Shift work, night work, and the risk of prostate cancer
A meta-analysis based on 9 cohort studies
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Abstract

Background: Epidemiology studies suggested that shift work or night work may be linked to prostate cancer (PCa); the relationship, however, remains controversial.

Methods: PubMed, ScienceDirect, and Embase (Ovid) databases were searched before (started from the building of the databases) February 4, 2017 for eligible cohort studies. We pooled the evidence included by a random- or fixed-effect model, according to the heterogeneity. A predefined subgroup analysis was conducted to see the potential discrepancy between groups. Sensitivity analysis was used to test whether our results were stale.

Results: Nine cohort studies were eligible for meta-analysis with 2,570,790 male subjects. Our meta-analysis showed that, under the fixed-effect model, the pooled relevant risk (RR) of PCa was 1.05 (95% confidence interval [CI]: 1.00, 1.11; P = .06; I² = 24.00%) for men who had ever engaged in night shift work; and under the random-effect model, the pooled RR was 1.08 (0.99, 1.17; P = .08; I² = 24.00%). Subgroup analysis showed the RR of PCa among males in western countries was 1.05 (95% CI: 0.99, 1.11; P = .09; I² = 0.00%), while among Asian countries it was 2.45 (95% CI: 1.19, 5.04; P = .02; I² = 0.00%); and the RR was 1.04 (95% CI: 0.95, 1.14; P = .40; I² = 29.20%) for the high-quality group compared with 1.21 (95% CI: 1.03, 1.41; P = .02; I² = 0.00%) for the moderate/low-quality group. Sensitivity analysis showed robust results.

Conclusions: Based on the current evidence of cohort studies, we found no obvious association between night shift work and PCa. However, our subgroup analysis suggests that night shift work may increase the risk of PCa in Asian men. Some evidence of a small study effect was observed in this meta-analysis.

Abbreviations: CI = confidence interval, NOS = Newcastle–Ottawa Scale, PCa = prostate cancer, RR = relevant risk, SIR = standard incidence ratio.

Keywords: cohort studies, meta-analysis, night work, prostate cancer, shift work

1. Introduction

Prostate cancer (PCa) is the most common form of cancer for men in developed countries and the 4th most common cancer in developing countries. In 2017, the American Cancer Society estimated that 161,360 new cases of PCa will be diagnosed, of which 26,730 men will die from PCa in the United States.

Although the incidence of PCa dropped more than 10% from 2010 to 2013 each year, PCa remains the leader in both occurrence and death in the United States for cancer. Working status has been linked closely to health. Shift work is very common among office workers, and is considered the main cause of circadian rhythm disorder. According to American and European surveys, approximately between 15% and 30% of adult workers are engaged in different degrees of shift work, with 32% to 36% of shift workers falling asleep at work more than once a week.

Several epidemiology studies suggest that a disrupted circadian rhythm may increase the risk of PCa. In a large Japanese cohort study, Kubo et al revealed that rotating shift work is significantly associated with an increased risk of PCa. Several case–control studies also found that shift work or night work may be linked to an increased PCa risk while some other cohort studies showed no association. An earlier meta-analysis by Rao et al summarized 8 observational studies and found that night shift work was associated with a higher risk of PCa. However, the substantial heterogeneity and potential recall bias from case–control studies warrants caution about their conclusions.

In this study, the evidence was updated, based on cohort studies, to verify whether night shift work increases the risk of PCa This meta-analysis was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.
2. Methods

2.1. Literature search

A comprehensive literature search was conducted based on PubMed, ScienceDirect, and Embase (Ovid). These databases were searched before (started from the building of the databases) February 4, 2017 by 2 independent reviewers, without language limitation. We also screened the reference lists of relevant studies manually. We used the following search terms to develop the strategy: sleep disorders, shift work, shift work, night work, rotate shift work, night shift work, prostate cancer, cancer, prostate tumor, and prostate neoplasm. The detailed search strategies for the 3 databases are presented in a supplementary file (Table S1; http://links.lww.com/MD/B958).

2.2. Inclusion criteria

The inclusion criteria was developed ex ante, and eligible studies were included if they satisfied the following criteria: based on prospective or retrospective cohort design; the exposure was to shift work, night work, or occupation related with shift work (e.g., airline crew)[12]; the endpoint was any stage of PCa, and only primary cancer was considered; the potential population was male; and peer-reviewed publications and available data could be extracted. Two authors screened the literature and any disagreement was resolved by discussion. Conference abstracts, gray literature, and commentary were excluded from the search.

2.3. Data extraction and transformation

Data items were extracted by 2 authors with the following information: first author’s name, publication year, region, population information (e.g., mean age at entry), follow-up years, exposure, endpoint, and effect sizes (relevant risk, RR) with 95% confidence interval (CI). We only extracted the multivariable controlled RR to minimize potential bias. The 2 authors checked each other’s data after the extraction process.

