BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015751
Article Type:	Research
Date Submitted by the Author:	30-Dec-2016
Complete List of Authors:	Åkerstedt, Torbjørn; Stockholm University, Stress Research Institute Narusyte, Jurgita; Karolinska Institute, Clinical Neuroscience Svedberg, Pia; Karolinska Institute, Department of Clinical Neuroscience Kecklund, Göran; Stockholm University, Stress Research Institute; Radboud University, Behavioural Science Institute Alexanderson, Kristina; karolinska institutet, Department of Clinical Neuroscience
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine
Keywords:	shift work, work hours, cohort study

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

Torbjörn Åkerstedt[1,2], Jurgita Narusyte[1], Pia Svedberg[1], Göran Kecklund[2,3], Kristina Alexanderson[1]

1.Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
2. Stress Research Institute, Stockholm University, Stockholm, Sweden
3. Behavioral Science Institute, Radboud University, Nijmegen, The Netherlands

Correspondence: Dr Torbjorn Akerstedt, Department of Clinical Neuroscience, Karolinska Institutet, 17177 Stockholm Sweden
Email: torbjorn.akerstedt@ki.se
Phone: +46 737078928

Key words: shift work, longitudinal, night work, cancer

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 12322 men.

Setting: Individuals in the Swedish Twin Registry.

Participants: 12322 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.

Key words: shift work, night work, men, twins, Sweden

Strength and weaknesses 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 studies also addresses heredity in relation to shift work and prostate cancer

•A disadvantage is the subjective information on exposure and covariates

• 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.

Within the European Union (27 countries) 18.7% of the work force work night time (2200-0600h) at least once per month, according to the 5th European Working Conditions Survey (www.eurofound.europa.eu). Night work disrupts the sleep wake cycle and it has been suspected that this may increase the risk of cancer. In 2007 the International Agency for Research on Cancer (IARC) carried out a review of available knowledge on the association between breast cancer in women and shift work [7] and concluded that six out of eight studies showed excessive risk for female workers with night shifts to develop breast cancer (Odds Ratios (OR) = 1.3-1.8). This lead the IARC to classify shift work in category two on the list of causes of cancer, that is, as a ”probable causative link”. The effect of duration of exposure was not clear, but a duration of 20 years was suggested by Kolstad [8], who found limited evidence for an association between night shifts and breast cancer. Several reviews, but not all, point in the same direction [9-13].

The association between shift work and prostate cancer has not been clearly established and studies on the topic are still rare. However, a recent meta-analysis of 8 very heterogenous studies concludes that there is a weak link (Rao et al 2015), 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.

The mechanism of the association between night work and cancer is hypothesized to be influenced by light at night on the level of melatonin, as well as disturbances of the circadian rhythm [7]. Virtually all studies of mechanisms has been focused on breast, and not, prostate cancer. But from the breast cancer studies it appears that, for example, blind women have a lower risk for breast cancer than seeing women[22]. Animal studies have shown that human breast cancer tumors implanted in mice can be manipulated in terms of growth by changing the flow of melatonin [23 24]. High levels of melatonin seem to protect also healthy cells from carcinogenic processes [23 24]. To phase advance the light exposure in mice increases the malign progression in tumour cells [25]. Female rats with implanted human breast cancer tumours show growth when the light intensity is increased and melatonin secretion decreased. Melatonin also suppresses the uptake of fatty acids during the night [24].

The objective of the present study was to increase the knowledge level regarding the association between night work and prostate cancer through using data from the Swedish Twin Registry 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 linked to the incidence of prostate cancer.

Method

Design and participants

The design was a prospective cohort study. Twins born in Sweden before 1959 who participated in the Screening Across the Lifespan Twin (SALT) study conducted by the Swedish Twin Registry (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 12322 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 [26]. 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 to all others. In addition, further categorization 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 categorization at ≥30 years,

hence the following categorization 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 Cancer Register 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 (BMI – 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). 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 Chi-square 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 Hazards Ratios (HR) with 95% Confidence Intervals (CI). 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. Potential familial confounding was controlled for by analyzing twin pairs discordant for prostate cancer (i.e., one twin in a pair was diagnosed with prostate cancer during the follow-up, whereas the twin partner not). Conditional Cox Proportional Hazard regression was applied, where each twin pair was provided with their own baseline hazard. All analyses were performed using SAS.9.4.

