Open Access

ORIGINAL ARTICLE

Prostate Cancer

Risk of prostate cancer in men with spinal cord injury: a systematic review and meta-analysis

Arcangelo Barbonetti[1], Settimio D'Andrea[2], Alessio Martorella[2], Giorgio Felzani[1], Sandro Francavilla[2], Felice Francavilla[2]

A lower risk of prostate cancer has been reported in men with spinal cord injury (SCI) as compared to that observed in able-bodied subjects. As injury-related consequences can have opposite effects on prostate pathophysiology, this meta-analysis aimed to (1) establish the existence/quantify the extent of decreased prostate cancer risk following SCI and (2) find out if there is any statistically significant difference in prostate-specific antigen (PSA) levels between SCI and able-bodied subjects. MEDLINE, Cochrane Library, Scopus, CINAHL, and ScienceDirect databases were used. Only studies reporting a prostate cancer diagnosis and/or PSA levels following SCI and in able-bodied controls were included. Five studies provided information about prostate cancer on 35 293 subjects with SCI and 158 140 controls. Six studies were included in PSA analysis which reported information on 391 men with SCI and 1921 controls. Pooled estimates indicated that SCI reduced the prostate cancer risk by approximately 50% as compared to controls, whereas differences in PSA levels were not statistically significant. Funnel plots suggested the presence of publication bias only in PSA analysis. Between-study heterogeneity was established and when, according to meta-regression models, analysis was restricted to studies including men with mean age over 55 years, prostate cancer risk in SCI decreased up to 65.0% than that in controls with no heterogeneity ($P = 0.33$, $I^2 = 9\%$). In conclusion, in men over 55 years old, SCI decreases the prostate cancer risk up to 65.0% than that in controls. The large between-study heterogeneity on PSA confirms its poor reliability as a screening tool for prostate cancer in SCI.

INTRODUCTION

Every year, spinal cord injury (SCI) occurs in 17 000 individuals in the United States and approximately 80% of these individuals are males.[1] Yet, with advancements in technology and routine checkups, the life expectancy for these patients has improved substantially and approached to that of the general population,[2] with the result that most patients with SCI are likely to go through age-related problems. Age, in particular, represents a well-known risk factor for prostate cancer, which is the most frequently diagnosed cancer among males aged 65–74 years; it is also the third leading cause of cancer-related death in the United States.[3] Therefore, it is expected that a larger number of patients with SCI may develop prostate cancer later in their lives. Moreover, the techniques of management of neurogenic bladder, including catheterization, predispose the patients to recurrent urinary tract infections following SCI. The resultant chronic inflammation of the prostate may increase the risk of developing prostate cancer in these subjects, which can be concluded on the basis of an established association between prostatitis and prostate cancer, as documented by population-based case–control studies.[4] Nevertheless, a lower prevalence of prostate cancer has been reported among individuals with SCI as compared to able-bodied age-matched individuals. The low levels of circulating androgens,[5–9] along with the loss of neurogenic

stimulation of prostate growth and activity,[10–12] peculiar to individuals with SCI, could prove to be protective to some extent, thus contributing to explaining a lower risk of prostate cancer, which, for all practical purposes, usually discourages screening programs in this population. In reality, the utility of enrolling men with SCI in screening programs is not clear because of the uncertainty in the efficiency of the use of prostate-specific antigen (PSA) as a screening tool for prostate cancer in these subjects. On the one hand, a low prostate volume, peculiar to males with chronic SCI,[13–17] would be associated with lower levels of PSA when compared to age-specific reference ranges; on the other hand, chronic prostate inflammation, catheterization, and repeated manual bowel evacuation are expected to yield falsely elevated PSA levels. As a result, several case–control studies have produced conflicting results, reporting either lower, similar or higher serum PSA levels in males with SCI as compared to that in able-bodied age-matched subjects.[10] In this scenario, where the actual level of the decreased prevalence of prostate cancer in SCI has not yet been determined, the limited use of screening programs could be the reason why prostate cancer would be diagnosed at an advanced stage and grade in this population.[18]

In order to assess the relationship of SCI with prostate cancer and PSA levels comprehensively, we carried out a meta-analysis of the available case–control studies, aiming to answer the following

[1]Spinal Unit, San Raffaele Sulmona Institute, Sulmona 67039, Italy; [2]Andrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila 67100, Italy.
Correspondence: Dr. A Barbonetti (arcangelobarbonetti@virgilio.it)

questions: (1) "Does, and to what extent, the presence of SCI decrease the risk of prostate cancer with respect to the general population?" and (2) "Is there any statistically significant difference in PSA levels between males with SCI and their able-bodied age-matched controls?"

MATERIALS AND METHODS

The study was conducted according to the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement;[19] it also complies with the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE).[20] PRISMA and MOOSE Checklists have been presented as **Supplementary Table 1** and **2**. The International prospective register of systematic reviews (PROSPERO) registration number is CRD42017057672.