Some prospective studies used the standard incidence ratio (SIR) as the measurement of risk for PCa. The relationship between SIR and RR can be expressed as follows[11]:

\[
\text{SIR} = \frac{\text{RR}}{\text{PE} \times \text{RR} + (1 - \text{PE})}
\]

where PE is the expected prevalence of PCa, we considered SIR as similarly equal to RR, since the expected prevalence of PCa is very low.[2]

2.4. Quality assessment

For included studies, we used the Newcastle–Ottawa Scale (NOS) for cohort studies, which evaluate the design quality and the implementation approach of original studies. We considered a study to be of high quality when it met 7 or more of the recommended items.

2.5. Statistical analysis

We used RR to reflect the risk of PCa when exposed to night shift work. The RRs were pooled across the studies by a random- or fixed-effect model, according to the heterogeneity tested by I² statistics. Briefly, the I² statistics range from 0% to 100%, and the value of I² ≥ 50 suggests substantial heterogeneity and that a random-effect model would be selected. The inverse variance method was used to combine the effect sizes.

We also conducted a predefined subgroup analysis by country, work type, study quality, mean age at entry, effect size, and follow-up years to determine the potential discrepancy between these subgroups. A one-by-one-omitted sensitivity analysis was conducted to confirm whether our results were stable. We used the Egger test to assess publication bias. All the statistical analyses were accomplished by Stata 12.0 software (Stata Corporation, College Station, TX). Ethical approval was not necessary due to the nature of meta-analysis.

3. Results

In total, 1573 primary records were retrieved from the databases, 308 of which were duplicates. The title and abstract were screened and 1185 publications were rejected as being not relevant. Therefore, 80 articles remained and required further screening by reading the texts in full. Of these, 71 studies did not meet the criteria and were subsequently excluded. Finally, 9 cohort studies were eligible for meta-analysis, involving a total of 2,570,790 male subjects (Fig. 1).

The mean age at entry of these subjects varied from 30.39 to 55.5 years, with an average value of 44.69 years. Among the 9 cohorts, 8 studies were based on a prospective design and 1 study was based on a historical design. Five studies were conducted in European counties, 2 studies were conducted in the United States, and 2 studies were conducted in Asian countries. The mean follow-up was 20.19 years, ranging from 6.5 to 30 years (Table 1).

Regarding the quality of the included studies, we deemed 6 studies to be of high quality, while 3 studies[18,19,22] were deemed to be of moderate to low quality. The mean quality score was 7, and the range was from 5 to 9 (Table S2; http://links.lww.com/MD/B958).

3.1. Night shift work and risk of PCa

Nine studies investigate the relationship between night shift work and the risk of PCa. Figure 2A and B presents the pooled results based on a fixed- and random-effect model. Our meta-analysis showed that, under the fixed-effect model, the pooled RR of PCa was 1.05 (95% CI: 1.00, 1.11; \(P = .06\); I² = 24.00%), for men who had ever engaged in night shift work; and under the random-effect model, the RR was 1.05 (95% CI: 1.00, 1.11). The RR for men who had ever engaged in night shift work was not significantly different from 1, but the risk of PCa was increased for men who had engaged in night shift work for more than 5 years (Table 2).

![Figure 1](https://example.com/figure1.png)
### 3.2. Subgroup analysis

Our subgroup analysis was conducted by country (western countries and Asian countries), work type (shift work and night work), mean age at entry (50 years or older and 50 years or younger), effect size (RR and SIR), follow-up years (>20 years and ≤20 years), and study quality (high-quality vs. moderate or low-quality). Table 2 presents the results. Our subgroup analysis showed that, when grouped by country, the RR of PCa among males in western countries was 1.05 (95% CI: 0.99, 1.11; \( P = 0.09; I^2 = 0.00 \%), while among Asian countries it was 2.45 (95% CI: 1.19, 5.04; \( P = 0.02; I^2 = 0.00 \%). When grouped by effect size, the RR was 1.04 (95% CI: 0.95, 1.14; \( P = 0.00; I^2 = 29.20 \%)) for the RR group compared with 1.21 (95% CI: 1.03, 1.41; \( P = 0.02; I^2 = 0.00 \%)) for the SIR group. When grouped by study quality, the RR was 1.04 (95% CI: 0.95, 1.14; \( P = 0.00; I^2 = 29.20 \%)) for the high-quality group compared with 1.21 (95% CI: 1.03, 1.41; \( P = 0.02; I^2 = 0.00 \%)) for the moderate/low-quality group. Other means of subgroup analysis showed no obvious discrepancy between subgroups.

### 3.3. Sensitivity analysis and publication bias

Our one-by-one-omitted sensitivity analysis showed that the whole pooled result was stable (Fig. 3). The Egger test showed some evidence of publication bias: the \( P \) value of bias was 0.05 (Fig. 4). A trim and fill analysis by both the fixed-effect model (RR = 1.04; 95% CI: 0.98, 1.10) and the random-effect model (RR = 1.05; 95% CI: 0.95, 1.15) showed that our results were stable (Fig. 5).

