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Circumcision and Prostate Cancer Mortality in the Cancer Prevention Study-I

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By

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Bachelor of Science

Virginia Commonwealth University

2017

Thesis Committee Chair: Michael Goodman MD, MPH

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

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ABSTRACT

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PROBLEM

Previous research has examined the role of sexually transmitted infections (STIs) on prostate cancer etiology. A meta-analysis of 34 case-control, 10 nested case-control, and 3 cohort design studies found that men with a history of any STIs had a 50% higher risk of prostate cancer. Circumcision has also been found to be associated with a lowered risk for some STIs, with the notable exception of gonorrhea. However, based on the literature, previous studies examining the association between circumcision and prostate cancer have been limited to 7 case-control and 1 cross-sectional studies. Thus far, no studies have attempted to examine the association with prostate cancer mortality as the main outcome and studied the association in a cohort study.

METHODS

The association between self-reported circumcision status and prostate cancer mortality was examined using data from 449,320 men in the Cancer Prevention Study I (CPS-I) cohort. Information on date and cause of death was collected by volunteers and verified using death certificates. Cox proportional hazards modeling was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS

During a median follow-up time of 12.8 years, 1,990 men died of prostate cancer. No statistically-significant association was found between circumcision and prostate cancer mortality (HR=0.96, 95% CI 0.85-1.08).

CONCLUSIONS

This study found no association between circumcision and prostate cancer mortality compared to seven out of eight case-control studies that found an inverse association between circumcision and prostate cancer incidence. Further studies should be conducted using more recent data.

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CHAPTER I: BACKGROUND AND LITERATURE REVIEW

BACKGROUND

Prostate cancer is the second most common type invasive malignancy and fifth leading cause of cancer-related mortality in men globally, making it a major public health concern both domestically and internationally (1,2). Prostate cancer etiology is largely uncertain, complicated by over diagnosis driven by widespread PSA screening beginning in the 1990s. A large proportion of cancers detected through PSA-screening may be indolent and are likely have a different etiology than aggressive prostate cancers (2). To circumvent the influence of indolent lesions to study the etiology of prostate cancer, researchers have focused on “aggressive” prostate cancer, defined based on as high Gleason scores, or fatal forms of the disease (2). Known risk factors for aggressive prostate cancer include age, race and ethnicity, family history, and inherited genetic variants (2). Researchers have also explored whether a history of sexually transmitted infections (STIs) is associated with an increased risk of prostate cancer (2-4). In 2014, a meta-analysis of 47 studies (34 case-control, 10 nested case-control, 3 cohort design) found that men who reported ever having “any STI” had a 50% higher risk of prostate cancer, compared to men who did not report any history; however, no associations were observed for individual STI types (4). The only exception was gonorrhea, which was associated with a 20% increase in prostate cancer risk (4).

Male circumcision is associated with a lowered risk for some STIs with the notable exception of gonorrhea (5, 6). However, research on the association between male circumcision and prostate cancer has been limited. Of the eight studies identified in a literature review (7 case-control, 1 cross-sectional), all but one found odds ratio (OR)

estimates less than 1.0 (Table 1.1) (3, 7-13). (3,7). It is important to point out, however, that most of these studies had limited sample sizes (number of cases ranged from $n = 94$ to $n = 1754$). In addition, a review of the current literature identified no cohort studies that examined the association between circumcision and prostate cancer. An advantage of examining circumcision and prostate cancer in cohort studies with prospective exposure collection is that the studies would be less prone to exposure misclassification. Also, in cohort studies, all prostate cancer outcomes can be collected and not influenced by survival bias in case-control studies that may miss the most aggressive prostate cancers.

