

The association between prostatitis and prostate cancer. Systematic review and meta-analysis

Gianpaolo Perletti^{1,2}, Elena Monti¹, Vittorio Magri^{3,4}, Tommaso Cai⁵, Anne Cleves⁶, Alberto Trinchieri⁷, Emanuele Montanari⁴

¹ Department of Biotechnology and Life Sciences, Università degli Studi dell'Insubria, Busto A., Italy;

² Department of Human Structure and Repair, Faculty of Medicine and Medical Sciences, Ghent University, Ghent, Belgium;

³ Urology Secondary Care Clinic, ASST-Nord, Milan, Italy;

⁴ Department of Urology, University of Milan Fondazione Ca' Granda IRCCS - Ospedale Maggiore Policlinico, Milan, Italy;

⁵ Department of Urology, Santa Chiara Regional Hospital, Trento, Italy;

⁶ Velindre NHS Trust Library, Cardiff University, Velindre Cancer Centre, Cardiff, UK;

⁷ Urology Unit, A. Manzoni Hospital, Lecco, Italy.

Summary

Objective: The main outcome of this review was the association between a history of clinical chronic prostatitis (NIH category II or III) and a histologically confirmed diagnosis of prostate cancer.

Materials and methods: Crude odds ratios and 95% confidence intervals (CI) were calculated to analyze dichotomous data. For analysis of pooled data we adopted a random-effects model and the inverse variance weighing method. Heterogeneity was assessed by calculating the I^2 value.

Results: Out of 2794 screened records, we retrieved 16 full-text articles written in English, reporting the data of 15 case-control studies, involving 422.943 patients. Pooled analysis resulted in a significant crude odds ratio of 1.83 (95% CI: 1.43 to 2.35; $P < 0.00001$). The total set of data showed considerable heterogeneity ($I^2 = 91\%$). Both the Egger's test and the Begg's test for funnel plot asymmetry did not reach statistical significance.

The 'trim and fill' method applied to the funnel plot imputed 3 missing studies and the resulting adjusted estimate of the odds ratio was 2.12 (95% CI: 1.38 to 3.22). According to GRADE criteria, the overall quality of the meta-analysis data is low, mainly due to the presence of bias, confounders and extreme effect size outliers. Five among the included studies reported data assessed in 8015 African-American subjects. Pooled analysis resulted in a non-significant crude odds ratio of 1.59 (95% CI: 0.71 to 3.57; $P = 0.26$), and considerable heterogeneity ($I^2 = 90\%$).

Conclusions: Meta-analysis of 15 case-control studies shows that a history of clinical chronic prostatitis can significantly increase the odds for prostate cancer in the general population, whereas such association in African-American individuals remains uncertain.

KEY WORDS: Prostate cancer; Prostatitis; Chronic prostatitis; Chronic pelvic pain syndrome; Meta-analysis; Case-control study.

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INTRODUCTION

Advanced age, family history, BRCA gene mutations and African descent are established risk factors for prostate cancer (1, 2).

Inflammation is known to be a major risk factor for various types of cancer. Strong epidemiological evidence demonstrates that chronic inflammatory diseases like

ulcerative colitis, *H. pylori* gastritis, acid reflux-related esophagitis/Barrett's syndrome and hepatitis can significantly increase the risk of developing malignant neoplasms. In the urological setting, the association between inflammation and urothelial bladder cancer has been recently demonstrated (3), and the interest for the role of inflammation in urolo-genital oncogenesis is increasing. In the last two decades, considerable effort has been devoted to investigate the linkage between inflammation and prostate cancer. For example, at the molecular and cellular level a model has been proposed whereby overexpression of the *Vav3* oncogene plays a key role in the transduction of aberrant signals leading to both chronic prostatitis and prostate cancer (4). At the tissue level, inflammation in the prostate can modify the organization of the glands and generate early cancer precursor lesions. Post-atrophic hyperplasia, a variety of 'proliferative inflammatory atrophy', is believed by some authors to be 'fertile ground' for development of preneoplastic lesions, as it appears to be implicated in lethal prostate cancer (5). At the clinical level, a number of studies investigated whether a history of clinical prostatitis may increase the risk of developing prostate cancer. The results of these studies have been meta-analyzed by Jiang *et al.* (6). This work, based on a literature search performed up to July 2012, confirmed previous findings (7) and indicated that clinical prostatitis may be significantly associated with prostate cancer. In subsequent years and up to the present day, new case-control studies have been performed on large patient populations. This systematic review is aimed to update and complement the meta-analytic data so far produced, focusing on the relationship between a diagnosis of prostate cancer (any grade) and previous exposure to clinical prostatitis.

