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MALE CIRCUMCISION, PENILE HUMAN PAPILLOMAVIRUS INFECTION, AND CERVICAL CANCER IN FEMALE PARTNERS

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ABSTRACT

Background It is uncertain whether male circumcision reduces the risks of penile human papillomavirus (HPV) infection in the man and of cervical cancer in his female partner.

Methods We pooled data on 1913 couples enrolled in one of seven case–control studies of cervical carcinoma in situ and cervical cancer in five countries. Circumcision status was self-reported, and the accuracy of the data was confirmed by physical examination at three study sites. The presence or absence of penile HPV DNA was assessed by a polymerase-chain-reaction assay in 1520 men and yielded a valid result in the case of 1139 men (74.9 percent).

Results Penile HPV was detected in 166 of the 847 uncircumcised men (19.6 percent) and in 16 of the 292 circumcised men (5.5 percent). After adjustment for age at first intercourse, lifetime number of sexual partners, and other potential confounders, circumcised men were less likely than uncircumcised men to have HPV infection (odds ratio, 0.37; 95 percent confidence interval, 0.16 to 0.85). Monogamous women whose male partners had six or more sexual partners and were circumcised had a lower risk of cervical cancer than women whose partners were uncircumcised (adjusted odds ratio, 0.42; 95 percent confidence interval, 0.23 to 0.79). Results were similar in the subgroup of men in whom circumcision was confirmed by medical examination.

Conclusions Male circumcision is associated with a reduced risk of penile HPV infection and, in the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer in their current female partners. (N Engl J Med 2002;346:1105-12.)

SINCE Hutchinson reported in 1855 that circumcision might prevent syphilis,[1] studies have suggested that circumcision may reduce the risk of penile cancer, urinary tract infections, and common sexually transmitted diseases, including human immunodeficiency virus (HIV) infection.[2-9] Little is known, however, about the effect of male circumcision on the risk of acquiring human papillomavirus (HPV). HPV causes genital warts in men and women, and it has been linked to cancers of the cervix, vulva, vagina, anus, and penis.[10,11] Cervical cancer is the second most common cancer among women worldwide, and up to 99 percent of all cases may be attributed to infection by oncogenic HPV genotypes.[12,13] Therefore, factors that reduce the probability of acquiring or transmitting HPV among men or women may reduce the risk of disease associated with these infections.

During the past 15 years the International Agency for Research on Cancer has performed several large case–control studies of cervical cancer in different countries. We used data from these studies to assess the effect of male circumcision on the risk of genital HPV infection in the men themselves and the risk of cervical cancer in their sexual partners.

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METHODS

Study Design

Study subjects were enrolled in one of seven case–control studies, five involving invasive cervical cancer and two involving cervical carcinoma in situ. The fieldwork for these studies was conducted from 1985 through 1993. Two studies each were conducted in Spain and Colombia, and one study each was conducted in Brazil, Thailand, and the Philippines. Details of the methods of each study, as well as the results of analyses of some risk factors for cervical cancer, have been published previously.[14-23] Female patients were women who had newly diagnosed, histologically confirmed cervical carcinoma in situ or invasive cervical cancer. Control women were recruited from the general population in the two studies of invasive cervical cancer in Spain and Colombia (population-based studies) and from the same hospitals as the patients in the case of the other studies (hospital-based studies). In all studies, control women were frequency-matched to the women with cervical cancer according to age. Since male and female risk factors for carcinoma in situ were similar to those for invasive cervical cancer, women with carcinoma in situ and controls were also included in the present analysis.[24]

Men who were eligible for the present study were the husbands or stable partners of the women with cervical cancer and the control women enrolled in each of these studies. A man was considered to be a stable partner of an enrolled woman if he reported having had regular sexual intercourse with the woman for at least six months, whether or not they were married or lived together.

All protocols were approved by the International Agency for Research on Cancer and the local ethics and research committees. Informed consent was obtained from all study subjects. Oral consent was obtained from the subjects in the Spanish and Colombian studies (which were initiated in 1985), consistent with the standard at the time. In the remaining studies, which were initiated later, written informed consent was obtained.

Questionnaire and Medical Examination

Subjects were interviewed with use of a standardized questionnaire administered in person by specially trained interviewers. Detailed information was collected on demographic and socioeconomic variables, sexual history, and circumcision status.

The circumcision status was assessed by a clinician in the case of 794 of the 815 men (97.4 percent) who were recruited in the studies in Brazil, Thailand, and the Philippines. After the exclusion of 4 men whose circumcision status was assessed as uncertain by the clinician, medical examination of the penis confirmed the self-reported circumcision status in 748 of 790 of the male partners (94.7 percent). Only 1.7 percent of men (5 of 287) who reported having been circumcised were considered by the clinician to be uncircumcised, and 7.4 percent of men (37 of 503) who reported not having been circumcised were considered by the clinician as having been circumcised (kappa, 0.89). On the basis of this high degree of reliability, the self-reported circumcision status was used for all analyses.

