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Circumcision and prostate cancer: a population-based case-control study in Montréal, Canada

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Objectives

To investigate the possible association between circumcision and prostate cancer risk, to examine whether age at circumcision influences prostate cancer risk, and to determine whether race modifies the circumcision–prostate cancer relationship.

Subjects and Methods

PROtEuS (Prostate Cancer and Environment Study), a population-based case-control study set amongst the mainly French-speaking population in Montréal, Canada, was used to address study objectives. The study included 1590 pathologically confirmed prostate cancer cases diagnosed in a Montréal French hospital between 2005 and 2009, and 1618 population controls ascertained from the French electoral list, frequency-matched to cases by age. In-person interviews elicited information on sociodemographic, lifestyle and environmental factors. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) between circumcision, age at circumcision and prostate cancer risk, adjusting for age, ancestry, family history of prostate cancer, prostate cancer screening history, education, and history of sexually transmitted infections.

Results

Circumcised men had a slightly lower risk, albeit not statistically significant, of developing prostate cancer than uncircumcised men (OR 0.89, 95% CI 0.76–1.04). Circumcision was found to be protective in men circumcised aged ≥36 years (OR 0.55, 95% CI 0.30–0.98). A weaker protective effect was seen among men circumcised within 1 year of birth (OR 0.86, 95% CI 0.72–1.04). The strongest protective effect of circumcision was recorded in Black men (OR 0.40, 95% CI 0.19–0.86, *P*-value for interaction 0.02) but no association was found with other ancestral groups.

Conclusion

Our findings provide novel evidence for a protective effect of circumcision against prostate cancer development, especially in those circumcised aged ≥36 years; although circumcision before the age of 1 year may also confer protection. Circumcision appeared to be protective only among Black men, a group that has the highest rate of disease. Further research into the differences in effect of circumcision on prostate cancer risk by ancestry is warranted, as is the influence of age at circumcision.

Keywords

circumcision, prostate cancer, ancestry

Introduction

Prostate cancer is the most common cancer in men worldwide [1]. Despite much research into the aetiological risk factors of prostate cancer, study results are inconclusive. To date, the only definitively established risk factors are African ancestry, advancing age, and a family history of prostate cancer [2]. On-going research is aimed at identifying modifiable risk factors that could ultimately lead to the prevention of prostate cancer.

Male circumcision may be one such modifiable preventive factor. Historically, prostate cancer was observed to be exceedingly rare in Jewish men, who, along with Muslims,

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compose the majority of circumcised males around the world. This observation led to the hypothesis that circumcision may confer protection against this malignancy [3]. Circumcision is typically performed in the neonatal stage or in early adolescence for religious or cultural reasons. Conversely, it is much less frequent during adulthood, when most circumcisions are done to treat pathological conditions of the foreskin or penile glans [4,5].

The hypothesised protective association between circumcision and prostate cancer seems plausible, as a history of various sexually transmitted infections (STIs) has been associated with an increased risk of prostate cancer, although findings regarding specific STIs have been inconsistent between studies [6–12]. Moreover, it has been shown that circumcised men have a lower chance of acquiring an STI than men with a foreskin [13–20]. Adding credence to the postulated link between circumcision and prostate cancer is the finding that circumcision is protective against the development of penile cancer, which is also thought to have an infectious cause [21].

Of the few epidemiological studies that have examined the relationship between circumcision and prostate cancer [22–27], all but one [27] were suggestive of a protective, although not statistically significant, association between circumcision and prostate cancer. However, except for the two most recent ones [22,24], studies have been based on limited sample sizes (ranging from 110 to 250 cases and 161 to 240 controls). Also, studies often did not consider potential confounders, e.g. family history of prostate cancer [23,25–27], ancestry [26], prostate cancer screening (PSA screening or DREs) [23,25–27], or STI history [23–27]. Furthermore, the effect of timing of circumcision on prostate cancer risk has received only cursory consideration, with previous studies dichotomising timing of circumcision as occurring at birth or later [25], or before or after first sexual intercourse [22].

Black men have an increased risk of prostate cancer compared with White men [28]. Although the reasons for this disparity in incidence are unknown, it is postulated that environmental, lifestyle, behavioural, and genetic factors may play a role [29,30]. Only one study has examined whether race may modify the circumcision–prostate cancer association [25]. It found a protective effect of circumcision in both Black and White men.

