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Shift work and breast cancer: a critical review of the epidemiological evidence

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Shift work and breast cancer: a critical review of the epidemiological evidence

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This report reviews critically the epidemiological literature that has addressed the possible relation between shift work and risk of breast cancer. Four published studies were identified that have directly investigated this relation, two cohort studies and two case-control studies. Each has different methodological strengths, and each has found some significant associations, sometimes with dose or duration response effects, albeit with varying size of risk and to different aspects of shift work. A potential mechanism for a relation between shift work and breast cancer risk would be via an effect of altered light exposure at night on levels of melatonin or other hormones that might affect cancer risk; this mechanism has not been established, however. Overall, the evidence for an association of breast cancer risk with shift work is appreciable but not definitive, and it remains unclear whether any association is causal or a consequence of confounding. Further epidemiological research is needed to clarify the relation.

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1 EXECUTIVE SUMMARY

This report reviews critically the epidemiological literature that has addressed the possible relation between shift work and risk of breast cancer, and suggests the directions of future research that might clarify this relationship. The idea that shift work might influence breast cancer risk derives from the hypothesis of Stevens[1], in 1987, that light exposure at night might affect breast cancer risk by a hormonal mechanism.

Four published studies were identified that have directly investigated whether shift work is associated with risk of breast cancer, two cohort studies and two case-control studies. Each has different methodological strengths, and each has found some significant relations, sometimes with dose or duration response effects, albeit to different aspects of shift work.

A potential mechanism for a relation between shift work and breast cancer risk would be via an effect of altered light exposure at night on levels of melatonin or other hormones that might affect cancer risk; this mechanism has not been established, however.

Overall, the evidence for an association of breast cancer risk with shift work is appreciable but not definitive, and it remains unclear whether any association is causal or a consequence of confounding. Several areas of research could be productive to clarify the relationship. Further epidemiological investigation is needed of whether breast cancer risk is raised in shift workers. The decisive results are likely to come from large cohort studies with well-designed questions on both shift and night work, and with extensive data on potential confounders. A second area of interest, although it would not resolve the underlying question of whether there is an association, would be research to understand the mechanism of an association, if one exists. If the Health and Safety Executive intends to undertake or sponsor research, important

considerations in deciding what to undertake will be the extent to which the HSE wishes to address directly the question of whether there is an association, the time-frame within which results are expected, and the scale of funds that can be committed.

2 INTRODUCTION & BACKGROUND

2.1 General

1 This report reviews critically the epidemiological literature that has addressed the possible relation between shift work and breast cancer, and assesses the extent to which there is evidence for a causal association and the nature of the association. It also suggests future research that might be undertaken to clarify this relationship. Studies that have directly investigated whether shift work is associated with risk of breast cancer, are considered in some detail below. In addition, there have been epidemiological studies of breast cancer risk in various other groups which are relevant – blind women and female aircraft cabin crew. Reference will be made to these, but they are not themselves about shift work and are not reviewed in detail.

2 The idea that shift work might relate to risk of breast cancer derives from a hypothesis put forward by Stevens in 1987[1] that exposure to light-at-night might lead to increased risk of breast cancer via impairment of pineal secretion of melatonin, which was itself based on an idea put forward by Cohen et al[2] that breast cancer development might be promoted by pineal hypofunction. Several different potential biological mechanisms for the proposed effect of melatonin on breast cancer risk have been proposed - for example via effects of melatonin on oestradiol levels or on free-radical scavenging, or via immune modulation. Information on these alternatives can be found in Schernhammer et al [3]. The melatonin hypothesis is not the focus of this review, but is discussed further in Sections 5 and 7. In the years since Stevens put forward his hypothesis, four studies have investigated whether shift work is related to breast cancer, although without any data on melatonin levels.

2.2 The aetiology of breast cancer

3 The findings on the relation of shift work to breast cancer risk need to be interpreted in the light of the general epidemiology of the causation of breast cancer, because a major complication in assessing the shift work literature is the possibility of confounding by other risk factors for breast cancer.