PATIENTS AND METHODS

No funding was received to support the present research.

Eligibility criteria

We included only full-text articles written in English, reporting case-control studies evaluating with various

epidemiological and statistical approaches the relationship between a history of 'prostatitis' and a subsequent diagnosis of prostate cancer.

Self-reported or physician-assessed clinical 'prostatitis' might include different symptomatic inflammatory conditions, characterized by chronic pain in the pelvic region, *lower urinary tract symptoms* (LUTS) and sexual dysfunction. These conditions are currently classified as NIH category II *Chronic Bacterial Prostatitis* (CBP) and NIH category III *Chronic Prostatitis/Chronic Pelvic Pain Syndrome* (CP/CPPS, formerly prostatodynia) (8).

Studies based exclusively on acute bacterial prostatitis were not included in this review and meta-analysis, as this condition is characterized by short duration and by prompt post-therapy remission. Subgroup data of patients affected by acute prostatitis were excluded from odds-ratio calculation and meta-analysis. Studies focusing exclusively on the assessment of inflammatory cell infiltrates in biopsy or radical prostatectomy specimens ('*histological prostatitis*', NIH category IV) were not included in the present analysis.

Patients of any ethnicity with a history of prostate cancer of any grade were eligible for the present study. Prostate cancer diagnosis could be documented by inspection of patient records or could be retrieved from community, hospital, medicare or other national private or public health insurance program databases/register.

Outcomes

The main and single outcome considered for this review is the association between a history of clinical chronic prostatitis and prostate cancer of any grade.

Search strategy and study selection

Search of published reports was performed by an information specialist (AC). Records were identified by searching international databases and trial registers including *Medline*, *PreMedline*, *Embase*, *Cochrane Library*, *Web of Science*, *LILACS*; *Scopus*, *OpenGrey*, *WHO International Clinical Trial Registry and clinicaltrials.gov*. All searches were performed starting from January 1st, 2000, and were assessed as up to date on January 31st, 2017. This time frame has been chosen to minimize the use of different definitions of prostatitis in included studies, as a new classification for clinical prostatitis was implemented in year 1999 and almost universally adopted thereafter (8).

In the text of the present review, included studies are referred to by the first author and year of publication.

Quality assessment

The *risk of bias* (ROB) of included studies was assessed independently by two researchers (GP, EM).

The quality of individual studies was rated using the case-control study version of the *Newcastle-Ottawa Scale* (NOS) (9), as recommended in chapter 13 of the *Cochrane collaboration handbook*, addressing the inclusion of non-randomized studies in systematic reviews and meta-analyses (*Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0*) (10).

The thresholds for converting the NOS scores to *Agency for Healthcare Research and Quality* (AHRQ) standards were:

Good quality: 3 or 4 stars in selection domain AND 1 or

2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

The NOS allowed to evaluate ascertainment bias/recall bias (exposure item of the NOS) and hospital control bias (hospital control section of the selection item of the NOS), according to *Sutton-Tyrrel* (11). Detection bias was evaluated separately, according to *Cochrane guidelines* (10).

Publication bias and small-study effect were investigated by visually assessing funnel plots and by performing both the *Egger's regression test* and the *Begg's rank correlation analysis* (12, 13).

The quality of the evidence resulting from analysis of pooled data was evaluated according to *GRADE criteria*, modified as recommended in Chapter 13 of the *Cochrane handbook* (10). Briefly, *GRADE* recommends rating as 'low' all meta-analytic evidence generated by pooling non-randomized studies. Evaluation may be upgraded to 'moderate' only in the presence of a large magnitude of effects or of lack of concern about confounders.

