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Circumcision and the risk of prostate cancer

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Abstract

Background—Several lines of evidence support a role for infectious agents in the development of prostate cancer (PCa). In particular, sexually transmitted infections (STIs) have been implicated in PCa etiology, and studies have found that the risk of acquiring a STI can be reduced with circumcision. Therefore, circumcision may reduce PCa risk.

Methods—Participant data collected as part of two population-based case-control studies of PCa were analyzed. Self-reported circumcision status, age at circumcision and age at first sexual intercourse were recorded along with a history of STIs or prostatitis. Multivariate logistic regression was used to estimate the relative risk of PCa by circumcision status.

Results—Data from 1,754 cases and 1,645 controls were available. Circumcision before first sexual intercourse was associated with a 15% reduction in risk of PCa compared to uncircumcised men (95% CI 0.73 – 0.99). This risk reduction was observed for cases with both less aggressive (OR 0.88, 95% CI 0.74 – 1.04) and more aggressive (OR 0.82, 95% CI 0.66 – 1.00) PCa features.

Conclusions—Circumcision before first sexual intercourse is associated with a reduction in the relative risk of PCa in this study population. These findings are consistent with research supporting the infectious/inflammation pathway in prostate carcinogenesis.

Introduction

Infections are reported to cause approximately 17% of incident cancers worldwide.[1] Causality between selected infectious pathogens and cancer are well established for stomach,[2] liver,[3] bladder, cervical[4] and penile[5] cancers. There are several potential mechanisms by which infectious agents may lead to cancer. Whereas direct cellular transformation by viruses can occur,[6] several changes in the tissue microenvironment can occur if a chronic inflammatory state is reached following infection. These include damage from reactive oxygen species along with cytokine induced angiogenesis and cellular proliferation, all of which may be involved in carcinogenesis.[7]

There are both epidemiologic and histologic data to support the inflammatory pathway in development of PCa. Pooled results from population-based studies of PCa risk have reported an 80% increased risk in PCa in men with a history of prostatitis,[8] although detection bias likely plays a role.[9] Proliferative inflammatory atrophy (PIA) is commonly seen in normal and cancerous prostates and is thought to represent a regenerative lesion following infection or trauma.[10] It has been suggested that PIA is a precursor lesion to PCa[11] and several

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genetic mutations have been identified in PIA, including GSTP1 hypermethylation, p53 mutations and alterations on Chromosome 8.[7]

Several lines of evidence support an infectious pathway in prostate cancer (PCa) development.[7, 12] In particular, sexually transmitted infections (STIs) have been implicated in PCa etiology in many,[7, 13-16] but not all studies.[17-19] A meta-analysis of 29 case-control studies found an increased relative risk of PCa in men with a history of any STI (OR 1.5, 95% CI 1.3 – 1.7).[16] Several sexually transmitted organisms have been detected in the prostate, including *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, Treponema pallidum*, human papilloma virus (HPV), herpes simplex virus (HSV) and human herpes virus type 8 (HHV8).[7] Serum antibody against HSV[13] and *Trichomonas*[15] in men have been associated with PCa risk while the presence of HPV DNA in prostate tissue[14] has also been associated with the risk of PCa. Finally, genes involved in infection susceptibility, such as *RNASEL*, may have a role in PCa development. A specific polymorphism in *RNASEL* has been reported to increase the risk of familial PCa[20] and men with this polymorphism may more commonly be found to have xenotropic murine leukemia-related virus (XMRV) in the prostate.[21] Recent evidence suggests that XMRV activity is enhanced in semen,[22] although it is unknown if XMRV is sexually transmitted. In total, these data support not only a potential infectious pathway for PCa development, but potentially a STI pathway.

