

RESEARCH ARTICLE

The Association of Circumcision and Prostate Cancer: A Meta-AnalysisYu-dan Li¹, Yang Teng², Yu Dai¹, Hui Ding^{1*}**Abstract**

Background: To investigate the association circumcision with prostate cancer. **Materials and Methods:** We searched PubMed, EMBASE, the Cochrane Library, and Chinese biomedicine literature database up to August 2015. All case-control studies were identified in which investigated the association circumcision with prostate cancer. Three authors independently assessed study quality and extracted data. All data were analyzed using RevMan 5.3 and STATA version 11.0. **Results:** Six case-control studies met the inclusion criteria. The pooled meta-analysis showed that there was a lower incidence of circumcision in prostate cancer patients compared with control (OR=0.90, 95% confidence interval [CI] 0.82-0.98, $P=0.01$). The results of meta-analysis also showed that no significant difference was found between circumcision and less aggressive prostate cancer (OR=0.93, 95% CI 0.83-1.04, $P=0.19$); however, there was a lower incidence of circumcision in more aggressive prostate cancer compared with control (OR =0.84, 95% CI 0.72-0.97, $P=0.02$). The Egger's results did not show any evidence of publication bias ($P=0.798$). **Conclusions:** In summary, within the limits of available data, male with circumcision appears to have a lower incidence of prostate cancer. In the future, high-quality multicenter studies are needed to thoroughly verify the outcome.

Keywords: Circumcision - prostate cancer - meta-analysis

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Introduction

According to Global Cancer Statistics, prostate cancer (PCa) is the second most commonly diagnosed cancer in males worldwide, and it is estimated that new cases are about 1.1 million in 2012 (Torre et al., 2015). Because lacking of effective therapy, the investigators are trying to search effective prevention measures in the occurrence of PCa. Currently, few definitively confirmed risk factors were found in PCa except for race, increasing age and family history (Lightfoot et al., 2004).

Emerging evidences indicated that there was a positive correlation between infections and cancers, such as bladder cancer, penile cancer, cervical cancer and gastric cancer (Huang et al., 1998; Bosch et al., 2009; Chau and Cubilla, 2012). A previous meta-analysis showed that it produced a positively protective effect on invasive penile cancer in childhood/adolescent circumcision (OR=0.33; 95% CI 0.13-0.83) (Larke et al., 2011). Male circumcision also may reduce the risk of cervical cancer in female sex partners, although no statistical significance was found (Bosch and Albero, 2009). Likely, it is reported that infections or inflammation may be related to prostate carcinogenesis (De Marzo et al., 2007). For example, although not all studies, many studies implicated that sexually transmitted infections (STIs) have a positive

association with PCa (Mandel and Schuman, 1987; Hayes et al., 2000; Dennis et al., 2009). Furthermore, a previous meta-analysis including 29 case-control studies demonstrated that there was higher relative risk of PCa in male with a history of STIs (OR=1.5, 95% CI 1.3-1.7) (Taylor et al., 2005). Another meta-analysis from 20 case-control studies showed that there was a statistical association between PCa and prostatitis (pooled OR=1.50, 95% CI: 1.39-1.62) (Jiang et al., 2013). Based on these findings, it seems plausible that circumcision may also decrease the risk of PCa through reducing the incidence of STIs.

In the past few years, a number of epidemiological studies have been done to assess the association between circumcision and PCa risk. However, these results were inconsistent (Ewings and Bowie, 1996; Rosenblatt et al., 2001; Wright et al., 2012; Spence et al., 2014). And for the relatively small sample size of the published studies, it is necessary to accumulate data from different studies to provide evidence on the association of circumcision with PCa risk. Moreover, more studies and large sample studies have been published in recent years (Wright and Lin, 2012; Spence and Rousseau, 2014). Therefore, we performed a systematic review and meta-analysis to further estimate whether circumcision can reduce PCa risk in male populations.

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Materials and Methods

Publication search

The following databases were searched: Pubmed (1966-August 2015), Embase (1974-August 2015) the Cochrane Library (2015, Issue 8) and Chinese biomedicine literature database (1978-August 2015) using the following search terms: 'Circumcision*' AND ('prostate cancer*' or 'Prostate Neoplasm*' or 'Prostatic Cancer*' or 'Prostatic Neoplasm*') to identify all relevant articles on the subject. We also searched the references of included studies to identify additional potentially relevant studies. Hand searching of the reference lists of included studies and reviews was undertaken and contact was made with experts in the field, unpublished studies were not sought. The search was not restricted by publication year or language.