Data collection and statistical analysis

Data extraction was performed by two independent researchers (GP, EM).

To analyze dichotomous data we calculated crude (unadjusted) *odds ratios* (OR) and log-odds ratios. Analysis included the calculation of 95% *confidence intervals* (CI), and Z statistics. For meta-analysis we adopted a random-effects model and the inverse variance weighing method. Heterogeneity was assessed by calculating the I^2 value. We performed *Galbraith's plot analysis* to identify outliers contributing substantially to heterogeneity.

Heterogeneity was tentatively investigated by excluding from meta-analysis studies showing small sample sizes, major effect estimate outliers, or specific study design characteristics deviating from the rest of included studies. The 'trim and fill' missing study imputation approach was applied to funnel plots, and adjusted overall effect sizes were calculated according to *Duval and Tweedie* (14).

In the presence of a prevalence of exposure in controls (Pctr) higher than 10%, a *risk-ratio* (RR) approximation was calculated according to *vanRhee and Suurmond* (15).

Pooled analysis was performed using the *RevMan 5.3* software. Funnel plots, *Galbraith's plots*, the *Egger's* and *Begg's tests*, and 'trim and fill' effect size adjustments were performed with the *Meta-Essentials Excel workbook 1.0* (*Erasmus Research Institute of Management, Erasmus University, Rotterdam, The Netherlands*). Optimal information size for meta-analysis was calculated with the *G*Power 3.1* software (assuming an α level equal to 0.05 and a $1-\beta$ error equal to 0.95).

RESULTS

A PRISMA flow-chart of the search and screening process is shown in Figure 1 of Supplementary Materials. A total of 2794 de-duplicated records were identified using our

search strategy. From 29 potentially relevant articles selected by two independent reviewers on the basis of title and abstract content, 16 articles met the inclusion criteria for the present review (16-31). These articles report the results of 15 case-control studies including a total population of 422.943 subjects. The *Cheng 2010* and *Chao 2010* articles (20, 21) contained essential data from a single study (the *California Men's health Study*), whereas it was not sure whether the *Rosenblatt 2001* study and the *Rothman 2004* study focused on the same case and control populations (28, 30).

The sample size of our meta-analysis complied "optimal information size" criteria, as recommended by the GRADE guidelines (32, not shown).

Table 1 of Supplementary Materials summarizes the main characteristics of the 15 included studies and the data extracted for the present systematic review.

Table 2 of Supplementary Materials presents the quality and bias assessments for the present review.

The median score and mode of the Newcastle-Ottawa scale were 5* and 5*, respectively (NOS range: 0 to 9). NOS scores were converted to AHRQ standards. 11 studies were rated as 'poor', 2 studies were rated as 'fair' and 2 studies were rated as 'good' (is shown in Table 2 of Supplementary Materials).

Detection bias, evaluated separately, was present in virtually all included studies, mainly due to the increased probability of prostate cancer detection in prostatitis patients subjected to intensive follow-up assessments.

The prostate cancer cases were 13.942, of which 1,806 were previously exposed to clinical chronic prostatitis, whereas controls were 409.001, of which 57.203 had a history of clinical chronic prostatitis. Pooled analysis resulted in a significant crude odds ratio of 1.83 (95% CI: 1.43 to 2.35; $P < 0.00001$). Figure 1 (panel A) shows the forest plot, study data and statistics.

The total set of data shows 'considerable' heterogeneity (Cochrane handbook, chapter 9) (10), as the calculated value of I^2 was 91%.

The *Hosseini 2010* study (22) appeared to be the major determinant of heterogeneity. This study yielded an odds ratio equal to 32.3, and thus appeared to be an extreme outlier in our analysis. A Galbraith plot was generated, and the *Hosseini 2010* study was confirmed to be an effect size outlier (is shown in Figure 2 of Supplementary Materials). The authors of the study were asked to verify whether any error in data analysis/reporting had occurred, or whether exposure vs. non-exposure data had been accidentally swapped. *Hosseini et al.* collaborated fully in this investigation by re-assessing the study database and statistics, and confirmed the original results of their study.