Systematic search strategy

We conducted a systematic search in MEDLINE, Cochrane Library, Scopus, CINAHL, and ScienceDirect to identify all relevant studies in English language with the terms: ("spinal cord injur*" OR "spine injur*" OR "spinal injur*" OR paraplegia OR tetraplegia OR quadriplegia) AND (prostate OR "prostate specific antigen" OR PSA OR "prostate tumour" OR "prostate neoplasm" OR "prostate adenocarcinoma"). If it was not clear from title and abstract whether the paper contained relevant data, the full paper was retrieved. The references cited in all full-text articles were also hand-searched in an effort to obtain additional studies for inclusion.

Inclusion and exclusion criteria

The primary outcome of interest was the relationship between SCI and prostate cancer. The secondary outcome was the difference in serum PSA levels between males with SCI and able-bodied subjects. The eligibility criteria used for the study were: (1) observational case–control studies, enrolling individuals aged 18 years or older having SCI and an able-bodied control group; (2) availability of odds ratios (ORs) for prostate cancer or data for its calculation and/or mean ± standard deviation (s.d.) of PSA levels in both groups. Two independent reviewers (AB and SDA) assessed the eligibility of each selected paper; any disagreement was resolved via discussion involving a third reviewer (FF).

Data extraction

Data were extracted from the selected articles by including the first author, publication year, geographic region, and mean age of participants. From the studies evaluating prostate cancer, we extracted the number of events (prostate cancer) and the total number of participants in cases (males with SCI) and controls (age-matched able-bodied subjects); from the studies reporting PSA levels, we obtained mean ± s.d. of PSA measurement along with the total number of participants in cases and controls. Where data were missing or inconsistent, the authors were contacted to obtain the necessary information.

Quality assessment

The quality of studies was assessed through the "star system" of the Newcastle–Ottawa Quality Assessment Scale (NOS).[21] The minimum number of stars was 0 and the maximum that could be awarded was 9 stars. Those getting scores ≥7 were regarded as high-quality studies. The quality assessment was performed by two reviewers (AB and FF). Any disagreement was resolved by a third author (SF) who reevaluated the original study.

Statistical analysis

The relationship between SCI and prostate cancer was assessed using OR and 95% confidence interval (95% CI) as well as by Mantel–Haenszel

estimates. The differences in PSA levels were assessed by calculating the standardized mean difference (SMD). In the presence of significant heterogeneity, data were combined using random effects models, which assumed that the included studies have varying effect sizes, thus providing a conservative estimate of the overall effect. For nonsignificant heterogeneity, the results were pooled in a fixed effects model.

The Cochran's Chi-square (Cochran's Q) test and the I^2 test were carried out to analyze statistical heterogeneity between the results of different studies. $I^2 < 25\%$ was considered as no heterogeneity, whereas $I^2 > 50\%$ and/or $P < 0.05$ indicated substantial heterogeneity. In order to illustrate heterogeneity that may not be fully conveyed by 95% CI, 95% prediction intervals were also included in the summary results of random effects models, as previously reported.[22]

Meta-regression and subgroup analyses were conducted to investigate between-study heterogeneity, by taking into account covariates that could affect the estimates. In particular, predictors which might be potential sources of heterogeneity, such as publication year, geographic region, NOS quality score of the studies, sample size, and mean age of the participants, were included in linear meta-regression models where the regression coefficient (β) described how the outcome variable (the estimate) changed with a unit increase in the explanatory variable (the potential effect modifier). Publication bias was graphically identified using funnel plots.

The extracted data were analyzed using the R statistical software (version 3.0.3; R Foundation for Statistical Computing, Vienna, Austria) and the Review Manager (RevMan) of the Cochrane Library (version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Study selection and quality assessment

The electronic search yielded 1159 studies. Three articles were retrieved from the manual search. After removal of duplicate, 839 studies were left, 802 of which were excluded as they were irrelevant on the basis of titles and abstracts. Hence, as shown in **Figure 1**, a total of 37 studies were identified; however, only 9 of them met the inclusion criteria.[12,13,16–18,23–26] The details of the selected articles are reported in **Table 1**.

Five studies evaluated the difference in the prevalence of prostate cancer between males with SCI and able-bodied controls.[12,16–18,26] In all the studies, the included males were diagnosed with prostate cancer
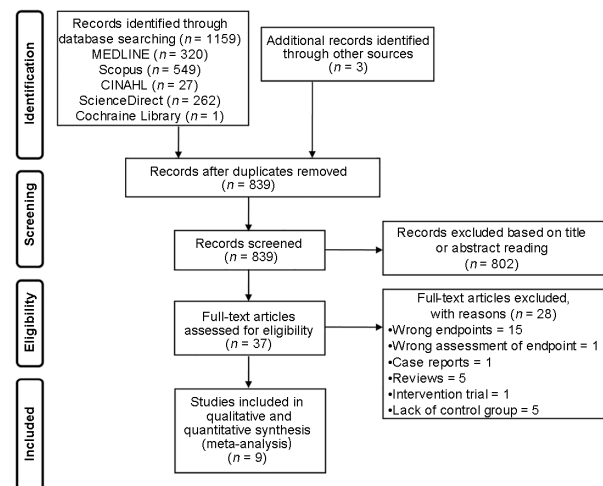
Figure 1: Flow diagram showing an overview of the study selection process.