The main objective of the present study was to investigate the possible association between circumcision and prostate cancer risk in the context of a large population-based case-control study, while controlling for potential confounders. Secondary objectives included examining whether age at circumcision influences prostate cancer risk, and determining whether race modifies the circumcision–prostate cancer relationship.

Subjects and Methods

Study Design and Population

PROtEuS (Prostate Cancer and Environment Study) is a population-based case-control study conducted in the predominantly French-speaking population in Montréal, Canada. The study has been described earlier [31]. In brief, study subjects had to be Canadian citizens, aged <76 years at diagnosis or recruitment, enumerated on Québec's French permanent electoral list, and residents in the Montréal metropolitan area across 39 electoral districts. Cases were diagnosed with histologically confirmed incident prostate cancer between September 2005 and August 2009. They were actively ascertained through pathology departments across seven of nine French hospitals in which prostate cancer is diagnosed in the Montréal metropolitan area. Ascertainment covered >80% of all cases diagnosed in the base area. Controls had not had a prostate cancer diagnosis at the time of interview. Concurrently to cases, they were randomly selected from the population-based provincial French permanent electoral list, which is thought to represent a nearly complete listing of Canadian citizens residing in the province of Québec. Controls were frequency matched to cases by age (within 5 years).

Data Collection

Between 2006 and 2011, trained interviewers conducted in-person interviews, mainly in respondents' homes. Information was obtained on sociodemographic characteristics, lifestyle factors (including sexual behaviour, history of STIs, smoking history, alcohol use, recreational physical activities, and diet), medical history (including prostate cancer screening), along with a detailed occupational history. For the main exposure variable, circumcision status, study respondents were asked 'Are you circumcised?' Subjects who responded 'yes' were then asked for their age at circumcision.

The study was approved by the ethics boards of all participating institutions, and all subjects provided written informed consent.

Statistical Analysis

Unconditional multivariate logistic regression models were used to estimate the odds ratios (ORs) and 95% CIs for the association between circumcision and prostate cancer. Circumcision status was dichotomised as 'Yes' or 'No'. Age at circumcision was categorised as follows: not circumcised, <1, 1–8, 9–20, 21–35, ≥36 years, where the thresholds for the last four categories derived from the distribution among control subjects who were circumcised at ≥1 year of age. Excluded from all analyses were subjects who preferred not to divulge whether they were circumcised (two cases, two controls) or did not know whether they were circumcised (27 cases, 29 controls). In addition, in order to respect the temporality of the exposure–outcome relationship, subjects who were circumcised at the same age or after their prostate cancer diagnosis or interview (six cases, one control) were excluded from all analyses.

As it was exceedingly rare that a subject was circumcised at or after diagnosis, subjects who did not know their age at circumcision (57) were retained in the analysis on circumcision status. A sensitivity analysis was conducted, excluding the subjects who did not know their age at circumcision. Study findings remained unchanged (not shown).

Regression models included the following a priori variables: age at diagnosis or interview (continuous); first-degree family history of prostate cancer ('yes', 'no', 'do not know'); PSA screening and/or DRE ('≤2 years', '>2 years of index date', 'never', 'do not know'); ancestry ('White', 'Black', 'Asian', 'Other', 'do not know'); highest education level attained ('<high school', '≥high school', 'do not know'); and history of STIs ('yes', 'no', 'do not know', 'prefers not to answer'). STI history was based upon subject self-reported history of the following infections: gonorrhoea, syphilis, genital herpes, genital warts or condylomas, human papillomavirus, chlamydia, HIV, AIDS, trichomonas, and/or any other sexually transmitted disease. Linearity of the association between age and prostate cancer was graphically verified before including age as a continuous variable in models. Other potential confounding variables (history of prostatitis, history of diabetes, born in Canada, family income, number of female sexual partners, total number of sexual partners, and self-identified sexual orientation) were entered one at a time into models already containing the a priori variables, with the intention that those additional variables producing a minimum 10% change in the OR between circumcision and prostate cancer would be included in the final models. None of these variables met the inclusion criterion.

Polytomous logistic regression models, adjusted for the a priori variables listed above, were used to determine whether circumcision status affected the severity of prostate cancer. Gleason scores obtained from pathology reports were used to classify cancer cases as less aggressive (Gleason score ≤3 + 4) and more aggressive (Gleason score ≥4 + 3) [32].