4 Breast cancer is the most common cancer in women in Britain. The great majority of case occur at postmenopausal ages. Epidemiological studies have shown that its causation involves genetic, behavioural and environmental factors, acting at many stages of life, possibly starting in utero and continuing until the menopause and beyond. Established risk factors include young age at menache, late age at menopause, late age at first birth, nulliparity, hormone replacement therapy, ionising radiation exposure, benign breast disease, and probably alcohol consumption; a review can be found in Henderson et al[4]. Some factors, at least, appear to act differently at premenopausal and postmenopausal ages. The complex mixture of causes, the close relations of several of them with general lifestyle, and the wide range of ages at which they act, make it particularly difficult to deal with confounding when examining relations to new postulated causal factors such as shift work.

3 METHODS

5 In order to find, as far as possible, all of the epidemiological literature relevant to shift work and risk of breast cancer, three methods were used in combination:- (i) a computerised search on appropriate keywords using PubMed; (ii) a search of the references given in the publications discovered in (i); and (iii) personal knowledge of the author and references suggested by the Health & Safety Executive. The publications thus found were then critically reviewed, with particular concentration on their methodological quality, and potential biases and other artefacts. Consideration was also given to the ways in which future research could build on the existing literature.

4 EPIDEMIOLOGICAL STUDIES OF BREAST CANCER RISK IN RELATION TO SHIFT WORK

4.1 Norwegian maritime radio operators cohort

6 Tynes et al [5] conducted a cohort study of 2619 Norwegian women certified to work as radio and telegraph operators during 1920-80, 98% of whom had worked at sea on merchant ships. The study was intended primarily to investigate the effect of radiofrequency radiation exposure on breast cancer incidence, which was followed from 1961-91, with breast cancers identified from the Norwegian Cancer Registry. Only 41 women were lost to follow-up (plus 103 emigrated).

7 Fifty breast cancers occurred in the cohort during follow-up. In a nested case-control study, shift work variables for these 50 cases were compared with those for 4 - 7 matched controls per case from the same cohort, who were alive at the time of diagnosis of the case and matched to the case on year of birth. Detailed job histories for merchant ships had been collected from seamen's records, and shift work had been classified for each year by research assistants who had knowledge of the histories of the merchant ships (but it is implied that they did not have direct information for each individual being studied as to whether they had personally done shift work). Individuals were classified with regard to shift work as 0, 1, 2 or 3, but the paper does not state what these levels mean. Shift work was stated to reflect presence in the radioroom, but again it is not quite clear what this statement means. No association was found between shift work and risk of breast cancer at ages under 50, but for breast cancer at ages 50 and above there was a significant trend in risk ($p = 0.01$) for a three-category analysis of shift work (the categories being composed of the 0, 1, 2 and 3 classification above multiplied by the number of years

worked in each class of occupation). The relative risk of breast cancer for the top category in the analysis vs. no shift work was 6.1 (95% confidence interval 1.5 to 24.2). The extent of shift work before the age of 30 was also significantly related to breast cancer risk at ages 50 and above ($p = 0.02$). There was a strong correlation (Spearman rank = 0.79) between the extent of shift work and the duration of employment, and the latter was itself significantly associated with breast cancer risk. After adjustment for duration of employment, shift work effects were still marked but not significant. Further analyses were made adjusting for a composite fertility variable (categorised as no births/first birth under age 25/first birth at age 25 or more), but this was only possible for six of the 21 cases aged 50 and above, and did not make a large difference to the results.

4.1.1 Comments

8 The study has the methodological strength of a nested case-control study within a good quality cohort study which had a high follow-up rate and cancers ascertained from a good cancer registry. There should therefore have been no selection bias in the study, and the data source avoids recall bias. There was a lack of information on potential confounders and only very limited adjustment for reproductive-related confounders, both in terms of the number of variables for which adjustment was made and the very small number of individuals for whom this was possible. On the other hand, the overall cohort may provide an exceptional circumstance where shift work was not confounded by most other variables, because both the shift workers and non-shift workers were, equally, radio and telegraph operators on merchant ships, and thus they might be (although there is insufficient information to be certain) similar with regard to many variables that select individuals into such an occupation. The paper notes, for instance, that this occupational group have only one year of education beyond obligatory schooling, and by implication this was similar for shift work exposed individuals and non-shift workers. It is not

entirely clear what the shift work variables or indeed what shift work overall means in this paper, but at one point in the Discussion it is noted that this indicates exposure to work or light at night in the radioroom.

