categorise people into three different 'chronotypes': early types (larks), normal types, and late types (owls). They argue that shift workers who work at times that mismatch their chronotype will suffer greater health impact than those whose chronotype matches their schedule. Hansen and Stevens[70] showed in a nested case-control study that women who were classed as a morning-type and worked a high number of night shifts (more than 884 shifts cumulatively) had the highest risk (odds ratio 3.9 with confidence interval 1.6 – 9.5, compared to morning types who did not work nights). The risk for women who were evening types was not significantly raised, even amongst those with the highest cumulative exposure (odds ratio 2.0, CI 0.7 – 5.8). The risk for evening types was lower and there was no observed increase in risk for women who were classed as 'normal' types. The authors argue that if chronotype is confirmed as a risk for breast cancer in night shift workers then this should be used in selecting people for night shift work.

Hoffman *et al.*[71] report statistically significant associations between single nucleotide polymorphisms associated with the CLOCK genes and breast cancer risk, which were modified by oestrogen receptor/progesterone receptor (ER/PR) status. Where there was more than one risk allele present the risk was only significantly increased in those with positive ER/PR status. Zienolddiny *et al.*[72] , in a large study of Norwegian nurses, showed that in women with long-term working for three consecutive night shifts, the risk of breast cancer was reduced in those with some variant alleles of CLOCK, PER3 and several other genes or melatonin signalling pathways. However, the associations were not reproducibly found in women who had worked four on more consecutive nights. Zhu *et al.*[73] identified that long-term shift work exposure promotes hypomethylation of CLOCK and hypermethylation of CRY2 genes. In a small study (10 day workers and 10 long-term shift workers), Shi *et al.*[74] identified circadian-relevant epigenetic changes in shift workers. They argue that these changes suggest that long-term night shift work results in down-regulation of miR-219, which may result in the down-regulation of immunomediated antitumor activity and an increase in breast cancer risk. While these studies add some support for the causality of night work for breast cancer they shed little light on the causal mechanism.

Shorter sleep duration is common amongst night shift workers, although sleep duration is not clearly related to circulation melatonin concentrations.[49] In recent research studies and a meta-analysis of sleep duration and cancer risk there was no evidence that short duration of sleep was associated with an increased risk of breast cancer.[75,76] Similarly, Qian[77] found no association between self-reported sleep duration and breast cancer overall, but identified a significantly reduced risk for oestrogen positive (ER+) and progesterone positive (PR+) receptor breast tumours for short sleep duration. This pattern is contrary to what would be expected if the risk was linked to melatonin status and shift work, and the results have been criticised because of potential bias in the exposure measurements. Hurley *et al.* [78] in a study of over 100,000 Californian teachers, found that compared to average sleepers, long sleepers (10+ hours per night) had a small increase in risk for the group of oestrogen-mediated cancers that included breast cancer, but no increased risk amongst short duration sleepers (<6 hours). Overall, there is little persuasive evidence for shorter sleep duration being an important cause of increased breast cancer amongst shift workers.

An IARC working group has considered the evidence for a causal link between vitamin D status and cancer.[79] From a meta-analysis of observational studies they found a risk of colorectal cancer and colorectal adenoma with low serum 25-hydroxyvitamin D (25(OH)D) levels. However, there is no conclusive evidence to suggest that vitamin D is involved in breast or prostate cancer aetiology. Subsequently, Bauer *et al.*[80] carried out an exposure-response meta-analysis of prospective epidemiological studies to assess the association between circulating 25(OH)D and breast cancer risk, stratified by menopause status. They found no association for premenopausal women, but amongst postmenopausal women there was a decreased risk of breast cancer for those with 25(OH)D levels above about 30 ng/ml. There was no apparent increased risk for those with low vitamin D status. Wang *et al.*[81] carried out a similar meta-analysis using data from prospective cohort and nested case-control studies. They also did not find any risk associated with 25(OH)D in premenopausal women, but they showed that in postmenopausal women each 10 ng/ml increase in circulating 25(OH)D concentration was associated with a statistically significant 3.2% reduction in breast cancer risk. Ward *et al.*[82] investigated the association between working patterns and vitamin D status in over 6,000 adults in Britain at age 45 years. They found 25(OH)D concentrations were 8% lower in female night workers compared with others (equivalent to a difference of 1.7 ng/ml), but there were no statistically significant differences between male day and night workers. A recent review and meta-analysis of randomised controlled clinical trials provided no evidence that vitamin D supplementation reduced the risk of breast cancer in postmenopausal women.[83] Based on the available evidence it seems unlikely that low vitamin D status from night shift work is an important risk factor for breast cancer.

It has been argued that shift working can promote stress, fatigue, physiologic dysfunction, and poor health choices such as smoking, increased alcohol consumption, lack of exercise and poor diet.[84,85] In addition, the timing of eating may affect the ability of the body to metabolise the food, with gain in body weight being greater when food was available in the evenings compared to mornings. Several studies have shown that shift workers are more likely to be obese than other workers[86-88] and obesity is a risk factor for postmenopausal breast cancer and is associated with poorer outcomes for this disease. Disruption of peripheral circadian clocks may be linked to the development of obesity because of the effect on metabolism[88,89], e.g. food consumed between midnight and 6am may be less

effectively metabolised. Consumption of alcohol is causally associated to pre- and post-menopausal breast cancer, including at low intake levels, e.g. around 10g alcohol equivalent to 1–2 drinks per day. It has been suggested that the critical risk period may be during early life and the pattern of consumption may be important, with one epidemiological study reporting that binge drinkers had an increased relative risk for breast cancer compared to other women of 1.33.[90] Active smoking, particularly amongst women who start before the birth of their first child, is also associated with increased risk of breast cancer.[91] Women who have worked night shifts are more likely to have used oral contraception and hormone therapy for the menopause[92], which may also increase risk of breast cancer.

Overall, the most likely candidate causal mechanism for breast cancer amongst female night shift workers is suppression of melatonin production due to exposure to light at night. However, other direct or indirect processes may be involved, particularly the tendency for shift workers to be overweight or obese.

Findings from the papers relating to health and safety

Potential Interventions

Within the research identified for this review a number of different interventions have been suggested and are presented below (full list in

Table 6). The interventions are discussed in relation to the current evidence available and where possible their feasibility in the workplace.

Melatonin

As identified in the review of mechanisms, melatonin has been implicated in the causal pathways relating to breast cancer. A number of potential interventional approaches have been suggested as a result of this.

The phase-shifting and sleep promoting effects of melatonin are not totally understood, but measurement of serum levels of melatonin shows a circadian rhythm with the highest plasma levels reported between three and four am. Boivin *et al.* identified that oral supplements of melatonin can be used to promote daytime sleep and this effect was greater in participants with difficulties in getting to sleep.[93] However, this effect is only found when internal melatonin levels were low. Additionally, studies in shift workers did not see an improvement in daytime sleep quality when melatonin was administered.[93-95] Thus the use of supplemental melatonin to improve daytime sleep quality in night workers does not seem to be an effective method, based on the studies to date, especially as there is still a lack of understanding of effective dosage in such workers or the safety of such an intervention and possible long-term health consequences.[95]

Exposure to light at night does cause disruption to melatonin levels. This can be seen as a positive in relation to those working night shifts where reduced melatonin levels were measured and daytime sleeping was improved.[93] There appear to be two schools of thought in relation to bright light at work for those working night shifts. The first is to filter the shorter light wavelengths out (below 540 nm) to counteract melatonin suppression.[93,95] Alternatively, Fritschi suggests the use of blue lamps causes melatonin suppression.[96] Further research is required to identify which is less damaging to the individual; attempting to cause a phase-shift in melatonin production, which may reduce sleepiness at work, or allowing the melatonin cycle to continue without disruption. Where there is consensus in relation to light exposure, is to try and reduce exposure to light on completion of the shift and in the sleeping area by using dark glasses and blackout blinds.[95-97]

Although melatonin has been implicated in the mechanism of shift work and breast cancer, there is still limited knowledge of what is preferable in relation to either phase-shifting the melatonin cycle or trying to prevent disruption of the melatonin cycle. Phase-shifting may reduce sleepiness while at work, and through this decrease accident risk, there is no guidance available at the current time in relation to safe dosage of melatonin. However, other suggestions of reducing illumination levels to keep the melatonin cycle in place do bring other hazards such as reduced visibility in the workplace and increased sleepiness.

Shift Design

In the last 40 years there has been a large body of research carried out in relation to the design of shift systems to promote safe and healthy work; although this has not been in relation to the prevention of workplace cancer. Those research studies that have considered shift design in relation to cancer have examined this from a more theoretical standpoint in relation to the potential mechanisms of cancer from shift work.

Fritschi identified that there is no simple solution when designing shift work due to the differences that individuals have in response to sleep loss, sleep disruption and for some, transition across time zones.[96] There does appear to be consensus in relation to trying to minimise the impact of shift work on circadian disruption.[94,98] Thus in trying to avoid internal desynchronisation, no more than 4 night shifts at a time should be scheduled.[94]

Reed highlights the importance of trying to minimize circadian disruption.[98] Grundy *et al.* suggest that the rapidly rotating shift pattern investigated (two 12-hour days, two 12-hour nights, 5 days off) or exposure to low light levels while working at night may not importantly disrupt melatonin synthesis.[61]

It is not just the timing of the shifts in a rotating system that are important, it is also important to consider the length of shifts and the break allowance within each shift.[96] These should be designed to allow task recovery within each shift as well as time for recovery between shifts.

Yong and Nasterlack suggested that measures to counteract the negative effects of shift work are more "eminence-based" than "evidence-based".[14] Their recommendations including selecting individuals who are more tolerant to shift work as well as using systems that are forward rotating (morning, afternoon then night shift). Erren *et al.* suggest that prevention of chronodisruption could be achieved by simply asking individuals "Compared to other people, how would you rate your coping with transmeridian travel and or shift work?".[9]

Shift schedules can probably be organised in ways that aim to minimise the associated health risks. A number of authors recommend the use of fast forward rotating shift systems,[12,14] with no more than one or two subsequent nights shifts can be supported on the basis of our experience.[14] In addition, the length of shift time and the breaks allowed within the shift can also be an important influence on health and wellbeing.

Cancer Screening

Tsai *et al.* examined adherence to breast, cervical and colon cancer screening by women who worked shifts other than day shifts.[99] In a sample of 9009 females adherence to screening tests was evaluated for workers aged 50-74 for breast cancer; 21-65 years for cervical cancer and 50-75 years for colorectal cancer. Participants were interviewed and a description of the hours they worked was obtained. The analysis identified that workers on alternative shifts were 35% ($p<0.001$) more likely to be non-adherent to breast cancer screening and 10% ($p<0.05$) for colorectal cancer screening. No significant differences were identified for cervical cancer screening but this was a younger population.

The paper by Tsai *et al.* broke the data down into different sectors and identified that those employed on alternative shifts in manufacturing; health and social care; arts, entertainment and recreation; hotel and food services; food preparation and service; office and administrative support; production and personal care were significantly more likely to not adhere to breast screening recommendations.[99] The study also considered confounding and interaction between risk factors and adherence to screening. For colorectal cancer screening, those employed on alternative shifts in manufacturing, hotel and food service, transportation and material moving, food preparation and servicing and production were more likely to be non-adherent to screening.

These data are important in highlighting that for individuals not working day shifts and in particular sectors do not adhere to cancer screening regimes. There may be several reasons for this including ability to access services when not working. Thus improving access to screening services, perhaps facilitated by employers, would appear to be an obvious solution.

There has been discussion about the use of screening tests including mammography for breast cancer and an IARC Working Group confirmed that for women aged 50 to 69 years that remains a net benefit in attending screening sessions.[90] As a result of this the employer could play a role in encouraging employees to attend screening sessions. Further considerations should be made for those who are at a genetically increased risk of breast cancer.

Pharmacological interventions

A number of pharmacological interventions have been suggested to improve wakefulness and reduce accidents. Boivin *et al.* examined the use of psychostimulants (modafinil) to reduce sleepiness in 209 workers.[93] This study found that there were improvements in subjective and objective measurements of sleepiness, and increased sleep latency compared to the placebo group. Caffeine as a stimulant has also been examined by taking before the onset of night work. Boivin *et al.* identified that having a nap before starting a night shift and taking 300 mg of caffeine improved performance on vigilance tasks. However, day time sleep length was reduced because of the nap.[93]

The use of hypnotics such as benzodiazepines as a means of improving daytime sleep was also reported.[93,94] The use of temazepam was found to increase the length of daytime sleep but compared to controls, the differences became smaller as the number of night shifts increased; possibly due to adaptation of the sleep cycle in the control group.[93] However, before using such drugs medical assessment of the severity of sleep problems must be carried out.

At this juncture, the use of pharmacological intervention has been limited and although does show some potential, the benefits and potential costs of such pharmaceutical interventions must be properly evaluated.

Lifestyle, diet, health and wellbeing

The review by Antunes *et al.* identified that being overweight or obese is more prevalent in shift workers when compared to day workers.[88] Furthermore, there is evidence that shift workers gain weight more often than day workers. The review focuses on the fact that there is evidence to show that shift work is associated with an increased risk of obesity, diabetes and cardiovascular disease. There may be dietary advice required by shift workers but understanding the reasons why shift workers gain more weight may allow a better understanding of the impact of shifts on metabolism. As mentioned previously (mechanistic section), the timing of eating may not coincide with the ability to metabolise food e.g. food consumed between midnight and 6am may be less effectively metabolised. As obesity is a risk factor for postmenopausal breast cancer, managing weight must be a concern for those managing shift workers.

In conclusion, those involved in night work and their employers need further evidence and advice on diet, time of eating, lifestyle behaviours and sleep hygiene. The importance of health surveillance and health promoting activities have been highlighted by a number of authors.[12,14] As Pan *et al.* points out, there has been no high quality evaluation of these interventions in relation to the health of shift workers including any potential cancer risk.[22]

Strategic Napping

Two papers within the review examined napping when working shifts as a means of improving alertness. Boivin *et al.* describe these as prophylactic naps (naps taken prior to night shifts) and recuperative naps (those taken during night shifts).[93] Prophylactic naps have the potential to counteract sleep deprivation and have been found to improve alertness during work time.[93] However, consideration has to be made of the negative impact that napping can have when awakening from sleep and “sleep inertia”, in situations where immediate wakefulness is required, the potential hazard from sleep inertia should be evaluated.

Bracci *et al.* examined the impact of recuperative napping on nurses working night shifts.[100] Measurement of urinary melatonin and 17-β-estradiol found that 17-β-estradiol levels were higher in participants who did not nap during night shifts. Although this was a small study it may indicate that napping should be encouraged where possible on night shifts.

While napping can be used to reduce sleep debt in a 24-hour period, this is not always going to be a solution in all workplaces.

Reducing exposure to night work

There appears to be an exposure-response effect relating to the cumulative years of work occurring within the research reviewed. If this is confirmed by future research it indicates that individuals may well be advised to restrict night working after a specific time period has elapsed. At the current time an exact figure cannot be given but in line with other research in relation to different health risks including cardiovascular disease and gastro-intestinal ill health and age, night work after 50 years of age should be limited.

Employer and Worker Education

In relation to workplace hazards, there is a duty of care in relation to exposure to hazards and risk reduction measures. Shift work and night work can be considered a hazard and as such health screening has to be provided to individuals who work nights in the UK. This is described as a free health assessment that must be carried out at regular intervals. In supporting the health and wellbeing of night workers it is important that structured and sustained health promotion programmes specifically tailored to night workers are provided.[14]

Review of guidance identified in review process

A number of guidance documents were identified as part of the data gathering stage of this review (see **Table 7**). The guidance provided on the whole does acknowledge the potential link between shift and night work and cancer. However, at the current time very little information is provided in relation to prevention. This is because the mechanisms behind shift work and cancer are not thoroughly understood, although the melatonin pathway does appear to be the most feasible. What the guidance does provide is information on other health aspects including health assessments, maintaining good health behaviours and the importance of risk assessments by employers. It is hoped that maintaining health and wellbeing in this occupational group that levels of other cancer risk factors (such as obesity or smoking) can be reduced.

Current and future research on shift work and cancer

The response to our enquiries of prominent researchers and funding institutions are set out in Appendix 1.