SIGNIFICANCE

Replicated associations between circumcision and prostate cancer would support current national and consensus recommendations for circumcision and support a role of STIs in prostate carcinogenesis. The procedure of male circumcision is a highly debated topic with current trends showing a decrease in popularity of the practice in many parts of the world. While the prevalence of male circumcision remains relatively high in the United States (71.2%) prevalence is much lower in other nations such as in Australia (26.6%), the United Kingdom (20.7%), France (14.0%), Germany (10.9%), and Sweden (5.1%) (15,16). The global prevalence of male circumcision is estimated to be between 36.7% (95% CI 33.4 – 43.9) and 38.7% (95% CI 31.4 – 42.0) (15,16). The American Academy of Pediatrics currently recommends male circumcision due to health benefits including lowered risk of transmission of some sexually transmitted infections, including HIV (14). Better evidence of the long-term health consequences of circumcision are needed for informed decision making. If circumcision is found to be associated with

lower risk prostate cancer mortality, then increasing the prevalence of male circumcision may reduce the overall disease burden of this common malignancy.

Table 1.1. Comparisons of Selected Characteristics of Analytic Epidemiologic Studies Investigating Male Circumcision in Relation to Prostate Cancer

Study, Year	Study Type	Population	Ethnicity (Age in years)	# Cases/ Controls	Endpoint	OR/RR	Potential Confounders/ EMMs
(7) Ewings, <i>et al.</i> , 1996	Case- Control	Hospital- based Somerset, England	Not given (± 5)	159/325	Incidence PCa	0.62 (0.39 – 0.98)	Confounding: frequency matched with age
(8) Mandel, <i>et al.</i> , 1987	Case- Control	Hospital cases & hospital & neighborhood matched controls MN, USA	White (under 75; HB matched ± 3 , NB matched ± 5)	226/240	Incidence PCa	HB: 0.98 (0.65 – 1.48) NB: 0.82 (0.55 – 1.24)	Confounding: matched on age, race, sex
(9) Newell, <i>et al.</i> , 1989	Case- Control	Hospital- based TX, USA	Non-Jewish White (48-86)	94/167	Incidence PCa	1.89 (1.13 – 3.18)	Confounding: matched on age
(3) Spence, <i>et al.</i> , 2014	Case- Control	Population- based Montreal, QC, Canada	White – 84%, Black – 5%, Asian – 4%, Other – 7%, (40-76)	All: 592/637 White: 526/525 Black: 22/31	Incidence PCa	All: 0.89 (0.76 – 1.04) White: 0.95 (0.80 – 1.12) Black: 0.40 (0.19 – 0.86) Less aggressive 0.90 (0.76 – 1.07) More aggressive: 0.86 (0.69 – 1.09)	Confounding: adjusted for STI history

(10) Ross, <i>et al.</i> , 1987	Case- Control	Population- based CA, USA	White ,Black (65 – 70, ±1)	White: 142/142 Black: 142/142	Incidence PCa	White: 0.50 (p-value <0.05) Black: 0.60 (p-value <0.05)	
(11) Wright, <i>et al.</i> , 2012	Case- Control	Population- based WA, USA	White = 93%, Black (35-74)	1754/1645	Incidence PCa	C1 ^a : 0.87 (0.75 – 1.07) C2 before: 0.89 (0.75 – 1.07) C2 ^b after: 1.26 (0.79 – 2.01) C3 ^c : 0.88 (0.74 – 1.04)	Confounding: matched on age EMM: possible suggestion of EMM by race
(13) Wynder, <i>et al.</i> , 1971	Case- Control	Hospital- based NY, USA	White (87%), Black (35 – 89)	172/142	Incidence PCa	1.03 (0.55 – 1.91)	

HB, hospital-based; NB, neighborhood-based

^aC1 = Circumcision status 1: Categorized by whether they ever had a circumcision, regardless of age of circumcision with never circumcised as referent group.

^bC2 = Circumcision status 2: Categorized on whether the circumcision was performed before first sexual intercourse or after first sexual intercourse with the uncircumcised as the referent group.

