Male Circumcision and Serologically Determined Human Papillomavirus Infection in a Birth Cohort

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Abstract

Circumcision has been reported to protect against infection with human papillomavirus (HPV) in men, but results have been inconsistent. We followed males in a birth cohort born in Dunedin, New Zealand, in 1972 and 1973 from age 3 to 32 years. Seropositivity at age 32 years for the oncogenic types HPV-16 and 18, and the nononcogenic types 6 and 11, was studied in relation to maternal reports of circumcision status at age 3 for 450 men. Seropositivity to any of these types was associated with lifetime number of sexual partners ($P = 0.03$), and lower moral-religious emphasis of the family of origin ($P < 0.001$). Circumcision was not found to be protective, with the adjusted odds ratio (95% confidence interval) for HPV6/11/16/18 seropositivity among the circumcised compared with the uncircumcised being 1.4 (0.89-2.2). (Cancer Epidemiol Biomarkers Prev 2009;18(1):177–83)

Introduction

The importance of a male factor in the etiology of cervical cancer was understood before identification of the sexually transmitted human papillomavirus (HPV) as the causal agent (1, 2). Exploration of the possible relationship between male circumcision and cervical cancer has a long history (3). Early ecologic studies showed that cervical cancer was less common in populations—such as Jewish people—among whom male circumcision was widespread (4). Subsequent studies of individuals, however, did not find a clear association between circumcision of partners and women's risk, although in most cases, only husbands were studied (5). Following the detection of the viral cause, a number of studies have investigated the association between circumcision and DNA-detected HPV infection in men (6-13). The results have been conflicting, with one of the suggested reasons being variability in methods for taking genital samples from men (11). Serologic assays for HPV, based on IgG to HPV capsids, have been extensively validated as a marker of cumulative HPV exposure (14-16). HPV seropositivity is strongly associated with the lifetime number of sexual partners, both for women (17) and for men (18). Both women and men are usually HPV seronegative before initiation of sexual activity (19). Sensitivity for detection of current sexually acquired HPV infection is ~50% to 60% and the specificity is considered high (14). In addition, seropositivity seems to be long-lasting with persistence of antibodies documented for at least 10 years (14, 20, 21). By contrast, most women with detectable HPV DNA become HPV DNA negative within a year and it is not clear whether this reflects a biological clearance of the virus or an inability of HPV DNA tests to detect continued presence of a latent infection (22). Hence, serologic assays are useful for epidemiologic studies that aim to investigate relative differences in cumulative infection rates between or within populations. Moreover, sampling of serum is readily standardized and reflects the exposure of the subject, without bias related to the exact bodily location sampled.

We have tested the hypothesis that circumcised men are less likely to acquire HPV-16 and 18 (the most common oncogenic types) and/or HPV-6 and 11 (the most common types causing genital warts). The prevalence of antibodies to these viruses at age 32 years was determined in the male members of a birth cohort whose early childhood circumcision history had been assessed at age 3 years. These men subsequently provided detailed information on their sexual behavior at ages 21, 26, and 32 years, allowing exploration for potential confounding factors.

Materials and Methods

Study Sample. The sample was enrolled in the Dunedin Multidisciplinary Health and Development Study, a longitudinal study of a birth cohort born in Dunedin, New Zealand, in 1972 and 1973 (23). The children were enrolled at age 3 years when 535 of the eligible male children participated. Subsequently, they were assessed on 10 occasions, the most recent being at age 32 years. At the age 3 years assessment, the mothers were asked whether their sons had been circumcised and, if so, at what age.

Questions about sexual behavior, based on those used in the 1990 British National Survey of Sexual Attitudes

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Note: N.P. Dickson and J. Ryding contributed equally.

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and Lifestyles, were presented by computer at ages 21, 26, and 32 years (24). Age at first intercourse was asked about at age 21 years. At each age, information was sought about condom use during heterosexual intercourse in the past year. At age 32 years, questions included whether men had ever had sexual contact with another man, and their lifetime number of female and male sexual partners.

The socioeconomic status of the study member's family of origin was based on parental occupation over the first 15 years of life using the Elley-Irving scale (25); that of the individual at age 32 years was based on their current or most recent occupation, classified using the New Zealand Socio-Economic Index (26). Although information on the family's religion was not obtained, the family environment was assessed at age 7 years using the Moos Family Environment Scale, within which was a measure of the family's emphasis on moral and religious issues (scored on a scale from 0-9; ref. 27). This was grouped as ''low'' (0-3), ''medium'' (4-5), or ''high'' (6-9) to give similar numbers in each group. Educational status was determined according to the highest educational qualification achieved by age 32 years.