Most of the responses drew our attention to recent published work which is also listed in the appendix. Work is ongoing to utilising the Nordic Occupational Cancer Study (NOCCA) to look at in-depth studies of the effects of work on cancer risk; shift work features within this. In the US, the National Cancer Institute's Epidemiology and Genetics Research Program is examining breast cancer risk in younger nurses. Work continues on the US Nurses' Health Study. A recent analysis has been published as a conference abstract[101] and importantly showed that although their earlier analysis of breast cancer mortality showed that 30+ years of rotating night shift work was associated with a significant increase in risk, adding a further 12 years of follow-up, breast cancer risk was no longer relevant, RR = 0.95 (0.77 to 1.17, p=trend = 0.95). They concluded that long-term night shift work particularly early in career may be associated with an increased risk of breast cancer, which appears to diminish after night work ceases, and further research is required to confirm this finding. In the Netherlands, the Rijksinstituut boor Volksgezondheid (RIVM) and Erasmus University are conducting studies on the long-term effects of shift work on health outcomes. In Canada, the Canadian Breast Cancer Foundation is funding two studies, one looking at breast cancer subtype and the other at epigenetic factors. Finally, in the UK, the Health and Safety Executive has funded the University of Oxford to carry out an analysis of shift work in the million women study. Our understanding is that this paper may be published some time during 2016.

DISCUSSION

The epidemiological evidence

Excluding the recent publication by Travis *et al.*[36], we identified 15 reviews and meta-analyses from a mixture of prospective and retrospective cohort and case-control studies published in the last 10 years in relation to breast cancer and night shift work or work as a flight attendant. The meta-analyses published before the IARC review, [5,6,102] tended to display relative risks of around 1.5 in both shift workers and flight attendants. The evidence came from a mixture of cohort studies, nested case-control and case-cohort studies and population-based case-control studies, and of the studies published since 2013, around half were prospective in design.

The two earliest meta-analyses in **Table 1** didn't explicitly examine exposure-response relationships, but rather concentrated on ever having worked as a night shift worker or a flight attendant.[7,9] In his critical review of the epidemiological evidence, Kolstad concluded that the evidence for an association between night shift working and breast cancer risk was limited; the evidence was restricted to North America and Europe at this time.[10] The meta-analysis by Viswanathan and Schernhammer gave similar summary relative risks as the two earlier meta-analyses, but for the first time provided some evidence of an exposure response indicating that in a study of nurses, the relative risk was statistically significantly elevated for nurses who worked rotating night shifts for 30 years or more.[11] It wasn't until the advance publication of the results of the IARC monograph meeting in 2007 that epidemiological work in this area received more attention.[5] Although the IARC working group concluded that there was evidence of the carcinogenicity of chronodisruption in experimental animals and an increased risk of breast cancer from work that involved disruption of the circadian rhythm, they expressed concerns about the lack of adjustment for the many potential confounding factors that could affect the breast cancer risk. This, together with vague and inconsistent definitions of shift work, caused the IARC working group to stop short of stating that the epidemiological evidence was sufficient and therefore that work involving circadian disruption was definitely carcinogenic in humans. There were candidate mechanisms, most notably suppression of night time melatonin production, which could explain the epidemiological findings.[5,6,102] Yong and Nasterlack thought that there was more uncertainty in the evidence than that portrayed by the working group suggesting that there was considerable heterogeneity in the exposure-response relationship and that some of the elevated risks were restricted to post-menopausal women and that time spent flying wasn't always a good indicator of circadian disruption in flight attendants.[14] Other reviews published since the IARC review, attempted to better characterise the different shift patterns in relation to exposure-response for breast cancer risk. In their review of studies published to 2012, Ijaz *et al.* found an increased relative risk per 5 years of working at night, with the risk mainly elevated in the case-control rather than cohort studies.[103] However, they thought none of the studies they looked at had a low overall risk of bias and concluded that the overall evidence was of low quality. Wang *et al.* in their meta-analysis concluded that there was a positive gradient of breast cancer risk with years of night shift work.[18] By contrast, Kamdar *et al.* didn't find a linear or other exposure-response relationship.[20] He *et al.* in the most detailed meta-analysis carried out to date, calculated that there was an overall increased risk of breast cancer associated with circadian disruption and that in case-control studies the relative risk per 10 years of shift work exposure was significantly elevated. However, overall they concluded that there was insufficient evidence to support a dose-response relationship between breast cancer and shift work.[21] This latter conclusion may be due to the lack of consistency in findings between the studies and also because of the difficulty of dealing with recall bias in the context of retrospective case-control studies. It's possible that some researchers in their enthusiasm for carrying out meta-analyses, irrespective of whether or not it's part of a systematic review, are not using the approach in the cautious way that has been advocated.[104] The inconsistency in deciding which studies to include in a review or meta-analysis in this area (**Table 2**) is evidence that no matter how careful the study protocol is written, a lack of consistency on this aspect will not lead easily to a consensus position in the literature. The recent meta-analysis of prospective studies is the most persuasive evidence to date that shift work does not increase the relative risk of breast cancer.[36]

In order to examine the recent epidemiological evidence for breast cancer more thoroughly, we identified the latest year we thought was routinely covered by the most recent reviews as 2013 - and looked at the epidemiological evidence from the beginning of that year onwards. What is immediately noticeable about the studies published from 2013 onwards is that they are all of high quality according to our scoring of the studies on the Newcastle-Ottawa scale (Wells *et al.* – see

http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Not counting the three studies included in Travis *et al.*[36], we found ten relevant studies in total. In a detailed retrospective population-based case-control study carried out in Australia[25], in which exposure to shift work and other factors causing circadian disruption were assessed by expert judgement from in-person interviews and analyses were adjusted for potential confounding factors, there was a 16% non-significant excess relative risk for ever having worked graveyard (work between midnight and 5 am) shifts.

Phase shift, where the central sleep-wake cycle becomes adjusted to being awake at night, was associated with significantly increased breast cancer risk. However, the trend of duration of exposure showed a significantly decreasing risk of breast cancer with increasing years of exposure. In a retrospective population-based case-control study in Germany[26,105] in which detailed shift work data were obtained from a subsequent telephone interview, and the analysis adjusted for potential confounding factors, no excess breast cancer risk was found for ever worked shifts or night shifts. However, in analyses by duration of exposure, they found evidence of increased risk for long-term exposure to night shift work particularly for oestrogen receptor-negative breast cancers. In a retrospective population-based case-control study in France[27] in which exposure data and data on confounders were collected by in-person interviews, the risk of breast cancer from ever having worked shifts and worked overnight shifts were around 30% raised and of borderline statistical significance.

Examining duration of exposure, the risk for work for more than 4.5 years was slightly higher and similar to the level of risk for those who worked less than 3 nights per week on average, but again were both of borderline statistical significance. In the same French population-based case-control[29], a significant excess breast cancer risk was for ever having worked nights and there was also an increased risk for working nights for 2 years or more compared with working less than 2 years. In a Swedish prospective population-based cohort study[30], a non-significant excess of breast cancer was found in shift work without night work, but in shift work with night work, the excess became statistically significant. In a prospective Dutch population-based cohort study[31], which obtained data on shift work from face-to-face or telephone interviews, and where the analysis was adjusted for some, but not all potentially confounding factors, no excess relative risk was observed for risk of hospital admission for breast cancer. A retrospective population-based case-control study in Spain[32] which obtained data on shift work and confounding factors from face-to-face interviews, found a non-significant excess relative risk of breast cancer of just under 20% for ever worked nights, for ever worked permanent nights and for ever worked rotating nights. Various metrics were examined to look for exposure-response relationships, but none was statistically significant. A Swedish prospective population-based cohort study obtained data on shift work and potential confounding factors from telephone interviews.[33] The overall relative risk for those who worked 1-45 years at night was around one, and there was some evidence of an increased risk for those who worked from 21-45 years at night.

In a nested case-control study in the textile industry in Shanghai[34], there was some evidence of a decreasing breast cancer risk in this Chinese population with increasing length of time worked rotating shifts. Three recently published prospective cohort studies utilising the Million Women Study, EPIC-Oxford and UK Biobank, when analyses were adjusted for potential confounding factors found no evidence of an increased risk for night shift work in relation to breast cancer and concluded that night shift work including long-term night shift work had little or no effect on breast cancer incidence.[36]

The two papers that initiated epidemiological research in this area, contained relative risks of 1.6 for graveyard shift work and 1.36 for nurses who work 30 years or more on the night shift.[106,107] Initial subsequent studies suggested typical relative risks of 1.5. However, more recent studies have tended to provide evidence of lower relative risks, with the most recent meta-analysis[108] suggesting relative risks of between 1.1 and 1.2. Exceptions to this are studies of flight attendants where the relative risk is still around 1.5. This gradual decreasing of relative risk over time as more methodologically robust studies are conducted, suggests a reduction in relative risk caused by better control for confounding factors. This has culminated in the prospective studies in Travis *et al.* showing no increased risk.[36]

Night work, or rotating shifts involving night work will almost certainly not suit everyone, although this may not be restricted to chronotype, but may depend on other factors such as psychological and domestic circumstances. As such, women may drop out of shift work at a relatively early stage. If

their breast cancer experience is different to the women who remain working night shifts, then this could affect the relative risks seen in some studies. It is clear that more recent studies have made better attempts at adjusting for confounding factors. However, case-control studies will still suffer from the effects of differential recall bias (in which women with breast cancer will more readily recall or over-estimate the amount of shift work they did). One way to resolve this is using prospective cohort studies that have well documented evidence of shift work patterns, prior to date of cancer diagnosis. Attempts have been made to do this, but unfortunately, it is difficult to collect data on confounding factors in these populations. As has been called for by several authors included in this review, what is needed are prospective cohort studies of women where accurate documentation of shift work is obtained in conjunction with good information on potentially confounding factors. This has now been partly addressed by the recent studies in Travis *et al.*[36], but the data on shift work are still self-reported and below the standard called for by the IARC working group. Case-control studies may still suffer from the effects of differential recall and differential participation/selection bias.

We now turn our attention to epidemiological reviews of shift work in relation to cancers other than breast cancer. We found 10 reviews and meta-analyses informative on this. The meta-analysis by Erren *et al*. also examined the risks of prostate cancer in relation to night shift work or work as a pilot[9]. Overall a 40% increase in risk was found. In his critical review of the epidemiological evidence Kolstad found some evidence in relation to colorectal cancer and prostate cancer.[10] Two studies found an increased risk for prostate cancer in relation to fixed and rotating night shifts and one for colorectal cancer showed no increased risk the same study showing an increased risk with increasing duration of night shift work. In their review of the epidemiological evidence, Viswanathan and Schernhammer found a single study of nurses with an increased risk of endometrial cancer for having worked 20 years or more on rotating night shifts.[11] Costa in his review makes reference to the IARC monograph[5,102] and the critical appraisal by Kolstad[10] and mentioned sporadic indications of cancer of the endometrium, colorectum, prostate and for non-Hodgkin's lymphoma. Wang *et al.* in their review describe the evidence for prostate cancer as inconsistent and for colorectal cancer was limited and inconsistent.[13] A meta-analysis by Sigurdardottir *et al.* included 16 studies examining prostate cancer, 15 of which were suggestive of an association, 10 of which were statistically significant [23] Yong and Nasterlack in their review pointed out that two new studies of prostate cancer had been published since the IARC review, neither of which had showed a significant excess and that little new information had emerged in relation to other cancer types.[14] Pan *et al.* review drew our attention to an excess of non-Hodgkin's lymphoma in men with exposure to night shift work and that a Canadian study that looked at several cancer sites found several excesses for various cancer sites, none of which had a significant exposure-response relationship.[22] They reported that studies of nurses showed increased risks for colorectal cancer and endometrial cancer for those with the longest duration of rotating shift work. However, they concluded that for cancers other than breast, too few studies have yet been published to reach meaningful conclusions in relation to shift work. In their meta-analysis of colorectal cancer, Wang *et al.* found a significant excess risk for ever done night shift work and also a statistically significant excess relative risk per 5 years increase in length of night shift work.[24] However, they concluded that further work was needed before definitive conclusions could be drawn.

Eleven individual epidemiological studies have been published since 2013 in relation to cancers other than breast cancer and night shift work, seven of which were prospective and four retrospective. In a retrospective population-based case-control study of incident ovarian cancer, data on shift work and potential confounding factors were obtained from in-person interviews.[38] Overall significant excesses in risk for night shift work were observed for invasive tumours and for borderline tumours. In a prospective cohort study of US nurses[39], a significant excess of lung cancer was observed in nurses working nights for 15 years or more and there was a significant increasing trend in risk with increasing duration of exposure. A Japanese prospective cohort study found no association between shift work and mortality from pancreatic cancer.[40] In a Spanish retrospective population-based case-control study of incident prostate cancer, a small non-significant increase in relative risk was observed for ever having done night work and for ever having done permanent night work.[32] The same was seen for ever having worked rotating night shifts. However, no significant trends were observed with respect to duration of night work. In a prospective population-based cohort study of fatal ovarian cancer in the USA, data on shift work and potential confounding factors was obtained by questionnaire.[42] A statistically significantly increased risk was obtained for rotating shifts, but not for fixed afternoon/evening or fixed night shifts. The same cohort study was used to examine fatal prostate cancer.[43] No significant excesses were observed for any type of work pattern. A

retrospective occupational cohort of US industrial workers found a non-significant excess of non-Hodgkin's lymphoma in shift workers.[44] A retrospective cohort study at a German chemical factory looked at prostate cancer, colorectal cancer and non-Hodgkin's lymphoma in relation to shift work. No excesses of cancer were seen.[44] A prospective population-based cohort study in Japan found a non-significant excesses of biliary and extrahepatic bile duct cancers.[47] In a US prospective cohort study of nurses there was some evidence of a trend of increasing risk of lung cancer, but no evidence for ovarian, pancreatic, or colorectal cancers or for non-Hodgkin's lymphoma.[39] In a prospective case-cohort study in China there was no evidence of an increased risk of lung cancer.[46]

On the whole, although there is some evidence that shift work may be associated with prostate cancer and colorectal cancer, the epidemiological evidence remains patchy and inconsistent. As for breast cancer, prospective cohort studies with good data on shift work and potential confounding factors for these cancers are required.

The strength of our study is that it has supplemented the evidence from recent epidemiological reviews and meta-analyses with recent studies not covered by the reviews. A key outcome remains the lack of prospective studies with well characterised data on shift work up to the standards suggested by the IARC working group. There remains a need to definitively clarify whether or not working shifts or night shifts increases the risk of cancer. For breast cancer, recent evidence suggests that it is now more likely than not that breast cancer risk is not increased in shift workers.

Two further studies of shift workers have recently been published. The first of these concludes that shift workers spend more time walking than non-shift workers and there are no other differences in levels of physical activity between shift workers and non-shift workers[109]. The other concludes that shift workers have similar diet quality to day workers, but a higher energy intake[110].

The Mechanistic evidence

Based on our examination of the mechanistic evidence, the most likely causal mechanism for a breast cancer risk amongst night shift workers, should one exist, is suppression of melatonin because of exposure to light at night, although the risk may be modified by other factors such as chronotype. However, it is also plausible that there may be direct or indirect causal pathways because of the general tendency for shift workers to be obese, and have other lifestyle risk factors for breast cancer. We examine both of these potential mechanisms in the context of potential interventions in the following section.

Potential Interventions

For those studies that examined potential interventions relating to health and safety, it was apparent that the research in this area is fragmented and groups of researchers have examined various aspects of either the melatonin cycle or pharmacological interventions. Furthermore, at the current time, there is limited research in relation to prevention of cancers and much of the research is focused on improving sleep or other lifestyle factors that may be implicated in the development of other cancers.

In relation to melatonin, the usefulness of this drug as a supplement depends on individual blood levels of melatonin (lower) and there is a lack of information on optimum dosage levels and the timing of doses. This is balanced against the argument of using light to lower melatonin levels when working at night as a means of improving wakefulness, but this has the potential to result in chronodisruption. What the research does agree is that to improve ease of going to sleep in the day, reduction of exposure to light on the way home and during sleep is essential.

There appear to be a number of agreements in relation to shift design and that the fast forward rotating shift system (morning, afternoon, night) may be less harmful. Although shift length can also be a factor, as can break allowance within shifts. An important point may also be to identify individuals who are able to cope better with shift work at the outset as there may be a healthy survivor effect occurring within the shift working population. This could have the impact of under-reporting of health issues because a number of people who are diagnosed with cancer in later life stopped shift working earlier and so may not be included in the enumerated cohorts

Health surveillance and workplace health promotion are important issues in maintaining the health of the shift work population. When examining the precursors to cancer, obesity is one such risk factor and as Antunes *et al.* highlighted that being overweight or obese is more common in shift workers[88]. Whether this is due to metabolism or other factors is still being discussed, but the importance of healthy diet and sufficient physical activity cannot be understated and employers can have a role in providing that advice and opportunities for workers on all shifts.

Lack of adherence to cancer screening was also identified in shift workers undergoing breast, colon and cervical cancer screening. The paper by Tsai *et al.* highlights that workers on alternative shifts were less likely to attend breast cancer screening sessions[99]. 318 Tsai The reasons for this have not been fully examined but there may be a need to improve access to screening services (current UK government plans for a 24/7 NHS) and to specifically encourage those involved in night work to attend.