Studies have reported a reduction in the risk of other STIs in men undergoing circumcision.[23-25] Recently, randomized controlled trials have found a reduction in the risk of acquiring human immunodeficiency virus (HIV) in men who are circumcised.[26] Therefore, if we assume that STIs play a role in PCa, and accept that circumcision can reduce the incidence of STIs, it is then plausible that circumcision may also reduce the risk of PCa. Although such a hypothesis has previously been postulated, only a few studies have explored this relationship.[27-29] We previously reported on circumcision status from a PCa case-control study of 1,456 men.[17] In that study, we found a non-significant relative risk reduction in those reporting circumcision (OR 0.86, 95% CI 0.67 – 1.10) adjusting for age, family history of PCa and number of PSA tests in the preceding 5 years. This present analysis combines those results with a second PCa case-control study of 1,943 men allowing for an increase in study power to further evaluate this hypothesis. In addition, we evaluate sexual history, prior STIs and prostatitis and the temporal relationship between date of circumcision and date of first sexual intercourse.

Materials and Methods

Study Population

This study uses data from men who participated in one of two population-based case-control studies of PCa.[30, 31] Cases were residents of King County, Washington with PCa identified from the Seattle-Puget Sound SEER cancer registry. In the first study, cases were diagnosed between January 1, 1993 – December 31, 1996. In the second study, cases were diagnosed between January 1, 2002 – December 31, 2005. Controls were matched by 5-year age groups and identified using random digit telephone dialing of male residents living in the same county with no history of PCa. Controls were enrolled evenly throughout the study period. A total of 2,244 eligible cases were identified and 1,754 (78%) participated in the study interview; 2,448 eligible controls were identified and 1,645 (67%) were interviewed.

Data Collection

Subjects completed in-person interviews conducted by trained staff that collected information about demographic and lifestyle factors, medical and family history, and PCa

screening history (PSA and DRE). Men were asked if they had undergone a circumcision and if yes, the date of the circumcision. Men were also asked about age at first sexual intercourse and number of lifetime sexual partners. Men were asked if they had ever been diagnosed with a disease transmitted through sexual contact and a showcard was used for reporting the specific type of infection (i.e., gonorrhea, syphilis, urethritis, genital herpes, genital warts, chlamydia, other-specify). A self-reported history of prostatitis was also recorded.

Clinical information on PCa cases was obtained from the SEER cancer registry. Gleason score, tumor stage (SEER summary stage) and PSA at diagnosis were available. Pathological stage was used for cases undergoing radical prostatectomy whereas clinical staging was used for other cases.

Statistical Analysis

Three definitions of circumcision status were considered. First, men were categorized by whether or not they ever had a circumcision, regardless of age of circumcision. Second, men were categorized based on whether the circumcision was performed before or after their reported age at first sexual intercourse: (A) no circumcision, (B) circumcised before first sexual intercourse, or (C) circumcised after first sexual intercourse. Finally, those men whose circumcision occurred after the age of first sexual intercourse were combined with those who were uncircumcised: (A) no circumcision or circumcised after first sexual intercourse, or (B) circumcised before first sexual intercourse. This was done as the hypothesis is that circumcision reduces risk of acquiring a STI and if PCa develops as a result of the STI, only circumcision prior to first sexual intercourse can potentially alter risk of PCa.

Multivariate logistic regression was performed to estimate the relative risk of PCa based on circumcision status. In each model, adjustment variables included age, family history of PCa, PSA tests within the 5 years before diagnosis (cases) or referent date (controls), race, history of any STI, history of prostatitis and number of male and female sexual partners. To evaluate possible effect modification (by age, race, family history of PCa, self-reported history of prostatitis or STI, study, income level, education) on risk related to circumcision status, we compared the reduced model, without the interaction term, with the full model, containing the interaction term, using a likelihood ratio test. Polytomous logistic regression was used to calculate risk estimates by disease aggressiveness (controls, less aggressive cases, more aggressive cases). Disease aggressiveness was based on a composite variable incorporating Gleason score, stage and PSA where more aggressive cases were defined by a Gleason score of 7(4+3) or greater, or non-localized stage, or PSA > 20 ng/mL at time of diagnosis. All statistical analyses were conducted using STATA software, Version 11 (Stata, Inc., College Station, TX).

