

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Night work and prostate cancer in men – a Swedish prospective cohort study
AUTHORS	Åkerstedt, Torbjørn; Narusyte, Jurgita; Svedberg, Pia; Kecklund, Göran; Alexanderson, Kristina

VERSION 1 - REVIEW

REVIEWER	William B. Grant Sunlight, Nutrition and Health Research Center United States
REVIEW RETURNED	23-Jan-2017

GENERAL COMMENTS	<p>An alternate hypothesis that should be addressed is that since night shift workers generally sleep during daytime, they do not spend much time in the sun, thus, they have lower 25-hydroxyvitamin D concentrations. Low concentrations may be a risk factor for prostate cancer although the findings regarding UVB exposure and 25OHD concentrations and risk of prostate cancer are not as strong as for several other types of cancer. On the other hand, high UVB exposure and 25OHD concentrations significantly reduce risk of breast cancer. An analysis of cancer incidence in Nordic countries found no significant correlation between outdoor occupation and incidence of prostate cancer but did find one for breast cancer [Grant, 2012]</p> <p>Papers to consider citing: Alefshat E, Abu Farha R. Determinants of vitamin d status among Jordanian employees: Focus on the night shift effect. <i>Int J Occup Med Environ Health</i>. 2016;29(5):859-70. Grant WB. 25-Hydroxyvitamin D and breast cancer, colorectal cancer, and colorectal adenomas: case-control versus nested case-control studies, <i>Anticancer Res</i>. 2015;35(2):1153-60. Grant WB. Low 25-hydroxyvitamin D concentrations may explain the link between breast cancer risk and shift work. <i>Int Arch Occup Environ Health</i> 2015;88:819. Grant WB. Low ultraviolet-B exposure may explain some of the link between night shift work and increased risk of prostate cancer. <i>Int J Cancer</i>. 2015 Aug 15;137(4):999. Grant WB. Role of solar UV irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. <i>Dermatoendocrinol</i>. 2012;4(2):203-11. Peters CE, Demers PA, Kalia S, Hystad P, Villeneuve PJ, Nicol AM, Kreiger N, Koehoorn MW. Occupational exposure to solar ultraviolet radiation and the risk of prostate cancer. <i>Occup Environ Med</i>. 2016 Nov;73(11):742-748. Romano A, Vigna L, Belluigi V, Conti DM, Barberi CE, Tomaino L, Consonni D, Riboldi L, Tirelli AS, Andersen LL. Shift work and serum</p>
-------------------------	---

	<p>25-OH vitamin D status among factory workers in Northern Italy: Cross-sectional study. <i>Chronobiol Int.</i> 2015;32(6):842-7.</p> <p>Sauvé JF, Lavoué J, Parent MÉ. Occupation, industry, and the risk of prostate cancer: a case-control study in Montréal, Canada. <i>Environ Health.</i> 2016 Oct 21;15(1):100.</p> <p>Schwartz GG. Vitamin D, sunlight, and the epidemiology of prostate cancer. <i>Anticancer Agents Med Chem.</i> 2013;13(1):45-57.</p> <p>Xu Y, Shao X, Yao Y, Xu L, Chang L, Jiang Z, Lin Z. Positive association between circulating 25-hydroxyvitamin D levels and prostate cancer risk: new findings from an updated meta-analysis. <i>J Cancer Res Clin Oncol.</i> 2014 Sep;140(9):1465-77.</p>
--	--

REVIEWER	Hui Hu University of Florida, USA
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	<p>This is an interesting manuscript and a timely investigation on night work and prostate cancer. The data used is a great resource to perform this investigation, although it suffers from the same limitations as most other studies do: the lack of information between the interview and the outcome/censoring. My main concerns are the way how the authors analyzed the data and how the survival time was defined. It is unreasonable to define the survival time as the time since interview when the information on exposure and many covariates were not available after the interview. Please find my detailed commented below:</p> <ol style="list-style-type: none"> 1. Please fix the citation format across the manuscript: ".1" instead of "1." 2. Page 4, line 54: it is not rare if there are already 8 studies 3. Page 4, line 56: please fix the citation format for (Rao et al. 2015) 4. Page 6, line 55: instead of categorizing the number of years, the authors can use polynomial terms of the continuous exposure to model the potential nonlinear relationship. 5. Page 7, line 19: the authors may also include cancer stage at diagnoses as a covariate. Please also specify what age was included as a covariate. Is it the age at interview? 6. Page 8, line 1: please perform multiple imputations to assess how the missing covariates may impact the results. 7. Page 8, line 15: please specify how survival time is generated. Is it age at diagnoses or number of years between the interview and diagnoses? It seems unreasonable if the authors use time since interview as the survival time since the exposure were measured from birth to interview. 8. Page 8, line 30: please check whether the proportional hazard assumption for the Cox model was met.
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