CONCLUSIONS

The relative risk of breast cancer for ever versus never working nights is lower in recent epidemiological studies than when it first came to the attention of the scientific community more than 15 years ago. There are increasingly well conducted epidemiological studies that look at a range of measures associated with chronodisruption and which account for a large number of known and potential confounding factors. It is possible that these higher quality studies provide better adjustment for other risk factors for breast cancer in shift workers. Some studies provide evidence of an increasing risk with increased duration of working nights. However, the heterogeneity in exposure-response means that a casual determination remains elusive. Very recent epidemiological evidence from prospective cohort studies suggests that there may be no elevated risk of breast cancer. The epidemiological evidence for cancers other than breast cancer remains limited. Thus there remains considerable uncertainty as to whether night shift work or prolonged night shift work increases the risk of cancer and so whether the association is causal. The need for preventive action depends on the need for precaution.

The main candidate mechanisms for the increased cancer risk are suppression of nightly melatonin production, with its known anti-carcinogenic properties, from exposure to light at night and/or poorer lifestyle opportunities for night workers resulting in higher than average levels of obesity.

A number of interventions have been tried out in practice, none of which appears to have been properly evaluated for efficacy or effectiveness in relation to reducing breast cancer risk. Measures to reduce exposure to natural light when returning home to sleep during daylight would appear to have benefits in aiding sleep. Given that shift workers tend to be less compliant than non-shift workers, employers should be encouraged to facilitate shift workers access to national cancer screening programmes. Employers should encourage female shift workers aged over 50 years of age to attend screening to detect breast cancer. Health promotion, in which employers actively provide healthy diets, opportunities to exercise and discourage tobacco smoking and alcohol consumption need to have particular prominence among night shift workers. Employers should access and use the wealth of advice that is currently available in relation to shift work; it may reduce cancer risk even if that is not its primary focus. We also believe that measures to alter shift patterns to make workers more alert and which are primarily to prevent accidents and improve the accuracy of work, may have the indirect benefit of reducing cancer risk. Although this requires evaluation, we believe that a responsible employer should seek to implement these interventions now.

There remains a need for further epidemiological investigation of the potential carcinogenic effects of night shift work through high quality studies that have well characterised working patterns (up to the standards required by the IARC working group) and can adequately control for other risk factors for breast cancer. Factors that disrupt the circadian rhythm including sleep disturbance and ability to adapt to shift work remain worth investigating. Regular monitoring of melatonin metabolites in urine would also be useful adjunct to any study.

RECOMMENDATIONS

IOSH should remain cautious in its advice in relation to shift work and cancer, as the association is not yet causal. It should encourage employers to be precautionary via the following:

- Provision of health and nutritious food and access to exercise for night shift workers and to reinforce public health programmes on smoking cessation and moderation of alcohol consumption;
- Use best practice in shift design to maintain alertness and reduce fatigue which primarily prevent accidents and improve the accuracy of work, may also have an indirect benefit of reducing cancer risk; and
- Facilitate access to national cancer screening programmes.

Current interventions such as optimum type of rotating shift pattern should be appropriately evaluated.

IOSH should consider commissioning a prospective epidemiological study of shift worker and cancer that includes collection of detailed information on shift working patterns and all relevant known and potential confounding factors including those that impact on the circadian rhythm and to monitor melatonin levels.

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Table 1 Reviews and meta-analyses of shift work or circadian rhythm disruption and breast cancer, 2005-2015

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Costa et al, 2010[12] Years covered not explicitly stated.	Reference made to the 2007 IARC review of 9 epidemiological studies[34] and the critical appraisal by Kolstad[5]	Of the 9 studies published so far, 6 were positive.	Not examined.	The IARC Working Group's concerns about the lack of precision in shift work definition and lack of adequate control for confounding were reiterated. This study doesn't add to the IARC evidence and the vote counting approach to summarising studies doesn't inform on effect size.
Dickerman & Liu, 2012[15] 2001 to date	N = 11 Nu = 11 3 C, 8 CC	Nurses who worked rotating shifts have increased risk compared to permanent day shift workers. No significant difference found between nurses who worked evenings and those who worked permanent day shifts. Suggestion that nurses who worked at least 5 years with 6 or more consecutive night shifts per month suggesting that risk might be proportional to number of consecutive nights worked.	Studies have reported a dose-dependent relationship between breast cancer risk and increased years and hours per week of night-shift work.	
Erren et al, 2008[9] Studies to 2007	N = 19 11 C, 8 CC 6 US, 13 E 12 FA, 6 OS	Meta-RR FA studies 1.7 (1.4 to 2.1) Meta-RR OS 1.4 (1.3 to 1.6)	Not explicitly examined.	Fixed effect meta-analyses. Random effects also carried out, but no significant heterogeneity.

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
He et al, 2014[21] Studies to 2014	N = 28 15 shift work, 3 FA, 7 short sleep duration, 6 light at night 10 C, 18 CC 12 E, 9 USA, 7 Other countries conducted in Europe, 9 in the USA and 7 in other countries	Overall meta-RR for circadian disruption 1.14 (1.12 to 1.56). RR shift work 1.19 (1.08 to 1.32) RR exposure to light at night 1.12 (1.12 to 1.12) RR sleep deficiency 0.96 (0.86 to 1.06) Employment as a flight attendant 1.56 (1.10 to 2.21). RR case-control studies 1.21 (1.11 to 1.32) RR cohort studies 1.04 (0.95 to 1.30) RR studies with >80% follow-up/response rate 1.16 (1.08 to 1.25) RR lower quality (Newcastle-Ottawa scale) 1.16 (1.08 to 1.25) RR European studies 1.32 (1.12 to 1.56).	CC studies per 10 years of shift work exposure RR 1.16 (1.06 to 1.27) C studies RR per 10 years of shift work exposure 1.03 (0.95 to 1.11). Insufficient evidence to support a dose-response relationship between breast cancer and shift work.	No significant heterogeneity. Evidence of publication bias. No association from two studies that examined turning light on during sleep. No dose-response for sleep deficiency from four studies.
Kolstad, 2008[10] Studies to 2007	N = 8 3 C, 1 NCC, 4 CC 4 E, 4 NA	5 of 8 studies indicated increased risks.	3 studies reported a significantly increased risk for long-term nightshift work beyond 20-30 years. Virtually no effects were found for shorter durations.	Limited evidence of a causal association between nightshift work and breast cancer.

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Leonardi et al, 2013[16] Studies to 2011	N = 12 4 C, 8 CC 4 US, 7 E, 1 A	A positive correlation between shift work and breast cancer risk was described in 6 out of 8 CC studies (2 from the USA, 6 from Europe). 4 prospective cohort studies, two results showing a positive association in US nurses, but a European and an Asian study that didn't	Some evidence presented in the tabulated results showing an increased risk with cumulative exposure to shift work in case-control and cohort studies.	The authors propose to carry out a case-control study including biopsy specimens from patients with night shift work exposure.
Ijaz et al, 2013[17] Studies to 2012	N = 16 5 CC,7 NCC, 4 C 5 N, 1 RT, 1 T, 1 M, 8 V 4 US, 10 E, 2 A	Not examined – focus on exposure-response.	RR for working at night per 5 years 1.05 (1.01 to 1.10) RR for working at night per 5 years C studies 1.01 (0.97 to 1.05) RR for working at night per 5 years CC studies 1.09 (1.02 to 1.20). RR per 300 night shifts 1.04 (1.00 to 1.10) RR per 300 night shifts C studies 1.00 (0.97 to 1.04) RR per 300 night shifts CC studies 1.07 (1.00 to 1.10).	No study had an overall low risk of bias and 6 studies were of moderate risk. Looking at effect of type of occupation, site of study, and shift system (rotating, fixed, rotating and fixed together), none was significant in the meta-regression. Restricting to better quality studies did not alter results. No significant publication bias. Overall quality of the evidence considered low.
Kamdar et al, 2013[20] Studies to 2012	N = 15 10 C, 5 CC 4 N, 3 FA, 1 RT, 1 T, 5 V 5 US, 8 E, 2 A	Overall meta-RR 1.21 (1.00 to 1.47)	Meta-RR short-term workers (duration < 8 y) 1.13 (0.97 to 1.32) Meta-RR longer duration (≥ 8 y) 1.04 (0.92 to 1.18) No linear or dose-response relationship between breast cancer risk and duration of employment	No significant publication bias.

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Megdal et al 2005[7] 1960 to 2005	N = 13 7 FA; 6 OS 8 E, 5 US 11 C, 2 CC	Meta-RR for all studies 1.48 (95% CI: 1.36 to 1.61) Meta-RR for female cabin crew 1.44 (1.26 to 1.65) Meta-RR for female night workers 1.51 (1.36 to 1.68)	Not explicitly examined.	Fixed effect meta-analysis. Some evidence found for confounding due to incomplete adjustment for breast cancer risk factors, with smaller effects in the studies that more completely adjusted for reproductive history and other confounders (evidence from meta-regression). No statistically significant publication bias. Mortality studies not included. Mention made of an air cabin crew study that had an SMR 1.11 (95% CI: 0.82 to 1.46).
Pan et al, 2015[22] Studies to 2013	N = 16 5 C, 6 CC, 5 NCC,	Overall most studies found some association between exposure to shift work and increased risk of breast cancer although a few studies reported no such association. Of the 9 retrospective studies showing an association, 8 were conducted in Europe and 1 in the USA. Of those not showing an association, two were conducted in Europe and 1 in the USA. Three of four prospective studies have provided evidence in favour of an association between shift work and breast cancer, one of which was in the USA, one in Europe and one in China.	The risk appears to primarily apply for women with longer durations of nightshift work.	The authors conclude there is compelling evidence that shift work increases the risk of breast cancer.

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Stevens et al, 2011 (incorporating Straif et al, 2007 and IARC, 2010)[5,6,102] 1996-2006	N = 9 3 C, 2 NCC, 4 CC 5 E, 4 US	No obvious difference in results from these studies according to their varied definitions of shift work. All studies reported significant and similarly strong associations of 'shift work' with risk, except for 2 studies which found no overall effect.	Exposure categories presented from the different studies, but not the associated risks.	Future studies should ensure that the measurement of shift work incorporates as many relevant factors as possible and that the metrics used by comparable across studies.
Viswanathan & Schernhammer, 2009[11] Years covered not explicitly stated.	N = 8 3 C, 5 CC (some nested within cohorts)	Meta-RR 1.40 (95% CI: 1.19 to 1.65)	One study of nurses had a RR of 1.36 (95% CI: 1.04 to 1.78) for working rotating night shifts for 30 years or more. Another study of nurses had a RR of 1.79 (1.06 to 3.01) for 20 years or more working rotating night shifts. Both studies controlled thoroughly for breast cancer risk factors.	Mention made of an additional 7 studies of flight attendants indicating an increased breast cancer risk, with a meta-RR of 1.44 (1.26 to 1.62).
Wang et al, 2011[13] Studies to 2009	Secondary review (review of reviews) 1 C, 5 reviews	The authors conclude there is suggestive evidence for an association between night work and increased risk of breast cancer.		

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Wang *et al.* 2013[24] 1971-2013	N = 10 3 C, 3 NCC, 4 CC 5 N, 1 M, 4 V 4 US, 5 E, 1 A	Overall meta-RR 1.19 (1.05 to 1.35)	RR overall per 5 years of night-shift work 1.03 (1.01 to 1.05) RR CC studies per 5 years of night shift work 1.06 (1.02 to 1.09) RR C studies per 5 years of night shift work 1.02 (1.00 to 1.04) RR per 500 night shifts 1.13 (1.07 t 1.21). RR 3 nights per month 1.02 (0.97 to 1.09).	No significant publication bias. Positive gradient of breast cancer risk with the year of night shift work.
Yong & Nasterlack 2012[14] Those included in IARC review plus 2007-2011	N = 13 (8 of which were included in IARC monograph) 4 C, 4 NCC, 5 CC 5 Nu, 1 RT, 7 GP	Reference made to IARC review that 6 out of 8 studies (excluding female flight attendants) have shown modestly elevated risks, and the incidence of breast cancer was also modestly increased in most cohorts of female flight attendants. 6 studies published since the IARC review, half of which displayed some statistically elevated relative risks.	Reference made to the IARC review that breast cancer risks are elevated after having worked shifts for 30 years or after cumulative exposure to shift work of only 6 months, and also appear after having worked for a little more than 3 years, but only in women aged 50 or more. Thus considerable heterogeneity exists in dose-response. In the 6 studies published since the IARC review, 3 showed significantly elevated risks in the highest exposure categories.	Study critical of IARC working group's assumption that cumulative radiation dose in FAs can be interpreted as indicating level of circadian disruption, because of flights along the same meridian.

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Notes: FA = Flight attendants OS = Other shift workers E = Europe US = United States of America A = Asia C = Cohort NCC = Nest case-control CC = Case-control Nu = Nurses RT = Radio and telegraph operators V = Various M = Military T = Textile industry GP = General population				

Table 2 Table showing which studies are contained in which review or meta-analysis for breast cancer

Review/Paper	Megdal et al 2005 (breast cancer, flight attendants studied separately)	Mono 98 (breast, prostate, colorectal, colon, rectum, endometrial, lung, stomach, bladder and leukaemia, flight attendants studied separately)	Erren et al 2008 (breast and prostate cancer, flight attendants studied separately)	Kolstad 2008 (breast, prostate and colon cancer)	Viswanathan and Schernhammer 2009 (breast and endometrial cancer)	Stevens et al 2011 (breast cancer)	Yong et al 2012 (breast, prostate, ovarian, skin melanoma and non-Hodgkin's lymphoma)	Leonardi et al 2012 (breast cancer)	Dickerman and Liu 2012 (breast cancer)	Wang et al 2013 (breast cancer)	Ijaz et al 2013 (breast cancer)	Kamdar et al 2013 (breast cancer)	He et al 2014 (breast cancer)	Pan 2015 (breast, prostate, colorectal, endometrial, non-Hodgkin's lymphoma, ovarian, skin, lung, colon, bladder, rectum, pancreatic, stomach, kidney, oesophagus and melanoma)
Taylor et al 1972		√		√										
Tynes et al 1996	√	√	√	√	√	√	√	√			√	√		√
Davis et al 2001	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Hansen 2001	√	√	√	√	√	√	√	√			√	√	√	√
Schernhammer et al 2001	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Reynolds et al 2002												√	√	
Linnersjo et al 2003												√		
Rafnsson et al 2003												√	√	
Schernhammer et al 2003		√		√										√
Travis et al 2004		√		√										√
Kojo et al 2005													√	
Schernhammer and Hanksinson 2005		√											√	
Verkasalo et al 2005													√	
Kubo et al 2006		√	√	√										√

Review/Paper	Megdal et al 2005 (breast cancer, flight attendants studied separately)	Mono 98 (breast, prostate, colorectal, colon, rectum, endometrial, lung, stomach, bladder and leukaemia, flight attendants studied separately)	Erren et al 2008 (breast and prostate cancer, flight attendants studied separately)	Kolstad 2008 (breast, prostate and colon cancer)	Viswanathan and Schernhammer 2009 (breast and endometrial cancer)	Stevens et al 2011 (breast cancer)	Yong et al 2012 (breast, prostate, ovarian, skin melanoma and non-Hodgkin's lymphoma)	Leonardi et al 2012 (breast cancer)	Dickerman and Liu 2012 (breast cancer)	Wang et al 2013 (breast cancer)	Ijaz et al 2013 (breast cancer)	Kamdar et al 2013 (breast cancer)	He et al 2014 (breast cancer)	Pan 2015 (breast, prostate, colorectal, endometrial, non-Hodgkin's lymphoma, ovarian, skin, lung, colon, bladder, rectum, pancreatic, stomach, kidney, oesophagus and melanoma)
Lie et al 2006	√	√	√	√	√	√	√	√	√	√	√	√		√
McElroy et al 2006													√	
O'Leary et al 2006		√	√	√	√	√	√	√	√	√	√	√	√	√
Pinheiro et al 2006			√										√	
Schernhammer et al 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Conlon et al 2007		√	√	√										√
Schwartzbaum et al 2007		√		√	√	√	√	√			√	√	√	√
Viswanathan et al 2007		√			√									√
Kakizaki et al 2008													√	
Lahti et al 2008							√							√
Nagata et al 2008									√					
Wu et al 2008													√	
Pukkala et al 2009							√							√
Lie et al 2010													√	
Pesch et al 2010						√	√	√	√	√	√	√	√	√
Pronk et al 2010							√	√	√	√	√	√	√	√

