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Association between multiple sclerosis and prostate cancer risk: A systematic review and meta-analysis

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Abstract. Prostate cancer (PCa) risk in patients with multiple sclerosis (MS) remains to be elucidated. The present study conducted a meta-analysis to assess the relationship between MS and PCa. PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched to identify studies on the PCa risk in patients with MS up to September 2022. A random effects meta-analyses model was performed to estimate the relative risk (RR) and the 95% confidence intervals (CI). All eight studies involving 210,943 patients with MS were identified and included in the meta-analysis. The present study revealed that there was no significant association between MS and the risk of PCa (RR=0.78, 95% CI: 0.56-1.08, P<0.0001). Subgroup analyses verified this conclusion when stratified by regions. However, after adjusting for potential confounders, the findings suggested conflicting results. The current evidence shows that compared with the population control, patients with MS have no relationship with PCa risk and further large samples and long-term trials are needed to verify these results.

Introduction

Prostate cancer (PCa) is one of the most common cancers and the fifth leading cause of cancer death in men (1). In 2022, the American Cancer Society estimated 268,490 new cases of prostate cancer and 34,500 mortalities (2).

Multiple sclerosis (MS) is an immune-related disease of the central nervous system (3), with a high rate of teratogenicity (4) and mortality (5) and its associated complications are the leading causes of mortality, including infections, respiratory failure, and cardiovascular diseases. Previous studies have shown a strong relationship between immune-related disorders and cancer (6,7). While some studies show an increase risk of cancer in individuals with MS, others show the opposite or no association at all (8,9).

Results on the association between MS and PCa are conflicting. For instance, Bosco-Lévy *et al* (10) suggested that MS was associated with an increased risk of PCa [hazard ratio (HR)=2.08; 95% CI: 1.68-2.58], while Kingwell *et al* (11) showed that MS was not associated with the risk of PCa [standardized incidence ratio (SIR)=0.91; 95% CI: 0.64-1.27]. Marrie *et al* (12) showed different results. To address this problem, a meta-analysis was performed to clarify the relationship between MS and risk of PCa.

Materials and methods

The present study followed the PRISMA statement (13). A systematic review and meta-analysis was conducted.

Search strategy. PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com), Web of Science (https://www.webofscience.com/) and Cochrane Library databases (https://www.cochranelibrary.com/) were searched for related studies that investigated the PCa risk in patients with MS up to September 2022. The following search terms were used (multiple sclerosis) OR (Sclerosis, Multiple) OR (Sclerosis, Disseminated) OR (Disseminated Sclerosis) OR (MS (Multiple Sclerosis) OR (Multiple Sclerosis, Acute Fulminating) OR (Multiple Sclerosis, Relapsing-Remitting) OR (Multiple Sclerosis, Chronic Progressive) AND (Prostatic Neoplasms) OR (Prostate Cancer) OR (Prostatic Cancer) OR (cancer).

Data extraction. The titles and abstracts of all articles retrieved from the initial search were screened to determine their relevance and all relevant articles were further evaluated to determine their qualifications for inclusion in the meta-analysis. Two authors independently extracted data according to the standardized process, including the author's name, year of publication, country, follow-up time, number of patients and adjusted confounding factors, Any differences arising during the study were resolved through discussion with the third Examiner (Jiawu Wang).

Quality assessment. Two authors evaluated the quality of the included studies according to the Newcastle Ottawa Scale (14), Based on the different quality scores, each study could obtain up

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Abbreviations: CS, cohort study; CCS, control-case study; NA, not applicable; MS, multiple sclerosis; PCa, prostate cancer