after they sustained SCI. Six studies reported serum PSA levels between the two groups of subjects.[13,16,17,23–25]

Quality rating of the studies, based on the NOS score, is outlined in **Table 2**. Quality scores ranged from 5 to 8. Eight articles were considered to be of high quality,[12,13,16–18,24–26] scoring ≥7; one article was assessed to be moderate.[23] In the study by Lynne *et al.*[23] a selection bias could not be ruled out since that study enrolled only volunteers and comparability could not be ensured by adjusting either on age or other variables.

Synthesis of results
Overall, five studies evaluating the risk of prostate cancer[12,16–18,26] provided information on 35 293 males with SCI and 158 140 able-bodied controls. As shown in **Figure 2a**, pooled OR suggested that the presence of SCI reduces the risk of prostate cancer by almost one-half as compared to that in able-bodied males (OR = 0.47, 95% CI: 0.27 to 0.83, $P = 0.009$). Between-study heterogeneity was revealed by I^2 value >50% ($P_{\text{for heterogeneity}} = 0.06$, $I^2 = 56\%$).

The six studies that reported PSA levels[13,16,17,23–25] provided information on 391 males with SCI and 1921 able-bodied controls. As shown in **Figure 2b**, the overall difference between the two groups was not found to be statistically significant (pooled SMD: 0.11, 95% CI: −0.46 to 0.68, $P = 0.7$; $P_{\text{for heterogeneity}} < 0.00001$, $I^2 = 95\%$).

Publication bias and heterogeneity evaluation
As shown in **Figure 3a**, the reasonably symmetrical shape of funnel plot suggested the absence of obvious publication bias among studies investigating the risk of prostate cancer. On the contrary, a clear asymmetry was observed in the funnel plot of studies analyzing PSA levels (**Figure 3b**).

As between-study heterogeneity in the pooled analyses was found (**Figure 2**), linear meta-regression analyses were performed in order to detect possible covariates responsible for this variability.

It was observed that only the mean age of study population contributed significantly to the source of heterogeneity in the analysis of prostate cancer: the older age of the participants was significantly associated with a higher decrease in OR for prostate cancer in SCI as compared to the controls ($\beta = -0.10$; 95% CI: −0.19 to −0.01; $P = 0.02$). Accordingly, in a subgroup analysis (**Figure 4a**), where we excluded the study by Torricelli *et al.*[17] and the largest study by Lee *et al.*[12] both reporting a mean age of participants to be <55 years, the pooled OR for the association between SCI and prostate cancer further decreased up to 0.35 (95% CI: 0.22 to 0.56, $P < 0.0001$) with no heterogeneity ($P_{\text{for heterogeneity}} = 0.33$, $I^2 = 9\%$).

As far as PSA levels were concerned, in the linear meta-regression models, both sample size and NOS quality score of the studies contributed significantly to heterogeneity: lower values of SMD, indicative of lower PSA levels in SCI as compared to that in controls, were associated with a higher NOS quality score ($\beta = -1.48$; 95% CI: −1.92 to −1.04; $P < 0.0001$) and a larger sample size of the study population ($\beta = -0.03$; 95% CI: −0.06 to −0.001; $P = 0.03$). In a subgroup analysis (**Figure 4b**), where we excluded the study by
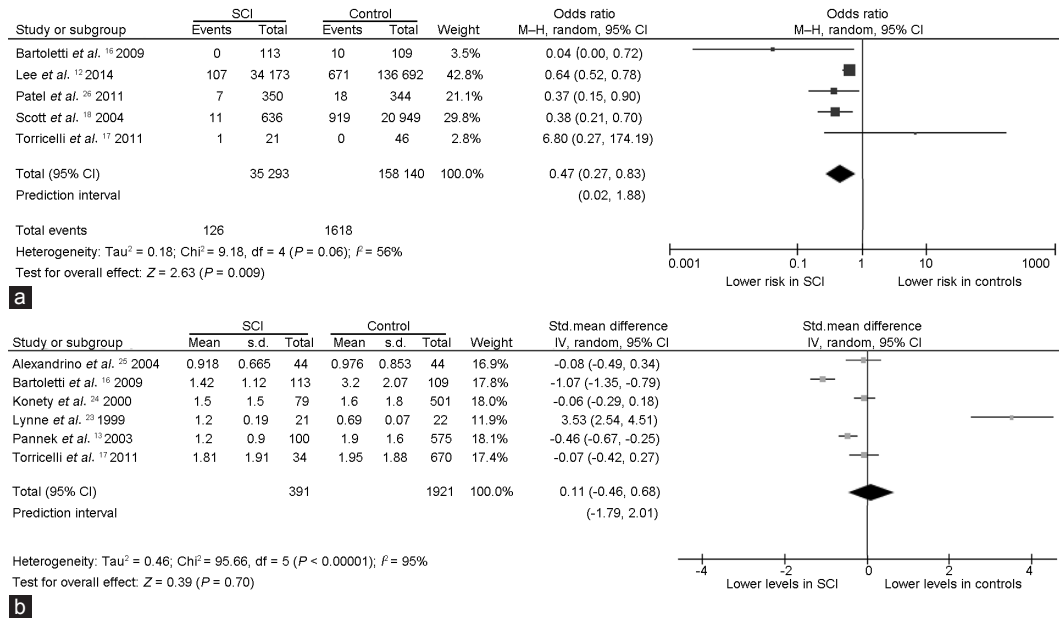
Table 1: Characteristics of the nine studies included

