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Night work and prostate cancer in men: a Swedish prospective cohort study

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ABSTRACT

Objectives Prostate cancer is the most common cancer and the second leading cause of cancer-related deaths among men, but the contributing factors are unclear. One such may be night work because of the day/night alternation of work and the resulting disturbance of the circadian system. The purpose of the present study was to investigate the prospective relation between number of years with night work and prostate cancer in men.

Design Cohort study comparing night and day working twins with respect to incident prostate cancer in 12 322 men.

Setting Individuals in the Swedish Twin Registry.

Participants 12 322 male twins.

Outcome measures Prostate cancer diagnoses obtained from the Swedish Cancer Registry with a follow-up time of 12 years, with a total number of cases=454.

Results Multiple Cox proportional hazard regression analysis, adjusted for a number of covariates, showed no association between ever night work and prostate cancer, nor for duration of night work and prostate cancer. Analysis of twin pairs discordant for prostate cancer (n=332) showed no significant association between night work and prostate cancer.

Conclusions The results, together with previous studies, suggest that night work does not seem to constitute a risk factor for prostate cancer.

Strength and limitations of this study

- Only a few studies have addressed the issue of night work and prostate cancer, and the results are conflicting. The strength of the present study is that it adds a rather large cohort with complete follow-up in national registers.
- A second advantage is that the study also addresses heredity in relation to shift work and prostate cancer.
- A disadvantage is that only subjective information on exposure and covariates is available.
- Another disadvantage is the lack of information on number of night shifts.

INTRODUCTION

Prostate cancer is the most common cancer and the second leading cause of cancer-related deaths among men.[1] The causes may be age, race/ethnicity and family history,[2] as well as soy and carrots.[3 4] Also firefighters may have an increased risk of prostate cancer.[5 6] The latter group is exposed to various carcinogens, but also to shift work, and such work hours interfere with the circadian system, particularly if they involve night shifts. Reviewing epidemiological and experimental literature, the International Agency for Research on Cancer concluded that night work is a probable causative risk of breast cancer in women, that is, placing night shifts in category 2 on the list of causes of cancer.[7] Furthermore, Kolstad found that the risk of breast cancer was increased after 20 years or more of exposure to night work.[7] Most, but not all, of subsequent reviews have found support for the link between night shifts and breast cancer in women.[8–12] This link may have important effects on public health since >18% of the population in the European Union is exposed to night work (www.eurofound.europa.eu).

In contrast, the association between shift work and prostate cancer has not been clearly established. However, a recent meta-analysis of eight very heterogeneous studies concluded that there is a weak link,[13] but only three studies show a significant association for 'ever shift work'.[14–16] Five other studies failed to find a significant association,[17–21] although the latter did find a significant association in the group with >28 years of exposure.

Apart from the involvement of disturbance of circadian rhythmicity in the putative effect of night work on cancer, it is thought that the suppression of melatonin through night-time exposure to light is a contributing factor.[22] Among the evidence is the finding that blind women have a lower risk for breast cancer than seeing women.[23] Furthermore, breast cancer growth may be increased by reducing melatonin flow to an implanted tumour in animals.[24 25] Phase advancing light exposure increases the rate of growth of cancer cells in mice.[26] When light exposure is increased and melatonin is decreased, cancer tumours increase in growth in female rats with implanted cancer tumours.[25]

The objective of the present prospective study was to increase knowledge regarding the association between night work and prostate cancer through using data from the Swedish Twin Registry (STR) in which familial factors (genetics and shared environmental) could be taken into account. Hence, a survey question on number of years of night work was used to predict the incidence of prostate cancer.

METHOD

Design and participants

The design was a prospective cohort study and is essentially identical to that of a previous study of night shifts and breast cancer in women.[27] Twins born in Sweden before 1959 who participated in the Screening Across the Lifespan Twin (SALT) study conducted by the STR and who, at the time of the interview, were 41–60 years old were included. Each individual participated in the SALT computer-assisted telephone interview once between 1998 and March 2003. The response rate was 74%, and the total sample encompassed 12 322 men. The interview included questions on the duration of night work and a number of items regarding different diseases and symptoms. The procedure for data collection has previously been described in detail.[28] The individuals were followed prospectively from the interview response date. Data on incident cancer were obtained from two registers at the National Board of Health and Welfare, the Swedish Cancer Registry and from the Cause of Death Register and linked to the twins by using the unique person identification number available for all Swedish citizens. The regional ethical committee of the Stockholm region approved the study.