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 107545. 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 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.

Table 1

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.

Table 2 here

The analysis of twin pairs discordant for prostate cancer did not show any significant associations, irrespective of exposure duration (see Table 3).

Table 3 here

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=0.40-1.03) for the exposure group with 21-45 hours of night-work (N = 5444).

Table 3 here

Discusssion

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 the previous five studies. Thus, six studies (including the present one) fail to associate night work with prostate cancer, while three do not. This will move the metaanalytic HR of Rao et al [27] closer to unity and uncertainty. There is clearly a need for more studies on the present topic.

The discrepancy in results may be due to lack of a common exposure metric, differences in the type of covariates adjusted for, or heterogenous 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 favor 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 [9-13]. 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, 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 generalizability. However, studies have shown that cumulative risks of cancer and mortality in twins do not differ from that in singletons [28]. A strength of the study was the linkage 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 needs 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.

Contributions: 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.

Funding: This study was funded by the AFA Insurance Company (grant number 120264)

Conflicting interests: None declared

Ethical approval: The ethical committee for the Stockholm Region

Provenance and peer review: Not commissioned, externally peer reviewed

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.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer Journal international du cancer 2010;**127**(12):2893-917.

2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA: a cancer journal for clinicians 2009;**59**(4):225-49.

3. van Die MD, Bone KM, Williams SG, et al. Soy and soy isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials. BJU international 2014;**113**(5b):E119-30.

4. Xu X, Cheng Y, Li S, et al. Dietary carrot consumption and the risk of prostate cancer. European journal of nutrition 2014;**53**(8):1615-23.

5. Pukkala E, Martinsen JI, Weiderpass E, et al. Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. Occupational and Environmental Medicine 2014;**71**(6):398-404.

6. LeMasters GK, Genaidy AM, Succop P, et al. Cancer risk among firefighters: a review and meta-analysis of 32 studies. Journal of Occupationa and Environmental Medicine 2006;**48**(11):1189-202.

7. Stevens RG. Testing the light-at-night (LAN) theory for breast cancer causation. Chronobiology International 2011;**28**(8):653-6.

8. Kolstad HA. Nightshift work and risk of breast cancer and other cancers--a critical review of the epidemiologic evidence. Scandinavian Journal of Work, Environment and Health 2008;**34**(1):5-22.

9. Bonde JP, Hansen J, Kolstad HA, et al. Work at night and breast cancer - report on evidence-based options for preventive actions. Scandinavian Journal of Work, Environment and Health 2012.

10. Jia YJ, Lu YS, Wu KJ, et al. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. Cancer Epidemiol 2013;**37**(3):197-206.

11. Wang F, Yeung KL, Chan WC, et al. A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. Annals of Oncology 2013;**24**(11):2724-32.

12. Ijaz S, Verbeek J, Seidler A, et al. Night-shift work and breast cancer--a systematic review and meta-analysis. Scandinavian journal of work, environment & health 2013;**39**(5):431-47.

13. Kamdar BB, Tergas AI, Mateen FJ, et al. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. Breast cancer research and treatment 2013;**138**(1):291-301.

14. Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. American Journal of Epidemiology 2006;**164**(6):549-55.

15. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology 2007;**18**(1):182-3.

16. Parent ME, El-Zein M, Rousseau MC, et al. Night work and the risk of cancer among men. American Journal of Epidemiology 2012;**176**(9):751-9.

17. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scandinavian Journal of Work, Environment and Health 2007;**33**(5):336-43.

18. Kubo T, Oyama I, Nakamura T, et al. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. International Journal of Urology 2011;**18**(3):206-11.

19. Gapstur SM, Diver WR, Stevens VL, et al. Work schedule, sleep duration, insomnia, and risk of fatal prostate cancer. American Journal of Preventive Mededicine 2014;**46**(3 Suppl 1):S26-33.