| Study	Geographic region	Endpoints of interest	Endpoint assessment	Age of SCI group (year)	Age of control group (year)	SCI level
Lynne *et al.*[23] 1999	USA	PSA	EIA	≥24	≥19	C: 38%; T: 52%; LS: 5%; Unknown: 5%
Konety *et al.*[24] 2000	USA	PSA	EIA	>40	≥40	NA
Pannek *et al.*[13] 2003	Germany	PSA	EIA	≥35	≥35	NA
Alexandrino *et al.*[25] 2004	Brazil	PSA	EIA	≥18	≥18	C: 17%; T: 80%; L: 3%
Scott *et al.*[18] 2004	USA	PSA[a] and prostate cancer	Cancer registry and clinic databases	>50	>50	NA
Bartoletti *et al.*[16] 2009	Italy	PSA and prostate cancer	PSA: EIA; prostate cancer: biopsy	≥52	≥58	T12 and above: 80.5%; L1 and below: 19.5%
Patel *et al.*[26] 2011	USA	Prostate cancer	Hospital registry	≥40	≥40	C: 48%; T: 43%; LS: 9%
Torricelli *et al.*[17] 2011	Brazil	PSA and prostate cancer	PSA: NA; prostate cancer: biopsy	≥33	≥36	NA
Lee *et al.*[12] 2014	China	Prostate cancer	Histological diagnosis on illness registry	≥20	≥20	NA

[a]The PSA values reported by Scott *et al.*[18] were not included in the meta-analysis as they were measured only in men with a diagnosis of prostate cancer. EIA: enzyme immunoassay; NA: not available; PSA: prostate-specific antigen; SCI: spinal cord injury; C: cervical; T: thoracic; LS: lumbosacral; T12: twelfth thoracic vertebra; L1: first lumbar vertebra

Table 2: Newcastle–Ottawa Quality Assessment Scale for case–control studies

Study	Selection				Comparability		Exposure			Total
	Definition of exposure	Representativeness	Selection of controls	Definition of controls	On age	On other risk factors	Assessment of exposure	Same methods of ascertainment for cases and controls	Non-response rate	
Lynne *et al.*[23] 1999	1	0	1	1	0	0	1	1	0	5
Konety *et al.*[24] 2000	1	0	1	1	1	1	1	1	0	7
Pannek *et al.*[13] 2003	1	1	1	1	1	0	1	1	0	7
Alexandrino *et al.*[25] 2004	1	1	1	1	1	0	1	1	0	7
Scott *et al.*[18] 2004	1	1	1	1	0	0	1	1	1	7
Bartoletti *et al.*[16] 2009	1	1	1	1	1	0	1	1	1	8
Patel *et al.*[26] 2011	1	1	1	1	1	0	0	1	1	7
Torricelli *et al.*[17] 2011	1	0	1	1	1	0	1	1	1	7
Lee *et al.*[12] 2014	0	1	1	1	1	1	1	1	1	8

Figure 2: Forest plots depicting (**a**) the odds ratios for prostate cancer in men with SCI and able-bodied controls, and (**b**) standardized mean difference in the serum levels of PSA between men with SCI and able-bodied controls. Diamonds indicate the overall summary estimates for the analysis (the width of the diamonds represents the 95% CI); boxes indicate the weight of the individual study in the pooled analysis. The serum PSA levels are reported with ng ml^{-1}. CI: confidence interval; df: degrees of freedom; IV: inverse variance; M–H: Mantel–Haenszel; s.d.: standard deviation; std.: standardized; PSA: prostate-specific antigen; SCI: spinal cord injury.
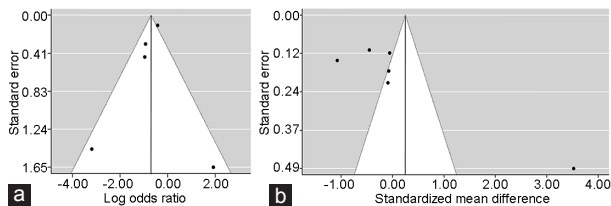
Figure 3: Funnel plots of an overall analysis of the relationship of spinal cord injury with (**a**) prostate cancer risk and (**b**) serum prostate-specific antigen (PSA) levels.