9 A difficulty in the results in terms of whether they might be aetiological is that there is no obvious reason why if there is a true effect it should be restricted to women aged 50 and above and not be apparent for breast cancer at younger ages. On the other hand the general idea of analysing breast cancer risks separately for these two age groups is reasonable given that there are several other reasons from general epidemiology to believe that aetiology might differ between pre- and post-menopausal women. It should also be noted that shipping workers (like aircraft workers, but unlike, for instance, nurses) will experience time-zone changes as well as shift work as a consequence of their occupation, and thus potentially they have a second chronobiologically disruptive effect on their lives. It is not clear whether the shift working and non-shift working members of the Norwegian cohort had similar degrees of time-zone shift.

4.2 US Nurses Cohort

10 Schernhammer et al [3] analysed breast cancer risks in 10 years follow-up of a cohort of 78,562 US nurses, in relation to exposure variables ascertained by questionnaire to the nurses in 1988. One of the questions had asked how many years in total the women had worked on rotating nightshifts with at least three nights worked per month in addition to days or evenings in that month. Two thousand four hundred and forty one breast cancers occurred in the cohort during follow-up. Analyses of breast cancer risk were undertaken with adjustment for an impressive list of potential confounders, including parity, age at first birth, body mass index, alcohol consumption, oral contraception use, postmenopausal hormone use, and menopausal status. Risk of breast cancer increased significantly with

number of years working rotating night shifts ($p = 0.02$), and risk for the longest category of exposure (≥30 years) compared with never working such shifts was significantly raised (RR = 1.36 (95% confidence interval 1.04 to 1.78)). Although there was an indication of a relation in both pre- and postmenopausal women, the trend and the risk in the highest exposure category were significant only in the latter. There was some evidence that the relation to shift work was specific to hormone-receptor-positive tumours. The body mass index tended to be slightly lower and the frequency of nulliparity slightly lower in never-shift workers than in ever-shift workers.

4.2.1 *Comments*

11 The paper by Schernhammer et al[3] comes from the Nurses Health Study (NHS), which is a highly impressive long-running US cohort study, although follow-up of it is less complete than ideal. The NHS is large and has produced important results in many areas, and its results need to be taken seriously. The paper shows a significant trend in risk with increasing duration of rotating nightshift work, after adjustment for an impressive list of potential confounders. There are no obvious known confounders missing from this adjustment. The pattern of results varied slightly between pre- and postmenopausal tumours, but was in the same direction in both, and although non-significant for the premenopausal tumours, there were much smaller numbers of premenopausal than postmenopausal cases.

12 There was no information in the study on intensity of light exposure, and no validation of self-reported duration of nightshift work, although the prospective design would avoid recall bias. Nightshift work appears to be a relatively objective, easily recalled variable, but the way in which the question was asked in the original

questionnaire about shift work may have led non-rotating (i.e. permanent) night workers to say that they were not shift workers (because the question asked only about rotating shift work). In principle this would generally be expected, however, to dilute the risks, not to create apparent risks artefactually, although the authors point out that with several exposure groups examined in the analyses biases in any direction are possible. The authors also point out reasons why rotating shift workers may have lower average melatonin levels than permanent nightshift workers, and therefore might provide a more potent test of the melatonin aetiology hypothesis than would permanent nightshift workers. It is possible that women who work night shifts differ from those who don't in aetiological ways that the study did not control for – for instance, lifestyle or hormone levels. These factors might either be a consequence of night work (i.e. an intermediate factor in the causal pathway), in which case they would not be confounding, or might be confounding.

13 In summary, the results are significant, not obviously due to bias, confounding or error, and come from a well-conducted and well-respected study. They give appreciable evidence in favour of an association between rotating nightshift work and risk of breast cancer incidence. The study on its own is not conclusive, however, and also the possibility of confounding by unknown factors remains.

4.3 Case-control study, Seattle U.S.

14 Davis et al [6] conducted a case-control study with 813 cases of breast cancer aged 20 to 74 years and 793 controls of the same ages who did not have breast cancer, and who were identified by random digit dialling. Data on shift work and many other potentially aetiological variables were obtained by in-person interview of the cases and controls.

Potential cases were identified from a population-based cancer registry, and the case response rate was 78%. The control response rate was 75% of women identified as eligible (95% of phone numbers were successfully resolved as to whether the number was residential and whether an eligible female lived in the household). It was also reported, however, that of 20148 phone numbers dialled only 1053 eligible women were selected as control subjects (i.e. only slightly more than 1 in 20 phone numbers generated an eligible woman).