Results

Selected characteristics of prostate cancer cases and controls are presented in Table 1. A family history of PCa was more common in cases (20.9%) than in controls (10.8%, $p < 0.001$). PSA values were missing for 7.7% and 17.5% of cases and controls, respectively. There was no difference in the self-reported history of STIs, although a diagnosis of prostatitis was more commonly reported by cases (12.5%) than controls (8.0%, $p < 0.001$). Of those with PCa, the majority had less aggressive disease (n = 1162 (66%)). As shown in Table 2, circumcision was reported in 68.8% of cases and 71.5% of controls. For 91% of the men who reported circumcision the procedure was done shortly after birth.

Circumcision was performed after the date of first intercourse in 3.9% (n = 68) and 2.5% (n = 41) of cases and controls, respectively. Caucasian men more commonly reported circumcision (69%) than African-American men (43%, $p < 0.001$). There were no differences in the frequency of circumcision according to family history of PCa in a first-degree relative or PSA screening history (data not shown).

Table 2 summarizes results of the multivariate regression analyses. Circumcision was associated with a reduction in the relative risk estimate for PCa. Having a circumcision after one's first sexual intercourse was not associated with risk of PCa. Men circumcised before their first sexual intercourse had a 15% reduction in the risk of PCa (95% CI 0.73 – 0.99) compared to those men uncircumcised and those circumcised after their first sexual intercourse. In the polytomous models, the relationship between circumcision status and PCa was observed for both less aggressive and more aggressive groups. There was no evidence for effect modification by age, STI status, study 1 vs. 2, history of prostatitis, family history of PCa, education or income level (all p-values for interaction > 0.4; data not shown). The specific type of STI was not associated with risk of PCa (data not shown). There was a suggestion of effect modification by race (p-value for interaction= 0.07), however the reduction in PCa risk with circumcision before first intercourse was observed in both groups in stratified analyses (Caucasians: OR 0.87, 95% CI 0.73 – 1.02; African-Americans: OR 0.64, 95% CI 0.39 – 1.08).

Discussion

In this analysis we found a reduction in the relative risk of PCa in men circumcised before their first sexual intercourse. These findings are consistent with research showing that an infectious/inflammatory pathway may be involved in prostate carcinogenesis.

Infections are estimated to be the cause of 17% of cancers worldwide.[1] Causal relationships have been identified for viruses (HHV-8 and Kaposi's sarcoma;[32] hepatitis B/C and liver carcinoma;[3] HPV and cervical/anal/genital carcinoma[4, 5]), bacteria (*Helicobacter pylori* and gastric carcinoma[2]) and parasites (*Schistosomiasis haematobium* and bladder carcinoma[33]). Several different mechanisms are postulated for how infectious agents may lead to cancer.[6, 7] Infections can result in a state of chronic inflammation with altered cytokine levels and generation of reactive oxygen species (ROS). ROS can lead to direct DNA damage, and the released cytokines promote angiogenesis and cellular proliferation. Another potential mechanism is direct viral integration into host DNA leading to cellular transformation. Finally, immune deviation caused by marked anti-infective immune response could lead to down-regulation of local cell mediated anti-tumor immune surveillance, impairing the ability to eradicate tumour cells.

A number of different observations support an infectious etiology for PCa. Several studies have explored the relationship between a history of STIs and PCa, and a number of sexually transmitted organisms have been identified in the prostate (*Mycoplasma genitalium, Chlamydia trachomatis, Trichomonas vaginalis*, HPV, HHV-8 and HIV).[34-37] A meta-analysis found that men with a history of any STI had an increased risk of PCa (OR 1.5, 95% CI 1.3 – 1.7).[16] Asymptomatic carrier status of several STIs is well known to occur as demonstrated by detection of organisms from the urine of asymptomatic individuals.[38-40] This suggests that the absence of a self-reported history of STIs does not preclude the possibility that exposure and prostatic localization has occurred. Perhaps partly as a result of this, some studies have also found that surrogates for extent of exposure to STIs (earlier age of first sexual activity[41] and a greater number of sexual partners[17, 42]) are associated with an increased risk of PCa.