Serologic Analyses. Virus-like particles (VLP) for HPV types 6, 11, 16, and 18 were kindly donated by Dr. Neil D. Christensen (Pennsylvania, USA) and Dr. Robert C. Rose (New York, USA). These were coated on to Luminex COOH beads (Bio-Rad) that had been precoated with Heparin salt at 50 μg/mL (Sigma-Aldrich), conjugated as recommended by the manufacturer. Optimal VLP coating concentration was determined for each type of VLP using a panel of serum samples with known reactivity to HPV-6, 11, 16 and 18 (17). The Luminex-based assay was applied to the previously used serum panel and verified to give similar results as the previously published VLP-based ELISA (28). The cutoff

Table 1. Socioeconomic characteristics and sexual behavior of circumcised and uncircumcised men

Characteristic	Circumcised (N = 180)	Uncircumcised (N = 270)	P
	Number (%)*	Number (%)*	
Average socioeconomic status of family			0.913
Low	32 (17.8)	51 (19.0)	
Medium	119 (66.1)	172 (64.2)	
High	29 (16.1)	45 (16.8)	
Highest qualification			0.817
High school or less	60 (33.3)	96 (35.7)	
Postsecondary, not University	82 (45.6)	114 (42.4)	
University	38 (21.1)	59 (21.9)	
Socioeconomic status at 32			0.863
Low	53 (29.4)	83 (31.3)	
Medium	95 (52.8)	133 (50.2)	
High	32 (17.8)	49 (18.5)	
Moral-religious emphasis of family			0.089
Low	37 (22.6)	75 (31.4)	
Medium	65 (39.6)	74 (31.0)	
High	62 (37.8)	90 (37.7)	
Age at first intercourse			0.337
14 or younger	28 (17.4)	44 (17.5)	
15-17	78 (48.5)	105 (41.7)	
18 or older	55 (34.2)	103 (40.9)	
Lifetime number of sexual partners †			0.478
0	1 (0.6)	3 (1.2)	
1	8 (4.6)	15 (5.9)	
2-4	25 (14.5)	28 (11.1)	
5-9	34 (19.7)	68 (26.9)	
10-19	42 (24.3)	55 (21.7)	
20 or more	63 (36.4)	84 (33.2)	
Same sex contact ever			0.420
No	157 (92.4)	236 (90.1)	
Yes	13 (7.7)	26 (9.9)	
Condom use in 12 mo before age 32 assessment			0.236
Usually or always	41 (23.7)	61 (23.6)	
Never or occasionally	123 (71.1)	173 (66.8)	
Not active	9 (5.2)	25 (9.7)	
Condom use in 12 mo before age 26 assessment			0.676
Usually or always	71 (41.0)	93 (36.9)	
Never or occasionally	95 (54.9)	147 (58.3)	
Not active	7 (4.1)	12 (4.8)	
Condom use in 12 mo before age 21 assessment			0.611
Usually or always	51 (34.5)	83 (37.6)	
Never or occasionally	88 (59.5)	129 (58.4)	
Not active	9 (6.1)	9 (4.1)	

NOTE: Totals for each characteristic vary due to missing values.
*Columns may not sum to 100.0% due to rounding.
† Includes male and female sexual partners.

Table 2. Seroprevalence of HPV infection according to socioeconomic characteristics and sexual behavior

Characteristic	Seroprevalence to HPV-6, 11, 16, or 18		
	n/N	%	*P*-value
Average socioeconomic status of family			0.039*
Low	14/83	16.9	
Medium	74/291	25.4	
High	23/74	31.1	
Highest qualification			0.262*
High school or less	32/156	20.5	
Post-secondary, not University	54/196	27.8	
University	25/97	25.8	
Socioeconomic status at 32			0.172*
Low	40/136	29.4	
Medium	51/228	22.4	
High	18/81	22.2	
Moral-religious emphasis of family			<0.001*
Low	42/112	37.5	
Medium	37/139	26.6	
High	24/152	15.8	
Age at first intercourse			0.365*
14 or younger	22/72	30.6	
15-17	47/183	25.7	
18 or older	35/158	22.2	
Lifetime number of partners †			0.030*
0	0/4	0.0	
1	4/23	17.4	
2-4	11/53	20.8	
5-9	23/102	22.6	
10-19	27/97	27.8	
20 or more	42/147	28.6	
Same sex contact ever			0.923 ‡
No	98/393	24.9	
Yes	10/39	25.6	
Condom use in 12 mo before age 32 assessment			0.729 ‡
Usually or always	27/102	26.5	
Never or occasionally	71/296	24.0	
Not active	10/34	29.4	
Condom use in 12 mo before age 26 assessment			0.443 ‡
Usually or always	45/164	27.4	
Never or occasionally	55/242	22.7	
Not active	6/19	31.6	
Condom use in 12 mo before age 21 assessment			0.109 ‡
Usually or always	29/134	21.6	
Never or occasionally	63/217	29.0	
Not active	2/18	11.1	