^cC3 = Circumcision status 3: Categorized based on whether the male was uncircumcised, or circumcision occurred after the age of first sexual intercourse or before first sexual intercourse with the uncircumcised and after category the referent group.

CHAPTER II: MANUSCRIPT

Circumcision and Prostate Cancer Mortality in the Cancer Prevention Study-I

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ABSTRACT

Problem. Previous research has examined the role of sexually transmitted infections (STIs) on prostate cancer etiology. A meta-analysis of 34 case-control, 10 nested case-control, and 3 cohort design studies found that men with a history of any STIs had a 50% higher risk of prostate cancer. Circumcision has also been found to be associated with a lowered risk for some STIs, with the notable exception of gonorrhea. However, based on the literature, previous studies examining the association between circumcision and prostate cancer have been limited to 7 case-control and 1 cross-sectional studies. Thus far, no studies have attempted to examine the association with prostate cancer mortality as the main outcome and studied the association in a cohort study.

Methods. The association between self-reported circumcision status and prostate cancer mortality was examined using data from 449,320 men in the Cancer Prevention Study I (CPS-I) cohort. Vital status information on death were collected by volunteers and verified using death certificates. Cox proportional hazards modeling was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results. During a median follow-up time of 12.8 years, 1,990 men died of prostate cancer. No statistically-significant association was found between circumcision and prostate cancer mortality (HR=0.96, 95% CI 0.85-1.08).

Conclusions. This study found no association between circumcision and prostate cancer mortality compared to seven out of eight case-control studies that found an inverse association between circumcision and prostate cancer incidence. Further studies should be conducted using more recent data.

INTRODUCTION

Prostate cancer is the second most common cancer in the United States, affecting 101.4 per 100,000 people in the United States alone in 2016 (1). However, due to, in part, widespread PSA screening beginning in the 1990s, etiology of clinically significant prostate cancer remains unclear (2). To understand this issue, researchers have focused on aggressive prostate cancer outcomes, including prostate mortality. Known risk factors for aggressive prostate cancer include age, race and ethnicity, family history, height, and inherited genetic variants (2).

The association between sexually transmitted infections (STIs) and prostate cancer is biologically plausible, and previous epidemiological studies have supported this relationship (2-4). In addition, risk of some STIs appears to be reduced in circumcised men (5,6). Thus, the association between circumcision and prostate cancer warrants investigation. Previous studies examining the association between circumcision and prostate cancer have been limited (7 case control, 1 cross-sectional) with most reporting an inverse association (3, 7-13). However, none of these studies used a cohort design and none looked at mortality, which is an important outcome if one is interested in most severe types of prostate cancer. Two studies did, however, examine circumcision in relation to more aggressive forms of prostate cancer (3,12). In one population-based case-control study, they found that the association of circumcision status between less

aggressive and more cancer did not differ greatly while in the other study they did find a difference between the two (3,12). These considerations served as the motivation for the current analysis.

As circumcision has been shown to reduce some STIs, an association between circumcision status and prostate cancer would support current recommendations for circumcision in the United States and provide indirect evidence of a role of STIs in prostate carcinogenesis. To overcome the potential biases of prior case-control studies, the Cancer Prevention Study (CPS)-I was utilized in this study to examine the association of prospectively collected circumcision status with subsequent mortality from prostate cancer.

METHODS

Study population. A total of 456,487 male participants at least 30 years of age were enrolled in the CPS-I cohort in 1959 from 25 U.S. states (17). Participants were recruited through American Cancer Society volunteers who requested friends and neighbors complete self-administered questionnaires on demographic, lifestyle, and medical factors. Participants who self-reported a history of any cancer besides non-melanoma skin cancer at baseline (n=7,167) were excluded from this analysis, leaving a total of 449,320 men in the analytical cohort.

Exposure. The main exposure for this analysis was circumcision status (Table 2.1). Circumcision status was self-reported on the 1959 baseline questionnaire where participants were asked “Are you circumcised?” Responses included “completely

circumcised (foreskin absent)” (27%), “some foreskin” (10%), “uncircumcised (full foreskin)” (46%), and “don’t know” (17%).