Inclusion and exclusion criteria

The included studies met the following criteria: (1) research categories-case-control study or a nested case-control study; (2) information evaluating the association between circumcision and PCa risk; (3) studies with sufficient data to perform a meta-analysis. The following studies were excluded: no control population, insufficient available data, and duplicated articles. The case-control studies were assessed with a modification of the Newcastle-Ottawa Scale (GA Wells, et al.). Scores 5 to 9 were defined as high quality, and a score <5 as low quality.

Data extraction

Data extraction will be carried out independently by the same authors using standard data extraction forms. Disagreements will be resolved in consultation with the third reviewer. For each study, the following characteristics were collected: first author's name, year of publication, ethnicity, and country of study population, design of experiment (population- or hospital-based controls), and the characteristics of the controls. The patient ethnicities were categorized as Caucasian, Asian or African and et al. When studies included subjects of more than one ethnicity, the data were extracted separately according to ethnicities for subgroup analyses.

Statistical analysis

The strength of association between circumcision and PCa risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The statistical significance of the summary OR was determined using the Z-test.

A chi-square-based Q statistics test and I^2 -test were used to assess the heterogeneity between the studies. Heterogeneity was considered significant if $P < 0.10$. The value of I^2 was used to assess the degree of heterogeneity ($I^2 < 25\%$, no heterogeneity; $I^2 25\% - 50\%$, moderate heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity). The Mantel-Haenszel method (fixed-effects) and the DerSimonian-Laird method (random-effects) were used to estimate the pooled ORs. Publication bias was assessed using inverted funnel plots. Funnel plot asymmetry was assessed using Egger's linear regression test. An asymmetric plot indicated possible publication bias. The

significance of asymmetry was determined using the t test, and $P < 0.05$ was considered to indicate a significant publication bias. Meta-analyses were performed using Review Manager, version 5.0, software (The Cochrane Information Management System, <http://ims.cochrane.org/revman>) and Software STATA version 11.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

A total of six case-control studies (Ewings and Bowie, 1996; Mandel and Schuman, 1987; Newell et al., 1989; Rosenblatt and Wicklund, 2001; Wright and Lin, 2012; Spence and Rousseau, 2014) investigating the status of circumcision in PCa patients met our inclusion criteria (Figure 1). These studies were published from 1987 to 2014. Six studies were from USA, Canada and UK, respectively. The race included white, black, asian and other. In all the studies, all controls were free of prostate cancer. A total of 4565 cases and 4892 controls were used to analyze the association of the circumcision and prostate cancer risk. The characteristics of each study are summarized in Table 1. Quality assessment showed that all studies were deemed as high quality.

Main Results of meta-analysis

The association between circumcision and prostate cancer: All studies reported the association between circumcision and prostate cancer. Because significant heterogeneity existed among these studies ($I^2 = 54\%$), fixed-effects and random-effects models were used to evaluate the stability of the results. The pooled results showed that there was a lower incidence of circumcision in PCa patients compared with control when fixed-effects model was used (OR=0.90, 95% confidence interval [CI] 0.82-0.98, $P=0.01$; Figure 2A); however, no significant difference was found between circumcision and prostate cancer when random-effects model was used (OR =0.90, 95% CI 0.78-1.05, $P=0.18$; Figure 2B).

Meanwhile, we found Newell's study existed significant heterogeneity, so we performed sensitivity analysis and found that the incidence of PCa risk was