The likelihood ratio test was used to examine potential effect modification of the association between circumcision status and prostate cancer, by ancestry. The test compared the full logistic regression model (a priori variables and the circumcision–ancestry product terms) to the reduced model (the full model without product terms). The existence of effect modification by ancestry was also assessed by entering circumcision–ancestry product interaction terms into the final model as dummy variables. Effect modification was considered to exist if *P*-values for any of the individual product terms were <0.05. ORs and 95% CIs were presented by ancestry strata.

All statistical analyses were done using STATA 12.0 (Stata Corporation, College Station, TX).

Results

The study consisted of 1590 prostate cancer cases and 1618 controls. Response rates among eligible subjects were 86% and 63% for cases and controls, respectively. Reasons for non-participation, among cases and controls, were refusal (94% and 86%), unable to trace (3% and 11%), death with no proxy respondent available (2% and 1%), and language barrier (1% and 1%). Additionally, 1% of eligible controls were too sick to participate with no available proxy. Proxy respondents, mostly spouses, provided information for 3% of cases and 5% of controls.

With the subject exclusions noted in the statistical analysis section above, the sample used to address our study objectives consisted of 1555 cases and 1586 controls. In all, 60 of the excluded subjects were not able to provide their circumcision status. Subjects who did not provide their circumcision status were more likely to have had a proxy respond to the interview (25.4%) compared with subjects who responded 'yes' or 'no' to being circumcised (3.0%). There were some demographic differences between subjects who provided their circumcision status and those who did not. The latter group, compared with the former, were respectively older [median (SD) age 69.5 (5.9) vs 65 (6.9) years], less likely to be born in Canada (46.7% vs 72.6%), less educated (61.7% vs 22.5% had <high school education), and were less likely to have White ancestry (75.0% v. 84.5%) and more likely to have Black ancestry (6.7% v. 5.7%) or Asian ancestry (10.0% v. 3.0%). Almost equal numbers of cases and controls did not know whether they were circumcised (27 cases and 29 controls) or preferred not to provide their circumcision status (two cases and two controls).

Table 1 presents select characteristics of cases and controls. Cases were slightly younger, less educated, and more likely to have a first-degree relative with prostate cancer than controls. Subjects with Black ancestry were more likely to be cases than controls and the reverse was true of subjects with Asian ancestry. Prostatitis was more common among cases, whereas diabetes was more common among controls.

Table 2 displays the associations between circumcision status, age at circumcision, and the risk of prostate cancer, both overall and by cancer aggressiveness. Circumcised men had a slightly lower risk of developing prostate cancer than uncircumcised men (OR 0.89, 95% CI 0.76–1.04), but the association did not quite achieve statistical significance.

Table 1 Select characteristics of subjects participating in the PROtEuS, Montréal, Québec, Canada, 2005–2009*.

Variable	Cases	Controls
N	1555	1586
N (%):		
Age, years:		
40–49	35 (2.3)	36 (2.3)
50–59	382 (24.6)	323 (20.4)
60–69	787 (50.6)	775 (48.9)
70–79	351 (22.6)	452 (28.5)
Born in Canada	1189 (76.5)	1092 (68.9)
Race:		
White	1340 (86.8)	1315 (83.7)
Black	103 (6.7)	75 (4.8)
Asian	25 (1.6)	70 (4.5)
Other	75 (4.9)	112 (7.1)
Marital status:		
Single	129 (8.3)	112 (7.1)
Married/common-law	1159 (74.5)	1211 (76.4)
Separated/divorced/widowed	258 (16.6)	256 (16.2)
Member of religious order	9 (0.6)	6 (0.4)
Highest level of education:		
Elementary school or less	375 (24.2)	333 (21.0)
≥High school	1178 (75.9)	1251 (79.0)
First-degree relative with prostate cancer	369 (24.5)	162 (10.5)
Number of female sexual partners:		
1	414 (28.4)	410 (27.9)
2–3	262 (18.0)	253 (17.2)
4–7	292 (20.0)	257 (17.5)
8–20	300 (20.6)	315 (21.4)
>20	191 (13.1)	234 (23.4)
Ever had male sexual partner	78 (5.1)	63 (4.1)
Ever had a STI	206 (13.5)	200 (12.8)
Timing of last prostate cancer screening:		
≤2 years	1542 (99.7)	1207 (78.3)
>2 years	2 (0.1)	186 (12.1)
Never screened	3 (0.2)	149 (9.7)
History of prostatitis	195 (12.8)	115 (7.3)
History of diabetes	230 (14.8)	319 (20.2)