Table 2.1. Frequency of Circumcision Status in CPS-I Participants (1959-1972)

Circumcision Status	N (%)
Uncircumcised	206,426 (45.9)
Some Foreskin	44,665 (9.9)
Completely Circumcised	121,019 (26.9)
Don’t Know	77,210 (17.2)

Outcome. The main outcome for this analysis was mortality from prostate cancer (n=1,990). Vital status was assessed by volunteers and then verified through review of death certificates to determine date and cause of death. In order to ascertain vital status, volunteers made personal inquiries annually to the participants they had enrolled. Additional follow-up occurred again by volunteers in 1971 and 1972 (17). International Classification of Diseases (ICD-7) code 177 was used to identify prostate cancer deaths for this analysis (17).

Statistical Analyses. Time-to-event was calculated from the date of enrollment in 1959 to the date of censoring event. Censoring events included date of death, date of last known contact, or the end follow up - September 30, 1972. Age-adjusted prostate cancer mortality rates were calculated for circumcision status exposure categories with rates standardized to the age distribution in the CPS-I cohort at baseline.

Hazards ratios (HR) and 95% confidence intervals (Cis) of the association between circumcision status and prostate cancer mortality were calculated using Cox proportional hazards regression stratified on single year of age at enrollment. Variables considered as potential confounders but not included in final model included race;

education; religion; marital status; first degree family history of breast, ovarian, pancreatic, or prostate cancers; height; body mass index (BMI); cigarette smoking packs per day; alcohol use; and frequency of intercourse. Effect modification by birth cohort, race, religion, and frequency of intercourse was evaluated comparing $-2 \log$ likelihood of models with and without interaction between circumcision status and the possible modifier of interest. The proportional hazards assumption was evaluated for the model using log-log survival curves, goodness of fit testing, and time-dependent covariate modeling. Alcohol use was found to violate the proportional hazards assumption when examining both the correlation between both the Schoenfeld residuals and survival time (p-value=0.02) and the interaction between alcohol use and log survival time (p-value=0.02). However, examination of the hazard functions plots showed multiple crisscrossing curves which suggests that the interaction with time is close to the null. Therefore, we treated alcohol use as if it met the proportional hazards assumption. All analyses were conducted in SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

During a median follow-up time of 12.8 years, 1,990 prostate cancer deaths occurred among study participants. Table 2.2 and Table 2.3 shows the distribution of demographic characteristics in the study population and the distribution of potential confounders, stratified on circumcision status, respectively. Most of the study participants were white (97%) and married (95%), regardless of circumcision status. Most of men (79%) were smokers; with 40% reporting smoking one pack of cigarettes a day. Participants who responded “don’t know” with regards to their circumcision status (n=77,210) had the lowest proportions of educational attainment with 47% reporting

having completed grammar school or less and only 7% reporting having received a college degree. Nearly all participants (96%) of Jewish faith reported being completely circumcised, precluding stratification of the association between circumcision and prostate cancer mortality by the Jewish faith.

Table 2.2. Frequencies of demographic and risk factor characteristics of study subjects in CPS-I (N = 449,320)

Variable	N	%
Birth Year		
1859 – 1897	101,729	22.6
1898 – 1905	113,060	25.2
1906 – 1911	117,226	26.1
1912 – 1929	117,305	26.1
Race		
White	435,395	96.9
Non-White	13,925	3.1
Education		
Grammar School or Less	110,221	24.5
Some High School	91,364	20.3
High School Graduate	80,793	18.0
Some College, Graduate Nurse, Registered Nurse, Junior College, Normal School	80,223	17.9
College Graduate	86,719	19.3
Religion		
Protestant/Other	366,597	81.6
Jewish	17,050	3.8
Catholic	65,673	14.6
Marital Status		
Married	425,140	94.6
Other	24,180	5.4
First-degree Family History of Site-Specific Cancers of Interest ^a		
No	424,531	94.5
Yes	24,789	5.5
Height (in Inches) – Mean (SD)	69.1 (2.7)	
Body Mass Index (BMI) – Mean (SD)	25.3 (3.2)	
Smoking Status (Cigarettes/Cigars)		
Never Smoker	94,677	21.1
Ever Smoker	354,643	78.9

