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Sexually transmitted infections and prostate cancer risk: A systematic review and meta-analysis

Saverio Caini [a,*], Sara Gandini [b], Maria Dudas [c], Viviane Bremer [d], Ettore Severi [e], Alin Gherasim [f]

[a] Unit of Molecular and Nutritional Epidemiology, Institute for Cancer Research and Prevention (ISPO), Italy
[b] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy
[c] Department of Infectious Disease Epidemiology, National Center for Epidemiology, Budapest, Hungary
[d] Division for HIV/AIDS, STI and Blood-Borne Infections, Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
[e] South East Regional Epidemiology Unit, Health Protection Agency, London, UK
[f] Swedish Institute for Communicable Disease Control, Solna, Sweden

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ABSTRACT

Prostate cancer (PC) is the second most incident cancer and the sixth cause of death by cancer in men worldwide. Despite extensive research efforts, no modifiable risk factors have been consistently identified for PC risk. A number of studies have focused on possible relationships between sexually transmitted infections (STIs) and PC. We performed a meta-analysis to explore the association between infection caused by *Neisseria gonorrheae*, *Treponema pallidum*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, Herpes Simplex Virus types 1 and 2, Human Herpes Virus 8 and Cytomegalovirus, and PC. We conducted a comprehensive, systematic bibliographic search of medical literature to identify relevant studies. We calculated summary relative risk (SRR) and 95% confidence intervals (CI) for the association between each STI and PC through random effect models. Subgroup, meta-regression and sensitivity analyses were carried out to detect between-study heterogeneity and bias. We included 47 studies published between 1971 and 2011. Men who reported having ever had any STI in lifetime had an increased PC (SRR 1.49, 95% CI 1.19–1.92). We found a significantly increased PC risk in men having had gonorrhoea (SRR 1.20, 95% CI 1.05–1.37). No other single STI was significantly associated with PC. Due to high incidence of both STIs and PC worldwide, prevention of STIs may help preventing a considerable number of PC cases.

1. Introduction

Prostate cancer (PC) is the second most incident cancer in men worldwide. In 2008 there were 903,500 estimated new cases and 258,400 estimated deaths worldwide, resulting as the sixth cause of death by cancer in men [1]. Despite extensive research effort, no modifiable risk factors have been consistently identified for PC, except perhaps smoking [2], obesity [3] and a sedentary lifestyle [4].

Sexually transmitted infections (STIs) represent a major public health problem worldwide. Human Papilloma Virus (HPV) and Herpes Simplex Virus (HSV) are common STIs worldwide [5,6], the former being also involved in the aetiology of cancer of cervix uteri and other anatomical sites [7,8]. Bacterial STIs are also emerging or re-emerging worldwide [9]. Cases of *Chlamydia trachomatis* have been increasingly reported during past 20 years [10–13]. Although this trend is partly attributable to extended screening efforts and more sensitive tests, several cases still go undiagnosed due to underreporting or asymptomatic disease, especially among women. Gonorrhoea is especially increasing in those countries with previously low incidence rates [10–15], despite being still at near-historic lows; more worryingly, resistance to 3rd generation cephalosporins is being increasingly reported [16]. Syphilis incidence is overall stable in developed countries, but on rise among middle-aged men and men who have sex with men [10,11,13,15]. Due to high proportions of asymptomatic cases, little is known on epidemiology of other STIs, such as infections with *Trichomonas vaginalis* or Human Herpes Virus 8 (HHV-8, also known as Kaposi's sarcoma-associated herpes virus).

* Corresponding author at: Institute for Cancer Research and Prevention (ISPO), Unit of Molecular and Nutritional Epidemiology, Via delle Oblate 2, 50141 Florence, Italy. Tel.: +39 3485828406.
E-mail addresses: saverio.caini@gmail.com, s.caini@ispo.toscana.it (S. Caini).

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The first claims of an aetiological role of STIs in the development of PC date back to the 1950s [17], and several mechanisms were subsequently proposed to explain this association. For gonorrhoea and other bacterial infections, the process was investigated that leads to PC through the phases of prostate inflammation and prostate atrophy, whereas for viral infections the emphasis was placed on the transforming properties of viruses, in particular herpes viruses [18]. It has also been hypothesized that multiple episodes of STIs and infections of longer duration (as in the case of infections not or inefficiently treated) may represent a greater risk for PC development, due to a higher cumulative risk of prostate involvement [18].

