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

Andrea R. Spence*, Marie-Claude Rousseau*†‡, Pierre I. Karakiewicz‡ and Marie-Élise Parent*†‡

*INRS-Institut Armand-Frappier, Université du Québec, Laval; †Department of Social and Preventive Medicine, University of Montréal, and ‡University of Montréal Hospital Research Centre (CRCHUM), Montréal, Canada

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]. Ongoing 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,
Circumcision and prostate cancer

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% vs 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 PROIEuS, Montréal, Québec, Canada, 2005–2009*.

| Variable | Cases | Controls |
|----------|-------|----------|
| 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.

| Circumcision status: | 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)* |
| 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 (0.60–2.20) |
| 9–20                 | 46 (3.0) | 45 (2.9) | 1.12 (0.71–1.78) | 31 (2.8) | 1.06 (0.64–1.76) | 13 (3.1) | 0.88 (0.46–1.79) |
| 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 screened in 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) | | |
| History of prostatitis, n (%) | | | | |
| First-degree relative with prostate cancer, n (%) | 334 (18.0) | 177 (16.4) | 8 (13.6) | 0.41 |
| Female sex 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.
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 0.40–1.56) 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.

Acknowledgements

This study was supported financially through grants from the Canadian Cancer Society, the Cancer Research Society, the Fonds de la recherche du Québec – Santé (FRQS), FRQS-RRSE, the Ministère du Développement économique, de l’Innovation et de l’Exportation du Québec, and the Canadian Institutes for Health Research. Marie-Élise
Parent and Marie-Claude Rousseau hold career awards from the FRQS.

We thank Mariam El-Zein and Deborah Weiss for their editorial comments about the manuscript. We wish to acknowledge the sincere dedication and hard work of the entire research team, which led to the successful completion of the PROtEuS Study.

**Conflict of Interest**

None disclosed.

**References**

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69–90
2. Key T. Risk factors for prostate cancer. Cancer Surv 1995; 23: 63–77
3. Apt A. Circumcision and prostastic cancer. Acta Med Scand 1965; 178: 493–504
4. Rickwood AM. Medical indications for circumcision. BJU Int 1999; 83 (Suppl. 1): 45–51
5. Hayashi Y, Koijima Y, Mizuno K, Kohri K. Prepuce: phimosis, paraphimosis, and circumcision. ScientificWorldJournal 2011; 11: 289–301
6. Taylor ML, Mainous AG 3rd, Wells BJ. Prostate cancer and sexually transmitted diseases: a meta-analysis. Fam Med 2005; 37: 506–12
7. Dennis MK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology 2002; 13: 72–9
8. Stark JR, Judson G, Alderete JF et al. Prospective study of Trichomonas vaginalis infection and prostate cancer incidence and mortality. Physicians’ Health Study. J Natl Cancer Inst 2009; 101: 1406–11
9. Sutcliffe S, Giovannucci E, Alderete JF et al. Plasma antibodies against Trichomonas vaginalis and subsequent risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006; 15: 939–45
10. Sarma AV, McLaughlin JC, Wallner LP et al. Sexual behavior, sexually transmitted diseases and prostatitis: the risk of prostate cancer in black men. J Urol 2006; 176: 1108–13
11. Fernandez L, Galan Y, Jimenez R et al. Sexual behaviour, history of sexually transmitted diseases, and the risk of prostate cancer: a case-control study in Cuba. Int J Epidemiol 2005; 34: 193–7
12. Dimitropoulos P, Lophatananon A, Easton D et al. Sexual activity and prostate cancer risk in men diagnosed at a younger age. BJU Int 2009; 103: 178–85
13. Gray RH, Kigozi G, Serwadda D et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. Lancet 2007; 369: 657–66
14. Bailey RC, Moses S, Parker CB et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007; 369: 643–56
15. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005; 2: e298
16. Tobian AA, Gray RH. Male foreskin and oncogenic human papillomavirus infection in men and their female partners. Future Microbiol 2011; 6: 739–45
17. Gray RH, Serwadda D, Kong X et al. Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. J Infect Dis 2010; 201: 1455–62
18. Tobian AA, Serwadda D, Quinn TC et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med 2009; 360: 1298–309
19. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS 2000; 14: 2361–70
20. Weiss HA. Male circumcision as a preventive measure against HIV and other sexually transmitted diseases. Curr Opin Infect Dis 2007; 20: 66–72
21. Larke NL, Thomas SL, Silva I, Weiss HA. Male circumcision and penile cancer: a systematic review and meta-analysis. Cancer Causes Control 2011; 22: 1097–110
22. Wright JL, Lin DW, Stanford JL. Circumcision and the risk of prostate cancer. Cancer 2012; 118: 4437–43
23. Mandel JS, Schuman LM. Sexual factors and prostatic cancer: results from a case-control study. J Gerontol 1987; 42: 259–64
24. Rosenblatt KA, Wicklund KG, Stanford JL. Sexual factors and the risk of prostate cancer. Am J Epidemiol 2001; 153: 1152–8
25. Ross RK, Shimizu H, Pagani-Hill A, Honda G, Henderson BE. Case-control studies of prostate cancer in blacks and whites in southern California. J Natl Cancer Inst 1987; 78: 869–74
26. EWings P, Bowie C. A case-control study of cancer of the prostate in Somerset and east Devon. Br J Cancer 1996; 74: 661–6
27. Newell GR, Fueger JJ, Spitz MR, Babaian RJ. A case-control study of prostate cancer. Am J Epidemiol 1989; 130: 395–8
28. Kheirandish P, Chinegwundoh F. Ethnic differences in prostate cancer. Br J Cancer 2011; 105: 481–5
29. Hatcher D, Daniels G, Osman I, Lee P. Molecular mechanisms involving prostate cancer racial disparity. Am J Transl Res 2009; 1: 235–48
30. Freedland SJ, Isacs WB. Explaining racial differences in prostate cancer in the United States: sociology or biology? Prostate 2005; 62: 243–52
31. Parent ME, Goldberg MS, Crouse DL et al. Traffic-related air pollution and prostate cancer risk: a case-control study in Montreal, Canada. Occup Environ Med 2013; 70: 511–8
32. Wright JL, Salinas CA, Lin DW et al. Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between cases with Gleason 4 + 3 and Gleason 3 + 4 tumors in a population based cohort. J Urol 2009; 182: 2702–7
33. Selvin S. Statistical Analysis of Epidemiologic Data, 3rd edn. New York: Oxford University Press, 2004
34. Coulter A, McPherson K. Socioeconomic variations in the use of common surgical operations. Br Med J (Clin Res Ed) 1985; 291: 183–7
35. Richters J, Smith AM, de Visser RO, Grulich AE, Rissel CE. Circumcision in Australia: prevalence and effects on sexual health. Int J STD AIDS 2006; 17: 547–54
36. Laumann EO, Masi CM, Zuckerman EW. Circumcision in the United States. Prevalence, prophylactic effects, and sexual practice. JAMA 1997; 277: 1052–7
37. Garg V, Raisch DW, Selig JP, Thompson TA. Health disparities in clinical practice patterns for prostate cancer screening by geographic regions in the United States: a multilevel modeling analysis. Prostate Cancer Prostatic Dis 2013; 16: 193–203
38. Rebbeck TR, Devesa SS, Chang BL et al. Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of African descent. Prostate Cancer 2013; 2013: 1–12
39. Brawley OW, Jani AB, Master V. Prostate cancer and race. Curr Probl Cancer 2007; 31: 211–25
40. Lawrence YR, Morag O, Benderly M et al. Association between metabolic syndrome, diabetes mellitus and prostate cancer risk. Prostate Cancer Prostatic Dis 2013; 16: 181–6
41. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006; 15: 2056–62