Lynne *et al.*[23] exhibiting both the lowest NOS score (**Table 1**) and the smallest sample size, the pooled SMD indicated lower PSA levels in SCI, which, however, were not statistically significant (SMD: −0.36; 95% CI: -0.74 to 0.02, *P* = 0.07) and associated with the persistence of large heterogeneity ($P_{for\ heterogeneity}$ < 0.00001, I^2 = 89%).

DISCUSSION

Although a lower risk of prostate cancer has been reported among males with SCI as compared to the able-bodied age-matched individuals, the actual decrease in its prevalence within this population has not yet been determined. The results from the present meta-analysis of five carefully selected observational case–control studies[12,16–18,26] suggest that the presence of SCI reduces the risk of prostate cancer by almost one-half as compared to their able-bodied age-matched subjects. Indeed, according to the results of the meta-regression models, when the analysis was restricted to males of mean age over 55 years, the risk decreased up to 65% than that in the controls, with a true population effect size between 44% and 78% (*P* < 0.0001), indicating that, as the prevalence of prostate cancer increases with an increase in the age of the general population, the "protective" effect of SCI becomes more evident.

The interruption of neural pathways to the prostate has been suggested to be a possible mechanism underlying the lower risk of prostate cancer in individuals with SCI.[10] In rats, where autonomic nervous system plays a key role in the growth of the prostate gland,[27] prostate denervation promotes changes in the cellular morphology, growth, and functions of the gland.[28] However, in humans, the influence of neurologic factors on the physiology/pathophysiology of the prostate remains largely unknown. Nevertheless, an increased risk of prostate cancer in paraplegic male subjects as compared to that in tetraplegic patients has been reported in two studies,[12,29] which supports the role of denervation in lowering the incidence of prostate cancer after SCI. A further and even more relevant role would be played by androgen deficiency, peculiar to this population. High rates of biochemical androgen deficiency, ranging from approximately 33% to 46%, have been reported in males having chronic SCI.[5–9] Whether and to what extent it can result in clinical hypogonadism is still unclear, because in the presence of SCI, the sexual symptoms, along with other putative clinical features of hypogonadism (*e.g.*, changes in body composition, osteoporosis, anemia, and mood disorders), overlap with direct or indirect consequences of neurological damage and disability. However, regardless of other putative clinical reflections, androgen deficiency could prove to be protective to some extent, resulting in a lower incidence of prostate cancer. Evidence shows that both the occurrence and progression of prostate cancer are influenced by androgens as (1) prolonged administration of high dosages of testosterone induces prostate cancer in rats, (2) malignancies of the prostate rarely occur in dogs and men castrated prior to puberty, and (3) androgen-ablative therapy inhibits the growth of prostate tumor.[30] In keeping with the notion of a major role of androgens in prostate cancer, meta-analyses indicate that shorter polymorphic cytosine-adenine-guanine (CAG) repeat sequences in the androgen receptor gene, which promote both a higher receptor binding affinity for androgens and a higher transactivation activity, are associated with an increased risk of prostate cancer.[31,32]

In the present analysis, a poor value of serum PSA levels as a screening tool for prostate cancer following SCI resulted from the large
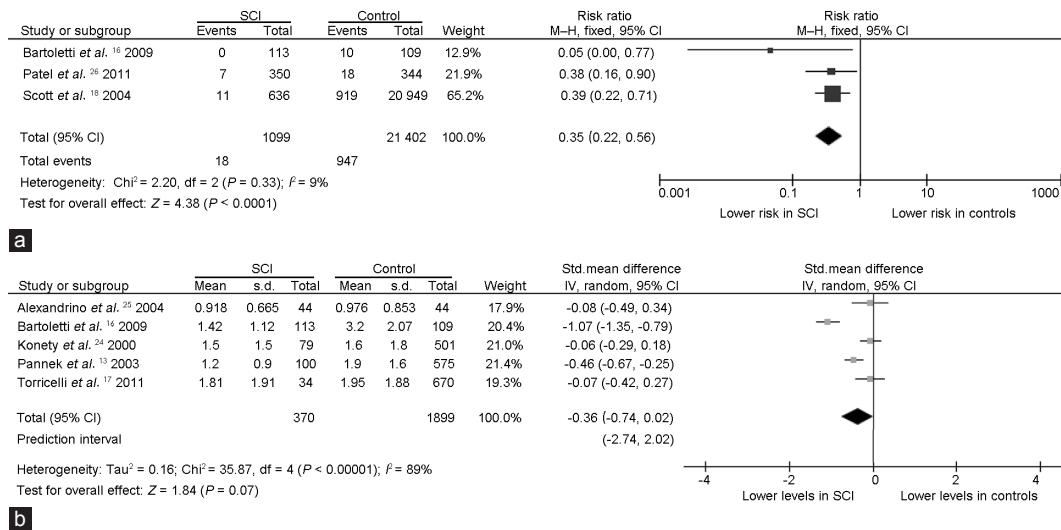
Figure 4: Forest plots depicting the results of the subgroup analyses on the relationship of SCI with (**a**) prostate cancer risk and (**b**) serum prostate-specific antigen (PSA) levels. After evaluation of heterogeneity, only studies carried out on samples with mean age >55 years were included in (**a**) the analysis of prostate cancer risk and the study from Lynne *et al.*[23] exhibiting both the lowest quality score at the Newcastle–Ottawa scale and the smallest sample size was excluded from (**b**) the analysis of serum PSA levels. The PSA levels are reported in ng ml^{-1}. CI: confidence interval; df: degrees of freedom; IV: inverse variance; M–H: Mantel–Haenszel; s.d.: standard deviation; std.: standardized; SCI: spinal cord injury.