Review/Paper	Megdal et al 2005 (breast cancer, flight attendants studied separately)	Mono 98 (breast, prostate, colorectal, colon, rectum, endometrial, lung, stomach, bladder and leukaemia, flight attendants studied separately)	Erren et al 2008 (breast and prostate cancer, flight attendants studied separately)	Kolstad 2008 (breast, prostate and colon cancer)	Viswanathan and Schernhammer 2009 (breast and endometrial cancer)	Stevens et al 2011 (breast cancer)	Yong et al 2012 (breast, prostate, ovarian, skin melanoma and non-Hodgkin's lymphoma)	Leonardi et al 2012 (breast cancer)	Dickerman and Liu 2012 (breast cancer)	Wang et al 2013 (breast cancer)	Ijaz et al 2013 (breast cancer)	Kamdar et al 2013 (breast cancer)	He et al 2014 (breast cancer)	Pan 2015 (breast, prostate, colorectal, endometrial, non-Hodgkin's lymphoma, ovarian, skin, lung, colon, bladder, rectum, pancreatic, stomach, kidney, oesophagus and melanoma)
Grundy et al 2011									√					
Klogg et al 2011							√						√	
Kubo et al 2011							√							√
Li 2011											√	√		
Lie et al 2011							√	√	√	√	√	√	√	√
Poole et al 2011							√							√
Schernhammer et al 2011							√							√
Villeneuve et al 2011							√							√
Hansen and Lassen 2012										√	√		√	√
Hansen and Stevens 2012							√	√	√	√	√		√	√
Menegaux et al 2012											√		√	√
Parent et al 2012														√
Pukkala et al 2012													√	
Knutsson et al 2013											√		√	
Bauer et al 2013													√	
Fritschi et al 2013													√	

Review/Paper	Megdal et al 2005 (breast cancer, flight attendants studied separately)	Mono 98 (breast, prostate, colorectal, colon, rectum, endometrial, lung, stomach, bladder and leukaemia, flight attendants studied separately)	Erren et al 2008 (breast and prostate cancer, flight attendants studied separately)	Kolstad 2008 (breast, prostate and colon cancer)	Viswanathan and Schernhammer 2009 (breast and endometrial cancer)	Stevens et al 2011 (breast cancer)	Yong et al 2012 (breast, prostate, ovarian, skin melanoma and non-Hodgkin's lymphoma)	Leonardi et al 2012 (breast cancer)	Dickerman and Liu 2012 (breast cancer)	Wang et al 2013 (breast cancer)	Ijaz et al 2013 (breast cancer)	Kamdar et al 2013 (breast cancer)	He et al 2014 (breast cancer)	Pan 2015 (breast, prostate, colorectal, endometrial, non-Hodgkin's lymphoma, ovarian, skin, lung, colon, bladder, rectum, pancreatic, stomach, kidney, oesophagus and melanoma)
Grundy et al 2013													√	
Girschik et al 2013													√	

Table 3 Reviews and meta-analyses of shift work or circadian rhythm disruption and cancers other than breast, 2005-2015

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Costa et al, 2010[12] Years covered not explicitly stated.	Reference made to the 2007 IARC review studies and the critical appraisal by Kolstad	Mention made of sporadic indications for cancer of the endometrium, 1 positive study, prostate (3 studies, 2 positive), colorectal (3 studies, 1 positive) and non-Hodgkin's lymphoma (1 positive study)	Not examined.	
Erren et al, 2008[9] Studies to 2007	N = 11 11 P 9 FP, 2 V 10 C, 1 CC 2 NA, 8 E, 1 A	Meta-RR FP studies 1.4 (1.1 to 1.8)	Not explicitly examined.	Fixed effect meta-analyses. Random effects also carried out, but no significant heterogeneity.
Kolstad, 2008[10] Studies to 2007	N = 4 2 Co, 1 Co&P, 1 P 2 C, 1 NCC, 1 CC 1 E, 2 NA, 1 A	2 studies showed increased prostate cancer risk for both fixed and rotating night shifts. 1 study showed an increased risk of colon cancer and another showed no increased risk.	1 study showed an increasing risk of colon cancer as the duration of rotating night shifts increased.	Insufficient evidence of a causal association for prostate cancer and for colon cancer.
Pan et al, 2015[22] Studies to 2013	N = 9 7 C, 2 CC 1 Co, 3 P, 1 E, 1 NHL, 1 Ov, 1 Sk, 1 V	In a Finnish study, there was an excess of NHL in men with exposure to night shift work. In a Canadian case-control study looking at several cancer sites, excess were observed for lung cancer, colon cancer, bladder cancer, prostate cancer, pancreatic cancer and NHL; however, there we no exposure-response relationships in this study.	In studies of nurses women with the longest durations of rotating shift work had modestly increased risks of colorectal cancer and endometrial cancer, but no association with ovarian cancer and risk of skin cancer decreased.	For cancers other than breast, too few studies have yet been published to reach meaningful conclusions in relation to shift work.

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Sigurdardottir et al, 2012[23] Studies to 2011	N = 4 3 C, 1 CC 1 E, 1 NA, 2 A Reference also made to an early meta-analysis of airline pilots Also included were study of sleep duration and light at night	16 studies included of which 15 were suggestive of a positive association, 10 of which were statistically significant.		The studies supporting the increase in prostate cancer risk are in line with the vast majority of the studies on shift work and breast cancer risk, although more studies are needed to draw definitive conclusions.
Stevens et al, 2011[6] (incorporating Straif et al, 2007 and IARC, 2010) 1996-2006		Increased risks for cancer of the prostate, colon and endometrium have been reported for shift workers and the earliest studies of airline pilots showed marked excesses of prostate cancer.		The prostate cancer studies may be limited by the potential for detection bias due a higher prevalence of screening in pilots.
Viswanathan & Schernhammer, 2009[11] Years covered not explicitly stated.	N = 1 1 E 1 C 1 NA		A single study of nurses showed an increased risk in women with 20 or more years work on rotating night shifts RR 1.47 (1.03 to 1.14).	No significant excess noted in leaner women (body mass index a known risk factor).
Wang et al, 2011[13] Studies to 2009	Secondary review (review of reviews) 1 C, 5 reviews	There is limited and inconsistent evidence for an association between shift work and prostate cancer, based on 3 studies. Evidence for an association between shift work and colorectal cancer is also limited and inconsistent. A single study found an association for non-Hodgkin's lymphoma in men, but not in women.		

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
Yong & Nasterlack [14] Those included in IARC review plus 2007-2011	N = 5 2 P, 1 Ov, 1 SM, 1 NHL 5 C 2 E, 2 NA, 1 A	After reiterating the IARC findings (see row above), two new studies have emerged on prostate cancer (since IARC review). Neither showed a significant excess in relation to shift work. Little new information has emerged on other cancer types, with no excesses for ovarian cancer, skin cancer or non-Hodgkin's lymphoma.		
Wang et al, 2015[24] 1996-2004	N = 6 3 C, 3 CC 6 Co	Meta-RR 1.32 (1.12 to 1.55) Meta-RR CC 1.63 (1.32 to 2.01) Meta-RR C 1.32 (0.96 to 1.22)	Meta-RR per 5 years increase in night shift work 1.11 (1.03 to 1.20)	No evidence of publication bias detected. The dose-response relation indicative that shift work could increase risk of colorectal cancer, but further research should be conducted to confirm the findings and clarify the biological mechanisms.

Notes:
P = Prostate cancer
Co = Colon cancer
E = Endometrial cancer
Ov = Ovarian cancer
SM = Skin (melanoma)
NHL = Non-Hodgkin's lymphoma
Sk = Skin
FP= Flight personnel
OS = Other shift workers
E = Europe
US = United States of America
A = Asia
C = Cohort
NCC = Nest case-control
CC = Case-control
Nu = Nurses
RT = Radio and telegraph operators

Reference, time period	Included studies	Assessment of risk for breast cancer for ever vs never exposed to shift work	Assessment of exposure-response for breast cancer	Additional information
V = Various M = Military T = Textile industry GP = General population				

Table 4 Studies published 2013-2015 informative in relation to breast cancer

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Fritschi et al, 2013[25]	Australia	Retrospective population-based case-control	1,785/1,202	58% for cases, 41% controls	Expert assessment from in-person interviews	Age, menopausal status, socioeconomic score, remoteness, education, country of birth, family history of breast cancer, number of children, breastfeeding, alcohol intake, physical activity, BMI, circadian type, circadian rhythm, circadian flexibility,	High	Ever/never graveyard shift Phase shift Duration of exposure graveyard shift <10 y 10-<20y 20+ y	1.16 (0.97 to 1.38), 381 exposed cases) 1.22 (1.01 to 1.47, 309) 1.25 (1.00 to 1.56, 199) 1.09 (0.79 to 1.50, 98) 1.02 (0.71 to 1.45, 84) (p-trend 0.04)

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Rabstein et al, 2013[26]	Germany	Population-based case-controls study	1143 cases/ 1155 controls	88% for cases, 67% for controls	Detailed shift work data from a subsequent telephone interview	Menopausal status, education, breast cancer in mother or sister, parity, age at first birth, duration of oral contraceptive use, duration of menopausal HRT use, BMI, smoking status, number of mammograms, lifetime breastfeeding	Medium	Ever vs never shift work Ever vs never nightshift work Worked <807 night shifts Worked 807 or more night shifts Ever worked more than 807 night shifts Ever Workers < 1055 night shifts (with >3 nights per month) Ever worked more than 1055 night shifts (with > 3 nights per month) Duration of night work years >1 - <5	0.98 (0.74 to 1.29, 112 exposed cases) (0.68 to 1.50, 55) 0.66 (0.39 to 1.11, 25) 1.78 (0.89 to 3.58, 23) 1.78 (0.89 to 3.58) 0,80 (0.47 to 1.36, 25) 1.66 (0.80 to 3.46, 20) 0.64 (0.34 to 1.24, 15)

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Menegaux et al, 2013[27]	France	Retrospective population-based case-control study	1232 cancer cases/ 1,317 controls	79% for cases, 76% for controls	In-person interviews	Age, study area, age at menarche, age at full-term pregnancy, parity, use of hormone replacement therapy, family history of breast cancer in first-degree relatives, BMI, alcohol consumption, tobacco consumption	High	Ever worked on night shifts Worked overnight shifts Duration of night work < 4.5 years Duration of night work ≥ 4.5 years Worked less than 3 nights per week on average Worked 3 nights or more a week on average	1.27 (0.99 to 1.64, 164 exposed cases) 1.35 (1.01 to 2.03, 120) 1.12 (0.78 to 1.60, 66) 1.40 (1.01 to 1.80, 98) 1.43 (1.01 to 2.03, 66) 1.14 (0.52 to 1.59, 80)
Knutsson et al, 2013[30]	Sweden	Prospective population-based cohort study	4,036	Probably 100%	Questionnaire	Number of children and alcohol intake	Medium	Shift without night versus day Shift with night versus day	1.23 (0.70 to 2.17, 10 exposed cases) 2.02 (1.03 to 3.95, 14)

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Truong et al, 2014[29]	France	Population-based case-control study	1126 cases/1,174 controls	79% for cases, 76% for controls	In-person interviews	Age, Study Area, Age at Menarche, Age at first full-term pregnancy, parity, current use of menopausal hormone therapy, BMI, alcohol consumption.	High	Ever did night work Work nights for ≥2 years vs < 2 years	1.32 (1.02 to 1.72, 153 exposed cases) 1.42 (1.08 to 1.88, 136)
Koppes et al, 2014[31]	Holland	Prospective population-based cohort	285,723 women	Coverage 95% complete	Face-to-face or telephone interviews from the Dutch Labour Force surveys	Age, origin, children in the household, education, occupational group, contractual working hours, job tenure	High	Hazard ratio of hospital admission for breast cancer Occasional night work Regular night work	1.04 (0.85 to 1.27, 102 exposed cases)) 0.87 (0.72 to 1.05, 117)

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Papantoniou et al, 2015[32]	Spain	Retrospective population-based case-control	1,708/ 1,778	On average 72% cases, 52% controls	Reported from face-to-face interview	Age, centre, education level, menopausal status, family history of breast cancer, body mass index, smoking status, oral contraceptive use, leisure time physical activity, alcohol consumption, sleep duration	High	Ever night work Ever permanent nights Ever rotating nights Cumulative years of night work: 1-4 5-14 ≥15 Cumulative years of working permanent nights: 1-4 5-14 ≥15 Cumulative years of rotating nights: 1-4	1.18 (0.97 to 1.43, 270 exposed cases) 1.19 (0.89 to 1.60, 97) 1.17 (.091 to 1.51, 139) P(trend) = 0.176 1.21 (0.83 to 1.76,58) 1.13 (0.83 to 1.53, 85) 1.21 (0.89 to 1.65, 91) P(trend) = 0.109 1.00 (0.59 to 1.66, 34) 1.17 (0.74 to 1.87, 36) 1.49 (0.88 to 2.53, 27) P(trend) = 0.369 1.58 (0.94

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Akerstedt et al, 2015[33]	Sweden	Prospective population-based cohort study	13,656 women from Swedish twins registry, with 3,404 exposed to night work	74% to telephone interview	Telephone interview	Age, education level, tobacco consumption, body mass index, having children, coffee consumption, previous cancer, use of hormones including oral contraceptives.	High	Worked nights (years): 1-45 1-5 6-10 11-20 21-45	 0.94 (0.73 to 1.22, 109 exposed cases) 0.92 (0.65 to 1.29, 57) 0.79 (0.45 to 1.38, 16) 0.77 (0.43 to 1.38, 18) 1.68 (0.98 to 2.88, 18)

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Li et al, 2015[34]	China	Prospective case-cohort study	1,709 cases/4,780 non-cases	54 breast cancer cases and 56 controls exclude due to missing baseline questionnaire or missing work history information	Data on shift work schedules obtained from factory records (80%), factory supervisors (12%) and in-person interviews (8%)	Age, reproductive history (number of liv births, lifetime duration of breast feeding) and alcohol consumption	High	Cumulative exposure on rotating night shifts (years): >0-12.8 >12.8-19.92 >19.92-27.67 >27.67 Cumulative exposure (years, 10 year lag) >0-12.8 >12.8-19.92 >19.92-27.67 >27.67 Cumulative exposure (years, 20-year lag) >0-12.8	P(trend) = 0.095 0.99 (0.83 to 1.17, 286 exposed cases) 0.97 (0.82 to 1.15, 290) 0.90 (0.76 to 1.06, 289) 0.88 (0.74 to 1.05, 287) P(trend) = 0.060 0.98 (0.84 to 1.15, 431) 0.99 (0.83 to 1.17, 266) 0.81 (0.67 to 0.98, 200) 0.91 (0.75 to 1.10, 235) P(trend) = 0.035 1.03 (0.89

Authors	Geographical location	Study design	No. cases/ controls or cohort size	Follow-up/ response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Gu et al, 2015[111]	USA	Prospective cohort study of nurses	74,862 females	82.2% of study population responded to questionnaire on shift work	Participants asked by questionnaire the total number of years during which worked rotating night shifts at least 3 nights per month	Age, alcohol consumption, physical exercise, multivitamin use, menopausal status, postmenopausal hormone use, physical examination in the previous 2 years, health eating score, smoking status, pack-years of smoking, and body mass index	High	Never worked night shifts 1-5 years 6-14 years ≥15 years P(trend)	1.00 (referent) 1.07 (0.90 to 1.26, 293 exposed cases) 0.99 (0.76 to 1.27, 79) 0.99 (0.74 to 1.33, 55) 0.83

Notes:
(1) Newcastle – Ottawa criteria: 7-9 stars high quality; 4-6 stars medium; 0-3 stars low

Table 5 Studies published 2013-2015, informative in relation to cancers other than breast cancer

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Bhatti et al, 2013[38]	USA	Prospective population-based case-control study	Ovarian	1,490 / 1,832	74.2 % cases / 78.2% controls	In –person interview	Age, county of residence, calendar year, duration of hormonal contraceptive use, number of full term pregnancies, and BMI	High	Night shift, invasive tumours Night shift, borderline tumours	1.24 (1.04 to 1.49, 293 exposed cases) 1.48 (1.15 to 1.90, 126)
Schernhammer et al, 2013[39]	USA	Prospective cohort study of 121,701 female registered nurses	Lung	78,612 included in analysis.	Not stated.	Questionnaire.	Smoking status, age started smoking, amount smoked, time since quitted smoking, fruit/vegetable intake, body mass index, use of oral contraceptives or postmenopausal hormones and menopausal status	High	Time working rotating shift 0 (ref) 1-5 6-14 ≥15 P(trend)	 1.00 1.02 (0.90 to 1.14, 573 exposed cases) 0.95 (0.80 to 1.13, 177) 1.28 (1.07 to 1.53, 164) 0.03