**Numbers within table may not sum to overall totals due to missing data.*

Further, there was an indication that circumcision performed within 1 year of birth provided some protection against prostate cancer (OR 0.86, 95% CI 0.72–1.04). Circumcision performed aged ≥36 years appeared to be highly protective against prostate cancer (OR 0.55, 95% CI 0.30–0.98). To better understand the lower risk of prostate cancer in men circumcised later in life, we compared subjects' demographic characteristics by age at circumcision (Table 3). Subjects circumcised aged ≥36 years, compared with subjects circumcised earlier and subjects not circumcised, had the lowest level of education and the greatest incidence of diabetes. Circumcision status did not, on the whole, appear to be associated with prostate cancer aggressiveness but there was an indication that circumcision before 1 year of birth may be protective of more aggressive prostate cancer (OR 0.86, 95% CI 0.69–1.07).

The likelihood ratio test, performed to examine potential effect modification of the association between circumcision status and prostate cancer by ancestry, was not significant ($P = 0.18$). It may not have reached statistical significance due to low power to detect effect modification [33], based on the small number of Black subjects (178) in our sample. However, there was a tendency towards a modifying effect of ancestry in the circumcision–prostate cancer relationship. The circumcision–prostate cancer associations, stratified by ancestry, are shown in Table 4. Specifically, circumcision exerted a strong protective effect in Black men (OR 0.40, 95% CI 0.19–0.86, *P*-value for interaction 0.02).

Discussion

This is a large-scale, population-based case-control study addressing the effect of circumcision on prostate cancer risk. The present data allowed us to identify several important observations. We showed a protective, albeit not statistically significant, effect of circumcision on prostate cancer risk. Only six studies have reported on this association, most of them were based on small samples. Five of the previous investigations found, like us, a negative association between circumcision and prostate cancer [22–26], although statistical significance was reached in only two of them [25,26]. The risk estimates for these five studies ranged from 0.5 to 0.98. The two largest studies, the former one using data from subjects who participated in the latter study and also data from another study, reported results for circumcision similar to ours (OR 0.87, 95% CI 0.74–1.02 (1754 cases, 1645 controls) [22] and OR 0.86, 95% CI 0.67–1.10 (753 cases, 703 controls) [24]). A smaller study (94 cases, 167 controls), which did not adjust for education level, found that circumcision conferred an increased risk of prostate cancer (OR 1.89, 95% CI 1.13–3.18) [27]. This finding may have been attributable to a higher education level amongst cases, which is associated with a greater tendency to be circumcised [34–36] and to undergo screening for prostate cancer by, either PSA screening and/or DRE [37].

In the present study, we observed a particularly strong protective effect of circumcision against prostate cancer among Black men. One study found that circumcision was protective against prostate cancer in both Black and White men, with the relative risks being about the same for each (0.6 and 0.5, respectively) [25]. It is well documented that prostate cancer has a greater incidence among men of African ancestry, in particular those from the USA, Caribbean, and Sub-Saharan Africa [38]. The underlying reasons for this have yet to be clearly established [39]. According to expectations, Black men in the present study, 78% originating from Haiti, had a 1.4-fold increased risk of prostate cancer compared with White men (OR 1.38, 95% CI 0.98–1.93). Interestingly, Black men in the present study were less likely to have been circumcised than White men (30% vs 40%, respectively), which may be one factor responsible for the differential in prostate cancer risk according to ancestry.

Table 2 Association between circumcision status, age at circumcision and prostate cancer, overall and by aggressiveness of cancer, PROtEuS, Montréal, Québec, Canada, 2005–2009.