Cigarette Packs Per Day		
Never Smoker (0 Cigarettes/Day)	94,677	21.1
<1 Pack per Day (1-19 Cigarettes/Day)	85,353	19.0
1 Pack per Day (20 Cigarettes/Day)	180,899	40.3
>1 Pack per Day (20+ Cigarettes/Day)	88,391	19.7
Alcohol Use (Drinks/Day)		
0 Drinks/Day	256,821	57.2
1 Drinks/Day	104,646	23.3
2+ Drinks/Day	87,853	19.6
Frequency of Intercourse (Times/Week)		
<1 Times/Week	140,180	31.2
1 Times/Week	191,979	42.7
>1 Times/Week	117,161	26.1

SD, standard deviation

^aFirst-degree family history of site-specific cancers of interest include breast, ovarian, pancreatic, or prostate cancers.

Table 2.3. Frequencies of potential confounders by circumcision status and hazard ratios (HR) and 95% confidence intervals (CI) from CPS-I (1959-1972)

Variables	Uncircumcised (N = 206,426)		Some Foreskin (N = 44,665)		Completely Circumcised (N = 121,019)		Don't Know (N = 77,210)		p- value ^a	Age-Adjusted HR (95% CI)
	N	%	N	%	N	%	N	%		
Race										<0.001
White	202,104	97.9	43,075	96.4	117,525	97.1	72,691	94.2		1.00
Non-White	4,322	2.1	1,590	3.6	3,494	2.9	4,519	5.9		1.82 (1.49, 2.22)
Education										<0.001
Grammar School or Less	46,843	22.7	7,550	16.9	19,196	15.9	36,632	47.4		1.00
Some High School	42,119	20.4	9,390	21.0	22,771	18.8	17,084	22.1		1.01 (0.89, 1.14)
High School Graduate	39,378	19.1	9,261	20.7	22,448	18.6	9,706	12.6		1.05 (0.90, 1.23)
Some College, Graduate Nurse, Registered Nurse, Junior College, Normal School	37,644	18.2	9,048	20.3	25,283	20.9	8,248	10.7		0.94 (0.82, 1.08)
College Graduate	40,442	19.6	9,416	21.1	31,321	25.9	5,540	7.2		0.85 (0.74, 0.98)
Religion										<0.001
Protestant/Other	175,182	84.9	38,110	85.3	88,259	72.9	65,046	84.3		1.00
Jewish	159	0.1	221	0.5	16,407	13.6	263	0.3		0.52 (0.36, 0.74)
Catholic	31,085	15.1	6,334	14.2	16,353	13.5	11,901	15.4		1.03 (0.89, 1.18)
Marital Status										<0.001
Married	196,517	95.2	42,648	95.5	115,205	95.2	70,770	91.7		1.00
Other	9,909	4.8	2,017	4.5	5,814	4.8	6,440	8.3		0.99 (0.85, 1.17)
First-degree Family History of Site-Specific Cancers of Interest										<0.001
No	194,548	94.3	42,149	94.4	114,032	94.2	73,802	95.6		1.00
Yes	11,878	5.8	2,516	5.6	6,987	5.8	3,408	4.4		1.60 (1.37, 1.86)