Several genes have been studied for their role in PCa development, and in some cases, (e.g., *RNASEL, TLR4, MSR1*) mutations or variants in these genes also increase an individual's susceptibility to infection.[12] A specific polymorphism in *RNASEL* (R462Q), has been shown to increase the risk of familial PCa[20] and men with this polymorphism more commonly harbor xenotropic murine leukemia-related virus (XMRV) in the prostate.[21] The role of XMRV in PCa is still not defined, although it has been associated with both overall and more aggressive PCa[43] and its replication has been shown to be androgen sensitive.[44]

Circumcision is associated with a reduction in the risk of incident HIV.[26] This is consistent with previous studies that have reported lower rates of different STIs (e.g., HPV, herpes simplex, syphilis, chancroid) in circumcised men.[45, 46] The mechanism(s) by which circumcision reduces acquisition of a STI is thought to be related to the microenvironment of the thin, lightly keratinized mucosal lining of the inner forskin.[26, 47] This tissue is subject to small tears allowing potential access of pathogens to the bloodstream. Circumcision may reduce these injuries due to the significant keratinization that occurs following the procedure. In addition, the moist environment under the preputial skin may help pathogens to survive for extended periods prior to direct infection. This space is obliterated with circumcision.

Combining the finding of a relationship between a history of STIs and PCa risk along with a reduction in STIs in circumcised men has lead to the hypothesis that circumcision might reduce PCa development by decreasing prostatic exposure to infectious agents and the associated inflammatory changes that may enhance carcinogenesis. Several prior studies have tested this hypothesis.[17, 27, 29, 48-51] In a study from 1987, population-based cases of PCa and age- and race-matched controls were interviewed in Los Angeles (a total of 284 case-control pairs).[28] Circumcision rates were 41% in African Americans and 60% in Caucasians. In both races, circumcision was associated with a reduction in the relative risk (RR) of PCa (RR = 0.5 in Caucasians, RR = 0.6 in African Americans). In another case-control study from the United Kingdom, 159 cases diagnosed between 1989 – 1991 were interviewed along with 325 age-matched controls.[27] Circumcision was more commonly reported by controls (33%) than cases (23%) and was associated with a significant reduction in the age-adjusted risk of PCa (OR 0.62, 95% CI 0.39 – 0.98). Family history of PCa was not available in either study and both were in the pre-PSA era. Finally, circumcision performed outside the neonatal period is often performed for men with phimosis and recurrent symptomatic balanitis. In penile carcinoma, some reports have found that the protective effect of early circumcision is not present when limited to those without a history of phimosis.[52] Whether this is also true for circumcision and PCa in unknown and should be addressed in future studies. We do not have data on phimosis to address this issue.

There are potential limitations to our study. We rely on self-reported circumcision status rather than medical examinations such that misclassification of exposure could occur, although studies have reported high agreement between self-reported and medical examiner determination of circumcision status.[53, 54] However, the prevalence of circumcision in our control population is similar to that reported from national surveys. [47, 55] We also evaluated self-reported history of STIs, age of first intercourse and number of sexual partners, all of which may be underreported due to the sensitive nature of these questions. However, a study of men over the age of 50 found that men reliably report these sexual histories.[56]

Conclusion

Infection and inflammation in the prostate may be important mechanisms enhancing the risk of subsequent development of PCa in some men. There is growing evidence to support a role for STI(s) in PCa etiology. Recent work has also shown that circumcision reduces risk

for acquiring STIs. We find a 15% reduction in the relative risk of PCa in men circumcised before their first sexual intercourse suggesting a biologically plausible mechanism through which circumcision may decrease risk of PCa.