heterogeneity between the included studies that reported its circulating levels in males with SCI and able-bodied controls (**Figure 2b**). In the crude analysis, although the overall difference between the two groups was not statistically significant, PSA levels were higher in SCI group. On the contrary, when, according to the results of the meta-regression models, the subgroup analysis was restricted to studies exhibiting both the highest NOS quality score and the largest sample size, the pooled estimate indicated lower PSA levels in SCI, which, however, were not statistically significant and showed persistent large heterogeneity (**Figure 4b**). Lower PSA levels in males with SCI would be in line with the low prostate volume, which has repeatedly been reported in this population.[13–17] Possibly, androgen deficiency and/or prostate denervation counteract the opposite impact of chronic inflammation, catheterization, and repeated manual bowel evacuation on prostate physiology/pathophysiology.

Some limitations of this meta-analysis have been recognized. Firstly, the inclusion of a limited number of studies. This, however, resulted from a strict screening and selection of the literature. Although only five studies were included in the quantitative analysis of prostate cancer, as a whole, they provided information on a very large number of males with SCI and their age-matched able-bodied controls. The study by Lee *et al.*[12] accounted for the largest proportion of the global study population; nevertheless, when this study, where the mean age was below 55 years, was excluded, according to the results of the meta-regression models, the pooled estimate remained statistically significant, with a further decrease (up to 65%) in the risk of prostate cancer in males with SCI as compared to that in their controls. Secondly, the availability of a limited number of studies refrained the authors from performing multivariable meta-regression analyses that would have helped detect possible independent associations of the different covariates with the estimates. A further limitation of this meta-analysis is that in the selected studies, information on the key factors having a potential impact on the pathophysiology of the prostate was largely incomplete. In particular, the lack of data on variables which can exert opposite effects on prostate growth and PSA levels in SCI (on the one hand, testosterone levels and the level of the lesion; on

the other hand, chronic prostate inflammation, catheterization, and repeated manual bowel evacuation) did not let the authors explain, by meta-regression analyses, their significance in contributing to the between-study heterogeneity in PSA levels. For instance, only the study by Bartoletti *et al.*[16] reported testosterone levels in 113 males with SCI and 109 age-matched able-bodied subjects; although the SCI group showed significantly lower testosterone levels, PSA values, prostate sizes, and prostate cancer prevalence, the independent association of testosterone with prostate endpoints was not investigated by multivariable regression models.

On the basis of the present study, it can be concluded that, in older males, chronic SCI represents a condition which reduces the risk of prostate cancer up to 65% as compared to that in able-bodied controls. The large between-study heterogeneity on serum PSA levels makes this marker a poor reliable screening tool for prostate cancer following SCI. This was mainly due to the interaction of opposite effects exerted by clinical variables peculiar to this population. These findings should be considered in defining more appropriate screening strategies for prostate cancer in males with SCI.

AUTHOR CONTRIBUTIONS

AB conceived the study, performed the systematic search to identify all relevant studies, assessed the eligibility of each selected study, assessed the quality of the studies, and performed data extraction and statistical analysis; SDA performed the systematic search to identify all relevant studies, assessed the eligibility of the full-text papers of the selected studies, and performed data extraction; AM participated in the systematic search and helped draft the manuscript; GF helped draft the manuscript; SF assessed the quality of the studies and critically revised the manuscript; FF conceived the study, evaluated for eligibility of the full text of the selected studies, assessed the quality of the studies, and wrote the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