Height (in Inches) - Mean (SD)	69.2 (2.7)	69.3 (2.6)	69.2 (25.2)	68.7 (2.9)	< 0.001 ^b	1.03 (1.01, 1.05)			
Body Mass Index (BMI) - Mean (SD)	25.4 (3.2)	25.2 (3.1)	25.2 (3.1)	25.2 (3.4)	< 0.001 ^b	1.01 (1.00, 1.03)			
Cigarette Packs Per Day						< 0.001			
Never Smoker (0 Cigarettes per Day)	43,553	21.1	8,048	18.0	22,805	18.8	20,271	26.3	1.00
<1 Pack per Day (1-19 Cigarettes/Day)	38,317	18.6	8,966	20.1	22,952	19.0	15,118	19.6	1.02 (0.89, 1.17)
1 Pack per Day (20 Cigarettes/Day)	82,533	40.0	17,727	39.7	48,180	39.8	32,459	42.0	1.01 (0.91, 1.13)
>1 Pack per Day (20+ Cigarettes/Day)	42,023	20.4	9,924	22.2	27,082	22.4	9,362	12.1	1.12 (0.95, 1.32)
Alcohol Use (Drinks/Day)						< 0.001			
0 Drinks/Day	119,028	57.7	24,633	55.2	62,926	52.0	50,234	65.1	1.00
1 Drinks/Day	47,037	22.8	10,489	23.5	30,879	25.5	16,241	21.0	1.04 (0.93, 1.16)
2+ Drinks/Day	40,361	19.6	9,543	21.4	27,214	22.5	10,735	13.9	1.12 (0.99, 1.27)
Frequency of Intercourse (Times/Week)						< 0.001			
<1 Times/Week	68,530	33.2	14,174	31.7	37,438	30.9	20,038	26.0	1.00
1 Times/Week	82,182	39.8	17,172	38.5	46,894	38.8	45,731	59.2	1.00 (0.91, 1.10)
>1 Times/Week	55,714	27.0	13,319	29.8	36,687	30.3	11,441	14.8	0.97 (0.83, 1.14)

^ap-value calculated using chi-square test for association at significance level $\alpha=0.05$, unless otherwise specified.

^bp-value calculated using ANOVA for association of means, at significance level $\alpha=0.05$

None of the selected potential confounders (Table 2.3) when controlled for in the model confounded the HRs of the association between circumcision and prostate cancer mortality by more than 10%. Therefore, interpretation of results is based on the age-adjusted associations. Stratified HRs for race, birth cohort, religion, and frequency of intercourse were also calculated to examine any potential effect modification, but no significant interaction was found (Supplementary Tables 1-4).

Compared to uncircumcised men, circumcision status was not significantly associated with mortality from prostate cancer (completely circumcised: HR=0.96, 95% CI 0.85-1.08 and some foreskin: HR=0.96, 95% CI 0.80 – 1.14, respectively; Table 2.4).

Table 2.4. Mortality rates and age-adjusted association of circumcision status with prostate cancer mortality, CPS-I (1959-1972)

Circumcision Status	Mortality Rate per 100,000 (95% CI)	Case (N)	Age-Adjusted HR (95% CI)	P-value
Uncircumcised	41.16 (38.5-43.8)	904	1.00 (ref.)	
Some Foreskin	38.54 (32.2-44.9)	147	0.96 (0.80-1.14)	0.60
Completely Circumcised	39.24 (39.2-35.3)	396	0.96 (0.85-1.08)	0.50
Don't know	45.27 (41.3-49.2)	543	1.06 (0.95-1.18)	0.30

DISCUSSION

In this large prospective cohort of 449,320 men including 1,990 deaths due to prostate cancer, no association was found between circumcision status and prostate cancer mortality. The association did not differ by race, religion, birth cohort, or frequency of intercourse.

The results from this study contrast with the seven out of eight previous case-control studies that found an inverse association with odds ratios (ORs) ranging from 0.40 to 0.98 (3,7-13); however, the CI from this study does include the lower bound of 0.80. The discrepancy with the previous studies may be due to using an older cohort for the analysis, limited sample size (number of cases ranged from n=94 to n=1,754 compared to the 1,990 cases in this study), the prospective collection of circumcision status, or differences in incidence compared to mortality outcomes.