15 For every job held for at least six months, questions were asked as to whether the job involved "graveyard" shift work, defined as 8 hours work between 7 pm and 9 am, and questions were also asked about day and evening work. Analyses of risk in relation to shift work were conducted with adjustment for four breast cancer risk factors, but these did not include age at first pregnancy, age at menarche, or menopausal status. Seven percent of cases and 5% of controls had ever-worked the graveyard shift in the 10 years before diagnosis, giving an odds ratio of 1.6 (95% CI 1.0 to 2.5; $p = 0.04$) for such work. There was a significant relationship of risk to hours per week worked on the graveyard shift in the 10 years before diagnosis, analysed as a continuous variable ($p = 0.03$) and analysed as quartiles ($p = 0.04$). There was a consistent trend between quartiles in the latter analysis and a maximal risk of 2.3 for the top category (≥5.7 hours per week). The relation of risk to number of years in the last 10 working at least one graveyard shift per week, was significant as a continuous variable ($p = 0.04$) but not significant as a categorized variable. Women who had ever-worked the graveyard shift at least once a week were more likely than other women to have ever-used oral contraceptives (76% vs. 62%) and to be nulliparous (16% vs 14%) and showed various other differences from non-shift workers. There was no information given on age at first pregnancy or age at menopause in shift workers vs non-shift workers.

4.3.1 *Comments*

16 The study was generally well conducted, although it is not entirely clear how the high reported response rate for controls accords with the low percentage of phone numbers for which an eligible control was found. Random digit dialling might in principle give some bias, depending on the type and extent of the population that could not be reached by phone, but this is likely to be relative low in the United States where phone penetration is high. There is also potential for selection bias if the hypothesis underlying the study was known to eligible individuals when they decided whether to take part in the study, but again given the reasonably high response rates reported, this seems unlikely to have been a major problem. The trends of risk found in relation to cumulative dose in the last 10 years and possibly with duration are points in favour of a real relation rather than an artefactual finding. Restriction of questioning to the last 10 years might have reduced misclassification of exposure, but also might have led to underestimation of risks if a longer period is relevant. A potentially serious deficiency of the study is the small number of potentially confounding variables that were included in the analyses. Women who chose to work nights are not random and might, for instance, be from poorer backgrounds, of atypical reproductive status, and atypical with regard to their alcohol consumption and possibly other variables. This was not fully taken into account in the adjustments, and potentially the results may at least in part be due to confounding.

4.4 Danish record-linkage case-control study

17 Hansen[7] conducted a record linkage case-control study in Denmark in which individual employment histories back to 1964 were gained from a nationwide pension scheme with compulsory membership, for 7035 women with breast cancer at ages 30-54

and born 1935-59, who were identified from the Danish Cancer Registry. Information about night working in different occupations was gained from a national survey of 2603 women in one year (1976). Occupations were counted as night work in the analyses of the breast cancer study if 60% or more respondents in the 1976 survey had "night-time schedules", and occupations were counted as not night work if less than 40% of respondents had reported night-time schedules in the 1976 survey (occupations with 40% to 59% of respondents with night-work schedules were omitted from the analyses). Women were counted as working at night in the breast cancer analyses if they were employed for at least half a year in an occupation deemed night work from the 1976 survey. Adjustments were made for socioeconomic status, based on job title, age at first and last birth of their children, and number of children, information on which was gained from a routine data source. Women with no employment history were omitted from the analyses. Controls were taken at random from the Central Population Register, matched to the cases on year of birth, sex, and being alive without cancer and having been an employee before the date of diagnosis of the case.

18 The odds ratio for breast cancer for women who had worked at night, as defined in the above sense, was 1.5 (95% CI 1.2 to 1.7). Only four occupations met the criterion of having 60% or more of respondents to the 1976 survey being night workers, and each of these showed a relative risk greater than 1.0 for breast cancer in the analyses, the greatest being 1.9 for air transport service workers. All four of the night-work occupations had greater mean alcohol consumption than female employees overall in the 1976 survey, and indeed each had alcohol consumption more than three times the median. (Alcohol consumption is a risk factor for breast cancer). It was stated that there was a positive trend of breast cancer risk with duration of work at night, but whether this trend was significant was not stated. The only data given on this was the relative risk for more than

six years of work at night, which was stated to be 1.7 (95% CI 1.3 to 1.7 *sic*). The above data were for a five year induction period of effect, but analyses with different induction periods or none had no great effect on the results. Hansen[8] subsequently noted that health workers, 41% of whom were night workers in their survey, and therefore who had been omitted from the above analyses, had a relative risk of breast cancer of 1.2 (95% CI 1.1 to 1.5).