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Lin et al, 2013[40]	Japan	Prospective cohort mortality study of men aged 40-65 during 1988-1990	Pancreas	22,224 include din analysis	Not stated	Questionnaire	Included age, height, weight, medical history, family history of cancer, smoking, alcohol consumption, job type, physical activity at work, whether worked indoors or outdoors, level of perceived stress, educational level and marriage status	High	Fixed night time work Rotating shift work	0.61 (0.22 to 1.50, 5) 0.83 (0.43 to 1.60, 11)

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Papantoniou et al, 2014[32]	Spain	Retrospective population-based case-control study	Prostate	1,095 / 1,388	74% cases/ 54% controls	In-person interviews	Family history of prostate cancer, leisure time physical activity, smoking status, past sun exposure and meat consumption	High	Ever night work	1.14 (0.94 to 1.37, 362 exposed cases)
									Ever permanent nights	1.10 (0.85 to 1.43, 156)
									Ever rotating nights	1.16 (0.92 to 1.46, 205)
									Cumulative years of night work:	
									≤10	1.10 (0.83 to 1.45, 128)
									11-27	0.94 (0.69 to 1.29, 92)
									≥28	1.35 (1.04 to 1.81, 138)
									P(trend)	0.047
									Cumulative number of night shifts:	
									>0 - ≤ 1152	1.03 (0.75 to 1.42, 85)
									1153-2856	1.09 (0.78 to 1.52, 71)
									≥2857	1.30 (0.97 to 1.74, 100)
									P(trend)	0.084

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Carreon et al, 2014[44]	USA	Retrospective cohort study of workers at a chemical manufacturing plant between 1946 and 2006.	Non-Hodgkin's lymphoma	1,874	Not stated.	Assignment to shift work based on job title and knowledge of factory production	Age, sex, calendar year	Medium	Duration of shift work (years) 0 >0-<1 >1	 2.59 (0.53 to 7.56, 3 cases) 2.22 (0.46 to 6.48, 3 exposed cases) 2.37 (0.77 to 5.52, 5)
Carter et al, 2014[42]	USA	Prospective population-based cohort study	Ovarian	161,004	99.4%	Questionnaire	Race, family history of breast or ovarian cancer, age at menarche, menopausal status, age at menopause, age at first birth, parity, duration of oral contraceptive use, postmenopausal oestrogen use, and previous tubal ligation	High	Rotating shifts Fixed afternoon/evening Fixed night	1.27 (1.03 to 1.56, 101 exposed cases) 0.62 (0.34 to 1.12, 11) 1.12 (0.57 to 1.87, 15)
Gapstur et al, 2014[43]	USA	Prospective population-based cohort study	Prostate	305,057	98.2%	Questionnaire	Race, education, BMI, smoking history, family history of prostate cancer, and frequent of painful urination	High	Rotating shifts Fixed afternoon/evening Fixed night	1.08 (0.95 to 1.22, 268 cases) 1.27 (0.97 to 1.65, 55) 0.72 (0.44 to 1.18, 16)

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Hammer et al, 2015[45]	Germany	Retrospective cohort study	Prostate	12,609 shift workers and 15,219 day workers	Over 90%	Occupational records	Age, sex, calendar year, smoking and duration of employment	High	Shift vs Day As above adjusted for smoking Shift vs day assuming 20 year latency Shift vs day adjusted for duration of employment	0.93 (0.73 to 1.18, 337 cases) 0.88 (0.69 to 1.13, 337) 0.89 (0.69 to 1.14, 322) 0.95 (0.75 to 1.21, 337)
Lin et al, 2015[47]	Japan	Prospective population-based cohort study	Biliary tract Extrahepatic bile duct	22,22 men aged 40-65	Not stated	Questionnaire based	Age, body mass index, history of gallstones, history of diabetes, alcohol consumption, cigarette smoking, sleep time and perceived stress.	Medium	Permanent nights Rotating shifts Permanent nights Rotating shifts	0.86 (0.31 to 2.36, 4 deaths) 1.31 (0.81 to 2.77, 12) 1.19 (0.43 to 3.31, 4) 1.93 (1.00 to 3,72, 11)

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Gu et al, 2015[111]	USA	Prospective cohort study of nurses	Lung	74,862 females	82.2% of study population responded to questionnaire on shift work	Participants asked by questionnaire the total number of years during which worked rotating night shifts at least 3 nights per month	Age, alcohol consumption, physical exercise, multivitamin use, menopausal status, postmenopausal hormone use, physical examination in the previous 2 years, health eating score, smoking status, pack-years of smoking, and body mass index	High	Never worked night shifts 1-5 years 6-14 years ≥15 years P(trend)	1.0 (ref) 1.05 (0.92 to 1.19, 523 exposed cases) 0.99 (0.83 to 1.18, 168) 1.25 (1.04 to 1.51, 150) 0.05
			Ovarian						Never worked night shifts 1-5 years 6-14 years ≥15 years P(trend)	1.0 (ref) 0.95 (0.77 to 1.18, 163) 0.89 (0.64 to 1.23, 47) 0.82 (0.55 to 1.22, 30) 0.27
			Pancreatic						Never worked night shifts 1-5 years 6-14 years ≥15 years P(trend)	1.00 (ref) 1.12 (0.90 to 1.40, 173) 1.14 (0.83 to 1.58, 52) 1.03 (0.70 to 1.51, 33) 0.77
			Colorectal						Never worked night shifts 1-5 years	1.0 (ref) 0.93 (0.79 to

Authors	Geographical location	Study design	Cancer(s) studied	No. cases/ controls or cohort size	Follow-up/response rate	Method of exposure assessment	Variables adjusted for	Quality, based on Newcastle-Ottawa criteria(1)	Exposure definition	RR (95% CI)
Kwon et al, 2015[46]	China	Retrospective case-cohort	Lung	267,400 in cohort; 1,559 lung cancer and 3,199 from sub cohort	Of the lung cancer cases and sub cohort (4,738) 11 non-cases and 53 cases excluded due to missing work history data. Machinist, wool and sanitation work history excluded 50 more cases and 145 non-cases.	Obtained by interview in conjunction with knowledge of shift work policies	Age, smoking status, parity, cumulative endotoxin exposure.	High	10 year lag, cumulative no. of years rotating night shift work 0 >0 to ≤17.1 17.1 to ≤24.9 24.9 to ≤30.6 >30.6 P(trend)	 0 (ref) 0.76 (0.63 to 0.93, 280 exposed cases) 0.90 (0.73 to 1.10, 260) 0.95 (0.77 to 1.18, 244) 0.82 (0.66 to 1.03, 253) 0.277
Notes: Newcastle – Ottawa criteria: 7-9 stars high quality; 4-6 stars medium; 0-3 stars low										

Table 6 Research evidence in relation to interventions

Author	Type of Study	What research question(s) does the study address?	Type of cancer(s) ?	Description of population	What data is provided on shift work?	What evidence is provided on the impact of shift working on the risk of cancer?	What evidence is provided on the steps that could be taken to reduce the risks of shift working?	Outcome Measures e.g., circadian rhythm, cancer, modifications
Bracci M, et al 2013[100]	Cross-sectional study	Investigate urinary 6-sulfatoxymelatonin , serum 17-B-estradiol levels in premenopausal shift nurses at the end of the night shift compared to a control group of daytime nurses.	Breast cancer	184 registered female nurses working in NHS hospital wards in Ancona, Italy. Of these, 31 shift working nurses were recruited and 31 daytime nurses.	Type of shift work.	Shift nurses experience changes in aMT6s levels after a night-shift. Napping habits influence 17-B-estradiol levels at the end of a night shift.	A short nap during night-shifts may exert a positive effect.	aMT6s levels.
Reed (2011)[98]	review	Shift work, light at night and the risk of breast cancer - a guide to administrative action for health care institutions	Breast cancer	not described	Light at night,	N/A	The paper has a section on 'how should health care institutions respond' and a section on 'options and recommendations' including; invoke the precautionary principle, minimizing exposure, scheduling that minimizes circadian disruption, promoting circadian entrainment, matching schedules with propensities and tolerances, environmental lighting,	N/A
Boivin et al 2007) [93]Working on atypical schedules. Netherlands:	Review	Countermeasures to improve adaptation to shift work	N/A	N/A	N/A	N/A	N/A	N/A

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Haus E, & Smolensky M, (2006)[94] Biological clocks and shift work: circadian dysregulation and potential long-term effects. Springer.	Mechanism and H&S review	Review of circadian dysregulation and long-term health effects	Breast; colon	N/A	N/A	None	Adaptation may be possible but not always feasible or desirable for rapidly rotating workers. Suggestions include the use of bright light and melatonin. Exposure to light at night has been attempted, but required use of dark sunglasses during daytime. Time of food intake may be important in some individuals. In rapidly rotating shifts, the individual should stay on the schedule dictated by their normal habits. Minimize, the number of consecutive night shifts should be no more than 4. The direction of rotation in rapid shifts is also of importance. Forward rotating shifts are more favourable than back rotating ones. Pharmacologic agents such as benzodiazepines may induce sleep and so be helpful in reducing fatigue, but doesn't act on the circadian system.	Circadian dysregulation

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Fritschi L, (2009)[96] Shift work and cancer. England:	Mechanisms review	Review of short and long term effects	Breast	N/A	N/A	None	Major differences in individual responses to sleep loss, sleep disruption, and time zone transitions make it impossible to develop a "one size fits all" shift schedule. Other researchers have concentrated on countermeasures that increase sleep duration, promote quick adaptation to night work, or improve subjective wellbeing at work. One possibility is to use our increasing understanding of the physiological control of the sleep-wake cycle to time our exposure to light and darkness for maximum adaptation. Using phototherapy lamps (especially those producing blue light, which is most efficient in resetting melatonin release time), wearing goggles, wearing sunglasses when driving home, and darkening bedrooms or wearing sleeping masks are being tried. Medications that are stimulants, hypnotics, or chronobiotics (substances that control the body clock) are also being used. It may also be possible to screen workers to select those with factors that seem to be associated with better tolerance of shift work, such as being an "evening person," having better family support, and having fewer responsibilities at home. Shift lengths should be shorter; rest breaks should be included; and researchers should educate shift workers and employers as to how sleep-wake cycles are controlled and how this knowledge can be used to maximise sleep quality, sleep duration, and alertness at work.	Cancer

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Schernhammer & Thompson CA(2011) [95] Light at night and health: the perils of rotating shift work. England:	Epi & Mechanisms review	Editorial for an epi study		N/A	N/A	None	Optimising shift schedules. Genetic screening tests to identify vulnerable populations. The use of exogenous melatonin in night workers. Changing light sources or filtering short wavelength (blue) light. By having night workers wear goggles. Determining which factors relate to shift schedules and what aspects of shift schedules are most detrimental to health.	Cancer

Author	Type of Study	What research question(s) does the study address?	Type of cancer(s) ?	Description of population	What data is provided on shift work?	What evidence is provided on the impact of shift working on the risk of cancer?	What evidence is provided on the steps that could be taken to reduce the risks of shift working?	Outcome Measures e.g., circadian rhythm, cancer, modifications
Rosenberg & Doghramji PP(2011) [97]	Review of treatment options for shift work disorder	Review of the epidemiologic and mechanistic evidence for the health effects of shift work and review of treatment options for shift work disorder	Breast; prostate; skin; ovarian	Various	Various	36% increased relative risk in nurses working nights for 30 years or more. Breast cancer 60% higher in women who worked night shift at least 1 time in the 10 years before diagnosis compared to those that did not. Rotating shift workers at significantly increased risk of prostate cancer than day workers, whereas the risk was not significantly increase for fixed night workers in the same study. Shift work has been associated with decreased risks of skin and ovarian cancer.	Napping to reduce urge for sleep. Use of timed bright light during work periods and restriction of morning light using night goggles in night shift workers during the drive home (use of two in combination). Administration of melatonin to improve adaptation to night-shift work. Use of hypnotics for insomnia and use of alerting agents for excessive sleepiness.	Cancer
Tsai RJ, et al (2014) [99]	Cross-sectional	Are shift workers adherent to cancer screening?	Cancer screening	9009 females who provided shift work information	Regular evening shift, regular night shift, rotating shift or some other schedule	27.4% of sample worked alternative shifts. Non-adherence for breast cancer screening was 35%, for colon cancer screening 10% and no differences between those who worked alternative shifts.	Shift work appears to affect attendance at screening appointments	N/A

Table 7 Guidance documents

Guidance document	Recommendations/advice
Associated Society of Locomotive Engineers and Firemen. Shift work, lifestyle and health section C. **This is an ASLEF booklet.**	**The DTLR Road Safety Research Report on (road) driver sleepiness found:** • That "caffeine (150mg) is an effective countermeasure to sleepiness, as is a short (less than 15 minutes) nap or doze. The two combined together (caffeine in the form of a caffeinated drink, then a nap) are particularly effective. The efficacy of these treatments will depend on the magnitude of the sleepiness. Even 'relaxing with the eyes closed' is worthwhile". However members need to be aware of the adverse effects of too much caffeine. **How do you risk assess shift schedules?** • The HSE published a report "validation and development of a method for assessing the risks arising from mental fatigue". A "Fatigue Index" is used to assess the risks from the impact of rostering on mental fatigue in safety critical work. o The Fatigue Index requires the calculation of 5 factors: shift start time (F1), shift duration (F2), rest period between shifts (F3), breaks during shifts (F4) and cumulative fatigue (F5). These are added together to give an overall index for the roster. **Impact of shift work and fatigue on safety and on mental and visual acuity:** *(main points/findings from Professor Folkhard paper)* • Safe duties are those between 8 and 10 hours (This fits well with ASLEF policy) • Second to fourth hour on duty is a SPAD risk and about 50% of all SPADs occur in this period. This has implications and suggests that longer, but less, turns are safer than shorter, but more turns. (An example would be that 4x10 hours = 40 is actually "safer" than 5x8 = 40 hours, as 4x 2/4 hour peak has one less 2/4 hour SPAD peak risk). • However, there is no real evidence to suggest that risk is significantly increased from working up to 12 hours. • The Report believes that "there is a strong case to be made for developing and piloting a set of guidelines for good practice on one or more TOCs. Drivers and Management's would set guidelines with benefit from expert advice. Trial would last 2/3 years. Then follow up with 6 monthly surveys. • Night turns – should be only 2/3 consecutive turns • Earlies again 2/3 consecutive turns • Rest Periods – minimum 14 hours (Now 12). • PNB's need research to find optimum times and duration. • Commuting time to and from work. No established maximum. DERA suggests max of 1 hour (Eurostar have this already). **Lifestyle training:** *ASLEF action, Reps should take account of:* • Knowledge of the effects of biological rhythms in the planning of shift rostering • Education of shift workers and their families • Environmental design changes, especially those aspects which can improve alertness such as temperature, lighting and comfort levels; • Provide medical advice for shift workers, especially for those with existing medical conditions. • The first and foremost control measure is to eliminate, or reduce as far as possible, the need for shift work. *How to improve sleep and fight "sleep debt":* • Before the first night shift try napping for 2 to 3 hours in the evening; • Inform your family that you need peace and quiet to be able to sleep in the daytime – you could use a "do not disturb" notice; • Make sure that the bedroom is dark and cool;

Guidance document	Recommendations/advice
	• Think about using earplugs; • Remember that tea and coffee are stimulants and also make you want to go to the toilet. Following your last night shift, try sleeping for only 3 or 4 hours, then stay awake all day and go to bed at your normal time. **Advice on nutrition for shift workers:** • Try to develop a regular eating schedule for the shift you are on; • Try to have your main meal of the day in the middle of your awake period and a couple of hours before commencing night duty; • Try to join your family for at least one meal a day, even if it is your 'breakfast' and their supper; • Eat lightly but nutritionally during the night; • Avoid caffeine if possible; • Control your sugar intake. • Take regular exercise, one or two hours before your shift will keep you more alert whilst on duty. • Avoid doing exercise within an hour or two of going to bed, as it increases your alertness and makes falling asleep more difficult. **Shift pattern recommendations (Wedderburn, 1991):** • Minimise permanent nights; • Minimise sequence of nights: only 2-4 night shifts in succession should be worked; • Consider shorter night shifts; • Avoid quick change-overs; • Plan rotas with some free weekends; • Avoid overlong work sequences; • Rotate forward (i.e. clockwise rotation morning/ evenings/ nights); • Avoid early starts.
Associated Society of Locomotive Engineers and Firemen Journal (2012). Stop Working Around The Clock. **ASLEF Journal, published monthly. This issue includes a feature on 'health at work is as important as safety' which includes shift work.**	**Shift working checklist:** • Minimise permanent nights • Minimise sequence of nights, working only 2-4 night shifts in succession • Consider shorter night shifts • Avoid quick change-overs • Plan rotas with some free weekends • Avoid overlong work sequences • Rotate forward (that is, clockwise rotation – morning/ evenings/ nights); • Avoid early starts • Ensure proper rest time between the end of one week's shifts and the start of the following weeks. Further guidance can be found in the health and safety section of the ASLEF web site. **Shift working checklist: for health and safety representatives:** • Find out if members have any problems working shifts. (Remember this can be a sensitive issue, has equal opportunities implications and that shift work is an issue for men and women). • Draw this article to your members' attention, especially the 'What should I do?' section • Find out if the people who set rosters and diagrams have had fatigue risk management training and if they take health issues into account