Variables

The exposed group was constituted of those who had worked at night for 1–45 years according to the response to the question: 'For how many years have you had working hours that meant that you worked nights at least now and then'. This group was compared with all others. In addition, further categorisation of exposure was based on intervals in multiples of 5, with observations that an effect may be expected for ≥30 years or ≥20 years. However, too few cases were obtained for categorisation at ≥30 years, hence the following categorisation was used: 1–5, 6–10, 11–20 and 21–45 years. In total, 4816 male SALT responders had been exposed to night work.

Prostate cancer was defined as having at least one incident cancer diagnosis after the date of the interview, either according to the Swedish Cancer Registry or to the Cause of Death Register.

The following variables were used as covariates: age, educational level (0=compulsory (reference), 1=more than compulsory); tobacco use (0=no tobacco (reference), 1=tobacco use (includes current or previous regular smoking/snuffing as well as occasional smoking or snuffing)); alcohol use (0=no alcohol consumption (reference), 1=alcohol consumption); physical activity (0=moderate exercise (reference), 1=low exercise, 2=high exercise based on this question in SALT: 'Of these 7 alternatives, which fits your annual exercise pattern?'); body mass index (height^2/weight) (0=normal weight (>18.5–25) (reference), 1=underweight (≤18.5), 3=overweight (>25–30), 4=obesity (>30)); only one participant was underweight and was removed; have children (0=no biological children (reference), 1=have biological children); coffee use (1=no coffee (reference), 2=1–2 cups a day, 3=3–4 cups a day; 4=≥5 cups a day); and previous cancer (0=no (reference), 1= yes) at the time of interview.

Statistical analysis

Frequencies were used to describe the background and covariates of the study population. The differences between day and night workers were tested by χ^2 test for categorical variables and t-test for continuous variables. In the analyses of associations, people with missing information on a specific covariate were excluded in the analyses including that covariate. Multiple Cox proportional hazard regression analyses for covariates were used to compute HRs with 95% CIs. Exposure was defined as night work (or not) with a subdivision for duration of exposure. All individuals contributed with time until date of the first prostate cancer diagnosis or censoring. Censoring events included other cancer diagnosis during the follow-up, date of death or end of follow-up time (31/12/2010), whichever came first. The analyses were adjusted for the statistical within-twin pair dependency.

The proportional hazards assumption was satisfied, which was examined by testing a model including an interaction between the night work (yes/no or categorised) and the survival time as a covariate. Potential familial confounding was controlled for, by analysing twin pairs discordant for prostate cancer (ie, one twin in a pair was diagnosed with prostate cancer during the follow-up, whereas the twin partner was not diagnosed). Conditional Cox proportional hazard regression was applied, where each twin pair was provided with their own baseline hazard. All analyses were performed using SAS V.9.4.

Some of the covariates had missing values, and we performed multiple imputations under the assumption that data were missing at random. The imputation was repeated 20 times using proc mi in SAS. The values of complete cases were compared with the imputed values, and only marginal deviations were observed.

RESULTS

The mean follow-up time was 8.7 years (range: 0–13). The total number of person-years in the cohort when participants were censored after death, time of diagnosis or after 31 December 2010 was 107 545. Prostate cancer occurred in 454 men between baseline and the last day of the complete follow-up, and 538 men died during follow-up.

Background information is presented in table 1. Night workers were slightly younger, used more tobacco, were

Table 1 Characteristics of the study population at baseline, N (%)

