Systematic Review and Meta-Analysis

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Shift work, night work, and the risk of prostate cancer

A meta-analysis based on 9 cohort studies

Hong-Bing Du, MD*, Kai-Yun Bin, BS, Wen-Hong Liu, BS, Feng-Sheng Yang, MD

Abstract

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

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; $P = .06$; $I^2 = 24.00\%$) 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; $P = .08$; $I^2 = 24.00\%$). Subgroup analysis showed the RR of PCa among males in western countries was 1.05 (95% CI: 0.99, 1.11; $P = .09$; $I^2 = 0.00\%$), while among Asian countries it was 2.45 (95% CI: 1.19, 5.04; $P = .02$; $I^2 = 0.00\%$); and the RR was 1.04 (95% CI: 0.95, 1.14; $P = .40$; $I^2 = 29.20\%$) for the high-quality group compared with 1.21 (95% CI: 1.03, 1.41; $P = .02$; $I^2 = 0.00\%$) 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.[1] 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.[2] 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.[1]

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,[3] 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.[4]

Several epidemiology studies suggest that a disrupted circadian rhythm may increase the risk of PCa.[5,6] In a large Japanese cohort study, Kubo et al[7] 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,[8–10] while some other cohort studies showed no association.[11,12] An earlier meta-analysis by Rao et al[13] 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.[14]

Editor: Meixia Lu.

Study design, literature search, data, and drafting the manuscript: H-BD; statistical analysis: H-BD and BK-Y; revise the manuscript and check the data and re-analysis the data: BK-Y, LW-H, YF-S.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2017) 96:46(e8537)

Received: 7 May 2017 / Received in final form: 29 September 2017 / Accepted: 12 October 2017

http://dx.doi.org/10.1097/MD.0000000000008537

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[15]:

$$SIR = RR/[P_E \times RR + (1 - P_E)]$$

where P_E 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) to assess quality.[16] The NOS checklist contains 9 items 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 I^2 statistics. Briefly, the I^2 statistics range from 0% to 100% and the value of $I^2 \geq 50$ suggests substantial heterogeneity and that a random-effect model would be selected. Likewise, if $I^2 < 50$, the fixed-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,[7,11,12,17–22] 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; $P = .06$; $I^2 = 24.00\%$) for men who had ever engaged in night shift work; and under the random-

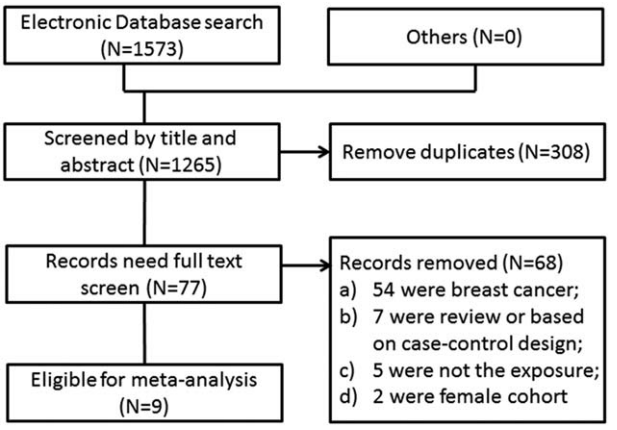

Figure 1. The flow diagram of the literature inclusion.

Table 1

Basic characters of included studies.

First author	Population information	Mean age at entry	Follow-up, y	Exposure	Endpoint	Adjusted RR	Adjusted item
Dickerman 2016	Prospective cohort in Finnish twins, with 11,370 participants and 620 cases (CIR: 5.45%)	40 (SD: 12.1)	30	Night work Shit work	Total prostate cancer	0.5 (0.1, 1.9) 1.0 (0.7, 1.2)	Age, education, BMI, physical activity, social class, smoking, alcohol, snoring, zygosity
Hammer 2015	Historical cohort in a German company, with 27,828 participants and 1073 cases (CIR: 3.86%)	40 (range: 32.5–50.5)	10	Shift work	Total prostate cancer Stage 4	0.95 (0.75, 1.21) 1.19 (0.21, 5.52)	Age and professional status, lifestyle factors, smoking
Gapstur 2014	Prospective cohort study of US adults, with 305,057 employed male participants and 4974 cases (CIR: 1.63%)	51.4 (SD: 8.5)	29	Night work Shift work	Fatal prostate cancer	0.72 (0.44, 1.18) 1.08 (0.95, 1.22)	Age, race, education, BMI, smoking status, family history of prostate cancer, urination
Hammer 2014	Prospective cohort of 10 countries (European and the United States), with 12,288 male participants and 114 cases (CIR: 9.3%)	About 49.7	21.7	Airline-related shift work	Prostate cancer death	1.23 (0.98, 1.53)	Standard mortality rate
Kubo 2011	Prospective cohort in Japan, with 4995 male participants and 17 cases (CIR: 0.34%)	About 55.5 (SD: 3.6)	25.9	Shift work	Total prostate cancer	1.79 (0.57, 5.68)	Age, body mass index, alcohol intake, smoking, exercise status
Pukkala 2012	Prospective cohort study of Nordic airline cabin attendants, with 1559 male and 24 cases (CIR: 1.54%)	Most of which <35 (mean: 30.39)	23.6	Airline-related shift work	Prostate cancer	1.11 (0.71, 1.65)	Standard incidence rate
Schwartzbaum 2007	Prospective cohort study of Swedish, with 2,102,126 male participants and 1319 cases (CIR: 0.06%)	About 42.09	18	Shift work	Prostate cancer	1.04 (0.99, 1.10)	Age, socioeconomic status, occupational position, county
Kubo 2006	Prospective cohort in Japan, with 14,052 working men and 31 cases (CIR: 0.22%)	About 51.9	6.5	Night work Shift work	Prostate cancer	2.3 (0.6, 9.2) 3.0 (1.2, 7.7)	Age, area, prostate cancer, BMI, smoking, alcohol drinking, work, stress, educational, marriage status
Pukkala 2002	Prospective cohort study in Nordic, with 10,032 male airline pilots and 466 cases (CIR: 4.65%)	About 41.3	17	Airline-related shift work	Prostate cancer	1.21 (0.93, 1.54)	Standardized incidence ratio