To assess to which extent the pooled effect size might have been inflated by the presence of extreme outliers, sensitivity analysis was performed by excluding the *Hosseini 2010* study. The resulting pooled effect size (crude odds ratio) was 1.55, and retained statistical significance (95% CI: 1.30 to 1.85, $P < 0.00001$) (Figure 1, panel B). Exclusion of *Hosseini 2010* from meta-analysis decreased the I^2 value to 81% ('substantial' heterogeneity).

The *Weinmann 2010* study differed from all other thirteen studies, as it included only lethal prostate cancer cases (19). However, tentative exclusion of this study

from the meta-analysis did not modify the I^2 value ($I^2 = 91\%$). To further explore heterogeneity, the *Pelucchi 2006* study was excluded, as data were collected as early as 1985, and exposure might be partly based on a dated definition and understanding of prostatitis (26).

The *Sutcliffe* study was also tentatively excluded, as analyses in this study included participants with missing prostatitis exposure information. In addition, case data were collected as early as 1985, and might be partly based on a pre-1999 definition of prostatitis (24). Exclusion of individual studies (*Pelucchi 2006* or *Sutcliffe 2006*) did not substantially alter heterogeneity, as the I^2 values were 92% and 91%, respectively.

The *Sarma 2006* study was also tentatively excluded as it included exclusively African-American patients (25), but also in this case heterogeneity was not substantially decreased ($I^2 = 90\%$).

Five among the included studies reported data assessed in African-American men (17, 20, 23, 25, 27), and meta-analysis in this specific ethnic subgroup was attempted. The total population included 8015 subjects; prostate cancer cases were 1066, of which 135 had a history of clinical chronic prostatitis, whereas the controls were 6949, of which 436 had been previously exposed to the disease. Pooled analysis resulted in a non-significant crude odds ratio of 1.59 (95% CI: 0.71 to 3.57; $P = 0.26$, Figure 2). When a fixed-effect model was applied to this analysis, the resulting odds ratio was 1.58 (95% CI: 1.23 to 2.03; $P = 0.0003$). In the frame of the present meta-analysis, the statistical significance of the odds-ratio calculated with such model should be interpreted conservatively.

Heterogeneity was 'considerable' ($I^2 = 90\%$), and appeared to be mainly generated by the *Sarma 2006* study (25), as its exclusion yielded a I^2 value of 73% ('substantial' heterogeneity). In this study, age distributions differed substantially between cases and controls, with older patients being present in the case cohort. This may imply that confounding factors (e.g., BPH confounder symptoms or higher number of 'historical' sexual partners in the cases cohort) might have played a role in the generation of the outlier odds ratio assessed in this study (crude OR: 5.02). Heterogeneity was not further explored, due to the small number of included studies.

Funnel plots were generated to analyze publication bias and small-study effects. The funnel plot (Figure 3, panel A) suggested a certain degree of asymmetry of the data distribution, though such visual impression was not confirmed by the Egger's test or by the Begg's rank correlation analysis, as neither test reached statistical significance (Egger's, $P = 0.631$; Begg's, $P = 0.125$).

The 'trim and fill' method applied to the funnel plot imputed 3 missing studies (Figure 3, panel A), and the resulting adjusted estimate of the overall effect size was 0.75 log-odds ratio (95% CI: 0.32 to 1.17), whose natural anti-logarithm is 2.12 (95% CI: 1.38 to 3.22). Such adjusted effect size is greater compared to the original finding of the pooled analysis (Log 1.83 = 0.60).

Again, the *Hosseini 2010* study (22) was a significant outlier in the funnel plot (Figure 3, panel A). Since *Hosseini 2010* shows the smallest sample size among all included studies (137 cases and 137 controls), a small-study effect may account for such a drift, in addition to other unique

Figure 1.