4.4.1 *Comments*

19 The analyses did not adjust for several potential confounding variables, including alcohol consumption and several reproductive-related factors. The study also has the weakness that there were no individual data collected on night work, and this was merely implied from a survey in one year of a modest number of women (2603 in total) whose representativeness is unclear. Because the analyses are effectively a comparison of four particular occupations with a large number of other occupations, it is possible that even if the results do relate to occupation rather than to confounding, they are a reflection of these particular occupations and their selective exposures or behaviours rather than to shift work *per se*. In a more general sense, the study raises the difficulty that occupations in which shift work is prevalent are atypical, and both their occupational and non-occupational exposures may be different from those of non-shift work occupations in ways relevant to breast cancer risk – the study particularly highlights alcohol consumption, but for instance oral contraceptive use and exercise levels might reasonably also be atypical in shift workers (exercise levels might be atypical either as a direct result of the occupation, for instance night shift nurses might have less occupational exercise than day shift nurses because many of the patients are asleep, or might be non-occupational, e.g. because shift workers spend much of the day sleeping rather than exercising, or because individuals who enjoy exercise might be more, or less, likely to

take nightshift jobs). Indeed a previous study in Finland had assessed breast cancer incidence (and found a significant excess) in airline cabin crew, and discussed this as a possible effect of cosmic radiation exposure, without any data or discussion on shift work[9]. It should be noted that if night workers tend to be lower social class than dayworkers, this would be expected to be associated with a decreased risk of breast cancer in shift workers (i.e. inverse confounding) not the increased risk that was found. The strengths of the study were that it was large, it had no opportunity for reporting bias because it was based on routine data already collected, and the misclassification of exposures was presumably non-differential and therefore conservative.

5 OTHER RELEVANT EPIDEMIOLOGY

20 Apart from the shift work studies reviewed in detail above, the most important epidemiological data that address the melatonin/breast cancer hypothesis have been case-control results on the relation of 'light at night' exposure to breast cancer risk[6] and studies of breast cancer risk in blind women[10-14]. There have also been several studies showing raised breast cancer incidence in airline cabin staff [9 15 16] and data showing low breast cancer incidence or mortality in women living in the Artic, with consequent winter darkness[17]. These studies are not about shift work and are not, therefore, reviewed here. A review can be found in Erren[17]. In brief, the results of the studies generally give support to the melatonin hypothesis, but not to the extent where it can be regarded as conclusively established. In particular there is great potential for confounding in the results for women who are blind, because they may have reproductive and lifestyle histories differing in many ways from other women. There is also considerable potential for confounding in studies of aircraft cabin staff, because of their lifestyle and because of their various occupational exposures, including cosmic radiation and sometimes pesticides sprayed in cabins [18]. Rates in arctic inhabitants will be confounded by genetic factors as well as behaviours and exposures.

6 CONCLUSIONS

21 Although few studies have yet been published on the relation of shift work to risk of breast cancer, and each of the studies has some weaknesses as outlined above, they have all found significant results, often with dose or duration response effects, albeit to different aspects of shift work. Furthermore, none of the studies are of poor quality and each has used a different methodology. Hence the overall evidence for an association (but not necessarily a causal association) between shift work and risk of breast cancer is now appreciable, although not definitive. The melatonin hypothesis furnishes a potential, but not established, mechanism for such an association.

22 An important inconsistency between the studies, which slightly weakens them as evidence for a true association with shift work, is the menopausal status group for which an association was found. Tynes et al[5] found a relation for postmenopausal women but none for premenopausal, and Schernhammer et al[3] found a similar magnitude of effect for pre- and postmenopausal women, but significantly only for the latter based on larger numbers. The other two studies did not analyse their data separately by menopausal status or by age, but that by Davis et al [6] was a population-based study of women aged 20-74 so presumably was largely postmenopausal, whereas that by Hansen[7] was a population-based study of women aged 30-54 and therefore, based on the age distribution in Danish cancer registry data[19], likely to be mainly premenopausal. Thus overall the evidence is stronger for postmenopausal than premenopausal women, but most of the available data are for the former.