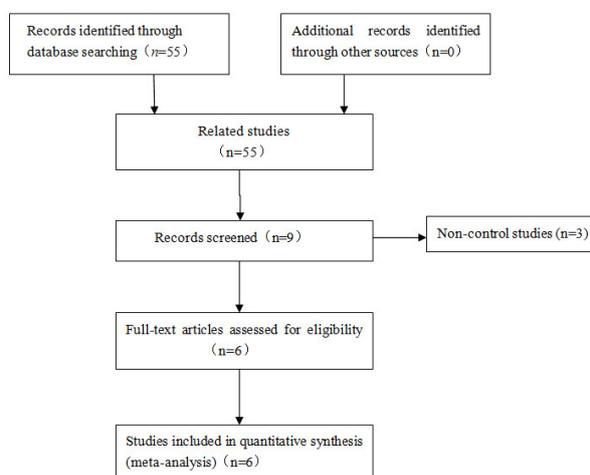


Figure 1. Flow Chart of Meta-analysis

Table 1. Characteristics and Quality Assessment of Included Studies

Study, first author	Country	Patients, (cases / controls)	Age range (years)	Race	Education Level (cases/controls)	History of STD, Prostatitis (cases/controls)	NOS score
Mandel 1987	United States	284/466	Cases:65.3 Hospital controls:64.9 Neighborhood controls:64.5	White	≥High school 53/36	-	5
Newell 1989	United States	110/220	41-86	White	≥High school 85/111	-	7
Ewings 1996	United Kingdom	159/325	-	-	≥High school 49/88	STD:4/4	6
Rosenblatt 2001	United States	753/703	40-64	White Black	≥High school 581/570	STD:126/110 Prostatitis:87/57	6
Wright 2012	United States	1754/1645	35-74	White Black	-	STD:270/242 Prostatitis:217/132	7
Spence 2014	Canada	1555/1586	40-79	White Black Asian Other	≥High school 1178/1251	STD:206/200 Prostatitis:195/115	7

NOS: Newcastle-Ottawa Scale; STD: Sexually Transmitted Disease.

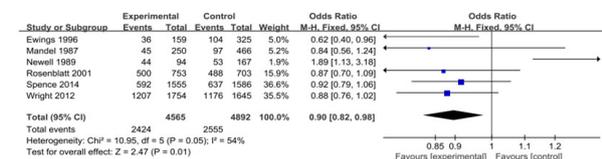


Figure 2A

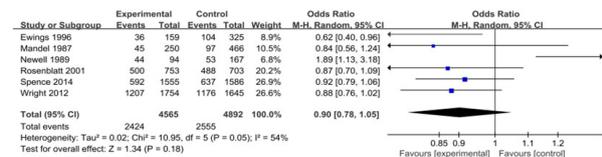


Figure 2B

Figure 2. A-Pooled results of the association of circumcision and prostate cancer (fixed-effects model); B-Pooled results of the association of circumcision and prostate cancer (random-effects model)

lower in circumcision patients than control (OR =0.88, 95% CI 0.80-0.96, $P=0.004$, $I^2=0\%$) when Newell's study was excluded.

The association between circumcision and prostate cancer aggressiveness status: Two studies including 3309 cases and 3231 controls reported the association between circumcision and prostate cancer aggressiveness status. The results of meta-analysis showed that no significant difference was found between circumcision and less aggressive prostate cancer (OR=0.93, 95% CI 0.83-1.04, $P=0.19$; Figure 3A); however, there was a lower incidence of circumcision in more aggressive prostate cancer compared with control (OR=0.84, 95% CI 0.72-0.97, $P=0.02$; Figure 3B).

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias. Egger's test was used to provide statistical evidence for funnel plot symmetry. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry, the Egger's results did not show any evidence of publication bias ($P=0.798$).



Figure 3A

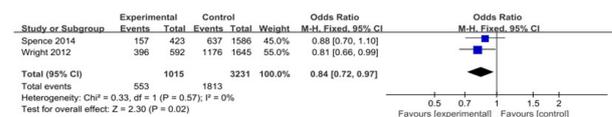


Figure 3B

Figure 3. A-Pooled results of the association between circumcision and prostate cancer less aggressiveness status; B-Pooled results of the association between circumcision and prostate cancer more aggressiveness status

Discussion

In the present study, we firstly performed a meta-analysis to evaluate the association between circumcision and risk for prostate cancer. In our meta-analysis, we used a precise search strategy, performed it with an independent librarian, and strengthened our meta-analysis reliability with sensitivity analysis. By doing so, we hoped to include all relevant studies, expecting to reduce the confounding bias, and draw a scientific and statistically robust conclusion. The pooled results demonstrated that there was lower prostate cancer risk in circumcised patients, especially in more aggressive prostate cancer.