Key words: multiple sclerosis, prostate cancer, meta-analysis

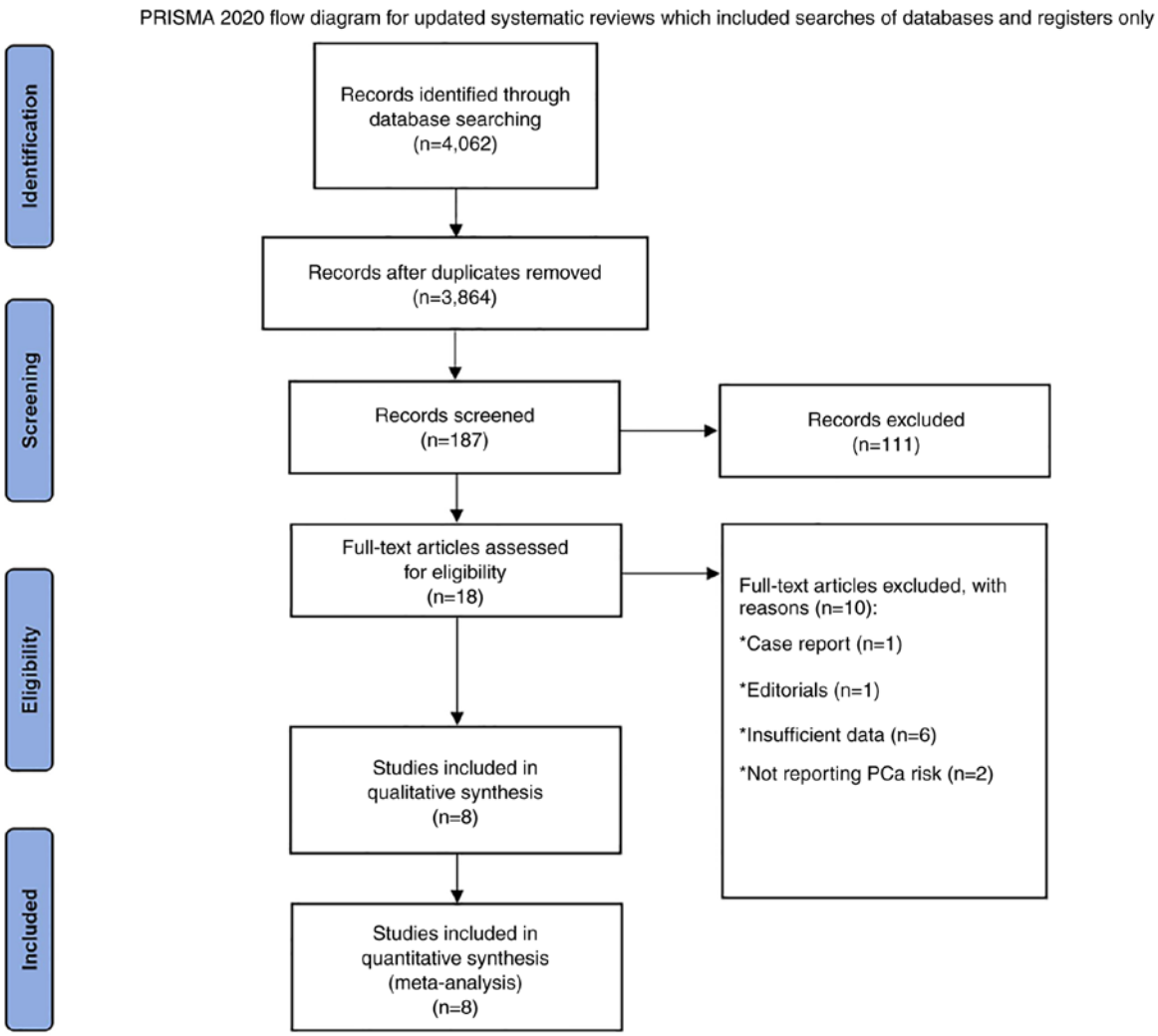

Figure 1. Flow diagram of study selection. PCa, prostate cancer.