Meta-analysis of case-control studies investigating the association between prostate cancer and a previous history of clinical chronic prostatitis. **A**, pooled analysis of the general population of included prostate cancer cases and controls; **B**, sensitivity analysis performed by excluding the Hosseini 2010 study (22) from the pooled effect size estimate.

The number of subjects allocated to cases or control groups, crude odds ratios, the 95% confidence intervals, the Z value for the overall effect, the significance of the pooled comparisons and heterogeneity data (Chi^2 , I^2), are presented. Data to the right of the vertical no-effect line of forest plots represent increased odds for prostate cancer in patients exposed to prostatitis. Diamonds represent overall effect sizes extending to the limits of the 95% confidence intervals of odds ratios.

Data are plotted according to the increasing weight of each study (top to bottom).

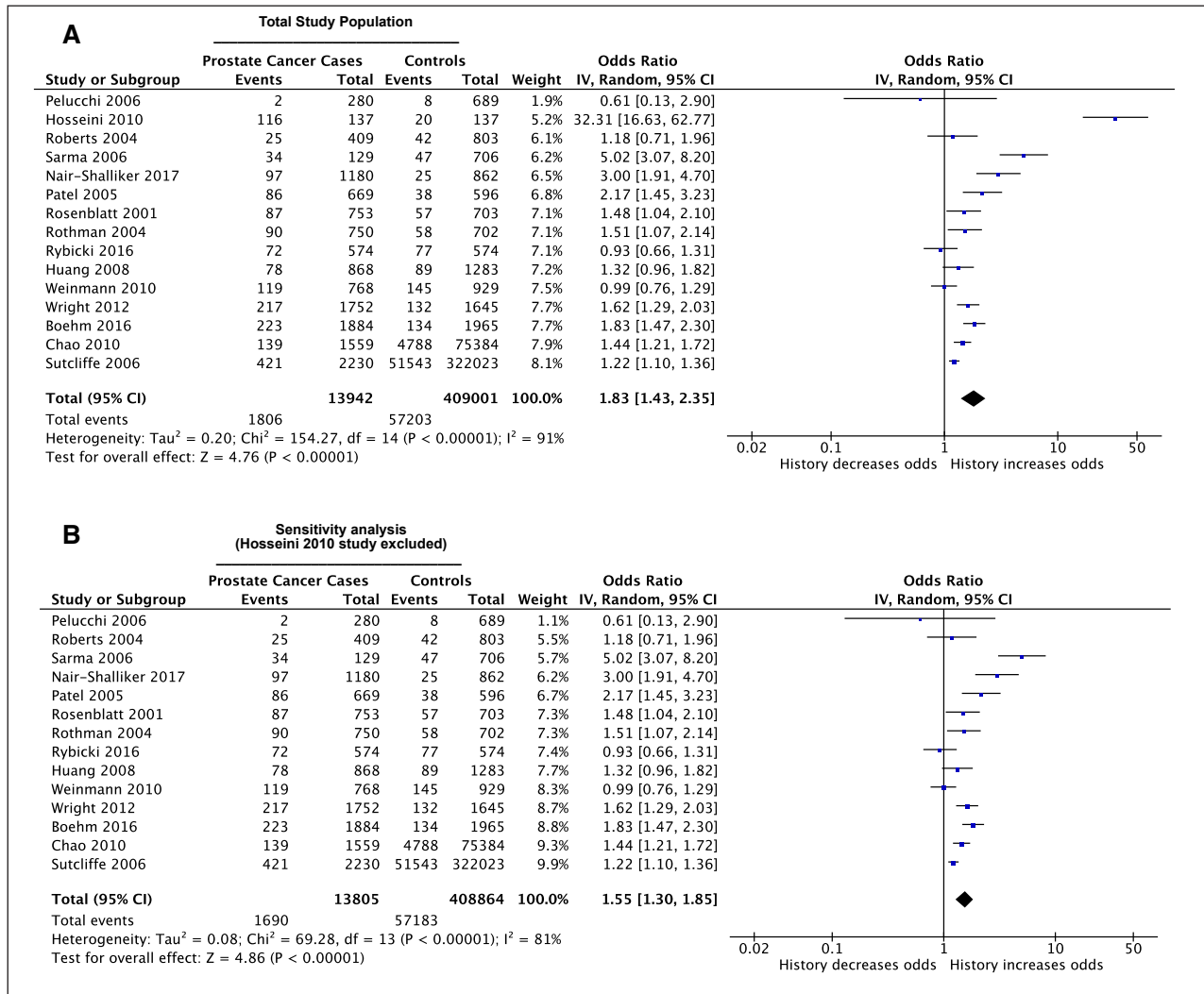


Figure 2.

Subgroup analysis performed on patients of African ethnicity (African-American).

Data are plotted according to the increasing weight of each study (top to bottom).

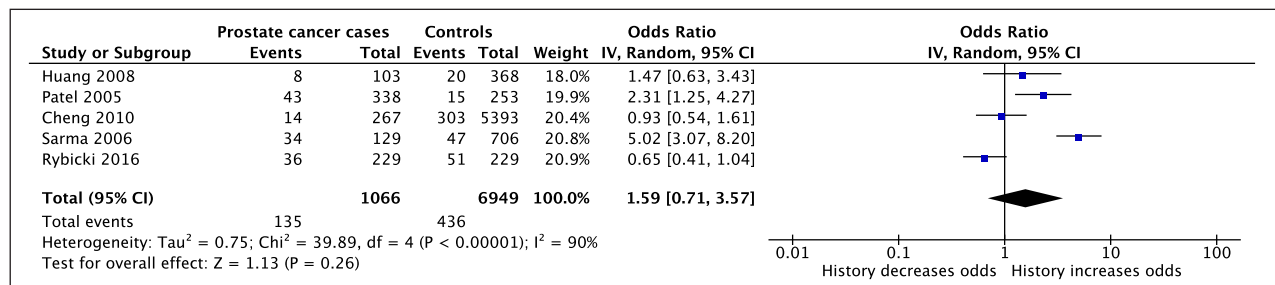
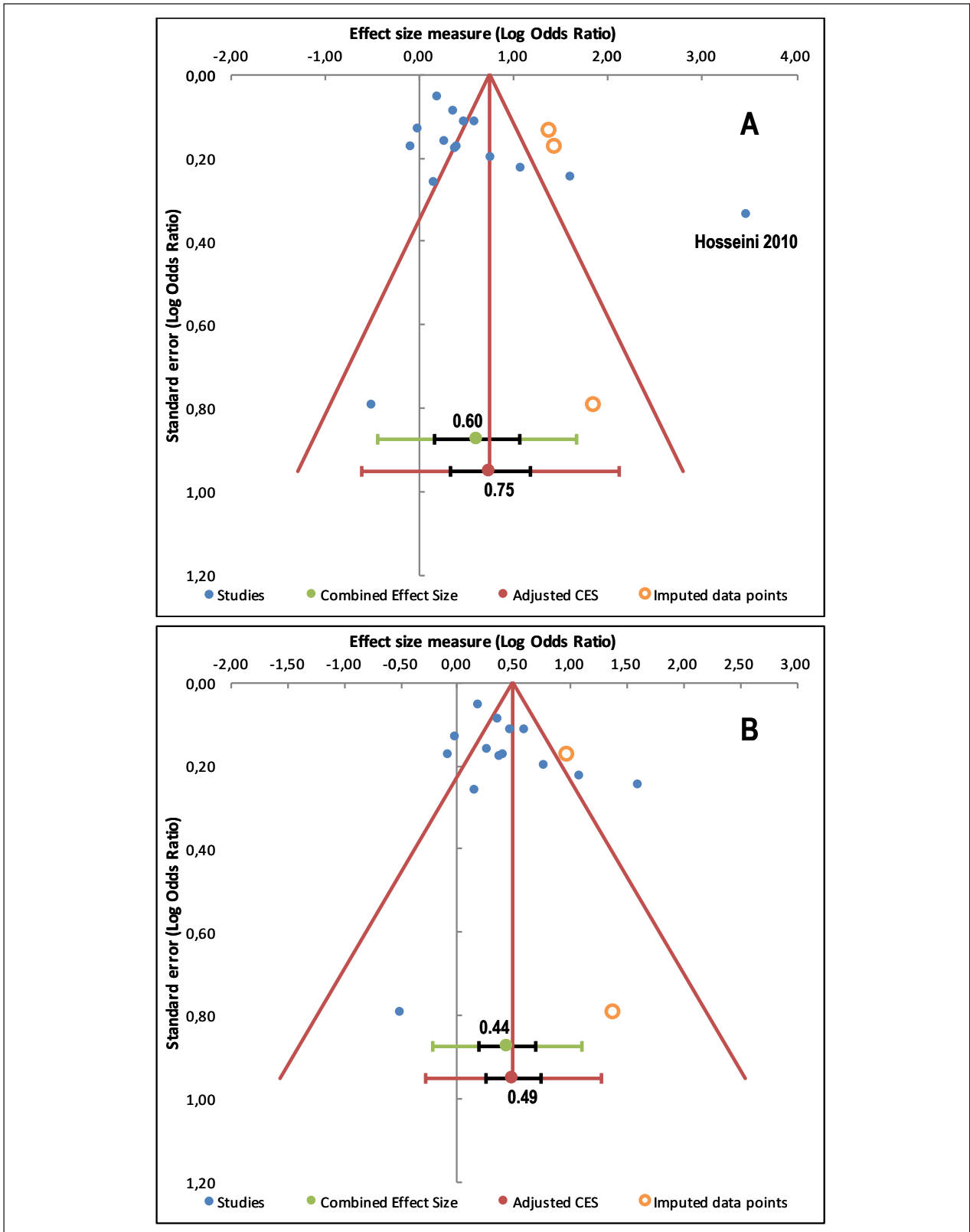