© 2014 The Authors. BJU International published by John Wiley & Sons Ltd on behalf of BJU International
42 Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 2004; 47: 1071–8

43 Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. *Prostate Cancer Prostatic Dis* 2013; 16: 151–8

44 Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006; 295: 1288–99

45 Szabo R, Short RV. How does male circumcision protect against HIV infection? *BMJ* 2000; 320: 1592–4

46 Anderson D, Politch JA, Pudney J. HIV infection and immune defense of the penis. *Am J Reprod Immunol* 2011; 65: 220–9

47 Patterson BK, Landay A, Siegel JN et al. Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. *Am J Pathol* 2002; 161: 867–73

48 Thomas AG, Tran BR, Cranston M, Brown MC, Kumar R, Tlelai M. Voluntary medical male circumcision: a cross-sectional study comparing circumcision self-report and physical examination findings in Lesotho. *PLoS ONE* 2011; 6: e27561

49 Urassa M, Todd J, Boërma JT, Hayes R, Isingo R. Male circumcision and susceptibility to HIV infection among men in Tanzania. *AIDS* 1997; 11: 73–80

50 Lissouba P, Taljaard D, Rech D et al. Adult male circumcision as an intervention against HIV: an operational study of uptake in a South African community (ANRS 12126). *BMC Infect Dis* 2011; 11: 253

51 Weiss HA, Plummer ML, Changalucha J et al. Circumcision among adolescent boys in rural northwestern Tanzania. *Trop Med Int Health* 2008; 13: 1054–61

52 Brown JE, Micheni KD, Grant EM, Mwenda JM, Muthiri FM, Grant AR. Varieties of male circumcision: a study from Kenya. *Sex Transm Dis* 2001; 28: 608–12

53 Bonner K. Male circumcision as an HIV control strategy: not a ’natural condom.’ *Reprod Health Matters* 2001; 9: 143–55

54 Risser JM, Risser WL, Eissa MA, Cromwell PF, Barratt MS, Bortot A. Self-assessment of circumcision status by adolescents. *Am J Epidemiol* 2004; 159: 1095–7

55 Templeton DJ, Mao L, Prestage GP, Jin F, Kaldor JM, Grulich AE. Self-report is a valid measure of circumcision status in homosexual men. *Sex Transm Infect* 2008; 84: 187–8

56 World Health Organization. Male circumcision: global trends and determinants of prevalence, safety and acceptability, 2007. Available at: http://www.who.int/hiv/pub/malecircumcision/globaltrends/en/. Accessed April 2014

57 Statistics Canada. 2001 Census of Canada. Institut de la Statistique du Québec, 2003. Available at: http://www.stat.gouv.qc.ca/statistiques/recensement/2001/recens2001_06/religion/religion06.htm. Accessed May 2013

Correspondence: Marie-Élise Parent, Unité d’épidémiologie et biostatistique, INRS-Institut Armand-Frappier Université du Québec, 531, boul. des Prairies, Laval, Québec H7V 1B7, Canada.

e-mail: marie-elise.parent@iaf.inrs.ca

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