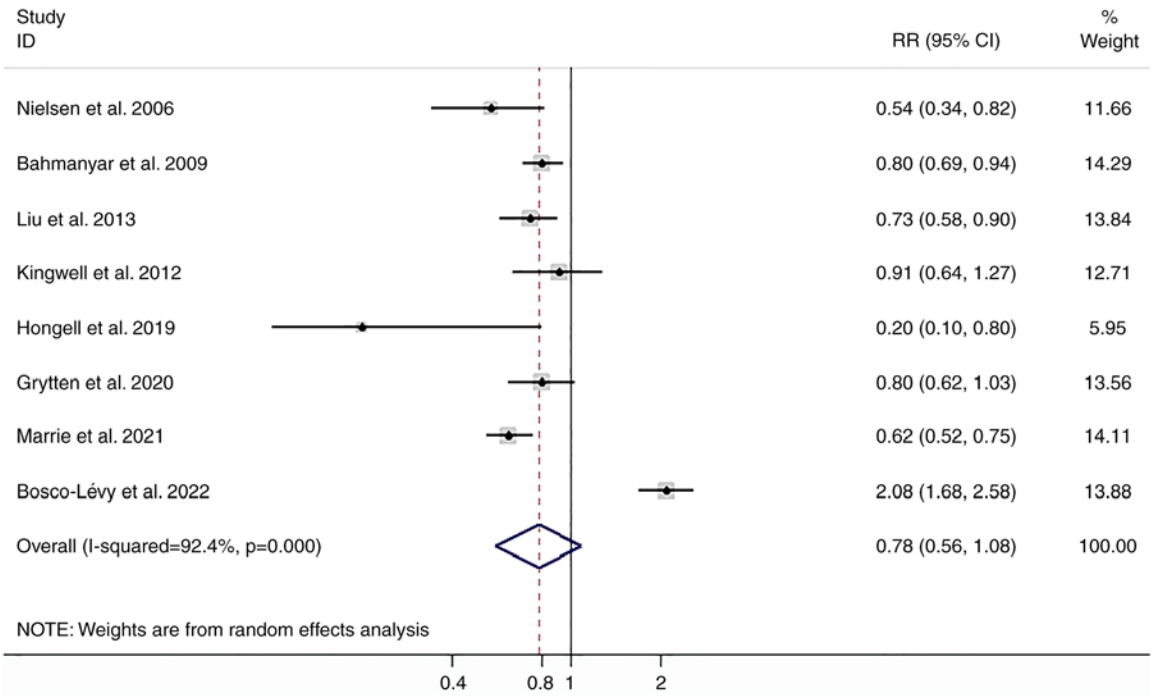

Figure 2. Meta-analysis on association between multiple sclerosis and prostate cancer risk. CI, confidence interval, HR, Hazard Ratio.

Table I. Characteristics of the included studies.

First author, year	Country	Study source	Study design	Population (MS/control)	PCa cases (MS/control)	Follow up duration	PCa risk (95% CI)	Adjusted confounding factors	(Refs.)
Nielsen, 2006	Denmark	Population-based	CS	11,817/NA	20/37.67	/	SIR (95% CI): 0.53 (0.34-0.82)	NA	(15)
Bahmanyar, 2009	Sweden	Population-based	CS	20,276/203,951	159/2,923	35 years	HR (95% CI): 0.80 (0.69-0.94)	Age, region of residence and socioeconomic index	(16)
Liu, 2013	Sweden	Population-based	CS	14,616/NA	86/NA	44 years	SIR (95% CI): 0.73 (0.58-0.90)	Obesity, chronic obstructive pulmonary disease	(17)
Kingwell, 2012	Canada	Population-based	CS	6,820/NA	35/NA	/	SIR (95% CI): 0.91 (0.64-1.27)	NA	(11)
Hongell, 2019	Finland	Hospital-based	CCS	1,074/10,740	2/86	/	OR (95% CI): 0.2 (0.1-0.8)	NA	(19)
Grytten, 2020	Norway	Population-based	CS	6,883/37,919	66/493	65 years	HR (95% CI): 0.80 (0.62-1.03)	Age, residence, and attained educational level	(18)
Marrie, 2021	Canada	Population-based	CS	53,983/269,915	NA/NA	10 years	IRR (95% CI): 0.62 (0.52-0.75)	Age, region, SES and comorbidity	(12)
Bosco-Lévy, 2022	France	Population-based	CS	95,474/95,474	253/122	/	HR (95% CI): 2.08 (1.68-2.58)	NA	(10)

CS, cohort study; CCS, control-case study; NA, not applicable; MS, multiple sclerosis; PCa, prostate cancer; CI, confidence intervals; SIR, standardized incidence ratio; HR, hazard ratio; OR, odds ratio; SES, socioeconomic status.