	All subjects (1555 cases and 1586 controls)			Less aggressive prostate cancer†‡ (N = 1127 cases)		More aggressive prostate cancer†‡ (N = 423 cases)	
	Cases n (%)	Controls n (%)	OR (95% CI)*	Cases n (%)	OR (95% CI)*	Cases n (%)	OR (95% CI)*
Circumcision status:							
No	963 (61.9)	949 (59.8)	1.00	693 (61.5)	1.00	266 (62.9)	1.00
Yes	592 (38.1)	637 (40.2)	0.89 (0.76–1.04)	434 (38.5)	0.90 (0.76–1.07)	157 (37.1)	0.86 (0.69–1.09)
Age at circumcision, years§							
Not circumcised	963 (63.4)	949 (60.7)	1.00	693 (62.8)	1.00	266 (64.7)	1.00
<1	408 (26.8)	435 (27.8)	0.86 (0.72–1.04)	309 (28.0)	0.91 (0.75–1.10)	98 (23.8)	0.77 (0.59–1.01)
1–8	35 (2.3)	49 (3.1)	0.88 (0.54–1.44)	22 (2.0)	0.76 (0.44–1.33)	13 (3.2)	1.18 (0.61–2.30)
9–20	46 (3.0)	45 (2.9)	1.12 (0.71–1.78)	31 (2.8)	1.06 (0.64–1.76)	15 (3.7)	1.28 (0.68–2.39)
21–35	48 (3.2)	46 (2.9)	0.89 (0.57–1.40)	35 (3.2)	0.89 (0.55–1.46)	13 (3.2)	0.91 (0.47–1.75)
≥36	20 (1.3)	40 (2.6)	0.55 (0.30–0.98)	14 (1.3)	0.54 (0.28–1.05)	6 (1.5)	0.56 (0.23–1.37)

**Adjusted for age at diagnosis for cases or interview for controls, ancestry, family history of prostate cancer, ever had STI, prostate cancer screening within the last 2 years, and highest educational level achieved. †Less aggressive prostate cancer refers to Gleason scores ≤7(3 + 4) and more aggressive prostate cancer refers to Gleason scores ≥7(4 + 3). ‡Gleason scores were missing for five cases. §22 circumcised controls and 35 circumcised cases did not know their age at circumcision.*

Table 3 Characteristics of subjects according to age at circumcision*, PROtEuS, Montréal, Québec, Canada, 2005–2009.

Variables	Not circumcised (N = 1912)	Circumcised aged ≤35 years (N = 1112)	Circumcised aged ≥36 years (N = 60)	P†
Mean (SD) age, years	64.6 (6.7)	63.2 (7.1)	66.4 (5.6)	<0.001
Born in Canada, n (%)	1280 (67.0)	905 (81.4)	44 (73.3)	<0.001
Ancestry, n (%)				
White	1604 (84.5)	946 (86.1)	51 (85.0)	0.01
Black	125 (6.6)	47 (4.3)	4 (6.7)	
Asian	69 (3.6)	26 (2.4)	0	
Other	101 (5.3)	80 (7.3)	5 (8.3)	
Marital status, n (%)				
Single	132 (6.9)	98 (8.8)	3 (5.0)	0.54
Married/common-law	1467 (76.7)	818 (73.6)	47 (78.3)	
Separated/divorced/widowed	304 (15.9)	189 (17.0)	10 (16.7)	
Member of religious order	8 (0.4)	7 (0.6)	0	
Highest level of education, n (%)				
Elementary school or less	459 (24.0)	210 (18.9)	18 (30.0)	<0.001
High school or more	1449 (75.8)	902 (81.1)	42 (70.0)	
First-degree relative with prostate cancer, n (%)	334 (18.0)	177 (16.4)	8 (13.6)	0.41
Number of female sexual partners, n (%)				
1	534 (30.1)	260 (24.9)	12 (22.2)	0.07
2–3	315 (17.8)	176 (16.8)	13 (24.1)	
4–7	322 (18.2)	208 (19.9)	8 (14.8)	
8–20	355 (20.0)	235 (22.5)	13 (24.1)	
>20	247 (13.9)	167 (16.0)	8 (14.8)	
Ever had male sexual partner, n (%)	77 (4.2)	63 (5.7)	1 (1.7)	0.08
Ever had an STI, n (%)	237 (12.7)	156 (14.2)	11 (18.3)	0.27
Timing of last screening, n (%)				
≤2 years	1675 (89.2)	975 (88.7)	50 (83.3)	0.15
>2 years	118 (6.3)	60 (5.5)	7 (11.7)	
never screened	84 (4.5)	64 (5.8)	3 (5.0)	
History of prostatitis, n (%)	209 (11.1)	93 (8.5)	6 (10.3)	0.07
History of diabetes, n (%)	356 (18.7)	170 (15.3)	18 (30.0)	0.003

** Numbers within table may not sum to overall totals due to missing data. †P-values from chi-square tests, except for the P-value for mean age, which was obtained from one-way ANOVA.*

Table 4 Association between circumcision status and prostate cancer, by ancestry, among subjects participating in the PROtEuS, Montréal, Québec, Canada, 2005–2009.