BMI = body mass index, CIR = cumulative incidence rate, RR = relevant risk, SD = standard deviation.

effect model, the pooled RR was 1.08 (0.99, 1.17; $P = .08$; $I^2 = 24.00\%$).

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 and ≤50 years), effect size (RR and SIR), follow-up years (>20 and ≤20 years), and study quality (high quality vs. moderate or low). 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; $P = .09$; $I^2 = 0.00\%$), while among Asian countries it was 2.45 (95% CI: 1.19, 5.04; $P = .02$; $I^2 = 0.00\%$). When grouped by effect size, the RR was 1.04 (95% CI: 0.95, 1.14; $P = .40$; $I^2 = 29.20\%$) for the RR group compared with 1.21 (95% CI: 1.03, 1.41; $P = .02$; $I^2 = 0.00\%$) for the SIR group. When grouped by study quality, the RR was 1.04 (95% CI: 0.95, 1.14; $P = .40$; $I^2 = 29.20\%$) for the high-quality group compared with 1.21 (95% CI: 1.03, 1.41; $P = .02$; $I^2 = 0.00\%$) 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 .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

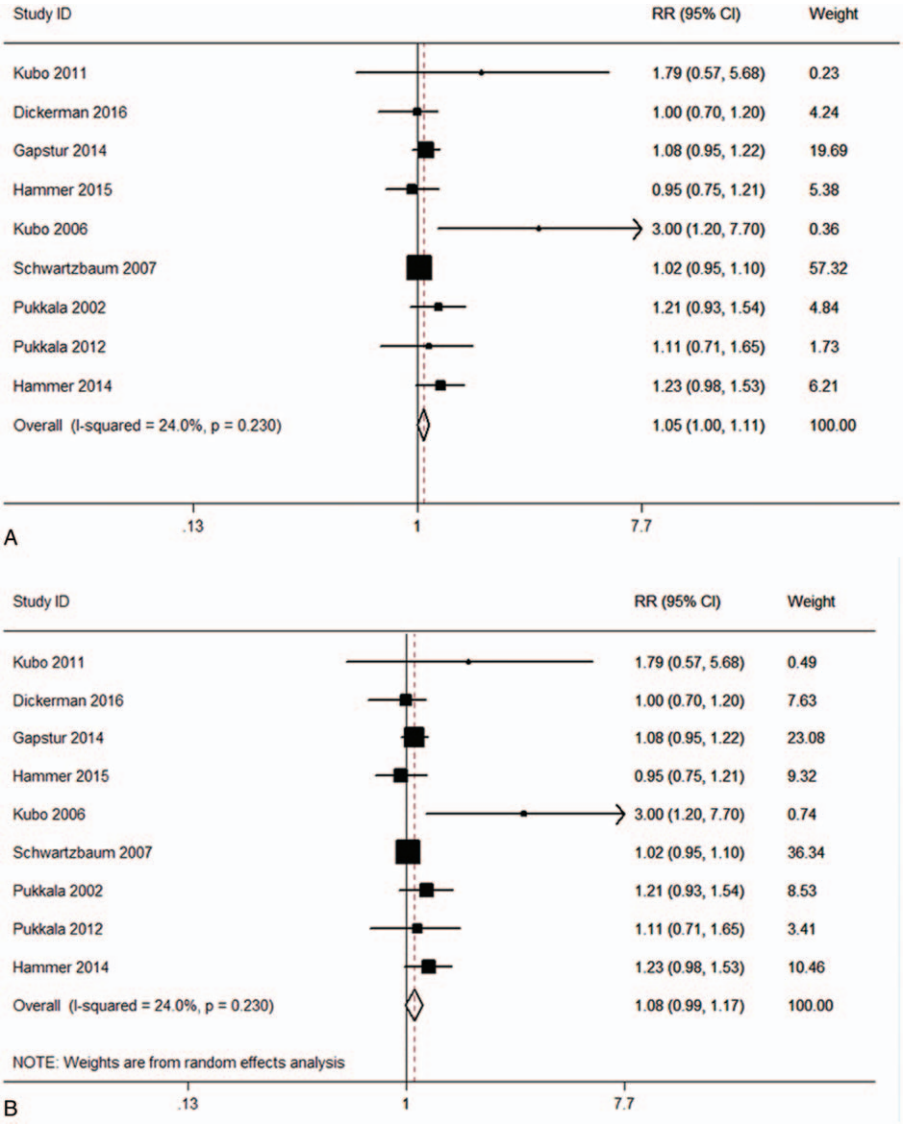