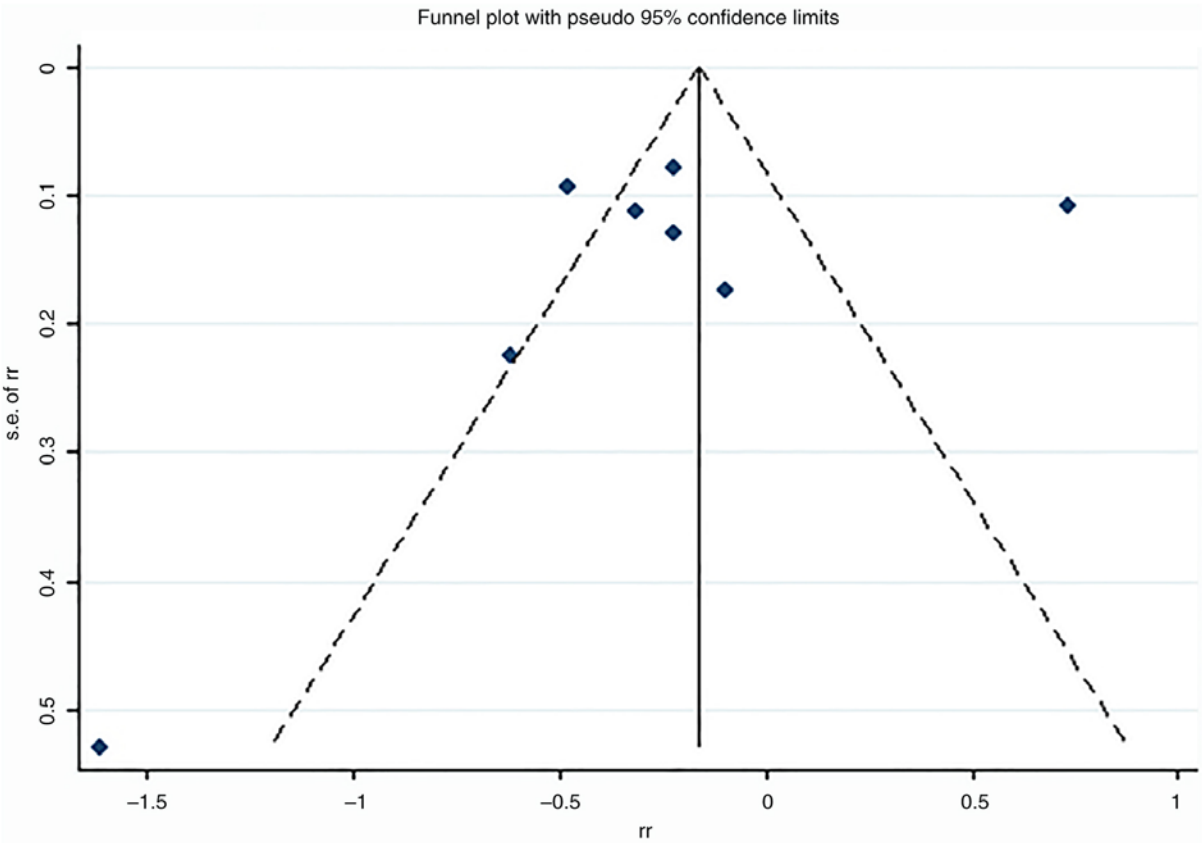

Figure 3. Funnel plot assessing of publication bias about the association between multiple sclerosis and prostate cancer risk. S.E., standard error; RR, relative risk.