Guidance document	Recommendations/advice
	when drawing rotas up • Raise any issues locally and with the Company Joint Safety Committee and Company Council. • Develop a Company Council shift-work policy and organise fatigue risk management training. • Inform your District Organiser and ASLEF's Executive Committee of any issues taken up and of any progress (or lack of it).
Electricity Industry Occupational Health Advisory Group (2008). Night work: Guidance note 3.3.	• Medical assessments and advice regarding fitness to work – health assessments o Employer must offer a free health assessment to any worker who is to become a night workers o Offer the opportunity to have further assessments at regular intervals
GMB, London Region Health and Safety Department. Reps guide to shift work.	A best practice approach based on the HSG65 guidelines is suggested for managing shift working arrangements: • Consider the risks of shift work and the benefits of effective management o What are the undesirable effects of shift work? o Consider the costs and benefits of effective management of shift working arrangements. • Establish systems to manage the risks of shift work. o Seek management's commitment to control the risks of shift work; o Identify individuals responsible for shift-working arrangements; and o Consult safety representatives "in good time" and their members. • Assess the risks associated with shift work in your workplace o Consider the risks that workers may be exposed to; o Establish who might be harmed by shift work; and o Consult safety representatives "in good time" and their members. • Take action to reduce those risks o Assess how severe the risks identified are and identify where improvements need to be made: o Improve the shift work schedule; o Improve the working environment; and o Apply appropriate control procedures. • Check and review your shift working arrangements regularly o Implement a system for early reporting of problems associated with shift work; o Monitor alterations to shift work schedules and/or conditions; o Periodically review the effectiveness of the shift working arrangements. While all workers are potentially at risk from shift work, employers should consider certain groups who are more vulnerable than others: • Young workers • Older workers • New and expectant mothers • Workers with pre-existing health conditions, which may be made worse by shift work, such as those with gastro-intestinal problems, coronary heart disease and sleeping problems • Workers taking time-dependency medication such as insulin • Temporary or older workers, such as sub-contractors and maintenance workers, who may not be familiar with or be able to adhere to current shift work schedules, or who have been on a different schedule with a previous employer;

Guidance document	Recommendations/advice
	• Workers, who following a standard day's work, have remained on call through the subsequent night or weekend
Health and Safety Authority (2012). Guidance for employers and employees on night and shift work	**Risk factors associated with shift work and practical advice on how to control them:** **Workload:** • Workload, Mental and physical demands, advice: o Plan an appropriate workload that accords with the length and timing of the shift. o If practical, schedule demanding work for periods when workers are most alert and least likely to be fatigued. o Where possible, demanding, dangerous and safety critical work should be avoided at night time, in the early hours of the morning or at the end of long shifts. o Where work is particularly demanding, consider shortening the length of the shift. **Work activity:** • Work activity, advice: o Where possible, schedule a variety of tasks into the shift and if practicable, allow workers some choice regarding their order of completion. **Shift pattern:** • Regular shifts, advice: o Permanent night shifts should be avoided where possible. o Ensure permanent night and early morning workers are aware of the risks through provision of information. o If practicable, offer workers the choice between permanent and rotating shifts. o Ensure there is adequate supervision. o Ensure adequate time at shift handover so that new shift team is fully aware of any issues in previous shift. • Rotating shifts – advice: o Plan the direction and speed of rotating shifts to assist a worker adapting to rotating shifts. • Forward versus backward rotation, advice: o Adopt forward rotating schedules where possible. o Ensure there is adequate rest time between shifts to comply with the 1997 Act: i.e. a minimum period of 11 hours. • Fast rotation versus slow rotation, advice: o Rotate shifts every two to three days where possible. o Avoid weekly/fortnightly rotating shift schedules where possible. o If fast rotation is not an option, then slow rotation over at least a three week period is the next best option. **Shift timing:** • Night shifts, advice: o Permanent night shifts should be avoided where possible. o Try to find alternatives to night work for those workers who cannot adapt to it. o The Night Work and Shift Work Regulations make allowance for transfer to day work where a night worker becomes ill as a result of night work. o Avoid demanding, monotonous and safety critical work during the night and early morning hours where possible. o Provide workers with information about the risks of night work. o In accordance with the provisions of the Night Work and Shift Work Regulations, ensure a health assessment is made available at regular intervals to night workers. o Where possible, provide the same or similar facilities and opportunities for night workers and day workers.

Guidance document	Recommendations/advice

	• Early morning starts, advice:
	  ○ Avoid early morning starts before 7a.m. where possible.
	  ○ Consider providing transport to work.
	  ○ Provide information to workers on the risks of shift work.
	• Afternoon starts, advice:
	  ○ Adopt afternoon starts in preference to night or early morning starts.
	• Daytime shifts, advice:
	  ○ Adopt day shifts in preference to night, early morning and afternoon starts where possible.
	Shift duration:
	• 8 hour shifts, advice:
	  ○ There are few differences in the effects of 8 and 12 hour shifts on workers and there are no clear advantages to either system.
	  ○ Eight hour shifts are preferable when the work is monotonous, demanding (physically or mentally) or safety critical.
	• 12 hour shifts, advice:
	  ○ Avoid 12 hour shifts when the work is monotonous, demanding (physically or mentally) or safety critical.
	  ○ Provide frequent and regular breaks to reduce the risk of fatigue.
	  ○ Limit 12 hour night shifts to 2 to 3 consecutive nights where possible.
	  ○ Be aware of the needs of vulnerable workers and transfer them to shorter shifts if necessary.
	  ○ Avoid shift overrun and overtime.
	  ○ Monitor shift swopping by workers.
	  ○ Discourage workers from doing second jobs on their free days.
	  ○ Make adequate arrangements to cover absentees.
	  ○ Consider additional day shifts to allow for absentees, training and development.
	• Shifts longer than 12 hours, advice:
	  ○ Avoid shifts longer than 12 hours.
	  ○ It is likely workers will not get the required minimum rest period of 11 hours under the 1997 Act.
	• Variable shift lengths, advice:
	  ○ Variable length shifts may be considered, as long as it is remembered that they require more planning.
	• Split shifts, advice:
	  ○ Avoid split shifts as they do not allow for adequate rest breaks between shifts.
	Rest breaks within shifts:
	• Rest breaks within shifts, advice:
	  ○ Under the 1997 Act workers are entitled to a 15 minute break after 4.5 hours and 30 minutes after 6 hours.
	  ○ Depending on the workload and length of shift, short regular breaks reduce the risk of fatigue.
	  ○ Allow workers some choice over when they take a break.
	  ○ Where work is machine/system controlled and not self- paced, introduce frequent breaks into shift schedule.
	  ○ Naps need close supervision and should not be allowed where safety critical decisions are made.
	  ○ If adopted, a break of 40 minutes is needed to allow workers a 20 minute nap and time to refresh themselves and regain alertness before resuming work.
	  ○ Make facilities available which encourage workers to take their longer breaks away from their work station.
	Rest breaks between shifts:
	• Rest breaks between consecutive shifts, advice:

Guidance document	Recommendations/advice
	○ Ensure the minimum time between shifts is 11 hours in order to comply with the 1997 Act and allow workers time to commute, eat, sleep and enjoy family and social life. • Rest days, advice: ○ Normally, a limit of five to seven consecutive working days should be set for standard (seven to eight hour) shifts. Where shifts are longer, for night shifts and early morning shifts a limit of two to three consecutive shifts followed by two to three rest days may be preferable. ○ Under the 1997 Act, workers are entitled to a 24 consecutive hours rest period per week, although rest days may be averaged over a fortnight. ○ When switching from day to night shifts or vice versa, make provision for a minimum of two nights of full sleep to enable workers adjust to a new schedule. ○ The 1997 Act states the rest period shall be a Sunday unless otherwise provided in the employee's contract of employment. **Provision of a health assessment and of workplace health promotion can prevent illness.** **Physical environment:** • Facilities, advice: ○ Where reasonably practicable provide similar facilities. ○ The requirements of the General Application Regulations (GAR) 2007, Regulations 18 to 25 (welfare and sanitary) and 163 to 166 (first aid) apply. • Lighting, advice: ○ Minimum compliance with Regulation 8 GAR 2007 ○ This is a technical area requiring specialist advice. • Temperature, advice: ○ Minimum compliance with Regulation 7 GAR 2007. ○ Allow workers control of the temperature if possible. Often outside night temperatures are cooler than daytime and additional warmth may be needed. • Ventilation, advice: ○ Minimum compliance with Regulation 6 GAR 2007. • Humidity, advice: ○ Air should be neither too dry nor too moist. **Management issues:** • Supervision, advice: ○ Minimum compliance with S8 and S10 of The Safety, Health and Welfare at Work Act 2005. ○ Shift supervisors should be trained to recognise risk factors leading to fatigue and be able to identify fatigued workers. ○ Consider increased supervision during periods of low alertness, night and early morning, following lunch and towards the end of long shifts. • Overtime, advice: ○ Avoid overtime where possible by having relief available to cover absences, emergencies etc. ○ If unavoidable, monitor individual hours worked to avoid excessive work hours especially where shift swapping is allowed. • Shift swapping, advice: ○ Monitor shift swapping to avoid excessive working hours. • Standby and on-call duties, advice: ○ Ensure adequate rest periods are provided for workers on standby and on call.

Guidance document	Recommendations/advice

	• Training and information, advice:
	  ○ Minimum compliance with S8 and S10 of 2005 Act is required.
	  ○ Provide information to workers and their supervisors on the risks of shift work and any relevant risk factors identified.
	  ○ Encourage workers to report any shift related problems.
	  ○ Encourage workers to adopt healthy behaviours and coping strategies outside of work.
	  ○ Provide training during their shift if possible.
	  ○ If workers have to attend training during their rest period, compensatory time off must be given.
	  ○ Consider additional shift teams to facilitate attendance at training and development.
	• Communication, advice:
	  ○ Encourage team working if possible.
	  ○ Ensure lone workers are contacted at regular intervals during the shift.
	  ○ Provide remote workers with phones and/or means of communication.
	  ○ Ensure adequate time is allowed to share information between shifts.
	  ○ Having a short overlap at the end of one shift and the start of the next will assist.
	  ○ Ideally information handover should be person to person.
	Health assessment, promotion and security:
	• Health assessment, advice:
	  ○ Comply with minimum requirements of Regulations 146 (health assessment for young persons), 151 (transfer to day work for pregnant workers) and 157 (health assessment for night workers) of GAR 2007 (see Section 6 of this guidance).
	  ○ Provide health assessment for night workers before starting work and at regular intervals.
	  ○ Transfer workers to day work where night shift causes or is likely to cause ill health effects.
	  ○ Encourage workers to inform their G.P. about their working arrangements.
	• Health promotion, advice:
	  ○ Where possible promote healthy behaviours such as healthy eating and exercise (see Section 5 of this guidance).
	• Security, advice:
	  ○ Ensure car parks are well lit and secure (security cameras may assist).
	  ○ Design shift start and end times around availability of public transport if possible.
	  ○ If not, consider providing transport to and from work.
	  ○ Ensure lone workers have access to telephones and are contacted regularly during shifts.
	
	Practical advice for employees:
	• Driving to and from work
	  ○ Get a lift, or use public transport or a taxi if possible
	  ○ Share lifts
	  ○ Drive carefully and do not speed
	  ○ Do not drive if overtired
	  ○ Stop for a quick rest if you feel sleepy while driving
	• Sleep pattern
	  ○ Find out if you sleep better by going to bed soon after returning home from work or waiting up and going to sleep before the next shift
	  ○ Have a short sleep before your first night shift

Guidance document	Recommendations/advice
	○ Have a short sleep after coming off night shifts and go to bed early that night • Sleep environment ○ Use your bedroom for sleep and not as an entertainment room (e.g. no television) ○ Avoid falling asleep in the living room ○ Choose a quiet room as your bedroom, where there is least disturbance from outside and internal noise and sounds ○ Blackout the bedroom as much as possible to keep out daylight, this will help you sleep and encourage melatonin production, vital for the suppression of tumours ○ Consider using heavy curtains or blinds, which can help in blacking out the room ○ Put your mobile on silent and landline ringing volume on low ○ Ask your family to keep the noise levels down from voice, radio, television and not to disturb you ○ If necessary let your neighbours know your schedule and request them to avoid use of noisy machines such as grass mowers and power tools when you should be sleeping ○ If they have a dog that barks a lot, ask them to bring it inside if possible ○ Use ear muffs and eye shields if necessary ○ Maintain a cool temperature: not too warm in the bedroom • Promoting sleep ○ Do some gentle exercise such as a short walk (but don't over exercise as it stimulates the body and raises temperature) ○ Get relaxed by reading or listening to music or watching a television programme ○ Have a shower or bath ○ Avoid drinking caffeine or other stimulants a few hours before going to sleep ○ Drink very little alcohol as it reduces the quality of sleep (see Section 5.7 stimulants and sedatives) ○ If you are hungry eat a light meal; don't go to bed hungry or overfed • Diet ○ Eat regular light meals as heavy meals can cause drowsiness ○ Avoid fatty foods as they are more difficult to digest ○ Choose foods that are easily digestible such as pasta, rice, bread, fruit and vegetables ○ Avoid sugary foods, which do provide a short energy boost, but then cause a dip in energy levels ○ Eat plenty of fruit and vegetables, which are a good option as their sugar is converted slowly into energy and they also provide vital vitamins, minerals and fibre ○ Drink plenty of water to avoid dehydration which affects both physical and mental performance; add a sweetener if you don't like water ○ However, don't drink too much before sleeping as it will result in you waking up early to relieve your bladder • Stimulants and sedatives ○ Caffeine is a mild stimulant found in coffee, tea, cola, energy drinks and in tablet form. It can improve reaction time and feelings of alertness for short periods. Occasional use of caffeine is fine, but it should not be used to keep you awake. You also need to be aware of what might happen when its effects wear off ○ Alcohol can promote the onset of sleep. However, it is associated with waking up early, disrupted sleep and poorer sleep quality. Excessive use can result in dependency and addiction and lead to long-term damage to your physical and mental health, work performance and family and social relations ○ Regular use of sleeping pills can lead to dependency and addiction • Physical exercise ○ General physical exercise advice, at least 30 minutes daily exercise.