According to a number of literatures reported, infections and inflammation are its possible mechanism. 17% of cancers are considered to be induced by infections including viruses, bacteria and parasites worldwide (Huang and Sridhar, 1998; Mostafa et al., 1999; Walboomers et al., 1999; Goktas et al., 2005; Backes et al., 2009). The potential mechanisms mainly included: (1) Infections can induce a chronic inflammation which changes cytokine levels and releases reactive oxygen species (ROS). The cytokines promote cellular proliferation and angiogenesis, and the released ROS can result in direct DNA damage.

(2) Virus is directly integrated into host DNA that causes cellular transformation. Finally, anti-infective immune response down-regulated local cell mediated anti-tumor immune monitoring, damaging the ability to kill tumour cells.

STIs have been confirmed to be closely related to PCa risk in case-control studies and meta-analysis. Many sexually transmitted organisms, including mycoplasma genitalium, HPV, HIV, HHV-8, trichomonas vaginalis and chlamydia trachomatis, have been found in the prostate. The previous studies (Weiss et al., 2006; Tobian et al., 2009) have reported that circumcision can reduce the incidence of STIs, the cause may be that circumcision changed the microenvironment, made the inner foreskin keratinized and kept balanus in a dry state, which avoided pathogens access to the bloodstream and reduced the risk of infection (Xu et al., 2007; Siegfried et al., 2009). This is the possible rationale that circumcision decrease the incidence of PCa.

In the USA, Morris et al. (2007) reported that the uncircumcised males had a 1.6-2.0-fold higher risk of prostate cancer compared with circumcised men, it is estimated that there is an extra cost of \$0.8-1.1 billion every year. In the Australia, male circumcision decreased 15-50% risk of PCa, approximately saved A\$1-2 million in prostate cancer and \$80 million in annual expenditure for the HPV vaccination (Morris et al., 2012). In our meta-analysis, the results showed that the uncircumcised males had a 1.1-fold higher risk of prostate cancer compared with circumcised men, while circumcised men reduced 12% incidence of PCa. It also indicated that circumcision decreased public health expenditure and should be advocated.

Up to now, only six studies reported the association, two of them were based on large samples. Two of the previous studies (Wright and Lin, 2012; Spence and Rousseau, 2014) found that there was a statistically negative association between circumcision and prostate cancer (OR 0.87, 95% CI 0.74-1.02 (1754 cases, 1645 controls) OR 0.86, 95% CI 0.67-1.10 (753 cases, 703 controls), while another study (Newell and Fueger, 1989) including 94 cases and 167 controls found that circumcision increased the risk of prostate cancer (OR 1.89, 95% CI 1.13-3.18). In the latter study, the reason which has higher incidence of prostate cancer and circumcision, may be attributed to receiving a higher education amongst cases and regularly screen serum PSA and/or DRE.

Ross et al. (1987) reported that circumcision could reduce prostate cancer risk in both Black and White men. Another study (Kheirandish and Chinegwundoh, 2011) indicated that there was higher risk of prostate cancer in Black men compared with White men. In this paper, two studies (Wright and Lin, 2012; Spence and Rousseau, 2014) reported whether race may change the circumcision-prostate cancer association, the results showed that there was a protective effect of circumcision for prostate cancer in Black men (OR 0.40, 95% CI 0.19-0.86; OR 0.64, 95% CI 0.39-1.08; respectively). Because lack of complete data, we are unable to quantitatively synthetic data using Review Manager software.

Some limitations should be noted in the present meta-analysis. First, all studies used self-reported or interview methods to assess circumcision status, it may produce report bias because of different education levels in population. Second, the age of circumcision and different race may be related to PCa, however, only one study completely reported detailed information, we are unable to evaluate the associations between PCa and the age, race in circumcision. Third, phimosis is defined as a condition of the penis where the foreskin cannot be fully retracted over the glans penis and is the most common medical indication for adult circumcision. The previous study (Larke, Thomas, 2011) found that circumcision may reduce the risk of penile cancer only when men had a history of phimosis not redundant prepuce. If a similar relationship is also applicable to prostate cancer, then the protective effect of circumcision may occur among men circumcised with phimosis. In future, the studies should compare phimosis with redundant prepuce in the role of PCa.

In summary, within the limits of available data, male with circumcision appears to have a lower incidence of prostate cancer. In the future, high-quality multicenter studies are needed to thoroughly verify the outcome.

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