An alternate hypothesis that should be addressed is that since night shift workers generally sleep during daytime, they do not spend much time in the sun, thus, they have lower 25-hydroxyvitamin D concentrations. Low concentrations may be a risk factor for prostate cancer although the findings regarding UVB exposure and 25OHD concentrations and risk of prostate cancer are not as strong as for several other types of cancer. On the other hand, high UVB exposure and 25OHD concentrations

significantly reduce risk of breast cancer. An analysis of cancer incidence in Nordic countries found no significant correlation between outdoor occupation and incidence of prostate cancer but did find one for breast cancer [Grant, 2012]

This is an interesting angle and we have added a reference to that effect. However, we have not developed any discussion since we did not obtain any positive results.

Reviewer 2

This is an interesting manuscript and a timely investigation on night work and prostate cancer. The data used is a great resource to perform this investigation, although it suffers from the same limitations as most other studies do: the lack of information between the interview and the outcome/censoring. My main concerns are the way how the authors analyzed the data and how the survival time was defined. It is unreasonable to define the survival time as the time since interview when the information on exposure and many covariates were not available after the interview. Please find my detailed comments below:

1. Please fix the citation format across the manuscript: ".1" instead of "1."

Right, done

2. Page 4, line 54: it is not rare if there are already 8 studies

Sorry, you are right, of course. We removed that part of the sentence.

3. Page 4, line 56: please fix the citation format for (Rao et al. 2015)

Done

4. Page 6, line 55: instead of categorizing the number of years, the authors can use polynomial terms of the continuous exposure to model the potential nonlinear relationship.

We agree that by studying night work as a categorical variable, we do not have any possibility to model a potential non-linear relationship. However, in this study we attempt to explain the association, instead of exactly predicting it, and therefore, we believe that categorization of night work makes the interpretation of the results more straightforward, as well as of a greater public health importance. It will also make it easier to compare with other studies, including being included in meta-analyses. So, we hope it is acceptable to retain the original approach

5. Page 7, line 19: the authors may also include cancer stage at diagnoses as a covariate. Please also specify what age was included as a covariate. Is it the age at interview? We do not have that information, unfortunately

6. Page 8, line 1: please perform multiple imputations to assess how the missing covariates may impact the results.

We have now performed multiple imputations (n=20) for the covariates with missing data and the mean values of the covariates with imputed values deviated only slightly from the mean values in the complete-case dataset (please see Table 1 below). We have added the following text in Methods:

"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 slightly deviances were observed." However, we did not enter the table in the manuscript since the differences were so small. If necessary we can do that, of course.

Table 1. Comparison of complete-case dataset and the dataset with imputed values for covariates with missing-values

Mean (SD)

Complete-case Multiple imputations (n=20)

Education 0.58 (0.49) 0.58 (0.004)

Tobacco use 0.89 (0.31) 0.89 (0.002)

BMI 1.71 (1.59) 1.71 (0.01)
Coffee consumption 3.14 (0.92) 3.14 (0.01)

7. Page 8, line 15: please specify how survival time is generated. Is it age at diagnoses or number of years between the interview and diagnoses? It seems unreasonable if the authors use time since interview as the survival time since the exposure were measured from birth to interview. We don't have information on when night work exposure occurred or when exposure for many of the covariates occurred. Thus, we think the reasonable solution would be to use baseline as a "start". We hope this is acceptable.

8. Page 8, line 30: please check whether the proportional hazard assumption for the Cox model was met.

The assumption was met and the text saying this is now found in the methods section, page 8.

VERSION 2 – REVIEW

REVIEWER	Hui Hu University of Florida, USA
REVIEW RETURNED	12-Apr-2017

GENERAL COMMENTS	Thanks the authors for addressing all my concerns. I do not have other comments.
-------------------------	--