*P-value from linear test for trend.
† Includes male and female sexual partners.
‡ P-value from Chi-square test for heterogeneity.

level was set by comparing the Luminex data to the previously used cutoff for the ELISA method. For HPV-16, we also tested the samples in this study in parallel using the Luminex method and the classic VLP-based ELISA (17). There was very high agreement (κ = 0.90), with the Luminex method being slightly more sensitive (12 samples were Luminex positive, ELISA negative, and 1 sample was Luminex negative, ELISA positive).

The Luminex multiscreen assay plates (Millipore) were prewetted with 150 μL of 1% bovine serum albumin (BSA) 0.1% Tween 20 PBS buffer and washed on a vacuum manifold. Human serum samples were diluted 1:30 and 1:90 and preincubated in 1% BSA, 0.1% Tween 20, 0.5% Polyvinylalcohol, 0.8% Polyvinylpyrrolidone buffer for at least 60 min. The wells were filled with 50 μL bead suspension and 50 μL per well of human serum and reacted for 1 h. After washing 5 times with 150 μL of 1% BSA 0.1% Tween 20 PBS buffer on a vacuum manifold, 50 μL/well of mouse anti-human IgG diluted ×1,000 in 11% BSA 0.1% Tween 20 PBS buffer were added to all plates and allowed to react for 90 min. After 5 further washes, 50 μL per well of R-phycoerythrin–conjugated goat anti-mouse IgG reporter antibody (Southern Biotech) diluted ×100 in 1% BSA 0.1% Tween 20 PBS buffer were added and reacted for 20 min. After 5 further washes, 100 μL/well 1% BSA, 0.1% Tween 20 PBS buffer were added and fluorescence was recorded using the Bio-Plex 200 system with Bio-Plex Manager Sofware 4.2. Uncoated beads were used as control. The background median fluorescent intensity of each serum was subtracted from the VLP reactivity, and then the median fluorescent intensity values were transformed into units using the ''parallel line'' method, as previously described (29).

Statistical Analysis. Potential socioeconomic and sexual behavior confounding factors were selected from variables known to be, or that might be, associated with

circumcision and HPV infection in men (16). Measures of these were collected as described earlier in the Materials and Methods, and are presented in Tables 1 and 2. The analysis was undertaken using Stata v.10. χ^2 tests for heterogeneity were used to determine the relationship between circumcision status and these measures of socioeconomic status and sexual behavior. Seropositivity to any of HPV-6, 11, 16, or 18 was studied in relation to these measures. A linear test for trend was performed using logistic regression and entering the actual measures before grouping where appropriate (for family's moral-religious emphasis, and number of sexual partners).

Odds ratios (OR) and 95% confidence intervals were calculated using a univariate logistic regression model to examine separately the relationship between circumcision and prevalence of HPV-16 and/or 18, HPV-6 and/or 11, or for any of these four types. The characteristics in Table 2 were explored as potential confounders. Such variables were judged to be confounders if adjustment resulted in a 10% change in the point estimate of the OR for circumcision, or if the confidence intervals changed to include or exclude 1.0 resulting in a change of statistical significance (30). First, the model with the strongest confounder was selected. Then remaining variables were entered into this model one by one using the above criteria to determine whether the resulting model should be adopted.

The study was approved by the Otago Ethics Committee and individual consent was given for the testing.

Results

Of the 523 male survivors at age 32 years, 450 (86.0%) had both information on their circumcision status reported by their mothers at age 3 and serum tested for antibodies to HPV (one of whom was not tested for HPV-16) at age 32 years. Of these 450 men, 180 (40.0%) had been circumcised by age 3 years; 154 in their first month of life and only 3 between the ages of 2 and 3 years.

There were no significant differences in the socioeconomic characteristics or sexual behavior of the circumcised and uncircumcised men (Table 1). A higher proportion of uncircumcised men (31.4%) came from a family where there was low moral-religious emphasis compared with circumcised men (22.6%), but the test for trend was not statistically significant.