Ancestry	Circumcised (N = 1216) †		Not circumcised (N = 1899)†		OR (95% CI) *	*P*-value for circumcision–ancestry interaction term
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)		
White	526 (50.0)	525 (50.0)	814 (50.7)	790 (49.3)	0.95 (0.80–1.12)	–
Black	22 (41.5)	31 (58.5)	81 (64.8)	44 (35.2)	0.40 (0.19–0.86)	0.02
Asian	6 (23.1)	20 (76.9)	19 (27.5)	50 (72.5)	1.09 (0.28–4.20)	0.92
Other	33 (38.4)	53 (61.6)	42 (41.6)	59 (58.4)	0.79 (0.40–1.56)	0.61

**Models adjusted for age at diagnosis for cases and age at interview for controls, family history of prostate cancer, ever had an STI, prostate cancer screening ≤2 years, highest education level achieved. †There were 13 circumcised and 13 uncircumcised men for whom ancestry was unknown.*

There were differences in STI exposure between circumcised and uncircumcised Black men, with the latter group more likely to have had an STI in the past (28% vs 10%, respectively). Such an STI pattern by circumcision status was not seen among White men. Although STI history was adjusted for within models, residual confounding may potentially explain the protective effect of circumcision in Black men.

Childhood circumcision, specifically, before initiation of sexual activity, may be the most opportune time in terms of prostate cancer prevention, as it precedes potential exposure to STIs [22]. In the present study, circumcision before the age of 1 year appeared to be associated with a slight decrease in prostate cancer risk. Two studies examined the effect of timing of circumcision on the risk of prostate cancer. Ross et al. [25] found that being circumcised at birth was protective against prostate cancer among Black men, whereas being circumcised later was protective among White men. However, these findings were based on a small case-control study (142 matched pairs of Black men and 142 matched pairs of White men), where only the subject age was considered within the analysis. Another case-control study (1754 cases, 1645 controls) observed a reduced risk of prostate cancer (OR 0.86, 95% CI 0.73–1.01) among men circumcised before their first sexual intercourse [22].

In the present study, there was a strong inverse association between prostate cancer risk and circumcision performed at ≥36 years of age. To our knowledge, such an association has never been documented. Our questionnaire did not collect information on the reasons for circumcision.

Men circumcised aged ≥36 years had a greater frequency of diabetes compared with men circumcised at a younger age and men never circumcised. Diabetes mellitus type 2 is associated with a reduced risk of prostate cancer [40–43], which has been attributed to lower testosterone levels found in diabetic men [44] or to reduced levels of circulating insulin experienced by long-term diabetics [43]. In addition, men in the present study who were circumcised late in life had a lower education level than those circumcised earlier. Education is positively associated with being screened, and thus diagnosed for prostate cancer [37]. However, as the protective effect of circumcision at a late age persisted after adjustment for education and diabetes, other factors appear to be at play.

The literature indicates that phimosis (an inability to retract the penile foreskin over the glans penis) is the most common medical indication for adult circumcision [4,5]. It has been reported that circumcision may be associated with a reduced risk of penile cancer only among men who had a history of phimosis [21]. If a similar relationship is applicable to prostate cancer, then the protective effect of circumcision may occur most readily among men circumcised later in life, as they are most likely to have had phimosis. As noted above, reasons for circumcision were not enquired of during the interview; hence, this conjecture could not be considered within the statistical analyses.

The biological mechanism by which circumcision may reduce the acquisition of STI infections, and thus potentially reduce prostate cancer risk, might be related to the anatomy of the penile foreskin. The inner surface of the foreskin is composed of mostly non-keratinised mucosal epithelium, which is more easily penetrated by microbes than the penile shaft and glans. In addition, during intercourse, the inner mucosal epithelial surface of the foreskin is directly exposed to genital secretions and it is more susceptible to trauma than the keratinised surfaces, which may provide passages of entry for pathogens [45,46]. Further, the preputial space under the foreskin provides a moist, warm environment that is conducive to the entrapment, survival, and growth of microbes [45]. Finally, the inner foreskin has a higher density of Langerhans' cells and CD4+ T lymphocytes, which are the target cells for HIV [47]. After circumcision, the urethral meatus is the only remaining penile mucosal tissue that is vulnerable to being breached by microbes.