20. Yong M, Blettner M, Emrich K, et al. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. Scandinavian Journal of Work, Environment and Health 2014;**40**(5):502-10.

21. Papantoniou K, Castano-Vinyals G, Espinosa A, et al. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. International journal of cancer Journal international du cancer 2015;**137**(5):1147-57.

22. Flynn-Evans EE, Stevens RG, Tabandeh H, et al. Total visual blindness is protective against breast cancer. Cancer Causes and Control 2009;**20**(9):1753-6.

23. Blask DE. Melatonin, sleep disturbance and cancer risk. Sleep Medicine Review 2009;**13**(4):257-64.

24. Blask DE, Hill SM, Dauchy RT, et al. Circadian regulation of molecular, dietary, and metabolic signaling mechanisms of human breast cancer growth by the nocturnal melatonin signal and the consequences of its disruption by light at night. Journal of Pineal Research 2011;**51**(3):259-69.

25. Filipski E, Delaunay F, King VM, et al. Effects of chronic jet lag on tumor progression in mice. Cancer Research 2004;**64**(21):7879-85.

26. Lichtenstein P, Defaire U, Floderus B, et al. The Swedish Twin Registry: A unique resource for clinical, epidemiological and genetic studies. Journal of Internal Medicine 2002;**252**:184-205.

27. Rao DP, Yu HF, Bai Y, et al. Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. Oncotargets Ther 2015;**8**:2817-26.

28. Oberg S, Cnattingius S, Sandin S, et al. Twinship influence on morbidity and mortality across the lifespan. Int J Epidemiol 2012;**41**(4):1002-9.

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

	Number of inviduals (%)		p-value
	Non-night workers (n=7 506)	Night workers (n=4 816)	
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%)	
BMI			<0.001
Normal weight	3570 (48%)	2099 (42%)	
Under weight	30 (0.4%)	10 (0.2%)	
Over weight	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. Hazard Ratios (HR) for shift work exposure groups applying multiple Cox analysis for prediction of prostate cancer[1] after baseline among male night workers, and with 95% Confidence Intervals (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)[a]**	**Follow-up to 60 years HR (95% CI)[b]**
No night work vs ever night work				
No night work [ref] Working nights for: (*unadjusted)*	0 1-45 years	294/7212 160/4656	1 0.84 (0.69-1.03)	1 **0.78 (0.64-0.96)**
No night work [ref] Working nights for: (*adjusted*) [2]	0 1-45 years	294/7212 160/4656	1 0.91 (0.74-1.12)	1 0.89 (0.72-1.09)
No night work vs years of shift work				
No night work [ref] Working nights for: (*unadjusted*)	0 years 1-5 years 6-10 years 11-20 years 21-45 years	294/7212 55/1729 31/800 38/968 36/1159	1 0.79 (0.60-1.06) 0.99 (0.68-1.43) 1.00 (0.72-1.41) 0.77 (0.55-1.09)	1 **0.72 (0.54-0.96)** 0.88 (0.61-1.27) 0.84 (0.60-1.18) 0.86 (0.61-1.21)
No night work [ref] Working nights for: (*adjusted*)[2]	0 years 1-5 years 6-10 years 11-20 years 21-45 years	294/7212 55/1729 31/800 38/968 36/1159	1 0.86 (0.63-1.17) 1.09 (0.74-1.61) 1.12 (0.78-1.63) 0.72 (0.50-1.05)	1 0.84 (0.62-1.15) 0.96 (0.65-1.42) 1.11 (0.77-1.60) 0.75 (0.52-1.09)

Note: [1] no cancer as reference;
[2] Adjusted for: age + education level + tobacco consumption + BMI + having children + coffee consumption + previous cancer
[a]: follow-up until December 31 2010, [b]: follow-up until the age of 60.

Table 3. Hazard Ratios (HR) for shift work exposure groups applying conditional Cox analysis of twin pairs discordant for prostate cancer[1] for prediction of prostate cancer after baseline among male night workers, and with 95% Confidence Intervals (CI). N=332.