560

REFERENCES

1 National Spinal Cord Injury Statistical Center. Spinal Cord Injury (SCI) facts and figures at a glance. Birmingham: University of Alabama at Birmingham; 2016. p1–2.
2 Strauss DJ, Devivo MJ, Paculdo DR, Shavelle RM. Trends in life expectancy after spinal cord injury. *Arch Phys Med Rehabil* 2006; 87: 1079–85.
3 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30.
4 Dennis LK, Lynch CF, Torner JC. Epidemiologic association between prostatitis and prostate cancer. *Urology* 2002; 60: 78–83.
5 Durga A, Sepahpanah F, Regozzi M, Hastings J, Crane DA. Prevalence of testosterone deficiency after spinal cord injury. *PM R* 2011; 3: 929–32.
6 Bauman WA, Fountaine MF, Spungen AM. Age-related prevalence of low testosterone in men with spinal cord injury. *J Spinal Cord Med* 2014; 37: 32–9.
7 Barbonetti A, Vassallo MR, Pacca F, Cavallo F, Costanzo M, *et al.* Correlates of low testosterone in men with chronic spinal cord injury. *Andrology* 2014; 2: 721–8.
8 Barbonetti A, Caterina Vassallo MR, Cotugno M, Felzani G, Francavilla S, *et al.* Low testosterone and non-alcoholic fatty liver disease: evidence for their independent association in men with chronic spinal cord injury. *J Spinal Cord Med* 2016; 39: 443–9.
9 Barbonetti A, Vassallo MR, Felzani G, Francavilla S, Francavilla F. Association between 25(OH)-vitamin D and testosterone levels: evidence from men with chronic spinal cord injury. *J Spinal Cord Med* 2016; 39: 246–52.
10 Shim HB, Jung TY, Lee JK, Ku JH. Prostate activity and prostate cancer in spinal cord injury. *Prostate Cancer Prostatic Dis* 2006; 9: 115–20.
11 Pannek J, Bartel P, Göcking K, Frotzler A. Prostate volume in male patients with spinal cord injury: a question of nerves? *BJU Int* 2013; 112: 495–500.
12 Lee WY, Sun LM, Lin CL, Liang JA, Chang YJ, *et al.* Risk of prostate and bladder cancers in patients with spinal cord injury: a population-based cohort study. *Urol Oncol* 2014; 32: 51.e1–7.
13 Pannek J, Berges RR, Cubick G, Meindl R, Senge T. Prostate size and PSA serum levels in male patients with spinal cord injury. *Urology* 2003; 62: 845–8.
14 Frisbie JH, Kumar S, Aguilera EJ, Yalla S. Prostate atrophy and spinal cord lesions. *Spinal Cord* 2006; 44: 24–7.
15 Hvarness H, Jakobsen H, Biering-Sørensen F. Men with spinal cord injury have a smaller prostate than men without. *Scand J Urol Nephrol* 2007; 41: 120–3.
16 Bartoletti R, Gavazzi A, Cai T, Mondaini N, Morelli A, *et al.* Prostate growth and prevalence of prostate diseases in early onset spinal cord injuries. *Eur Urol* 2009; 56: 142–8.
17 Torricelli FC, Lucon M, Vicentini F, Gomes CM, Srougi M, *et al.* PSA levels in men with spinal cord injury and under intermittent catheterization. *Neurourol Urodyn* 2011; 30: 1522–4.
18 Scott PA Sr., Perkash I, Mode D, Wolfe VA, Terris MK. Prostate cancer diagnosed in spinal cord-injured patients is more commonly advanced stage than in able-bodied patients. *Urology* 2004; 63: 509–12.
19 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
20 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000; 283: 2008–12.
21 Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, *et al.* Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7: iii–x, 1–173.
22 Riley RD, Higgins JPT, Deeks JJ. Research methods and reporting: interpretation of random effects meta-analyses. *BMJ* 2011; 342: d549.
23 Lynne CM, Aballa TC, Wang TJ, Rittenhouse HG, Ferrell SM, *et al.* Serum and semen prostate specific antigen concentrations are different in young spinal cord injured men compared to normal controls. *J Urol* 1999; 162: 89–91.
24 Konety BR, Nguyen TT, Brenes G, Lewis N, Saul M, *et al.* Evaluation of the effect of spinal cord injury on serum PSA levels. *Urology* 2000; 56: 82–6.
25 Alexandrino AP, Rodrigues MA, Matsuo T. Evaluation of serum and seminal levels of prostate specific antigen in men with spinal cord injury. *J Urol* 2004; 171: 2230–2.
26 Patel N, Ngo K, Hastings J, Ketchum N, Sepahpanah F. Prevalence of prostate cancer in patients with chronic spinal cord injury. *PM R* 2011; 3: 633–6.
27 McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, *et al.* Growth of the rat prostate gland is facilitated by the autonomic nervous system. *Biol Reprod* 1994; 51: 99–107.
28 Wang JM, McKenna KE, McVary KT, Lee C. Requirement of innervations for maintenance of structural and functional integrity in the rat prostate. *Biol Reprod* 1991; 44: 1171–6.
29 Frisbie JH. Cancer of the prostate in myelopathy patients: lower risk with higher levels of paralysis. *J Spinal Cord Med* 2001; 24: 92–4.
30 Wilding G. The importance of steroid hormones in prostate cancer. *Cancer Surv* 1992; 14: 113–30.
31 Nelson KA, Witte JS. Androgen receptor CAG repeats and prostate cancer. *Am J Epidemiol* 2002; 155: 883–90.
32 Zeegers MP, Kiemeney LA, Nieder AM, Ostrer H. How strong is the association between CAG and GGN repeat length polymorphisms in the androgen receptor gene and prostate cancer risk? *Cancer Epidemiol Biomarkers Prev* 2004; 13: 1765–71.