	Number of indivi(duals (%)		p Value
	Non-night workers (n=7506)	Night workers (n=4816)	
Age, years	51.7 (4.7)	51.2 (4.8)	<0.001
Education			0.06
Compulsory	3069 (41)	2071 (43)	
More than compulsory	4434 (59)	2744 (57)	
Missing	3 (0.04)	1 (0.02)	
Children			0.35
Have children	6122 (82)	3960 (82)	
Do not have children	1384 (18)	856 (18)	
Missing	–	–	
Tobacco use			<0.001
No	919 (12)	410 (8)	
Yes	6506 (87)	4359 (91)	
Missing	81 (1)	47 (1)	
Body mass index			<0.001
Normal weight	3570 (48)	2099 (42)	
Underweight	30 (0.4)	10 (0.2)	
Overweight	3325 (44)	2278 (47)	
Obesity	530 (7)	500 (10)	
Missing	51 (0.7)	19 (0.4)	
Physical activity			0.04
Moderate	1968 (26)	1209 (25)	
Low	2332 (31)	1509 (31)	
High	3192 (43)	2077 (43)	
Missing	14 (0.2)	21 (0.4)	
Alcohol consumption			<0.001
No alcohol	147 (2)	116 (2)	
Alcohol	3343 (45)	1954 (41)	
Missing	4016 (53)	2746 (57)	
Coffee consumption			<0.001
No coffee	471 (6)	311 (6)	
1–2 cups a day	1298 (17)	789 (16)	
3–4 cups a day	2595 (35)	1437 (30)	
5+ cups a day	3140 (42)	2272 (47)	
Missing	2 (0.03)	7 (0.2)	
Previous cancer			0.14
No	7319 (98)	4716 (98)	
Yes	187 (2)	100 (2)	
Missing	–	–	
New cancer diagnosis during follow-up			0.16
No cancer	6870 (92)	4419 (92)	
Prostate	294 (4)	160 (3)	
Other cancer	342 (4)	237 (5)	
Time to prostate cancer diagnosis (years(SD))	5.8 (2.7)	6.1 (2.7)	0.24

Significance levels based on t-tests or χ^2 tests.

Table 2 HRs for shift work exposure groups applying multiple Cox analysis for prediction of prostate cancer (no cancer as reference) after baseline among male night workers and with 95% CI. Reference: non-exposed. n=12 322, total number of cases=454

	Duration of exposure, years	Cases/no cases	Complete follow-up HR (95% CI)*	Follow-up to 60 years HR (95% CI)†
No night work versus ever night work				
No night work (ref)	0	294/7212	1	1
Working nights for: (*unadjusted*)	1–45 years	160/4656	0.84 (0.69 to 1.03)	0.78 (0.64 to 0.96)
No night work (ref)	0	294/7212	1	1
Working nights for: (*adjusted*)‡	1–45 years	160/4656	0.91 (0.74 to 1.12)	0.89 (0.72 to 1.09)
No night work versus years of shift work				
No night work (ref)	0 years	294/7212	1	1
Working nights for: (*unadjusted*)	1–5 years	55/1729	0.79 (0.60 to 1.06)	0.72 (0.54 to 0.96)
	6–10 years	31/800	0.99 (0.68 to 1.43)	0.88 (0.61 to 1.27)
	11–20 years	38/968	1.00 (0.72 to 1.41)	0.84 (0.60 to 1.18)
	21–45 years	36/1159	0.77 (0.55 to 1.09)	0.86 (0.61 to 1.21)
No night work (ref)	0 years	294/7212	1	1
Working nights for: (*adjusted*)‡	1–5 years	55/1729	0.86 (0.63 to 1.17)	0.84 (0.62 to 1.15)
	6–10 years	31/800	1.09 (0.74 to 1.61)	0.96 (0.65 to 1.42)
	11–20 years	38/968	1.12 (0.78 to 1.63)	1.11 (0.77 to 1.60)
	21–45 years	36/1159	0.72 (0.50 to 1.05)	0.75 (0.52 to 1.09)

*Follow-up until 31 December 2010.
†Follow-up until the age of 60.
‡Adjusted for: age + education level + tobacco consumption + BMI + having children + coffee consumption + previous cancer.
BMI, body mass index.

more overweight, consumed more coffee and did not differ from non-night workers on previous or later cancer or time to diagnosis of prostate cancer.

The cumulative incidence of prostate cancer was 3.3% among the night workers and 3.9% among non-night workers (χ^2=3.66, p=0.16). Table 2 shows that the incidence was higher in the group with the highest exposure. Results of the Cox regression analyses, regardless of years of night work exposure, did not show any significant association to prostate cancer after adjustment for covariates (table 2). No association with duration of night work was seen. The analysis of twin pairs discordant for prostate cancer did not show any significant associations, irrespective of exposure duration (see table 3).