Figure 2. The relationship between night shift work and the risk of prostate cancer: (A) fixed-effect model and (B) random-effect model.

Table 2

Subgroup analysis.

Subgroup items	Number	Pooled results	*P*	Heterogeneity (I^2), %
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.

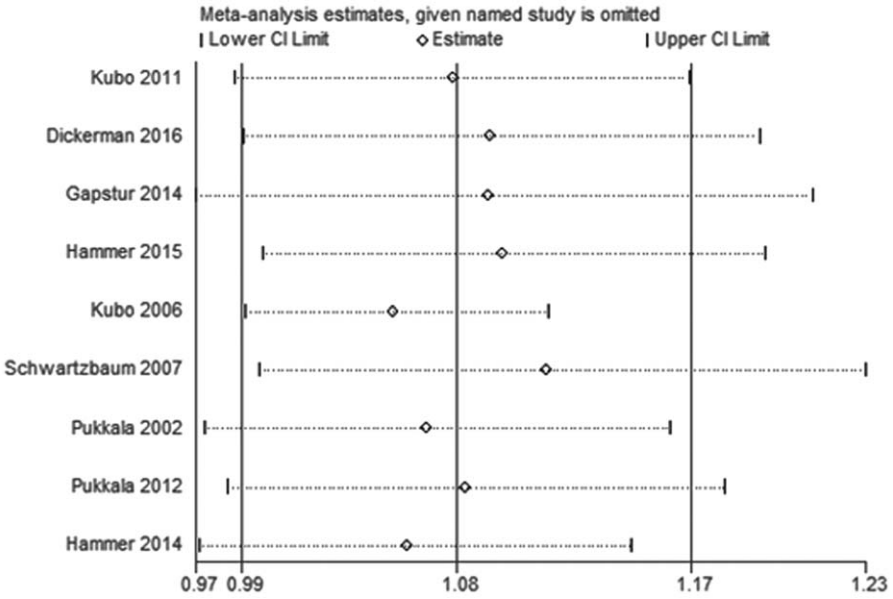

Figure 3. One-by-one-omitted sensitivity analyses.

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,[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.[23] Second, we conducted a predefined subgroup analysis to reveal any potential discrepancy among groups, avoiding selection bias.[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.[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.[26]

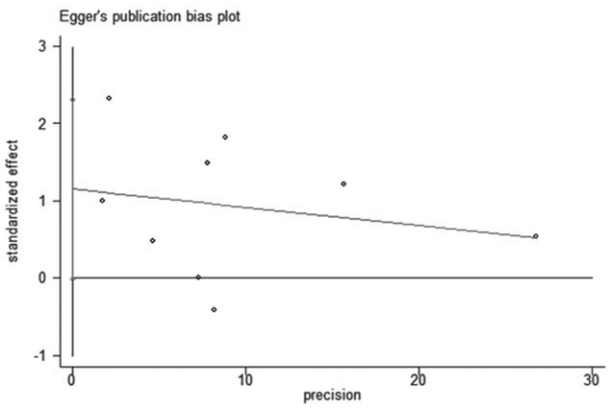

Figure 4. Publication bias by Egger test.

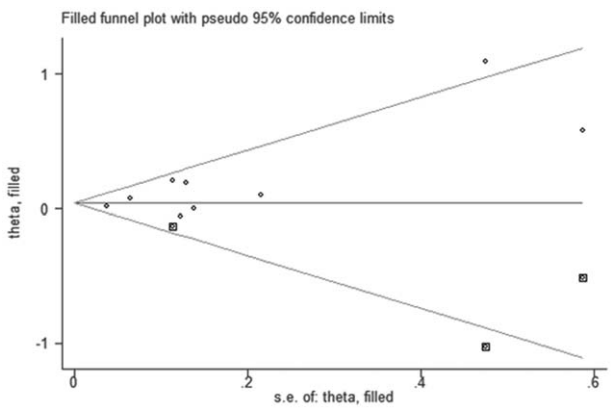

Figure 5. Filled funnel plot by trill and fill method.

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.

Acknowledgment

The authors thank Dr. X.H. Wang for his previous assistant on this meta-analysis.

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