The prevalence of antibodies to HPV-16 and 18 was 18.0% and 4.2%, respectively; and the prevalence of antibodies to HPV-6 and 11 was 4.4% and 1.1%, respectively. Overall, 21.1% of the men had antibodies to either HPV-16 or 18; 4.7% to either HPV-6 or 11; and 24.7% to any of the 4 types tested. There were statistically significant relationships between seropositivity to any of the HPV types and socioeconomic status of the participants' family of origin, moral-religious emphasis of their family at age 7 years, and their lifetime number of sexual partners (Table 2).

As shown in Table 3, the prevalence of antibodies to any of the HPV types tested was actually higher among circumcised men (27.2%) than among the uncircumcised (23.0%). For HPV-16 and/or 18, the respective proportions were 22.8% and 20.0%; and for HPV-6 and/or 11, 4.4% and 4.8%. None of these differences were statistically significant.

Adjustment for possible confounders did not alter these findings (Table 3).

The only factor that met our final criteria for a confounder for the comparison of any HPV type infection was age at first intercourse, which altered the OR for the circumcised compared with the uncircumcised from 1.3 (0.81-1.9) to 1.4 (0.89-2.2). Similarly, for HPV-16 and/or 18, only age at first intercourse met the criteria for confounding. For HPV-6 and/or 11, the final model included frequency of condom use in the 12 months before the age of 26 years. These adjusted results were similar to those unadjusted ORs obtained when the sample was restricted to those for whom data on the confounder were available.

Discussion

In this birth cohort, early childhood circumcision was not found to be protective against infection (by age 32 years) with the most common HPV types that cause cervical cancer or genital warts. The socioeconomic characteristics and the sexual behavior of the circumcised and uncircumcised men were remarkably similar; moreover, adjustment for potential confounding factors made little difference to the findings.

Strengths of this study are that it was population-based with a very high retention rate, that detailed information on sexual behavior was collected repeatedly using well-validated questions, and that computer presentation (with safeguards to protect confidentiality)

Table 3. Seroprevalence of HPV infection in circumcised and uncircumcised men

Type	Number (%)		Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
	Circumcised (N = 180)	Uncircumcised* (N = 270)		
HPV-16	35 (19.4)	46 (17.1)		
HPV-18	7 (3.9)	12 (4.4)		
HPV-16 or 18	41 (22.8)	54 (20.0)	1.2 (0.75-1.9)	1.4 (0.85-2.2) †
HPV-6	8 (4.4)	12 (4.4)		
HPV-11	0 (0.0)	5 (1.9)		
HPV-6 or 11	8 (4.4)	13 (4.8)	0.92 (0.37-2.3)	1.1 (0.43-2.8) ‡
Any HPV type	49 (27.2)	62 (23.0)	1.3 (0.81-1.9)	1.4 (0.89-2.2) †

*Reference category.
† Adjusted for age at first intercourse.
‡ Adjusted for frequency of condom use in the previous 12 mo at age 26.

was used to enhance disclosure. Parental reports of early circumcision in a face-to-face interview when the subjects were age 3 were used to assess circumcision status, including age at surgery. The proportion circumcised (40.0%) was very similar to that in another sample born in 1972 in a different New Zealand city (31). It was higher than the 30% circumcised in another New Zealand birth cohort born five years later (32), which is consistent with the decreasing local popularity of the procedure over this period (33).

Although a weakness of the study is that information about later circumcision was not sought, this is very uncommon in New Zealand compared with infant or early childhood circumcision (34). Other findings on circumcision and sexually transmitted infections from this cohort have been consistent with most recent studies from developed countries. We previously reported that circumcision did not protect against serologically determined herpes simplex virus-2 infection up to age 26 years (35), consistent with findings of the US National Health and Nutritional Examination Survey over a wide age range (36). Similarly, in this cohort, circumcision did not protect against any self-reported sexually transmitted infections (none were HIV) to age 32 years (34); this finding is consistent with a number of large population-based cross-sectional studies (37-39), although not with a study from another birth cohort (32).

Most emphasis should be placed on the results for HPV-16 and/or 18 and for any of the four HPV types as the low prevalence of HPV types 6 and 11 resulted in wide confidence intervals. As expected from our examination of the distribution of the possible confounders by circumcision status, adjustment for possible confounders made little difference to the findings. In fact, the slight differences present were due almost entirely to missing data for each of the socioeconomic and sexual behavior measures. Thus, the variables adjusted for in the final models may not be true confounders. Furthermore, adjustment for number of sexual partners and for moral/religious emphasis of the family (both of which were related to HPV seropositivity) did not alter our estimates.