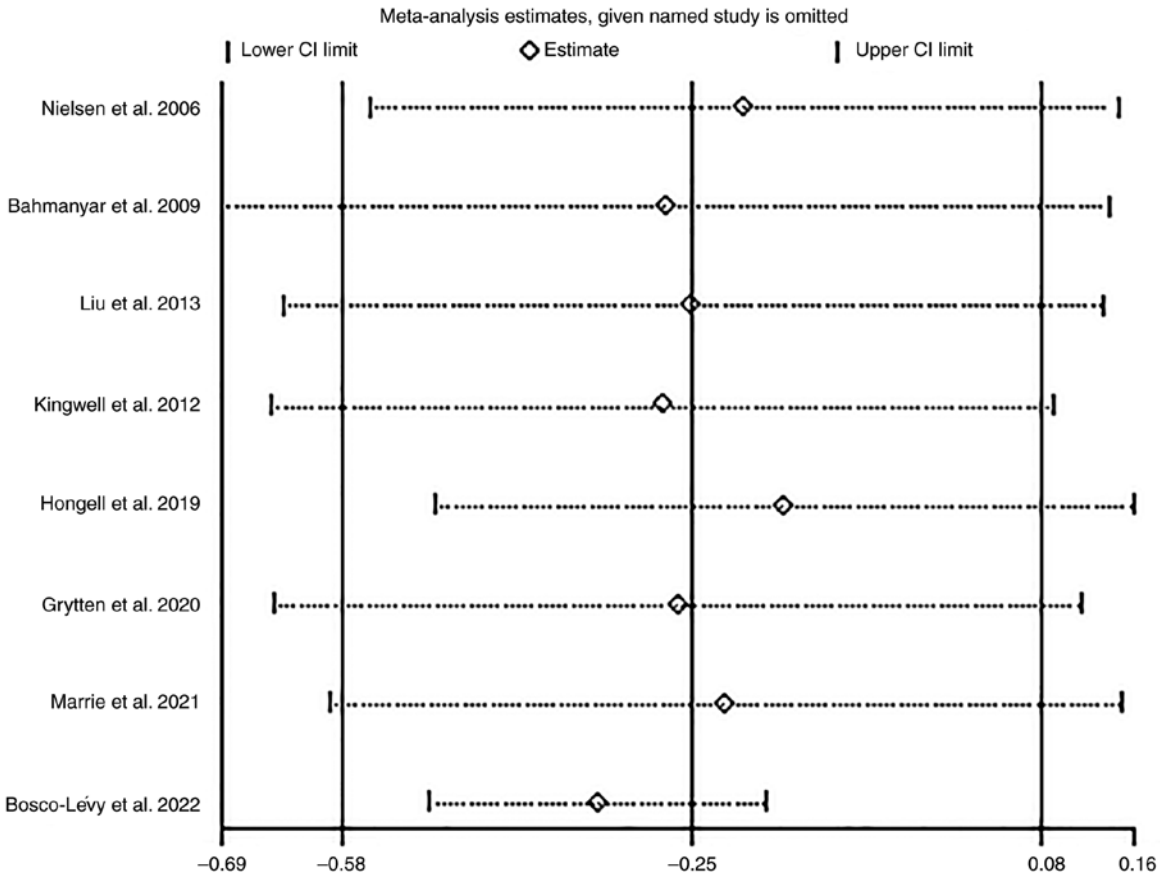

Figure 4. Sensitivity analysis investigating the influence of each individual study on the overall prostate cancer risk.

Table II. PCa risk in patients with multiple sclerosis.

	PCa risk		
Group	n	RR (95% CI)	Model
Overall	8	0.78 (0.56-1.08)	Random
Country			
European	6	0.78 (0.51-1.19)	Random
Other	2	0.73 (0.50-1.56)	Random
Adjustment for other factors			
Yes	4	0.73 (0.64-0.83)	Random
No	4	0.75 (0.33-1.67)	Random

PCa, prostate cancer; RR, relative risk.

to nine points, with total scores ranging from 0 to 9, including high quality (8-9 points), medium quality (6-7 points), and low quality (≤5 points). Third party reviewers resolved differences.

Statistical analysis. The data on all outcomes of interest were analyzed using Stata software version 12.0 (StataCorp LLC). Consistency indication, the incidence rate ratios, the odds ratios, the SIRs and the HRs, were directly considered as RRs in the meta-analysis. Heterogeneity was given by I^2, When $I^2 \geq 50\%$, it indicates that the heterogeneity is high, and the random effect model should be used; otherwise, a fixed effect model should be used. Subgroup analyses was stratified by country and confounding factors. Sensitivity analysis was used to evaluate the stability and consistency of the results. The Egger test and Begg test was used to determine publication deviations. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Study selection process. Based on the search strategy, the database search yielded 4,062 results. After excluding duplicate results and preliminary screening, 187 studies remained. After excluding non-relevant articles again, eight articles were included in the meta-analysis. The screening process is shown in the PRISMA flow chart (Fig. 1).

Study characteristics and methodological quality. The main characteristics of the included studies are summarized in Table I. These studies included seven cohorts studies (10-12,15-18) and one case-control study (19), summing 210,943 patients with MS. A total of two studies (16,17) from Sweden, two (11,12) from Canada, one (15) from Denmark, one (18) from Norway, one (19) from Finland and one (10) from France were included. Among these studies included in the meta-analysis, three studies were of high quality, and five were of moderate quality.