The inverse association between circumcision and prostate cancer persisted after adjustment for STI history. Further, it is possible that STI acquisition may be in the causal pathway between circumcision and risk of prostate cancer, and as such, adjustment for STI history would not be appropriate. In accordance with this, we also ran regression analyses excluding STI history from the models but including all other confounding variables as before (age, first-degree family history of prostate cancer, prostate cancer screening, ancestry, and education level). We found that results did not change when STI history was excluded (data not shown). According to these findings, STIs would not be thought to be an important explanatory factor for the observed protective effect of circumcision. However, the possibility of residual confounding by STIs remains, as misclassification of exposure based on self-reports probably occurred.

The present study had some inherent limitations. First, circumcision status was self-reported and largely could not be verified through hospital medical files. A few studies have examined the validity of self-reported circumcision status compared with that determined by physical examination. In those set in African countries, considerable discordance between these two methods of exposure measurement was observed [48–51]. This may relate, in part, to practices of circumcision that may vary widely in developing countries. For instance, differing amounts of the foreskin may be excised or none removed but instead, for example, incisions made in the foreskin [52,53]. On the other hand, in developed countries, the practice is more uniform. A study amongst adolescent boys in the USA [54] found a high preponderance of inaccuracies in self-reported circumcision status, possibly due to a lack of knowledge about this surgical procedure. By contrast, circumcision self-reports were found to be highly accurate amongst American homosexual men [55]. Nonetheless, the findings from these validation studies might not be applicable to the present study, as they are based in populations that are divergent from our study base.

Although circumcision status was self-reported in the present study, we have indicators suggesting that it was reasonably valid. First, it is estimated that 30% of males aged >15 years, excluding Muslims and Jews, are circumcised in Canada [56]. This rate is lower than the 40% circumcision frequency in control subjects in the present study but is comparable if we take into account that ≈9% of Montréal residents are Jewish or Muslims [57] and assume that most were circumcised. Further, if needed, interviewers provided respondents with a definition of circumcision. Finally, 22% of subjects had another person, primarily a spouse, present during the interview, which might have also aided in ensuring a more valid circumcision status.

Although having another person present during the interviews may have aided more valid reporting of circumcision status, there is also the possibility it may have precipitated further misclassification of STI histories. Nonetheless any misclassification would probably be non-differential, as many variables were collected during the interview and there is no reason to think responses would vary by case or control status. In addition, interviewers thought most respondents (96%) provided 'truthful' answers to the questions pertaining to sexual behaviour, which included STI histories.

Another study limitation relates to the fact that we did not know the reasons why adults were circumcised, limiting our ability to assess whether the protective effect of circumcision was limited to men with medical indications for surgical removal of the foreskin.

The protective effect of circumcision done later in life and the reduced risk found in Black men were discovered among limited groups of few subjects and need to be corroborated.

The present study was based on a case-control study design. It is hard to conceive that cases would have tended to under-report their circumcision status, as compared with controls, leading to a protective association. Misclassification probably occurred, but it was likely to be non-differential, yielding conservative estimates. Error in self-reports of circumcision would be expected to be of the same magnitude in the context of a cohort study.

Strengths of the present study include the large number of participants, making this among one of the largest studies on this issue, in-person interviews conducted by experienced interviewers, the relatively high response rates, and the comprehensiveness of data collection that allowed us to adjust for many potential confounders. Also, circumcision status was provided by nearly all study subjects. Prostate cancer cases were incident in nature and diagnoses were histologically confirmed.

In conclusion, the present findings provide additional evidence for a protective effect of circumcision against prostate cancer development. The protective effect seen was largely confined to Black men. Men circumcised aged ≥36 years also appeared to be at lesser risk of prostate cancer. The associations seemed to be independent of STI infections, although residual confounding by STIs remains a possibility. Very little evidence has accrued to date on the role of circumcision in prostate cancer risk among Black men, known to have the highest rates of the disease. This clearly deserves further research.

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Conflict of Interest

None disclosed.

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Abbreviations: OR, odds ratio; PROtEuS, Prostate Cancer and Environment Study; STI, sexually transmitted infection.