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

Note: [1] no cancer as reference;
[a]: follow-up until December 31 2010, [b]: follow-up until the age of 60.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p4
Objectives	3	State specific objectives, including any prespecified hypotheses p5
Methods		
Study design	4	Present key elements of study design early in the paper p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p6 & p8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up p6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p6
Bias	9	Describe any efforts to address potential sources of bias p7
Study size	10	Explain how the study size was arrived at p6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p7-8
		(*b*) Describe any methods used to examine subgroups and interactions p8
		(*c*) Explain how missing data were addressed p8
		(*d*) If applicable, explain how loss to follow-up was addressed p8
		(*e*) Describe any sensitivity analyses p9
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed p6
		(b) Give reasons for non-participation at each stage p6
		(c) Consider use of a flow diagram na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders p8
		(b) Indicate number of participants with missing data for each variable of interest na)(no missing data – complete follow-up
		(c) Summarise follow-up time (eg, average and total amount) p8
Outcome data	15*	Report numbers of outcome events or summary measures over time p8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included p9
		(*b*) Report category boundaries when continuous variables were categorized p7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p9
Discussion		
Key results	18	Summarise key results with reference to study objectives p10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p11
Generalisability	21	Discuss the generalisability (external validity) of the study results p11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015751.R1
Article Type:	Research
Date Submitted by the Author:	27-Mar-2017
Complete List of Authors:	Åkerstedt, Torbjørn; Stockholm University, Stress Research Institute Narusyte, Jurgita; Karolinska Institute, Clinical Neuroscience Svedberg, Pia; Karolinska Institute, Department of Clinical Neuroscience Kecklund, Göran; Stockholm University, Stress Research Institute; Radboud University, Behavioural Science Institute Alexanderson, Kristina; karolinska institutet, Department of Clinical Neuroscience
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine
Keywords:	shift work, work hours, cohort study

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

Torbjörn Åkerstedt[1,2], Jurgita Narusyte[1], Pia Svedberg[1], Göran Kecklund[2,3], Kristina Alexanderson[1]

1.Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
2. Stress Research Institute, Stockholm University, Stockholm, Sweden
3. Behavioral Science Institute, Radboud University, Nijmegen, The Netherlands

Correspondence: Dr Torbjorn Akerstedt, Department of Clinical Neuroscience, Karolinska Institutet, 17177 Stockholm Sweden
Email: torbjorn.akerstedt@ki.se
Phone: +46 737078928

Key words: shift work, longitudinal, night work, cancer

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 12322 men.

Setting: Individuals in the Swedish Twin Registry.

Participants: 12322 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.

Key words: shift work, night work, men, twins, Sweden

Strength and weaknesses 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 (IARC) 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 8 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 tumor 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 decreased, cancer tumors increase in growth in female rats with implanted cancer tumors..[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 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 Swedish Twin Registry (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 12322 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 to all others. In addition, further categorization 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 categorization at ≥30 years, hence the following categorization 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 Cancer Register 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 (BMI – 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). 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 Chi-square 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 Hazards Ratios (HR) with 95% Confidence Intervals (CI). 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 categorized) and the survival time as a covariate. Potential familial confounding was controlled for, by analyzing twin pairs discordant for prostate cancer (i.e., one twin in a pair was diagnosed with prostate cancer during the follow-up, whereas the twin partner not). Conditional Cox Proportional Hazard regression was applied, where each twin pair was provided with their own baseline hazard. All analyses were performed using SAS.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 107545. 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 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 here

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=0.40-1.03) for the exposure group with 21-45 hours of night-work (N = 5444).

Table 3 here

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 the previous five studies. Thus, six studies (including the present one) fail 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 favor 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, 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 generalizability. 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 needs 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.

Contributions: 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.

Funding: This study was funded by the AFA Insurance Company (grant number 120264)

Conflicting interests: None declared

Ethical approval: The ethical committee for the Stockholm Region

Provenance and peer review: Not commissioned, externally peer reviewed

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.