Supplementary Table 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (*e.g.*, Web address), and, if available, provide registration information including registration number.	Material and methods
Eligibility criteria	6	Specify study characteristics (*e.g.*, PICOS, le.*g*th of follow-up) and report characteristics (*e.g.*, years considered, language, publication status) used as criteria for eligibility, giving rationale.	Inclusion and exclusion criteria
Information sources	7	Describe all information sources (*e.g.*, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Systematic search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Inclusion and exclusion criteria
Data collection process	10	Describe method of data extraction from reports (*e.g.*, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction
Data items	11	List and define all variables for which data were sought (*e.g.*, PICOS, funding sources) and any assumptions and simplifications made.	Systematic search strategy
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Quality assessment
Summary measures	13	State the principal summary measures (*e.g.*, risk ratio, difference in means).	Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g.*, I2) for each meta-analysis.	Statistical analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (*e.g.*, publication bias, selective reporting within studies).	Statistical analysis
Additional analyses	16	Describe methods of additional analyses (*e.g.*, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Statistical analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results: Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (*e.g.*, study size, PICOS, follow-up period) and provide the citations.	Results: Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results: Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results: Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results: Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results: Figure 3
Additional analysis	23	Give results of additional analyses, if done (*e.g.*, sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results: meta-regression analyses and subgroup analysis [Figure 4]
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the str*e.g*th of evidence for each main outcome; consider their relevance to key groups (*e.g.*, healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (*e.g.*, risk of bias), and at review-level (*e.g.*, incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (*e.g.*, supply of data); role of funders for the systematic review.	Not available

From: Moher *et al.*[19]

Supplementary Table 2: MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported section
	Reporting of background should include	
1	Problem definition	Introduction
2	Hypothesis statement	Introduction
3	Description of study outcome (s)	Introduction/Material and methods
4	Type of exposure or intervention used	Material and methods
5	Type of study designs used	Material and methods
6	Study population	Material and methods: Inclusion and exclusion criteria
	Reporting of search strategy should include	
7	Qualifications of searchers (*e.g.*, librarians and investigators)	Material and methods
8	Search strategy, including time period included in the synthesis and key words	Material and methods: Systematic search strategy
9	Effort to include all available studies, including contact with authors	Material and methods: Systematic search strategy and data extraction
10	Databases and registries searched	Material and methods
11	Search software used, name and version, including special features used (*e.g.*, explosion)	Statistical analysis
12	Use of hand searching (*e.g.*, reference lists of obtained articles)	Figure 1
13	List of citations located and those excluded, including justification	Study selection and Figure 1
14	Method of addressing articles published in languages other than English	Not available
15	Method of handling abstracts and unpublished studies	Not available
16	Description of any contact with authors	Data extraction
	Reporting of methods should include	
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Material and methods: Quality assessment
18	Rationale for the selection and coding of data (*e.g.*, sound clinical principles or convenience)	Material and methods: Inclusion and exclusion criteria
19	Documentation of how data were classified and coded (*e.g.*, multiple raters, blinding and interrater reliability)	Material and methods: Quality assessment
20	Assessment of confounding (*e.g.*, comparability of cases and controls in studies where appropriate)	Material and methods: Quality assessment
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Material and methods: Quality assessment
22	Assessment of heterogeneity	Material and methods: Statistical analysis
23	Description of statistical methods (*e.g.*, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Material and methods: Statistical analysis
24	Provision of appropriate tables and graphics	Table 1, Table 2, Figures 1, 2, 3, 4
	Reporting of results should include	
25	Graphic summarizing individual study estimates and overall estimate	Synthesis of results: Figure 2, Figure 4
26	Table *g*iving descriptive information for each study included	Table 1
27	Results of sensitivity testing (*e.g.*, subgroup analysis)	Figure 4
28	Indication of statistical uncertainty of findings	Table 1
	Reporting of discussion should include	
29	Quantitative assessment of bias (*e.g.*, publication bias)	Publication bias [Figure 3] and heterogeneity evaluation
30	Justification for exclusion (*e.g.*, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Quality of included studies: Table 2
	Reporting of conclusions should include	
32	Consideration of alternative explanations for observed results	Discussion
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Discussion
34	Guidelines for future research	Discussion
35	Disclosure of funding source	Not available

From: Stroup *et al.*[20]