Figure 3.

Funnel plot for publication bias analysis. **A**, 'trim and fill' method (14) applied to the analysis of the total study population. The combined effect size (CES, green) and the adjusted estimate of the combined effect size (red) resulting from the imputation of three additional studies (orange) are shown. **B**, funnel plot analysis performed after excluding the Hosseini 2010 study (22). In these plots the effect sizes are expressed as the natural logarithms of the odds ratios.



features of the study. Exclusion of *Hosseini 2010* from the funnel plot analysis (Figure 3, panel B) confirmed the non-significance of the plot asymmetry tests (*Egger's*, $P = 1.0$; *Begg's*, $P = 0.352$). The 'trim and fill' analysis imputed 2 missing studies, and the adjusted estimate of the overall effect size was 0.49 log-odds ratio (95% CI: 0.25 to 0.74), whose natural anti-logarithm is 1.63 (95% CI: 1.28 to 2.09) (Figure 3, panel B). Such adjusted odds ratio is slightly higher compared to the original finding of the pooled analysis (without *Hosseini 2010*, $\text{Log } 1.55 = 0.44$). We did not assess for publication bias in the subgroup analysis of African-American patients, due to the small number of included studies.

According to GRADE criteria (32), the overall quality of the meta-analysis data is 'low', mainly due to the presence of bias, confounders and extreme outliers. Moreover, the magnitude of the effect size generated from meta-analysis and the assessed heterogeneity did not justify upgrading the quality evaluation to 'moderate'.

DISCUSSION

The present meta-analysis of fifteen case-control studies performed between year 2000 and January 31st, 2017 shows that a history of clinical chronic prostatitis can significantly increase the odds for prostate cancer of any grade (OR = 1.83, 95% CI: 1.43 to 2.35). Our results support and update previous findings, pointing to a significant association between prostate cancer and exposure to prostatitis (*Dennis et al.*, OR = 1.6, 95% CI 1.0 to 2.4; *Jiang et al.*, OR = 1.64, 95% CI: 1.36 to 1.98) (6, 7). Although calculation of the odds ratio is the most appropriate strategy to retrospectively quantify the association between a disease and a hypothetical risk factor, its interpretation is not always straightforward, and the perception of risk can be often overestimated by readers not familiar with its underlying statistics. Thus, we converted the 1.83 odds ratio resulting from our meta analysis to a risk-ratio estimate equal to 1.63 (95% CI: 1.23 to 2.17) (15).