Guidance document	Recommendations/advice

	• Social support
	  ○ Let your family and friends know about how shift work affects you. If they understand the problems, they can be more supportive
	  ○ Let them know your shift schedule well in advance. This means that social and family activities can be planned around your shift schedule
	  ○ Get involved as much as possible with family activities such as meals, household chores, sport and going out together
	  ○ Plan your domestic chores and duties so that they do not disrupt your rest and sleep schedule
	  ○ Try to carry out some social activities with work colleagues who share similar shift schedules to you as they may be available when family and friends are not
	• Keeping alert at work
	  ○ Exercise lightly before starting work
	  ○ Keep light levels bright
	  ○ Maintain adequate room temperature and ventilation
	  ○ Take regular short breaks if allowed
	  ○ Walk away from your work station during breaks
	  ○ If possible do more stimulating work when you begin to feel drowsy
	  ○ Keep in contact with colleagues

Health and Safety Executive (2006). Managing shift work: health and safety guidance.	**A systematic approach to assessing and managing the risks associated with shift work:**
	• Consider the risks of shift work and the benefits of effective management
	  ○ What are the undesirable effects of shift work?
	  ○ Consider the costs and benefits of effective n management of shift-working arrangements.
	• Establish systems to manage the risks of shift work.
	  ○ Seek management commitment to control the risks n of shift work.
	  ○ Identify individuals responsible for shift-working n arrangements.
	  ○ Involve safety representatives and workers
	• Assess the risks associated with shift work in your workplace.
	  ○ Consider the risks that workers may be exposed to.
	  ○ Establish who might be harmed by shift work.
	  ○ Consult workers and their safety representatives.
	• Take action to reduce these risks.
	  ○ Assess how severe the risks are and identify where n improvements need to be made.
	  ○ Improve the shift-work schedule.
	  ○ Improve the workplace environment.
	  ○ Apply good practice guidelines.
	• Check and review your shift-work arrangements regularly.
	  ○ Implement a system for early reporting of problems n associated with shift work.
	  ○ Monitor alterations to shift-work schedules and/or n work conditions.
	  ○ Periodically review the effectiveness of your shift- n working arrangements
	
	While all workers are potentially at risk from shift work, you should consider certain groups who are more vulnerable than others. These include:
	• Young workers;

Guidance document	Recommendations/advice
	• Older workers; • New and expectant mothers; • Workers with pre-existing health conditions, which may be made worse by shift n work, such as those with gastro-intestinal problems, coronary heart disease and sleeping problems; • Workers taking time-dependent medication such as insulin; • Temporary and other workers, such as sub-contractors and maintenance n workers, who may not be familiar with or be able to adhere to current shift work schedules, or who have been on a different schedule with a previous employer; • Workers, who following a standard day's work, have remained on call through the subsequent night or weekend **Consult workers and safety reps, including:** o Encourage workers to share their experiences of shift work; o Discuss which shifts are hardest and why; o Use assessment tools and techniques to highlight potential problems and n compare different shift schedules (see appendix 3); o Provide examples of different shift-work schedules; o Invite spontaneous contribution of ideas. **Improve the shift work schedule:** **Workload:** • Workload, Mental and physical demands, advice: o When planning work, plan an appropriate workload, according to the length and the timing of the shift. If practical, schedule demanding work for periods when workers are most alert and least likely to be fatigued. Where possible, demanding, dangerous and/or safety-critical work should be avoided during the night and early hours of the morning and towards the end of long shifts. When work is particularly demanding, consider shortening the length of the shift. **Work activity:** • Work activity, advice: o Where possible, schedule a variety of tasks into the shift plan and if practicable, allow workers some choice regarding their order of completion. **Shift pattern:** • Permanent shifts, advice: o Permanent night shifts should be avoided where possible, although some workers and supervisors may find them desirable. Ensure staff, especially those who work permanent night shifts or early morning shifts are aware of the risks, through provision of training and information. o If reasonably practicable, offer workers the choice between permanent and rotating shifts. o Ensure there is enough supervision of shifts to facilitate communication between workers and promote appropriate behaviour and rational decision making. o Improve communication at shift handover to ensure that new shift teams are fully aware of issues that have arisen during the previous shift. • Rotating shifts – comment: o Rotating shift schedules reduce the number of nights an individual has to work, as night work is shared between all workers. However, the constantly changing shift pattern means that workers may have difficulty adapting to the schedule. The direction and speed of rotation can influence how an individual adapts to rotating shifts.

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	• Forward versus backward rotation, advice:
	  ○ Adopting forward-rotating schedules rather than backward-rotating, may help reduce sleep loss and fatigue.
	  ○ Ensure there is adequate rest time between shifts. Under the WTR, the minimum time allowed between shifts is 11 hours.
	• Fast rotation versus slow rotation, advice:
	  ○ Rotating shifts every 2-3 days is recommended, as the internal body clock does not adapt and sleep loss can be quickly recovered, reducing the risk of fatigue and ill health.
	  ○ Weekly/fortnightly rotating shift schedules are not recommended. Avoid these where possible.
	  ○ If fast rotation is not possible, then slowly rotating shifts over at least a 3-week period is the next best option.
	Shift timing:
	• Night shifts, advice:
	  ○ Only a limited number of workers can successfully adapt to night work. Try to find alternatives to night work for those workers who cannot adapt. Where possible, permanent night shifts should be avoided.
	  ○ Consider the type of work being done and the workload. Where possible, avoid demanding, monotonous, dangerous and/or safety-critical work during the night and early hours of the morning.
	  ○ Provide training and information about the risks of shift work for workers and their families. Make staff aware of sources of information and support, such as child care and counselling services. Under the WTR, night workers have a right to receive free health assessments.
	  ○ Where reasonably practicable, provide similar facilities and opportunities for night workers as those available for your daytime workers.
	• Early morning starts, advice:
	  ○ Where early morning starts are not essential for business needs, avoid shift starts before 07.00 am. Consider if providing transport to and from the workplace would be beneficial.
	  ○ Provide training and information about the risks of shift work for workers and their families. Make staff aware of sources of information and support, such as child care and counselling services.
	• Afternoon starts, advice:
	  ○ Afternoon shifts are suitable for most workers and where practicable, you should adopt them in preference to night or early morning shifts.
	  ○ Provide training and information about the risks of shift work for workers and their families. Make staff aware of sources of information and support such as child care and counselling services.
	• Daytime shifts, advice:
	  ○ Where practicable, adopt day shifts rather than night or early morning shifts.
	Shift duration:
	• 8 hour shifts, advice:
	  ○ There are few differences in the effects of 8-hour and 12-hour shifts on workers and there are no clear advantages to either system. However, the nature of the work needs to be considered. 8-hour shifts are preferable when work is monotonous, demands concentration or vigilance, is isolated, is safety critical and/or there is exposure to work-related physical or chemical hazards.
	• 12 hour shifts, advice:
	  ○ Avoid shifts that are longer than 8 hours, where work is demanding, safety critical or monotonous and/or there is exposure to work-related physical or chemical hazards. Encourage and promote the benefit of frequent and regular breaks to reduce the risk of fatigue. Allow adequate recovery time between shifts and bear in mind that commuting times and availability of public transport

Guidance document	Recommendations/advice
	may contribute to the fatigue related to long shifts. Limit 12-hour night shifts to 2-3 consecutive nights. ○ Consider the needs of vulnerable workers: arrange for these workers to do shorter shifts if necessary. ○ Shifts should not be planned to be longer than 12 hours. Avoid overrun and discourage overtime. Monitor and control shift swapping. Make adequate arrangements to cover absentees. Discourage workers from taking second jobs. If this is a particular problem you could set this as a condition of employment in contracts of work. ○ Make adequate arrangements to cover absentees. Some companies include an extra shift in their rosters (usually days) to allow flexibility and time for training, development etc. Monitor and control shift swapping. • Shifts longer than 12 hours, advice: ○ Avoid shifts that are longer than 12 hours in length. Avoid overrun and discourage overtime. Monitor and control shift swapping. Make adequate arrangements to cover absentees. Discourage workers from taking second jobs. • Variable shift lengths, advice: ○ Consider if shifts of variable duration and/or flexible start and end times could offer a suitable compromise for your organisation. Bear in mind that schedule design will be more complex and require more planning and organisation. • Split shifts, advice: ○ If reasonably practicable, avoid split shifts, as they do not allow enough recovery time between shifts. If split shifts are necessary, ensure that suitable on-site catering and rest facilities are available. ○ Ensure workers are aware of the risks of shift work, through provision of training and information. **Rest breaks within shifts:** • Rest breaks within shifts, advice: ○ Encourage and promote the benefit of frequent and regular breaks to reduce the risk of fatigue. Under the WTR, workers are entitled to a 20-minute rest break if the working day is longer than six hours. But consider the length of the shift and the workload when planning the amount and length of breaks. A short break of 5-15 minutes every 1-2 hours may help maintain performance and reduce accidents, particularly when the work is demanding or monotonous. ○ If practicable, workers should be allowed some discretion over when they take a break from work. Ideally, workers should be allowed to rest before they experience fatigue. However, workers may not always act as the best judge of when a break is needed and should be strongly discouraged from saving up their rest time in order to leave earlier. Where the pace is out of the worker's control (e.g. machine/system paced), schedule frequent rest breaks in the shift plan. ○ Napping should be well supervised and only be used as a strategy in organisations where there is a high risk of involuntary sleeping, such as driving and night-time vigilance tasks. Do not adopt it in work environments where important decisions, especially safety-critical decisions, could be clouded by sleepiness. If napping is adopted, appropriate facilities should be provided with scheduled breaks of around 40 minutes to allow workers sufficient time to have a short nap, refresh themselves and regain alertness before resuming work. ○ Make facilities available and encourage workers to take their longer breaks away from their workstation. **Rest breaks between shifts:** • Rest periods between consecutive shifts, advice: ○ Workers need sufficient time between shifts to commute, eat meals, sleep and participate in domestic and social activities. Under WTR, the minimum time allowed between shifts is 11 hours. • Rest days, advice: ○ In general, a limit of 5-7 consecutive working days should be set for standard (i.e. 7-8 hour) shifts. Where shifts are longer than this, for night shifts and for shifts with early morning starts it may be better to set a limit of 2-3 consecutive shifts, followed by 2-3 rest days to allow workers to recover.

Guidance document	Recommendations/advice
	○ Consider if regular refresher training in complex procedures and time allowed for refamiliarisation/updating would help when there are extended rest periods (including holidays) between successive shifts. ○ Under WTR, workers are entitled to a 24-hour day off per week, although days off may be averaged over a fortnight. When switching from day to night shifts or vice versa, make provision to allow workers a minimum of 2 nights of full sleep to enable them to adjust to the new schedule. ○ Where possible, regular weekend breaks should be built into the shift schedule. **How factors in the workplace environment may increase the risks associated with shift work and offer advice on how to make improvements to reduce these risks.** **Physical environment:** • Facilities, advice: ○ Where reasonably practicable, provide similar facilities and opportunities for shift workers as those available for your daytime workers. Where this is not possible, it is important to make provision for workers to make a drink and heat up food and to allow workers to take their longer/meal breaks away from their workstation. First-aid facilities, and if possible, a trained first-aider should be made available for all shifts. • Lighting, advice: ○ You should take into account the extent of natural lighting, the reflective properties of the surrounding area and the work materials, the nature of tasks being undertaken and the age of the workforce when you consider workplace lighting. A combination of direct and indirect lighting (e.g. up lighting) will help reduce glare and areas of shadow. ○ The practical application of bright light exposure to shift-work schedules is a complicated area. As yet it is relatively untried, and may require considerable resource. Seek specialist advice when considering this as a means of increasing alertness. • Temperature, advice: ○ Monitor workplace temperature on a regular basis to determine if adjustments to the heating supply need to be made for particular shifts. For example, during the night, heating may need to be increased to compensate for the drop in body temperature; however, a warm, stuffy atmosphere can cause drowsiness. Allow workers control of local heating arrangements. Where maintaining a comfortable temperature is impractical, take all reasonable steps to achieve a temperature which is as comfortable as possible. These may include providing localised heating/cooling devices, appropriate clothing and provision of rest facilities. **Management issues:** • Supervision, advice: ○ Consider if increased supervision would be beneficial during key periods of low alertness, e.g. during the night and early hours of the morning, following lunch and towards the end of long shifts. Ensure supervisors are aware of the risks of shift work, through provision of training and information. Ensure that they are sufficiently trained to recognise the symptoms of fatigue, which may indicate that a worker is failing to cope with their current shift-work schedule or that there are general problems with the shift-working arrangements. • Overtime, advice: ○ Where possible, avoid overtime by establishing systems to provide relief staff to cover absentees, vacancies, increased workloads and emergencies. If overtime is unavoidable, review a worker's preceding work and rest periods before agreeing to it. You should also monitor and record the hours that individuals have worked to identify where action should be taken to avoid excessive working hours. This is especially important when an individual has opted out of WTR, in workplaces where shift swapping is permitted and during exceptional circumstances such as emergency workers attending an incident. • Shift swapping, advice:

Guidance document	Recommendations/advice
	○ Shift swapping should be monitored and recorded by supervisors. It is important to review a worker's scheduled work and rest periods before agreeing to a swap to avoid excessive hours being worked. • Standby and on-call duties, advice: ○ Under WTR, periods when workers carrying out standby and on-call duties are required to be at the workplace, whether working or not, is considered working time. Make provision in the work schedule to allow adequate rest for those workers carrying out standby/on-call duties. Ensure workers are aware of the risks associated with fatigue through provision of training and information. • Training and information, advice: ○ Tailored training and/or information regarding the risks associated with shift work should be available for workers, their families, their supervisors, safety representatives and management. Make workers aware of the potential impact fatigue may have on safety, health and well-being. Encourage workers to report shift work-related problems they may have and consider any suggestions workers make in relation to improving the shift-working arrangements. Encourage workers to take responsibility for their welfare outside work and promote the use of appropriate coping strategies to help workers and their families to adapt to shift work (see Appendix 2). ○ If possible, arrange/adapt training sessions to the shift pattern rather than restricting it to daytime hours. Alternatively, ensure that workers are given compensatory time off if they have to attend training during rest periods by establishing a system to provide relief staff when required. To help this, some companies include extra shifts in their rosters (usually on days) to allow flexibility and time for training and development. • Communication, advice: ○ Encourage interaction and if possible arrange for employees to work together or in teams. If an employee must work alone, encourage them to make contact with other workers at regular intervals. If they are located remotely then contact can be provided by telephone or similar communications devices. In case of emergency, provide an alarm or other communication device. Ensure information on workplace issues is made available to all staff. ○ Agree on, and make sure timing and procedures for transmitting information to the next shift team are clear, available to all staff and followed at all times. Avoid extending shifts by good planning of the handover, e.g. by building in a small overlap between start and finish times on consecutive shifts. Ideally, shift handovers should be conducted face-to-face and be two-way, with all participants taking responsibility for ensuring accurate communication, using both verbal and written means, be based on a pre-determined analysis of the information needs of incoming staff and be given as much time as necessary to ensure clear and accurate communication. **Welfare:** • Occupational health, advice: ○ Encourage workers to inform their doctor about their working arrangements, as this may help early diagnosis of any shift work-related ill health. Consider if alternative work is available for workers who have difficulties adapting to shift work or develop shift work-related health problems. This is particularly important for groups such as ageing workers and new and expectant mothers who might be more vulnerable to the risks of shift working. ○ Promote healthy living strategies like increasing exercise and improving diet, such as those included in Appendix 2. ○ Employers should seek specialist advice from a suitably qualified health care professional, when devising and assessing the results of health assessments. If a worker suffers from health problems that are caused or made worse by night work, you should, where possible, transfer him or her to day work. • Lone working/violence, advice: ○ Employers should take steps to make sure that the workplace and its surroundings are well lit, safe and secure. Consider if shift start and end times can be adjusted to fit in with the availability of public transport. If not, consider providing transport to and from the workplace. Promote car sharing and ensure car parks and entrances are well lit and secure. Encourage communication

Guidance document	Recommendations/advice
	between workers and ensure all, especially those who work alone, have access to telephones and alarm systems. Consider if you need to install security cameras and/or provide security staff.
Joint submission from social and public health sciences unit and the Scottish collaboration for public health research and policy.	This document is a response to the economy, energy and tourism inquiry. The document suggests there is some evidence that reorganisation of working schedules can have a positive impact on employees health (Bambra et al, 2008).
Labour Research Department: FACT Service (2012). Breast cancer link to working night shifts, 74(22).	This is a short overview of research in the area, highlighting the Danish compensation system for women suffering from breast cancer who had worked night shifts for longer than 20 years, paid for through employer insurance. This article highlights that advice from HSE and government is needed for employers so that they can reduce the risk of female workers developing breast cancer, such as through safer shift patterns.
Office of Rail Regulation (2012). Managing Rail Staff Fatigue. **Guidance document**	The document focuses on the management of fatigue of workers, not solely in relation to shift work. **Examples of controls for managing and mitigating fatigue risk for shift workers include:** • Shorter shifts • Fewer successive shifts without a rest day • Steps to reduce short-notice variations in planned start times • Enhanced fatigue education and training • How to recognise fatigue • Ensuring staff remain fit for duty throughout their shifts • Have a policy and agreed arrangements for shift exchange to prevent swapping shifts without proper assessment of the potential fatigue consequences • Monitor trends in shift exchange **Limits for hours worked and working patterns for safety critical workers are generally appropriate for:** • The maximum length of any work shift or period of duty; • The minimum rest interval between any periods of duty; • The maximum number of hours to be worked in any seven day period; • The minimum frequency of rest days; • The maximum number of consecutive day shifts; • The maximum number of consecutive night shifts and early-morning shifts; and • The maximum period of time between breaks, including breaks for meals. **Good practice for maximum shift lengths would be as follows (RSSB T059):** • Day shift – twelve hours • Night & early shifts – ten hours • Shifts starting before 0500 - eight hours.