Circumcision has been found to reduce the risk of acquiring human immunodeficiency virus (HIV) and some other STIs such as herpes simplex virus type 2, chlamydia, and syphilis, with the notable exception of gonorrhea (5,6). The role of STIs in prostate cancer outcomes have also been previously examined. A meta-analysis of 34 case-control, 10 nested case-control, and 3 cohort design studies found that men with a history of any STIs had a 50% higher risk of prostate cancer (4). However, the meta-analysis found that gonorrhea was the only individual STI to be significantly associated with an increased risk of prostate cancer, with an increased risk of 20% (SRR 1.20, 95% CI 1.05–1.37) (4). Future investigations regarding the role that STIs, most notably gonorrhea, on prostate cancer etiology should be considered. In addition, while direct analysis of history of STIs and lifetime history of sexual partners was not possible with this cohort, the high proportion of married participants (95%) in this study may help to control for these unmeasured variables.

This study benefits from the large sample size of the cohort, prospective exposure ascertainment, study population of birth cohorts during the changing patterns in circumcision practices and, use of aggressive prostate cancer outcome. A large sample

size is beneficial because it increases power for the study and reduces margin of error. In addition, the use of a large prospective cohort that measured prostate outcomes via mortality is also beneficial as it reduces ascertainment bias. This study took place between 1959-1972, before widespread PSA screening began in the 1990s that led to an over diagnosis of prostate cancer and indolent lesions in men (2). Because of the timeline of the study and outcome of prostate cancer mortality, this analysis was able to narrow its focus to aggressive forms of prostate cancer that lead to death and is also less prone to exposure misclassification due to disease and survival bias.

While circumcision was self-reported by participants in the study, it is likely that any bias in misreporting would be random to the outcome and cause a bias towards the null. In addition, while the generalizability of these findings are narrowed due to the older birth cohorts examined, this study still provides significant impact towards the limited research currently available on circumcision and prostate cancer outcomes and can provide considerations for future studies that attempt to examine similar circumcision prostate cancer hypotheses. Though controlling for known risk factors for prostate cancer disease did not affect the results for this analysis, it is possible that uncontrolled confounding may have impacted the findings. Examination of unmeasured variables that were unavailable such as number of sexual partners, history of STIs, contraception methods, and condom use would have been advantageous to control for potential confounding and to examine the relationship and possible etiology between circumcision, STIs, and prostate cancer more closely. However, analyses found little influence on results from measured marital status, religion, and frequency of intercourse variables, all of which may relate to the previously listed unmeasurable confounders.

This study found no association between circumcision and prostate cancer mortality. Yet, further studies should be conducted using more recent data and examining the relationship between STIs and prostate cancer in more detail.

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SUPPLEMENTARY TABLES

Supplemental Table 2.1. Age-adjusted hazard ratios (HR) and 95% confidence intervals (CI) of circumcision with prostate cancer mortality, stratified by race, CPS-I (1959-1972)

	White		Non-white		p-value for race interaction
	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	
Uncircumcised	866	1.00 (ref.)	38	1.00 (ref.)	0.1225
Some Foreskin	141	0.97 (0.81-1.16)	6	0.56 (0.24-1.34)	
Completely Circumcised	368	0.94 (0.83-1.06)	28	1.06 (0.65-1.74)	
Don't Know	508	1.06 (0.95-1.19)	35	0.69 (0.44-1.10)	

Supplemental Table 2.2. Age-adjusted hazard ratios (HR) and 95% confidence intervals (CI) of circumcision with prostate cancer mortality, stratified by birth year, CPS-I (1959-1972)