Subgroup meta-analysis focusing on men of African descent did not yield significant results when a random-effects model was adopted. It is indeed crucial to assess whether prostatitis may be a risk factor for prostate cancer in this population, as its incidence is approximately 60% higher and the mortality rate is 2-3 times greater compared with caucasian men (33). Thus, additional studies performed on large patient populations are warranted to provide unequivocal evidence in this respect.

Included studies were characterized by high risk of bias, mainly due to the presence a number of confounding factors, such as comorbidities (e.g., BPH) in both cases and controls, different intra-study or inter-study proportions of African-American subjects, difficulty in obtaining medical documentation of previous exposure to risk factors, different inter- and intra-study age ranges, issues in the selection of control populations, population size issues, etc.

Increased digital rectal examination, PSA or ultrasound assessment rates may expose patients affected by prostatitis or sexually-transmitted diseases to increased detection of indolent, clinically irrelevant cancers, thus potentially generating detection biases between cases and controls. In addition, recalling bias, due to subjective reporting of pro-

statitis exposure, might be universally present in the studies included in this review, also because prostatitis and BPH (likely prevalent in older subjects) are known to be cross-confounders, due to partial symptom overlap (34). These biases are intrinsically present in most case-control investigations, independently of the rigorousness of the study design.

Clinical diagnosis of chronic prostatitis presumes the presence of chronic inflammation of the prostatic tissue in diagnosed patients. However, the presence of inflammatory mononuclear cells is a very common finding in histological prostate specimens (up to 77%), especially in men beyond the age of 50 (35). Moreover, it has been demonstrated that the distribution of prostatic inflammation is similar for patients with and without chronic prostatitis-like symptoms (36). However, histological chronic inflammation has been associated to increased prostate cancer risk in several studies (e.g., 37), though this issue is controversial, as other studies have shown that inflammation may actually decrease the risk for prostate cancer (38-40). Thus, from our point of view clinical, symptomatic chronic prostatitis and histological evidence of chronic inflammation of the prostate should be provisionally investigated as separate entities, whose impact on prostatic oncogenesis may be based on distinct mechanisms of action at the tissue, cellular or molecular levels.

Clinical implications and key points

The prognostic and therapeutic implications of our findings, together with the findings of *Dennis et al.* and *Jiang et al.* (6, 7), may be of considerable importance. In this respect, it might be interesting to investigate whether aggressive therapeutic management of chronic prostatitis syndromes may have cancer-preventive potential.

CONCLUSIONS

Meta-analysis of 15 case-control studies shows that a history of clinical chronic prostatitis can significantly increase the odds for prostate cancer in the general population, whereas such association in African-American individuals remains uncertain.

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Correspondence

Gianpaolo Perletti, PhD (Corresponding author)

gianpaolo.perletti@uninsubria.it

Università degli Studi dell'Insubria

Department of Biotechnology and Life Sciences

Via A. Da Giussano, 12 21052 Busto A., Italy

Elena Monti, PhD

Università degli Studi dell'Insubria

Department of Biotechnology and Life Sciences

Via A. Da Giussano, 12 21052 Busto A., Italy

Vittorio Magri, MD

Urology Secondary Care Clinic, ASST-Nord, Milan, Italy

Tommaso Cai, MD

Department of Urology, Santa Chiara Regional Hospital, Trento, Italy

Anne Cleves, Mrs

Velindre NHS Trust Library, Cardiff University, Velindre Cancer

Centre, Cardiff, UK

Alberto Trinchieri, MD

Urology Unit, A. Manzoni Hospital, Lecco, Italy

Emanuele Montanari, MD

Department of Urology, University of Milan Fondazione Ca' Granda

IRCCS - Ospedale Maggiore Policlinico, Milan, Italy