MS and PCa risk. Random-effects meta-analysis showed MS was not associated with the risk of PCa (RR=0.78; 95% CI: 0.56-1.08), with substantial heterogeneity (I^2=92.4%; $P<0.001$; Fig. 2). The present study was unable to perform a subgroup analysis based on study design because of limited data. A subgroup analysis based on the distinct regions showed that RR of 0.78 (95% CI: 0.51-1.19) among European countries and the RR of 0.73 (95% CI: 0.50-1.06) among other countries (Table II). The studies that adjusted for potential confounders gave a RR of 0.73 (95% CI: 0.64-0.83), while the RR of other unadjusted studies was 0.75 (95% CI: 0.33-1.67) (Table II).

The Begg and Egger tests and funnel plot (Fig. 3) was used to determine publication bias, the results of Begg and Egger tests (Pb=0.711 and Pe=0.612) and almost symmetrical funnel plots showed there was no publication bias. Sensitivity analysis (Fig. 4) found that no individual study would significantly change the pooled RRs after removal, indicating that the results were reliable.

Discussion

The first comprehensive meta-analysis on the relationship between MS and PCa risk was published in 2015 (20), suggesting that MS reduced PCa risk. Notably, a study published in Cancer Hematology Review in 2016 also reported MS is associated with the reduction of PCa risk (21), while a cohort study in 2020 summing up more than 6,800 patients showed that during an average follow-up of 65 years, MS was not associated with PCa risk. However, a recent cohort study in 2022 found that MS increased the risk of PCa (10).

The risk of PCa in patients with MS is unknown and may be related to genetic and environmental factors, such as chronic inflammation and infection (22), which can cause tumor growth and escape by interfering with normal immune surveillance. Previous studies have shown that regulatory T-cell function is significantly impaired in patients with MS compared to normal function (23) and that regulatory T-cells can both promote tumorigenesis and inhibit the growth of some inflammatory tumors (24). Hormones also play an important role in patients with MS; studies have shown that testosterone levels are significantly lower in patients with MS and due to the significant anti-inflammatory properties of testosterone, some patients with MS opt for testosterone supplementation therapy, which may also have a relevant impact on PCa development due to the complex mechanism of action of testosterone (25-28). The treatment of MS may lead to the loss of immune protection against cancer or the activation of the immune system, making it a primary tumor (29). Moreover, the possible reasons include that studies conducted in different countries may have different factors that affect the results. For example, common risk factors for PCa include being elderly (30), diet (31) and independent protective factors including regular screening for PCa.

The present meta-analysis builds on previous meta-studies. Ghajarzadeh *et al* (32) summarized studies up to September 2019 and calculated a pooled RR estimate of 0.79 for cancer in patients with MS, thus they concluded that patients with MS would have a reduced risk of cancer. Nevertheless, due to the small number of studies, they did not summarize the PCa risk data, and no subgroup analysis was performed. Therefore the present study became necessary and it found a significant negative association between MS and PCa risk in subgroup

analysis adjusted for confounders, suggesting that some of the confounders may also confound the results.

The present study found strong heterogeneity. Possible reasons for this are: First, the number of studies was relatively small (eight studies). Second, the sample sizes were different across the studies. Finally, the reasons may be related to geographic region, with no reports of PCa risk in Asia. In addition, different types of studies, including cohort studies and controlled case studies, and differences in study populations may be other sources of heterogeneity.

Overall, the present study was the most recent and comprehensive study on the association between MS and PCa risk. Its conclusions are meaningful, and the results of the subgroup and sensitivity analyses further validate the reasonableness and reliability of the findings.

However, the present study had several limitations. First, the number of studies was relatively small. Second, different study methods and social factors of different study populations may also cause heterogeneity. Finally, observational studies themselves may be subject to information bias. Therefore, future high-quality studies should address these issues comprehensively.

In summary, the present study demonstrated there was no significant association between MS and PCa risk, and the correlation between treatment modalities and PCa needs to be further explored in the future.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

QJ contributed to the study conception and design. Data collection and analysis were performed by ZH, YF, JW and YL. The first draft of the manuscript was written by ZH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. ZH and YF confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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