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Table 1

Selected Characteristics of Prostate Cancer Population-Based Cases and Controls, King County, WA

	Cases N = 1,754	Controls N = 1,645	p-value
Age at reference date (years)			
35-49	139 (7.9)	154 (9.4)	0.25
50-54	258 (14.7)	251 (15.3)	
55-59	441 (25.1)	438 (26.6)	
60-64	518 (29.5)	430 (26.1)	
65-69	210 (12.0)	202 (12.3)	
70-74	188 (10.7)	170 (10.3)	
Race			
Caucasian	1,548 (88.3)	1,529 (93.0)	< 0.001
African-American	206 (11.7)	116 (7.1)	
First-degree family history of prostate cancer			
No	1,388 (79.1)	1,467 (89.2)	< 0.001
Yes	366 (20.9)	178 (10.8)	
PSA screening within the past 5 years			
None	415 (23.7)	606 (36.8)	< 0.001
1 – 2 PSAs	429 (24.5)	303 (18.4)	
≥ 3 PSAs	822 (46.9)	478 (29.1)	
Unknown	88 (8.0)	258 (15.7)	
PSA at diagnosis (cases) or interview (controls)			
0.0 – 3.9	228 (13.0)	1,259 (76.5)	< 0.001
4.0 – 9.9	976 (55.6)	81 (4.9)	
≥ 10	415 (23.7)	18 (1.1)	
Missing	135 (7.7)	287 (17.5)	
History of sexually transmitted infection (any)			
No	1,484 (84.6)	1,403 (85.3)	0.58
Yes	270 (15.4)	242 (14.7)	
Prostatitis			
No	1,535 (87.5)	1,513 (92.0)	< 0.001
Diagnosed ≤ 2 years of reference date	67 (3.8)	18 (1.1)	
Diagnosed > 2 years of reference date	150 (8.6)	114 (6.9)	
Number of female sexual partners			
0 – 1	366 (23.9)	391 (26.8)	0.03
2 – 14	843 (46.1)	802 (48.8)	
≥ 15	545 (31.1)	452 (27.5)	
Number of male sexual partners			
None	1,696 (96.7)	1,616 (98.2)	0.02
Any	58 (3.3)	29 (1.8)	

Table 2

Relative Risk Estimated for Prostate Cancer According to Circumcision Status, by Disease Aggressiveness [#]

	All			Less Aggressive PCa		More Aggressive PCa	
	Cases N (%)	Controls N (%)	OR* (95% CI)	Cases ^ N (%)	OR* (95% CI)	Cases ^ N (%)	OR* (95% CI)
Circumcision status (1)							
No	547 (31.2)	469 (28.5)	1.00 (Referent)	351 (30.2)	1.00 (Referent)	196 (33.1)	1.00 (Referent)
Yes	1,207 (68.8)	1,176 (71.5)	0.87 (0.74 – 1.02)	811 (69.8)	0.91 (0.76 – 1.09)	396 (66.9)	0.81 (0.66 – 1.00)
Circumcision status (2)							
No	547 (31.2)	469 (28.5)	1.00 (Referent)	351 (30.2)	1.00 (Referent)	196 (33.1)	1.00 (Referent)
Before 1st sexual intercourse	1,139 (64.9)	1,135 (69.0)	0.86 (0.73 – 1.01)	764 (65.8)	0.89 (0.75 – 1.07)	375 (63.3)	0.80 (0.65 – 1.00)
After 1st sexual intercourse	68 (3.9)	41 (2.5)	1.15 (0.75 – 1.77)	47 (4.0)	1.26 (0.79 – 2.01)	21 (3.6)	0.96 (0.54 – 1.70)
Circumcision status (3)							
No or after 1st intercourse	615 (35.1)	510 (31.0)	1.00 (Referent)	398 (34.3)	1.00 (Referent)	217 (36.7)	1.00 (Referent)
Before 1st sexual intercourse	1,139 (64.9)	1,135 (69.0)	0.85 (0.73 – 0.99)	764 (65.8)	0.88 (0.74 – 1.04)	375 (63.3)	0.82 (0.66 – 1.00)

[#]Disease aggressiveness based on a composite variable incorporating Gleason score, stage and PSA where more aggressive cases were defined by a Gleason score of 7(4+3) or greater, or non-localized stage, or PSA > 20 ng/mL at time of diagnosis

*OR= odds ratio adjusted for age, race, PSA tests within the 5 years before diagnosis or reference date, family history of prostate cancer, history of any sexually transmitted infection, history of prostatitis, number of male and female sexual partners

^Same control population as for all analysis