Guidance document	Recommendations/advice
	Good practice for the maximum number of consecutive shifts before a rest day would be as follows (RSSB report T059): • Day (including mixed patterns) – seven • Night – three • Early – five **Working patterns designed to:** • Minimise the build-up of fatigue by restricting the number of consecutive night or early-morning shifts; • Allow fatigue to dissipate by ensuring adequate rest between shifts and between blocks of shifts; and • Minimise sleep disturbance. **Features of work patterns to consider:** • Timing of shift start • Length of shift • Weekly work-rest ratio • Shift rotation • Predictability
Health and Wellbeing for UK Rail: Workshop 2: (2013). Institute for Manufacturing.	• This report is from a one day workshop mapping the future of health and wellbeing for the UK rail industry. It doesn't specify specific recommendations for shift working. • In the short term fatigue/shift patterns, the future occupational cancer burden/ shift work and fatigue/shift patterns were highlighted as a health and wellbeing challenge and opportunity under occupational health and the effect of work on health. In the medium term there is a challenge and opportunity for assistance in managing a shift work lifestyle to enable better sleep, eating habits and exercise.

The Young Foundation (2011). Rough Nights: The growing dangers of working at night.	**Advice and tips for night workers:**
	Getting enough sleep
	• Having a bedtime ritual that you follow before going to sleep. This could involve having a hot bath, avoiding stressful or stimulating activity directly before bed.
	• Lower the temperature of the room you are sleeping in – people sleep better in cooler environments
	• Try not to let your mind dwell on the upcoming shift or other stressful situations. Try to concentrate on innocuous relaxing activities such as walking on a beach/going to the park etc.
	• If you can't sleep, get up and do something in another room to distract yourself. It doesn't help lying in bed worrying that you can't sleep.
	• When sleeping in the day:
	  ○ Turn off mobile phones, disconnect landlines, consider putting up a notice at your door that you do not want to be disturbed
	  ○ Wear ear plugs and eye shades
	  ○ Use thick, light blocking curtains – these will also reduce other noises
	  ○ Ask family and friends at home to make sure it is a peaceful place during the day
	• Avoid alcohol before going to bed and don't drink caffeine for up to four hours before going to bed
	• Drink less fluid before going to bed to avoid trips to the toilet
	• Eat a small meal before going to bed to prevent hunger, but avoid heavy meals which are hard to digest
	• Avoid nicotine before going to bed; it is a stimulant
	• Drink less fluid before going to bed to avoid trips to the toilet

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	• Eat a small meal before going to bed to prevent hunger, but avoid heavy meals which are hard to digest • Avoid nicotine before going to bed; it is a stimulant • Regular exercise during the day helps sleep patterns **Get plenty of sleep before your first shift** • Try to have a long lie-in in the morning • Try staying up later the night before to adjust • Have a sleep in the afternoon, so that you are well rested before you start **Napping during your shift** • Try to have a short nap during the shift, as short as 20-40 minutes. They should be no longer than 45 minutes **Don't neglect your relationships** **Let your GP know you work night shifts** **Pay particular attention to your journey home** • Consider sharing lifts home • Have a nap if you are feeling sleepy • Consider using public transport **Stay vigilant when you are most vulnerable** **Keep the lights on during your shift** **Eat and drink properly** **Reduce your caffeine intake** **Be vigilant if operating heavy machinery or safety equipment**
UNISON. Gender, safety and health: a guide for UNISON safety reps.	• The Working Time Regulations require that health assessments are provided for all night shift workers: ○ UNISON believes that employers should offer advice on breast and prostate cancer awareness and breast and prostate examination as part of the health assessment. • It is recommended that women avoid or be relieved of irregular hours or rotating shifts during pregnancy.
UNITE the Union (2013). Unite guide to shift work and night work: a health and safety issue for Unite members.	All workers are potentially at risk if they do shift work – and some groups may be even more so: • Young workers and older workers • New and expectant mothers – women of childbearing age • Workers with pre-existing health conditions or disabilities e.g. heart disease, sleep apnoea • Workers taking medication e.g. the effectiveness of insulin for diabetics may be affected by changing routines • Temporary, agency or contract workers who may not be used to shift work and may not be aware of their legal rights. **Suggested guidelines for shift design:** • Plan an appropriate and varied workload. • Offer a choice of permanent or rotating shifts and try to avoid permanent night shifts.

Guidance document	Recommendations/advice
	• Either rotate shifts every 2-3 days or every 3-4 weeks - otherwise adopt forward rotating shifts. • Avoid early morning starts and try to fit shift times in with the availability of public transport. • Limit shifts to 12 hours including overtime, or to 8 hours if they are night shifts and/or the work is demanding, monotonous, dangerous and/or safety critical. • Encourage workers to take regular breaks and allow some choice as to when they are taken. • Consider the needs of vulnerable workers, such as young or ageing workers and new and expectant mothers. • Limit consecutive work days to a maximum of 5 -7 days and restrict long shifts, night shifts and early morning shifts to 2-3 consecutive shifts. • Allow 2 nights' full sleep when switching from day to night shifts and vice versa. • Build regular free weekends into the shift schedule. **Suggested guidelines for the work environment- employers should:** • Provide similar facilities as those available during the daytime – such as a canteen – and allow shift workers time for training and development. • Ensure temperature & lighting is appropriate and preferably adjustable. • Provide training and information on the risks of shift work and ensure supervisors and management can recognise problems. • Consider increasing supervision during periods of low alertness. • Control overtime, shift swapping and on-call duties and discourage workers from taking second jobs. • Set standards and allow time for communication at shift handovers. • Encourage interaction between workers and provide a means of contact for lone workers. • Encourage workers to tell their GP that they are shift workers. • Provide free health assessments for night workers. • Ensure the workplace and surroundings are well lit, safe and secure. **Practical issues for safety reps to consider with members when negotiating agreements:** • Hours • Training • Welfare and other issues to be considered **Other important provisions of the working time regulations:** • Daily rest • Breaks • Maximum weekly working time • Annual leave • Changes to the employment contract • Agency workers • Personal injury claims

Appendix 1 Current, ongoing and planned research

Funding recently awarded for research on shift work and cancer, identified through funders and researchers:

- Eero Pukkala received funding from the Nordic Cancer Union Research Grant for the project "Work and cancer: in-depth studies initiated by the NOCCA project" in 2011, 2012 and 2013.
- National Cancer Institute's Epidemiology and Genetics Research Program is funding a study titled "Nurses' Health Study II: Risk Factors for Breast Cancer Among Younger Nurses." This project is looking at a number of risk factors for post-menopausal breast cancer, including shift work.
- RIVM and ErasmusMC University in Rotterdam are conducting studies on the effects of long-term shift work on health outcomes.
- There are currently two ongoing grants funded by the Canadian Breast Cancer Foundation:
    - Dr. John Spinelli, BC Cancer Agency (Vancouver, British Columbia). Grant funded in 2014: Occupational and other risk factors in relation to breast cancer subtype
    - Dr. Olga Kovalchuk, University of Lethbridge (Lethbridge, Alberta). Grant funded in 2012: Shift work and breast cancer: an epigenetic connection

Recent work that has been published on shift work and cancer, identified through funders and researchers:

Erren, T. C., Herbst, C., Koch, M. S., Fritschi, L., Foster, R. G., Driscoll, T. R., ... & Liira, J. (2013). Adaptation of shift work schedules for preventing and treating sleepiness and sleep disturbances caused by shift work. The Cochrane Library.

Åkerstedt, T., Knutsson, A., Narusyte, J., Svedberg, P., Kecklund, G., & Alexanderson, K. (2015). Night work and breast cancer in women: a Swedish cohort study. BMJ open, 5(4), e008127.

Erren, T. C., & Morfeld, P. (2014). Computing chronodisruption: How to avoid potential chronobiological errors in epidemiological studies of shift work and cancer. Chronobiology international, 31(4), 589-599.

Erren, T. C., Morfeld, P., & Groß, V. J. (2015). Night shift work, chronotype, and prostate cancer risk: Incentives for additional analyses and prevention. International Journal of Cancer.

Fernandez, R. C., Peters, S., Carey, R. N., Davies, M. J., & Fritschi, L. (2014). Assessment of exposure to shiftwork mechanisms in the general population: the development of a new job-exposure matrix. Occupational and environmental medicine, 71(10), 723-729.

Fritschi, L. (2009). Shift work and cancer. BMJ, 339.

Fritschi, L., Erren, T. C., Glass, D. C., Girschik, J., Thomson, A. K., Saunders, C., ... & Heyworth, J. S. (2013). The association between different night shiftwork factors and breast cancer: a case–control study. British journal of cancer, 109(9), 2472-2480.

Fritschi, L., Glass, D. C., Heyworth, J. S., Aronson, K., Girschik, J., Boyle, T., & Erren, T. C. (2011). Hypotheses for mechanisms linking shiftwork and cancer. Medical hypotheses, 77(3), 430-436.

Girschik, J., Heyworth, J., & Fritschi, L. (2010). Re:"Night-shift work and breast cancer risk in a cohort of Chinese women". American journal of epidemiology, 172(7), 865-866.

Hammer, G. P., Emrich, K., Nasterlack, M., Blettner, M., & Yong, M. (2015). Shift Work and Prostate Cancer Incidence in Industrial Workers: A Historical Cohort Study in a German Chemical Company. Deutsches Ärzteblatt International, 112(27-28), 463

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Ongoing work on shift work and cancer identified during data extraction:

Reference	Type of Study	What research question(s) does the study address?
Demers, P., Martinsen, J. I., Weiderpass, E., Kjærheim, K., Lynge, E., Sparén, P., & Pukkala, E. (2011). Cancer incidence among Nordic firefighters. Occupational and Environmental Medicine, 68(Suppl 1), A19-A20.	Abstract of epi study.	Examine the risk of cancer among firefighters.
Fritschi, L., Erren, T., Glass, D., Saunders, C., Girschik, J., Boyle, T., El-Zaemey, S., Thomson, A.K., Roger, P., Peters, S., Slevin, T., D'Orsogna, A. De Vocht, F., & Heyworth, J. (2013). 205 Biological mechanisms that underlie shiftwork as a risk factor for breast cancer. Occupational and Environmental Medicine, 70(Suppl 1), A69-A70.	Abstract of case-control study.	Investigate hypotheses for the association between shift work and breast cancer.
Girschik, J., Heyworth, J., & Fritschi, L. (2010). Re:"Night-shift work and breast cancer risk in a cohort of Chinese women". American journal of epidemiology, 172(7), 865-866.	Letter to the editor	Night shift work and breast cancer risk in a cohort of Chinese women
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Ijaz, S. I., Verbeek, J., Ojajaarvi, A., & Neuvonen, K. (2013). 354 Correlations between night shift work and the development of breast cancer: systematic review. Occupational and Environmental Medicine, 70(Suppl 1), A120-A121.	Abstract of systematic review	Assess the strength of association between exposure to night shift work and breast cancer incidence.
Kogevinas, M.K., Papantoniou, Gomez Acebo, Merino Salas, Peiro, Perez, Alguacil. (2013). Night shift work and prostate cancer risk in a population-based case-control study in Spain. Occup Environ Med, 70(1), A121.	Abstract of case-control study.	Evaluate prostate cancer risk and night shift work.
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Reference	Type of Study	What research question(s) does the study address?
Papantoniou, K., Kogevinas, M., Sanchez, V. M., Moreno, V., Pollan, M., Moleón, J. J. J., Ardanaz, E., Maltzibar, J., Peiro, R., Tardon, A., Alguazil, J., Navarro, C., Gomez-Acebo, I., Castano-Vimyals, G. (2014). 0058 Colorectal cancer risk and shift work in a population-based case-control study in Spain (MCC-Spain). Occupational and environmental medicine, 71(Suppl 1), A5-A6.	Oral presentation of case-control study.	Evaluate colorectal cancer risk in relation to night and rotating shift work and genetic variation.
Pijpe, A., Vermeulen, R., Slottje, P., van Leeuwen, F., & Rookus. (2011). The Nightingdale Study: A Prospective Cohort Study on Shift Work and Breast Cancer Among Nurses in the Netherlands. J Epidemiol Community Health, 65(1), A289.	Poster presentation of cohort study.	Provide insight into the potential association between occupational exposures and the risk of cancer and other diseases.
Rabstein, S., Harth, V., Pesch, B., Justenhoven, C., Baisch, C., Schiffermann, M., Heinze, E., Brauch, H., Hamann, U., Ko, Y., & Brüning, T. Associations of polymorphisms in circadian genes, shift work and breast cancer in the German GENICA study.	Abstract of case-control study.	Investigate association between polymorphisms, shift work and breast cancer.
Rabstein, S., Pesch, B., Harth, V., Justenhoven, C., Hamann, U., Brauch, H., Ko, Y., & Bruening, T. (2014). 0181 Associations between pre-defined occupational job tasks and breast cancer risk. Occupational and environmental medicine, 71(Suppl 1), A84-A84.	Poster presentation of case-control study.	Investigate the association of job tasks in the industrial and health sector and breast cancer.
Tsc, L. A., Wang, F., Chan, W. C., Wu, C., Li, M., Kwok, C. H., Leung, S.L.., Yu, W.C., & Yu, I. T. (2014). 0076 Long-term nightshift work and breast cancer risk in Hong Kong women: results update. Occupational and environmental medicine, 71, A7-8.	Oral presentation of case-control study.	Report updated results on long-term nightshift work and breast cancer risk.
Tse, Wang, Chan, Kwok, Leung and Yu. (2013). Preliminary results of a case-control study of night shift work and breast cancer among Hong Kong women. Occup Environ Med, 70(1), A54.	Abstract of case-control study.	Night shift work and breast cancer.
Wang, F. W., & Yu, T. (2013). 353 Night-shift work and risk of breast cancer: a meta-analysis. Occupational and Environmental Medicine, 70(Suppl 1), A120-A120.	Abstract of meta-analysis.	Association between night-shift frequency and cumulative night-work and breast cancer.

Appendix 2 Search Protocol

SHIFT WORK AND CANCER SEARCH PROTOCOL

The following document describes the search protocol that will be used for the review of shift work and cancer.

Research Question

What is the impact of shift working on the risk of cancer, and what are the steps that could be taken to reduce the risks, to help build an international perspective of the problem?

Population

Employed

Intervention

Workplace interventions

Shift planning

Shift Scheduling

Outcomes

Cancer(s)

Search Databases

For academic research the following databases will be used to identify the different types of studies listed below: Cochrane Database of Systematic Reviews (CDSR), Current Contents, EMBASE, MEDLINE, Scisearch, BIOSIS Previews, PsychInfo, Toxfile ,and Scopus.

Grey literature searches will be carried out using Google Scholar, Open Grey, and relevant websites.

Types of Studies

Systematic reviews, reviews, meta-analysis, cohort studies, case-control studies, intervention studies

Inclusion Criteria

Published 2005 onwards, English Language

Exclusion Criteria

Published pre-2005, non-English language. Results looking at all cancers combined.

Search Strategies (Peer reviewed literature)

<u>Systematic reviews and meta-analyses</u>

("shift work" OR shift-work OR shiftwork OR "night work" OR ("work patterns" and (rotat* OR shift))) AND ("breast cancer" OR "prostate cancer" OR "colon cancer" OR "endometrial cancer" OR "colorectal cancer" OR "bladder cancer" OR "ovarian cancer" OR "gastro-intestinal cancer" OR (hormone-dependent AND cancer) OR cancer OR (womb AND cancer) OR (uterus AND cancer)) AND ("systematic review" OR review OR meta-analysis OR "cohort study" OR "case-cohort study" OR "case-control study" OR "intervention study" OR "experimental study")

Major Studies that post-date the most recent reviews

("shift work" OR "shift-work" OR "shiftwork" OR "night work" OR ("work patterns" and (rotat* OR shift))) AND ("breast cancer" OR "prostate cancer" OR "colon cancer" OR "endometrial cancer" OR "colorectal cancer" OR "bladder cancer" OR "ovarian cancer" OR "gastro-intestinal cancer" OR (hormone-dependent AND cancer) OR cancer OR (womb AND cancer) OR (uterus AND cancer))

Mechanisms of cancer and shift work

("shift work" OR "shift-work" OR "shiftwork" OR "night work" OR ("work patterns" and (rotat* OR shift))) AND ("breast cancer" OR "prostate cancer" OR "colon cancer" OR "endometrial cancer" OR "colorectal cancer" OR "bladder cancer" OR "ovarian cancer" OR "gastro-intestinal cancer" OR (hormone-dependent AND cancer) OR (womb AND cancer) OR (uterus AND cancer)) AND (mechanism OR mechanistic OR pathway OR "phase shift" OR "sleep disruption" OR "sleep disorder" OR "sleep-wake cycle" OR "sleep-wake schedule" OR "lifestyle factors" OR chrono-disruption OR chronodisruption OR "biological night" OR "biological clock*" OR "circadian dis*" OR "circadian rhythm" OR (low* AND "Vitamin D") OR (low* AND melatonin) OR ("light at night"))

Note: The search terms have been tested by running the searches in our online Dialog databases which include the databases listed under "Search databases" above, and separately in PubMed since this database highlights any search terms not found in the searches.

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