### 4. Discussion

In our meta-analysis, we reviewed the evidence in respect of night shift work and the risk of PCa, based on cohort studies. We found that, based on our pooled results, night shift work is not associated with an increased risk of PCa for the total population, regardless of mean age, work type, or follow-up years. However, in our subgroup analysis, we found that, among males in Asian countries, night shift work may increase the risk of PCa, but this effect was not observed in western countries.

Interestingly, our subgroup analysis, based on study quality, reveals that for high-quality studies, the pooled results were not statistically significant; while for moderate- or low-quality studies, the pooled results showed a significant increase in PCa risk. This suggests that our meta-analysis may have been affected by the “small study effect.” The Egger test for publication bias also supports this hypothesis. By a series of additional analyses (e.g., subgroup analysis, sensitivity analysis, and trim and fill analysis) we provided evidence to suggest that night shift work is not linked to PCa risk in the total population.

Some evidence of publication bias was detected, and the small-study effect may have influenced our results. In our subgroup analysis, we found the pooled results of moderate- or low-quality...
Figure 2. The relationship between night shift work and the risk of prostate cancer: (A) fixed-effect model and (B) random-effect model.

Table 2
Subgroup analysis.

| Subgroup Items     | Number | Pooled results | P    | Heterogeneity (I²), % |
|--------------------|--------|----------------|------|-----------------------|
| Country            |        |                |      |                       |
| Western countries  | 7      | 1.05 (0.99, 1.11) | .09  | 0                     |
| Eastern countries  | 2      | 2.45 (1.19, 5.04) | .02  | 0                     |
| Work type          |        |                |      |                       |
| Night work         | 6      | 1.04 (0.95, 1.14) | .22  | 29                    |
| Shift work         | 3      | 0.85 (0.43, 1.69) | .24  | 30                    |
| Mean age           |        |                |      |                       |
| >50                | 3      | 1.11 (0.98, 1.25) | .19  | 61.80                  |
| ≤50                | 6      | 1.04 (0.98, 1.11) | .20  | 0                     |
| Effect size        |        |                |      |                       |
| Relative risk      | 6      | 1.04 (0.95, 1.14) | .4   | 29.20                  |
| Standard incidence ratio* | 3 | 1.21 (1.03, 1.41) | .02  | 0                     |
| Follow-up year     |        |                |      |                       |
| >20                | 5      | 1.10 (1.00, 1.22) | >.05 | 0                     |
| ≤20                | 4      | 1.09 (0.91, 1.31) | .38  | 58                    |
| Study quality      |        |                |      |                       |
| High quality       | 6      | 1.04 (0.95, 1.14) | .4   | 29.20                  |
| Moderate/low quality* | 3 | 1.21 (1.03, 1.41) | .02  | 0                     |

* Subgroups with statistical significant pooled results.
studies tended to be positively associated with PCa risk. When pooled, the whole effect tended to trend positively. However, our overall pooled results were still negative, which indirectly demonstrates that night shift work may not increase the risk of PCa in the total population. The trim and fill analysis presenting stable results also supported our results.

A previous meta-analysis by Rao et al.\cite{13} based on 5 cohorts and 3 case-controls, concluded that night shift work may increase the risk of PCa and there may be a dose–response effect. However, their pooled results showed substantial heterogeneity between studies. The 3 case-control studies they included may have also introduced potential bias since these are based on historical design. In this meta-analysis, we only pooled cohort studies, conducted a series of additional analyses, and found that night shift work may increase the risk of PCa among Asian males only.

It is not clear what may underlie these differences. One potential explanation is that the different effect of night shift work on Asian men compared with European and American men may be due to differing lifestyles and genotypes. Another possibility for the differences may be due to the varying types of jobs undertaken by the subjects. However, further research is required to investigate these differences.

There were several strengths in our meta-analysis. First, only cohort studies were included, with no case–control studies, which reduced bias.\cite{23} Second, we conducted a predefined subgroup analysis to reveal any potential discrepancy among groups, avoiding selection bias.\cite{24} Third, we conducted a series of additional analyses that all supported our main findings. However, there were still several limitations to our study. First, the number of included studies was relatively small. Although the sample size was sufficient, only part of the sample was researched, which may not be representative of the total population. Second, in several included studies, eligible subjects were all from a certain company, lowering the representativeness of the sample. Third, the small study effect may have positively influenced our results. The real effect may be more conservative than the current pooled effect.\cite{25} Fourth, for subgroup analysis, only 2 studies involved Asian men. Although the pooled effect in this group was significant, the results may be at risk of a type II error due to the limited study numbers.\cite{26}
5. Conclusion

Based on the current evidence of cohort studies, we found no obvious association between night shift work and PCa. However, our subgroup analysis suggests that night shift work may increase the risk of PCa in Asian men. Some evidence of a small study effect was observed in this meta-analysis.

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