Table 2 Alcohol consumption was not entered into the main analysis, since the internal loss of data was >50% for this variable. However, a separate analysis showed that the estimates with adjustment for alcohol was HR=0.64 (95% CI 0.40 to 1.03) for the exposure group with 21–45 hours of night work (n=5444).

DISCUSSION

In this prospective cohort study of Swedish twins, we did not find any statistically significant association between the amount of night work and prostate cancer. Familial influences on the association were of minor importance. The results are similar to those of five previous studies,[17–21] but at least three studies did show a significant association for 'ever night work' and prostate cancer.[14–16] The present results add another negative finding to the previous five studies. Thus, six studies (including the present one) fail

Table 3 HRs for shift work exposure groups applying conditional Cox analysis of twin pairs discordant for prostate cancer (no cancer as reference) for prediction of prostate cancer after baseline among male night workers, and with 95% CI. n=332

	Duration of exposure, years	N (%)	Complete follow-up HR (95% CI)*	Follow-up to 60 years HR (95% CI)†
No night work (ref)	0 years	225 (68)	1	1
Working nights for:	1–5 years	42 (13)	1.02 (0.48 to 2.18)	0.88 (0.26 to 2.46)
	6–10 years	19 (6)	1.97 (0.64 to 6.02)	1.24 (0.26 to 5.82)
	11–20 years	22 (7)	0.88 (0.32 to 2.43)	0.87 (0.26 to 2.93)
	21–45 years	24 (7)	1.05 (0.39 to 2.84)	0.57 (0.13 to 2.45)

*Follow-up until December 31 2010.
†Follow-up until the age of 60.

to associate night work with prostate cancer, while three do not. This will move the meta-analytic HR of Rao *et al*[13] closer to unity and uncertainty. There is clearly a need for further studies on the present topic.

The discrepancy in results may be due to a lack of a common exposure metric, differences in the type of covariates adjusted for or heterogeneous occupational groups involved. Furthermore, selection into and out of night work occurs continuously, and this may attenuate any associations. It is also likely that the variability of results simply reflects a true lack of association between night work and prostate cancer. The present authors favour this latter explanation in view of the presently available data. Nevertheless, the issue of a potential association between night work and prostate cancer is far from settled.

It should be pointed out that also the association between night work and breast cancer in women is weak, even if meta-analyses in most cases produce significant results.[8–12] Also regarding breast cancer, about half of the studies fail to find significant associations between night work and breast cancer, but the total number of studies is about twice that of the studies of prostate cancer.

The present study had some additional limitations. Thus, the sample had an intermediate size, exposure was self-reported and information on occupation/work task was not available. Furthermore, there was no possibility of estimating exposure to night work after the baseline measure. Another limitation is that the result concerned Swedish twins, which may limit generalisability. However, studies have shown that cumulative risks of cancer and mortality in twins do not differ from that in singletons.[29] A strength of the study was the linkage of exposure at the individual level to nationwide register data through the social security number assigned to all persons living in Sweden. This resulted in an almost 100% complete follow-up of disease.

It is apparent that possible associations between night work and prostate cancer need to be studied in more detail. The present negative results add to the previous negative results, which dominate previously conducted studies. There is also a need for studies employing better research methods. This includes well-defined measurement of exposure, preferably using frequency of night shift in addition to duration of exposure. Future studies also need objective (company records) measures of exposure, rather than self-reported ones as well as repeated application of such measures. There is also a need for studying this in specific occupational groups.

To conclude, in this prospective study of Swedish twins, we found no evidence that night work, regardless of duration, is associated to prostate cancer. This agrees with the majority of the previous studies.

Contributors TÅ initiated the study, discussed the analyses and wrote the manuscript. JN discussed the design, carried out the analyses and commented on the manuscript. PS and KA discussed the design, supervised the analyses and commented on the manuscript. GK commented on the manuscript.

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Data sharing statement The data cannot be made publically available. According to the Swedish Ethical Review Act, The Personal Data Act and the Administrative Procedure Act, data can only be made available after legal review, for researchers who meet the criteria for access to this type of sensitive and confidential data. Readers may contact professor Kristina Alexanderson (Kristina.alexanderson@ki.se) regarding the data.

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