	1859 - 1897		1898 - 1905		1906 - 1911		1912 - 1929	
	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)
Uncircumcised	625	1.00 (ref.)	191	1.00 (ref.)	68	1.00 (ref.)	20	1.00 (ref.)
Some Foreskin	85	0.89 (0.71-1.12)	40	1.07 (0.76-1.50)	20	1.29 (0.78-2.13)	2	0.39 (0.09-1.65)
Completely Circumcised	243	0.94 (0.81-1.10)	95	0.97 (0.76-1.24)	44	1.06 (0.73-1.55)	14	0.98 (0.49-1.94)
Don't Know	423	1.02 (0.90-1.15)	94	1.23 (0.96-1.58)	17	0.89 (0.52-1.51)	9	2.05 (0.93-4.50)
p-value for birth cohort interaction								0.2317

Supplemental Table 2.3. Age-adjusted hazard ratios (HR) and 95% confidence intervals (CI) of circumcision with prostate cancer mortality, stratified by religion, CPS-I (1959-1972)

	Protestant/Other		Jewish		Catholic		p-value for religion interaction
	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	
Uncircumcised	793	1.00 (ref.)	1	1.00 (ref.)	110	1.00 (ref.)	
Some Foreskin	127	0.93 (0.77-1.13)	1	1.50 (0.09-24.50)	19	1.14 (0.70-1.85)	
Completely Circumcised	311	1.01 (0.88-1.15)	30	0.58 (0.08-4.38)	55	1.26 (0.91-1.75)	
Don't Know	484	1.10 (0.98-1.23)	0	<0.0001	59	0.82(0.60-1.13)	0.2605

Supplemental Table 2.4. Age-adjusted hazard ratios (HR) and 95% confidence intervals (CI) of circumcision with prostate cancer mortality, stratified by frequency of intercourse, CPS-I (1959-1972)

	<1 Time / Week		1 Time / Week		>1 Time / Week		p-value for frequency of intercourse interaction
	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	Case (N)	Age-adjusted HR (95% CI)	
Uncircumcised	378	1.00 (ref.)	415	1.00 (ref.)	111	1.00 (ref.)	
Some Foreskin	63	1.01 (0.77-1.31)	66	0.94 (0.72-1.22)	18	0.85 (0.52-1.40)	
Completely Circumcised	175	1.06 (0.88-1.27)	173	0.92 (0.77-1.09)	48	0.83 (0.59-1.16)	
Don't Know	158	1.04 (0.86-1.25)	357	1.09 (0.95-1.26)	28	0.86 (0.57-1.31)	0.4892

CHAPTER III: SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

SUMMARY

This study examined the association between circumcision status and prostate cancer mortality in a large U.S. cohort. No statistically-significant association was found between circumcision and prostate cancer mortality (HR=0.96, 95% CI 0.85-1.08). A limited number of studies have examined the role that circumcision status may have on aggressive forms of prostate cancer outcomes and no other studies have examined the association in cohort studies besides this one. Additional studies should be conducted that examine the association between circumcision and aggressive forms of prostate cancer outcomes and death and the role that sexually transmitted infections may have on prostate cancer outcomes.

PUBLIC HEALTH IMPLICATIONS

Circumcision was not found to be associated with prostate cancer mortality which contrasts with previous case-control study findings (3, 7-13). Replicated associations could indicate that there may be potential benefits for circumcision and support current recommendations for the procedure. In addition, the findings could also help to shed light on prostate cancer etiology and the role that sexually transmitted infections (STIs) may have in prostate cancer outcomes.

FUTURE CONSIDERATION

Future investigations into circumcision and prostate cancer mortality should consider examining more closely measures that may be associated with both circumcision and STIs. Additionally, the association between sexually transmitted infections and prostate cancer outcomes is necessary as well. In addition, researchers should consider the potential biases that may occur due to self-reporting of circumcision status. Providing informational resources to participants regarding how to know their status may be beneficial. Finally, future studies should consider the impact that PSA screening may have on certain generations of participants and attempt to prevent any potential biases this may have on exposure misclassification and survival.