23 Interpretation of the results overall and indeed the construction of future studies is hampered by the great potential for confounding, because several recognised (and perhaps other unrecognised) risk factors for breast cancer are likely to be associated with shift work[*]. Hence the possibility that shift work *per se* increases the risk of breast cancer cannot be dismissed, but on the other hand it remains possible that the apparent associations are due to confounding. Because breast cancer is so common (much the most common cancer in women in Britain [20] the possibility of even a modest occupational risk factor (e.g. say one resulting in a true relative risk of 1.5) would be of importance.

[*] *Such factors might be occupational or non-occupational, and are discussed below, under 'Further Research'.*

7 FURTHER RESEARCH

7.1 Research questions

24 The question whether breast cancer risk is increased by shift work can be broken down into several subquestions, for each of which further research might be productive:-

25. *Is there an increased risk of breast cancer in shift workers?* It should be noted that even this question can be broken down further, because it has varied between publications what shift has meant – one could either investigate whether risk is increased in those who work at night or in those who work time-varying shifts. For choice where possible, both questions need to be addressed, and the effects of each need to be separated.

26. *If there is a raised risk, does it apply to premenopausal or postmenopausal women, or both?* For the reasons discussed above, these questions need to be investigated separately.

27. *If there is a raised risk, is this because of an effect of shift/night work per se, or a consequence of factors associated with shift/night work?* It should be noted that although such factors would in epidemiological parlance be termed confounders, it would vary according to their origins as to whether from a health and safety point of view they should be viewed as artefacts or as of direct interest.

28 For instance, such confounders might be behaviours or exposures such as reproductive history or non-occupational alcohol consumption, that might be reasons for selection into night-work, which presumably would not be of direct interest from the

viewpoint of occupational health and safety. They might also be genotypic factors resulting in selection into shift work e.g. individuals who are genetically prone to sleep badly, or to be awake at night, might choose night work. Thus, it has been reported that "morning types" have more difficulty in adapting to night work and are more likely to give it up, and that they have an earlier onset of melatonin synthesis and perhaps other differences in melatonin profiles, than "evening types" [21]. Although it is not obvious why timing of melatonin synthesis, as opposed to say cumulative total (or peak levels) of melatonin, should matter to breast cancer risk, this highlights the possibility that if shift work is associated with breast cancer, this might be because of the intrinsic circadian rhythms or hormone levels of workers who can adapt to night work, rather than the effect of such work.

29 On the other hand, the confounders might be behaviours occurring during night work – for instance there might be more opportunity or incentive to drink alcohol while on a night shift, or night shift workers might get little exercise or eat differently while at work. Such factors might be considered of health and safety import. Alternatively, the confounders might be exposures that occur in occupations that happen to be shift work occupations, but these exposures are not actually a consequence of shift work (e.g. cosmic radiation exposure in airline staff[22]. They might also be non-occupational exposures consequent on shift work – for instance shift workers might take sleeping pills or oral contraceptives in order to be able to continue their job, and these behaviours consequent on shift work might have effects on breast cancer risk. It is beyond the scope of this report to decide which of these factors are or are not of interest to the Health & Safety Executive, but it is worth noting with regard to future research that distinguishing between different reasons for an association of cancer risk with shift work might be of great importance to the Executive.

30. *If there is an excess of breast cancer due to shift work per se, what is the mechanism?* Most of the research impetus for examination of the possible relation of shift work to breast cancer has come from the melatonin hypothesis – i.e. the hypothesis that melatonin secretion may diminish risk of breast cancer, and that night or shift work might alter melatonin secretion patterns and hence influence breast cancer risks. It is not the purpose of this review to review this hypothesis in detail, but it is notable that the epidemiological evidence on shift work and breast cancer risk is not dependent on whether the melatonin hypothesis proves to be correct; even if further research does not support the melatonin hypothesis, the relation of shift work to breast cancer risk would remain of interest. On the other hand, if the melatonin hypothesis were to become a well-established aetiological mechanism, this would increase the plausibility of the shift worker hypothesis. Although this review has been concerned solely with epidemiology, it is notable that in reaching an epidemiological judgment on the evidence on whether a cancer is caused by a posited aetiological factor such as shift work, one of the criteria to be considered[23] is biologically plausibility, and such plausibility would strengthen arguments for an aetiological relationship. The melatonin hypothesis is not the only hypothesised mechanism, however, that could explain a relation of night or shift work to cancer risk. Several other hormones have circadian rhythms, including for instance steroids, and thus findings on the relations of these to breast cancer risk could also alter the biological plausibility of the shift work hypothesis.