Detection of HPV DNA

Two samples of exfoliated cells were obtained from the penis: one from the distal urethra with the use of a very thin, wet, cotton-tipped swab and one from the external surface of the glans and coronal sulcus with the use of a standard-sized wet, cotton-tipped swab. Cervical exfoliated cells were collected from the women as previously described.[14-20] The detailed protocol used for the polymerase-chain-reaction (PCR) assay for the detection of HPV DNA in the cervical and penile specimens has been described previously.[14-23] Briefly, the L1 consensus primers MY09–MY11, as modified by Hildesheim et al.,[25] were used for the samples collected in the Colombian and Spanish studies. The GP5+/6+ general primer system was used for the samples collected in the remaining studies. PCR products were assessed for HPV DNA with the use of a cocktail of HPV-specific probes and were genotyped by hybridization of the PCR products with type-specific probes for 33 HPV types in the case of cervical samples and for at least 6 HPV types (6, 11, 16, 18, 31, and 33) in the case of penile samples.[26,27] Samples that were positive for HPV but that did not hybridize with any of the type-specific probes were called "HPV X." Amplification of a fragment of the β-globin gene served as an internal quality control for each specimen.

Statistical Analysis

We used unconditional logistic regression to estimate odds ratios and 95 percent confidence intervals in order to measure associations between specific variables and the risk of penile HPV infection or cervical cancer. All logistic-regression models were adjusted for the age of the male partner (in quartiles) and the study in which his partner was enrolled (seven categories). Covariables in the model for penile HPV infection included the male partner's level of education (primary school or less vs. secondary school or higher), the age at which he first had sexual intercourse ($\leq$16, 17 to 18, or $\geq$19 years), his lifetime number of sexual partners (1 to 5, 6 to 20, or $\geq$21), and his self-reported frequency of genital washing after intercourse (always vs. occasionally or never). The Wald test, adjusted for the same covariables, was used to assess the association of each variable with circumcision status. Further adjustment for case–control status or the presence of cervical HPV DNA did not substantially alter the point estimates, and these variables were not included in the analyses. Logistic-regression models for cervical cancer were also adjusted for the woman's age, her lifetime number of sexual partners, and the age at which she first had sexual intercourse. Fisher's exact test was used to assess the association between male circumcision status and the risk of penile HPV infection, with stratification according to several characteristics of the men.

We assessed whether the association of circumcision status with the risk of penile HPV infection and cervical cancer differed significantly according to the country in which the various studies were conducted by including in the fully adjusted logistic-regression model an interaction term combining country and circumcision status. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Study Subjects

Of the 3790 women (1896 women with cervical cancer and 1894 controls) who were enrolled in the seven case–control studies, 2800 (1329 women with cervical cancer and 1471 controls) reported having a husband or stable male partner at study entry. A total of 984 of the 1329 partners of women with cervical cancer (74.0 percent) and 937 of the 1471 partners of control women (63.7 percent) were interviewed. Of these, 807 partners of patients (82.0 percent of those interviewed) and 717 partners of control women (76.5 percent) provided cytologic specimens, of which 610 (75.6 percent) and 533 (74.3 percent), respectively, yielded a valid PCR result. Eight men whose circumcision status was unknown (four with a valid PCR result and four who did not provide samples) were excluded from the analyses.

Overall, the men whose HPV status could be confirmed by PCR assay were similar to the men whose HPV status could not be established with respect to age, level of education, circumcision status, and var-

iables related to sexual behavior. In Colombia, highly educated men were more likely than less educated men to have a valid PCR result. In Thailand, uncircumcised men and men who reported having had a large number of sexual partners were more likely to have a valid PCR result than their counterparts. However, the exclusion of men from Thailand did not substantially alter the magnitude of the associations.

Women whose partners participated in the study did not differ significantly from women whose partners did not participate with respect to age, level of education, or variables related to sexual behavior. Likewise, women whose partners were tested for HPV infection were similar to those whose partners were not tested.

Characteristics of the Subjects

The overall prevalence of self-reported circumcision was 19.3 percent (370 of 1913 men): 1.5 percent in Colombia, 6.1 percent in Brazil, 10.0 percent in Thailand, 11.5 percent in Spain, and 91.0 percent in the Philippines. As compared with uncircumcised men, circumcised men had a higher level of education, were less likely to report frequent genital washing after sex, and were more likely to have good genital hygiene, as assessed by a physician (Table 1).