References

1. Ferlay J, Shin HR, Bray F, *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;**127**:2893-917.

2. Jemal A, Siegel R, Ward E, *et a*l. Cancer Statistics 2009;**59**:225-49.

3. van Die MD, Bone KM, Williams SG, *et al.* Soy and soy isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials. BJU Int 2014;**113**:E119-30.

4. Xu X, Cheng Y, Li S, *et al*. Dietary carrot consumption and the risk of prostate cancer. Eur J Nutr 2014;**53**:1615-23.

5. Pukkala E, Martinsen JI, Weiderpass E, *et al*. Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. Occup Environl Med 2014;**71**:398-404.

6. LeMasters GK, Genaidy AM, Succop P, *et al*. Cancer risk among firefighters: a review and meta-analysis of 32 studies. J Occup Environ Med 2006;**48**:1189-202.

7. Kolstad HA. Nightshift work and risk of breast cancer and other cancers--a critical review of the epidemiologic evidence. Scand J Work Environ Health 2008;**34**:5-22.

8. Bonde JP, Hansen J, Kolstad HA, *et al*. Work at night and breast cancer - report on evidence-based options for preventive actions. Scand J Work Environ Health 2012.

9. Jia YJ, Lu YS, Wu KJ, *et al*. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. Cancer Epidemiol 2013;**37**:197-206.

10. Wang F, Yeung KL, Chan WC, *et al*. A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. Ann Oncology 2013;**24**:2724-32.

11. Ijaz S, Verbeek J, Seidler A, *et al*. Night-shift work and breast cancer--a systematic review and meta-analysis. Scand J Work, Evironment health 2013;**39**:431-47.

12. Kamdar BB, Tergas AI, Mateen FJ, *et al*. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 2013;**138**:291-301.

13. Rao DP, Yu HF, Bai Y, *et al*. Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. Oncotargets Ther 2015;**8**:2817-26.

14. Kubo T, Ozasa K, Mikami K, *et al*. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. Am J Epidemiol 2006;**164**:549-55.

15. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiol 2007;**18**:182-3.

16. Parent ME, El-Zein M, Rousseau MC, *et al*. Night work and the risk of cancer among men. Am J Epidemiol 2012;**176**:751-9.

17. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scand J Work EnvironHealth 2007;**33**:336-43.

18. Kubo T, Oyama I, Nakamura T, *et al*. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. Int J Urol 2011;**18**:206-11.

19. Gapstur SM, Diver WR, Stevens VL, *et al*. Work schedule, sleep duration, insomnia, and risk of fatal prostate cancer. Am J Prev Med 2014;**46**(3 Suppl 1):S26-33.

20. Yong M, Blettner M, Emrich K, *et al*. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. Scand J Work, Environ Health 2014;**40**:502-10.

21. Papantoniou K, Castano-Vinyals G, Espinosa A, *et al*. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. International journal of cancer Int J Cancer 2015;**137**:1147-57.

22. Stevens RG. Testing the light-at-night (LAN) theory for breast cancer causation. Chronobiol Int 2011;**28**:653-6.

23. Flynn-Evans EE, Stevens RG, Tabandeh H, et al. Total visual blindness is protective against breast cancer. Cancer Causes and Control 2009;**20**:1753-6.

24. Blask DE. Melatonin, sleep disturbance and cancer risk. Sleep Med Rev 2009;**13**:257-64.

25. Blask DE, Hill SM, Dauchy RT, *et al*. Circadian regulation of molecular, dietary, and metabolic signaling mechanisms of human breast cancer growth by the nocturnal melatonin signal and the consequences of its disruption by light at night. J Pineal Res 2011;**51**:259-69.

26. Filipski E, Delaunay F, King VM, *et al*. Effects of chronic jet lag on tumor progression in mice. Cancer Res 2004;**64**:7879-85.

27. Akerstedt T, Knutsson A, Narusyte J, et al. Night work and breast cancer in women: a Swedish cohort study. BMJ Open 2015;**5**(4):e008127.