31 As a consequence, research on how time-varying shift work, night work, and light at night affect total or peak melatonin levels (and how it affects other hormone levels) would be of value in considering the shift work hypothesis, even though it would not in itself answer the question as to whether shift work affects the risk of breast cancer.

Similarly, epidemiological studies that test the melatonin hypothesis are of interest in the context of the shift work hypothesis, but do not give information directly about it.

7.2 Future epidemiological studies of the relation of breast cancer to shift work

32 As there have only been four studies to date directly examining the relation of breast cancer risk to shift work, and these are suggestive without being conclusive, there is a considerable need for further studies to clarify the issue. These studies need, however, to dissect night/shift work further, and to improve control or avoidance of confounding, rather than simply to repeat the existing literature. The possibility of interaction with known risk factors also needs to be considered in these studies. Because disentangling the roles of shift and night work from potentially confounding variables is so difficult, it seems unlikely that any single study will completely resolve the breast cancer/shift work question, although one or two well designed and conducted studies could greatly clarify it. As illustrated by the experience from the existing literature reviewed above, there is potential for studies to be devised that minimise confounding and defects of study design. There may be potential for some investigation of these questions within existing cohort studies run by the Health & Safety Executive.

33 Particularly attractive are two avenues of investigation. The first is studies such as that by Tynes et al[5]. that take advantage of special occupational circumstances where there are likely to be few or minimal confounding differences between nightshift workers and non-nightshift workers. The second is large general cohort studies, like the Nurses Health Study[3], in which detailed data on confounders and (unlike the Nurses Health Study) detailed data on shift work and night work could be collected with the

methodological strengths of a cohort design. In principle, cohort studies that included melatonin assays would be of great interest, but there would be formidable technical and practical difficulties in gaining valid measures on a sufficiently large scale.

34 Given that only one interview case-control study of the breast cancer and shift work question has yet been published, and that such studies can gain data on shift/night work and confounders relatively quickly for large numbers of cases, there is also scope for further case-control investigation. Because of their potential for misclassification and bias, however, such case-control studies are unlikely to give decisive answers.

35 In conclusion, if there is a wish to try to resolve the central question – whether shift work causes raised risk of breast cancer and if so by how much – the decisive information is likely to come from cohort studies. Unless special occupational circumstances can be found where confounding is improbable, the studies will need to gain data on an extensive range of confounders, they will take several years to give results, and they will be expensive if they are to be of sufficient size. The cost and scale required make it unrealistic to suppose that such a study could be inaugurated specifically for the purpose of investigating the shift/night work hypothesis. The costs would be far lower, however, if data on shift work were collected as part of a cohort study already funded for other reasons. Alternatively, a case-control study could be inaugurated less expensively and with more rapid results than setting up a new cohort, but would be less likely to contribute definitive results.

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9 APPENDIX : A J SWERDLOW, BRIEF BIOGRAPHY

Anthony Swerdlow was educated in medicine at King's College, Cambridge and Balliol College, Oxford. After junior posts in clinical medicine, epidemiology and public health in the Oxford region and London, he worked in epidemiology as a senior lecturer at the University of Glasgow, and then at the Office of Population Censuses and Surveys in London, where he was responsible for national statistics on cancer incidence and mortality. He joined the London School of Hygiene & Tropical Medicine, University of London in 1987 and was Professor of Epidemiology there from 1996-2000. In July 2000, he moved to a post as Professor of Epidemiology and Director of the Department of Health Cancer Screening Unit at the Institute of Cancer Research (University of London). He holds doctorates in epidemiology from Glasgow and Oxford Universities, and is a Fellow of the Faculty of Public Health Medicine of the Royal Colleges of Physicians of the UK and a Fellow of the Academy of Medical Sciences. His research and teaching have been in chronic disease epidemiology, mainly on cancer, especially testicular cancer, breast cancer and melanoma. He has published widely on risks of cancer in relation to environmental and behavioural factors, and on the descriptive epidemiology of cancer in Britain. He has served also on various advisory committees on cancer-related issues, nationally and internationally.

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