Using serology has advantages over DNA sampling for detecting cumulative exposure to HPV because it also shows the effect of HPV exposures in the past, whereas detection of DNA reveals only current infection (40). HPV serology, however, will underestimate the total number of men who have ever been infected with these HPV types. In women, only ~50% to 60% of cervical HPV DNA-positive individuals are also seropositive (14). Men may be even less likely than women to mount a detectable antibody response (41). The specificity of IgG is considered to be high, based on the finding of very low rates of antibody detection in sexually inexperienced and monogamous adults and in children (19, 42). We tested the samples for antibodies to HPV-16 using ELISA and Luminex methods. Although slightly more samples were reactive using the Luminex test, when we analyzed the relationship between circumcision and HPV-16 seropositivity using these two methods, the findings were virtually the same: the adjusted OR using ELISA was 1.3 (0.76-2.3), and using Luminex was 1.3 (0.79-2.2). Moreover, if the imperfect performance of serologic testing were to reverse a protective effect of circumcision, circumcised men infected with HPV would need to be more likely to become seropositive than the uncircumcised, or be more likely to have false-positive results, or both.

Sexual exposure to HPV in men this can result in any of penile, oral, or anal infection. Oral HPV-16 infection is strongly related to certain orophayngeal cancers, the risk of which increases with the lifetime number of oral sex partners (43). The acquisition of oral infection in men would not be expected to be influenced by their circumcision status. Furthermore, healthy control adults are reported to have a relatively low prevalence of oral HPV-16 DNA (~4%; ref. 43). As not all oral infections are likely to result in seroconversion, the relative contribution of oral HPV to positive serology is likely to be small. In addition, anal HPV has been identified as being relatively common among men who have sex with men (44). When, in this study, we removed all the men who reported anal sex with another man, there was no change in the relationship between circumcision and HPV seropositivity (data not shown). Thus, oral or anal acquisition was unlikely to have strongly influenced our results.

This is the first population-based study to investigate circumcision and HPV infection using serologic testing for HPV. The only previous study of HPV serology and circumcision was undertaken in a sample of Korean students and also found no relationship (45). However, that study was unusual in that seroprevalence was not found to be higher among the sexually experienced men than the nonexperienced, suggesting that there might have been problems with the serologic testing and/or reporting of sexual activity.

There have been several published studies examining the relationship between circumcision and prevalent penile HPV DNA. Five cross-sectional studies found the prevalence of DNA-detected penile HPV to be lower in circumcised men (6-10), whereas three did not (11-13). It has been suggested that the anatomic site of sampling might explain some of the variation in results (11). A meta-analysis has been undertaken (46), but this has been criticized as ''biased, inaccurate, and misleading'' (47). One study has suggested that the higher prevalence of penile detected HPV DNA among uncircumcised men is due not to a higher incidence of infection but to more persistence, which would imply more risk of transmission to women (9).

Our finding of no relationship between circumcision and seroprevalence of HPV-6 and 11, which commonly cause genital warts, is consistent with 3 large population-based cross-sectional studies in the USA, United Kingdom, and Australia that all found no relationship between circumcision and self reported genital warts (37-39).

Several case-control studies of cervical cancer among women who had only ever had one male sexual partner have been undertaken, none of which found a clear overall relationship with his circumcision status (6, 48-50). When we combined the results of these in a meta-analysis, including the adjusted ORs from the 3 studies where this information was provided, and the unadjusted from the other, the OR for cervical cancer among those whose only partner had been circumcised was 0.80 (0.61-1.05), showing a protective effect of borderline significance. In one of these studies, a statistically significant protective effect was found if the

men had been circumcised when younger than 1 year of age (45). In another, male circumcision had a significant protective effect (0.42; 95% confidence interval, 0.23-0.79) for women whose sole male partner reported 6 or more partners but not among those with fewer partners (1.40; 95% confidence interval, 0.76-2.57; ref. 6). This was consistent with the authors' hypothesis that circumcision would be more protective among women whose male partners were at higher risk for HPV infection. If a protective effect of male circumcision on the risk of cervical cancer in women is confirmed, our results suggest this may be due to a lower risk of transmission to the women, rather than a lower risk of acquisition by the men.

In conclusion, we found no evidence that early childhood circumcision significantly reduced the risk of acquiring HPV infection by age 32 years, although a small protective effect cannot be ruled out. Although some studies suggest that circumcision might reduce the risk of penile HPV persistence in men, it is uncertain whether this results in a lower risk of transmission to women. On current evidence it would be premature to promote male circumcision as protection against cervical cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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