28. Lichtenstein P, Defaire U, Floderus B, *et al*. The Swedish Twin Registry: A unique resource for clinical, epidemiological and genetic studies. J Int Med 2002;**252**:184-205.

29. Oberg S, Cnattingius S, Sandin S, *et al*. Twinship influence on morbidity and mortality across the lifespan. Int J Epidemiol 2012;**41**:1002-9.

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

	Number of inviduals (%)		p-value
	Non-night workers (n=7 506)	Night workers (n=4 816)	
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%)	
BMI			<0.001
Normal weight	3570 (48%)	2099 (42%)	
Under weight	30 (0.4%)	10 (0.2%)	
Over weight	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. Hazard Ratios (HR) for shift work exposure groups applying multiple Cox analysis for prediction of prostate cancer[1] after baseline among male night workers, and with 95% Confidence Intervals (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)[a]**	**Follow-up to 60 years HR (95% CI)[b]**
No night work vs ever night work				
No night work [ref]	0	294/7212	1	1
Working nights for:	1-45 years	160/4656	0.84 (0.69-1.03)	**0.78 (0.64-0.96)**
(*unadjusted)*				
No night work [ref]	0	294/7212	1	1
Working nights for:	1-45 years	160/4656	0.91 (0.74-1.12)	0.89 (0.72-1.09)
(*adjusted*) [2]				
No night work vs years of shift work				
No night work [ref]	0 years	294/7212	1	1
Working nights for:	1-5 years	55/1729	0.79 (0.60-1.06)	**0.72 (0.54-0.96)**
(*unadjusted*)	6-10 years	31/800	0.99 (0.68-1.43)	0.88 (0.61-1.27)
	11-20 years	38/968	1.00 (0.72-1.41)	0.84 (0.60-1.18)
	21-45 years	36/1159	0.77 (0.55-1.09)	0.86 (0.61-1.21)
No night work [ref]	0 years	294/7212	1	1
Working nights for:	1-5 years	55/1729	0.86 (0.63-1.17)	0.84 (0.62-1.15)
(*adjusted*)[2]	6-10 years	31/800	1.09 (0.74-1.61)	0.96 (0.65-1.42)
	11-20 years	38/968	1.12 (0.78-1.63)	1.11 (0.77-1.60)
	21-45 years	36/1159	0.72 (0.50-1.05)	0.75 (0.52-1.09)

Note: [1] no cancer as reference;
[2] Adjusted for: age + education level + tobacco consumption + BMI + having children + coffee consumption + previous cancer
[a]: follow-up until December 31 2010, [b]: follow-up until the age of 60.

Table 3. Hazard Ratios (HR) for shift work exposure groups applying conditional Cox analysis of twin pairs discordant for prostate cancer[1] for prediction of prostate cancer after baseline among male night workers, and with 95% Confidence Intervals (CI). N=332.

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

Note: [1] no cancer as reference;
[a]: follow-up until December 31 2010, [b]: follow-up until the age of 60.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p4
Objectives	3	State specific objectives, including any prespecified hypotheses p5
Methods		
Study design	4	Present key elements of study design early in the paper p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p6 & p8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up p6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p6
Bias	9	Describe any efforts to address potential sources of bias p7
Study size	10	Explain how the study size was arrived at p6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p7-8
		(*b*) Describe any methods used to examine subgroups and interactions p8
		(*c*) Explain how missing data were addressed p8
		(*d*) If applicable, explain how loss to follow-up was addressed p8
		(*e*) Describe any sensitivity analyses p9
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed p6
		(b) Give reasons for non-participation at each stage p6
		(c) Consider use of a flow diagram na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders p8
		(b) Indicate number of participants with missing data for each variable of interest na)(no missing data – complete follow-up
		(c) Summarise follow-up time (eg, average and total amount) p8
Outcome data	15*	Report numbers of outcome events or summary measures over time p8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included p9
		(*b*) Report category boundaries when continuous variables were categorized p7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p9
Discussion		
Key results	18	Summarise key results with reference to study objectives p10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p11
Generalisability	21	Discuss the generalisability (external validity) of the study results p11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.