A recently published meta-analysis showed a weak association between HPV-16 and PC and no association for HPV-18 [19]. For other STIs, the most recent meta-analysis, published in 2005, found significantly increased PC risk in men with a history of gonorrhoea (1.35, 95% CI 1.05–1.83) and any STI (1.48, 95% CI 1.26–1.73), but not syphilis (1.42, 95% CI 0.76–2.64) [20]. Since 2001, year of publication of the most recent paper included in the latter meta-analysis, several epidemiological studies have been conducted to explore the association between STIs and PC risk. We performed a meta-analysis to explore the association between gonorrhoea, syphilis, and other STIs (other than HPV) and PC risk.

2. Materials and methods

2.1. Definition of outcome and exposures

We considered as outcome histologically confirmed prostate cancer, diagnosed through clinical examination or after consulting cancer registries.

We defined exposure as either self-reported history, clinical or serological diagnosis of infection caused by any of the following agents: *Neisseria gonorrheae*, *Treponema pallidum*, *C. trachomatis*, *T. vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, HSV types 1 and 2, HHV-8 and Cytomegalovirus (CMV).

We also considered for meta-analysis the association between reported history of "any STI" (either specified or not) and PC risk.

2.2. Data sources and search strategy

We identified eligible studies to be included in the meta-analysis by reviewing published reports listed in the following databases: PUBMED, Ovid Medline, EMBASE, and ISI Web of Science – Science Citation Index Expanded. To search for published papers, we used all possible combinations of MESH terms defining the outcome ("prostatic cancer" OR "prostate cancer") AND each of the aforementioned infective agents (see above) and STI caused by them (i.e., "gonorrhoea", "syphilis", "trachoma", "trichomoniasis", etc.). Additional studies were collected by searching through references lists of retrieved articles and previously published meta-analyses and reviews. A full copy was obtained of papers that were considered of interest after reading the abstract.

2.3. Criteria for including studies

Retrieved papers published up to August 31, 2013 were included in the meta-analysis if they met the following inclusion criteria: human observational studies; a cohort, case-control (including matched and nested case-control) or case-cohort design; reporting or providing sufficient information for estimating a measure of relative risk (RR) (incidence rate ratio, risk ratio, odds ratio, hazard ratio, standardized incidence ratio) with 95% confidence intervals (95% CI) or another measure of statistical uncertainty (standard errors, variance, or exact *p*-value of the significance of the estimates). No language or time restrictions were applied.

When two or more papers published results originating from the same study sample, as it may happen with cohorts analyzed at different points in time, we only considered the most recently published results.

2.4. Data extraction

Two authors (SC and ES) independently extracted the following information from each paper included in the meta-analysis: year of publication, country, study design, source of cohort members (for cohort, case-cohort and nested case-control studies) or of cases and controls (for case-control studies), type of matching (if any), mean/median age, ethnicity, inclusion of controls with familial history of PC, inclusion of controls suffering from cancers other than PC and/or benign prostatic hyperplasia (BPH), blind assessment of exposure status, type of diagnosis for exposure, and adjustments that were made for statistical analyses. Any discrepancies in study selection and data extraction (emerged by comparing the two database that were prepared) were handled by discussion between the authors; if no agreement could be reached, another co-author (SG) would decide.

For case-control studies with more than one control group we considered, for each association of interest, the odds ratio originating from the control group that was judged, on an a priori basis, to yield least biased estimates.

2.5. Statistical analysis

For any different pair of outcome and exposure, the most adjusted measure of association and the corresponding confidence intervals were transformed into log relative risk and corresponding variance, with the formula proposed by Greenland [21]. When only the *p*-value was provided as measure of uncertainty, we calculated a 'test-based' estimate of variance [21]. When estimates were not available from the paper but only crude data were provided (for example, as a 2 by 2 table), we calculated crude, exact odds ratios and 95% CI.

Summary relative risks (SRR) and 95% CI for the association between each STI and PC were obtained by pooling the study-specific estimates by random effects models, with maximum likelihood estimates and 95% CI based on *t*-distribution [22], to be conservative. SRR were only calculated when five or more estimates were available.

Heterogeneity across studies was evaluated using the I^2 parameter, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance. Meta-regressions and sub-group analysis were carried out to investigate the influence of variables assumed to potentially confound or modify the association between STI and prostate cancer, such as country, publication year, study design, study setting (hospital- versus population based), method of exposure assessment, and percentage of non-Caucasian people in the study sample. Sensitivity analysis was carried out to verify the effect of single studies on the stability of the summary estimates.

To verify whether publication bias might affect the validity of the estimates, funnel plots were investigated considering regression of ln(RR) on the sample size, weighted by the inverse of the pooled variance [23].

All analyses were performed with SAS software version 8.02 (SAS Institute Inc., Cary, NC, USA) and STATA software version 11 (Stata Inc., College Station, TX, USA).

3. Results

Overall, 109 papers were obtained and examined for inclusion (Fig. 1). Eleven papers were excluded because they were reviews and/or meta-analyses. Forty-eight papers were excluded because