Circumcision and Penile HPV Infection

HPV DNA was detected in 182 of the 1139 penile specimens (16.0 percent). The most common HPV genotypes were 16 (24.7 percent of all positive samples), 18 (4.9 percent), 6 or 11 (3.3 percent), 53 (3.3 percent), 31 (2.7 percent), and 33 (2.2 percent). The type could not be identified in the case of 51.1 percent of the positive samples. HPV types 35, 39, 45, 51, 52, 54, and 59 each accounted for less than 1.5 percent of the positive samples.

HPV was detected in 19.6 percent of uncircumcised men (166 of 847) and 5.5 percent of circumcised men (16 of 292). As compared with uncircumcised men, circumcised men had a lower prevalence of HPV infection in all subgroups defined according to base-line characteristics (Table 2).

The overall odds ratio for penile HPV infection associated with self-reported circumcision was 0.37 (95 percent confidence interval, 0.16 to 0.85), after adjustment for age, study location, level of education, age at first sexual intercourse, lifetime number of sexual partners, and frequency of genital washing after sex. The adjusted odds ratio associated with clinician-assessed circumcision was 0.44 (95 percent confidence interval, 0.17 to 1.13). There was an inverse association between circumcision and the risk of HPV infection in all studies (P for heterogeneity=0.87), and this finding persisted whether or not the female partner had cervical HPV infection or had been given a diagnosis of cervical cancer (data not shown). The only other

TABLE 1. CHARACTERISTICS OF UNCIRCUMCISED AND CIRCUMCISED MEN.*

CHARACTERISTIC	UNCIRCUMCISED MEN (N=1543)	CIRCUMCISED MEN (N=370)	P VALUE†
	no. (%)		
Study location			<0.001
Brazil	139 (9.0)	9 (2.4)	
Colombia	464 (30.1)	7 (1.9)	
Thailand	361 (23.4)	40 (10.8)	
Philippines	24 (1.6)	242 (65.4)	
Spain	555 (36.0)	72 (19.5)	
Age			0.43
≤37 yr	399 (25.9)	97 (26.2)	
38–46 yr	363 (23.5)	102 (27.6)	
47–56 yr	381 (24.7)	89 (24.0)	
≥57 yr	400 (25.9)	82 (22.2)	
Level of education			0.06
Never attended school	179 (11.6)	8 (2.2)	
Primary school	862 (55.9)	123 (33.2)	
Secondary school or higher	499 (32.3)	239 (64.6)	
Unknown	3 (0.2)	0	
Age at first sexual intercourse			0.14
≤16 yr	573 (37.1)	65 (17.6)	
17–18 yr	408 (26.4)	84 (22.7)	
≥19 yr	560 (36.3)	221 (59.7)	
Unknown	2 (0.1)	0	
Lifetime number of sexual partners			0.52
1–5	490 (31.8)	183 (49.5)	
6–20	483 (31.3)	115 (31.1)	
≥21	548 (35.5)	69 (18.6)	
Unknown	22 (1.4)	3 (0.8)	
Sexual intercourse with prostitutes			0.99
No	488 (31.6)	174 (47.0)	
Yes	1049 (68.0)	196 (53.0)	
Unknown	6 (0.4)	0	
Genital washing after intercourse			<0.05
Always	625 (40.5)	85 (23.0)	
Never or occasionally	916 (59.4)	285 (77.0)	
Unknown	2 (0.1)	0	
Physician's assessment of genital hygiene‡			<0.001
Good	281 (53.6)	207 (71.1)	
Fair or poor	224 (42.7)	80 (27.5)	
Unknown	19 (3.6)	4 (1.4)	
Condom use with regular partner‡			0.36
No	462 (88.2)	207 (71.1)	
Yes	62 (11.8)	83 (28.5)	
Unknown	0	1 (0.3)	
Condom use with prostitutes§			0.29
Never or occasionally	709 (67.6)	61 (31.1)	
Usually or always	337 (32.1)	134 (68.4)	
Unknown	3 (0.3)	1 (0.5)	
Current partner's lifetime number of sexual partners			0.84
1	1118 (72.5)	302 (81.6)	
2–3	376 (24.4)	58 (15.7)	
≥4	48 (3.1)	10 (2.7)	
Unknown	1 (<0.1)	0	

*Because of rounding, percentages may not total 100.

†Wald's test was used to assess the association between each characteristic and circumcision status, adjusted for study location, age, level of education, age at first sexual intercourse, lifetime number of sexual partners, and frequency of genital washing after sex.

‡Subjects from Colombia and Spain were excluded.

§The analysis is limited to men who had had sex with prostitutes.

TABLE 2. PREVALENCE OF PENILE HUMAN PAPILLOMAVIRUS (HPV) INFECTION AMONG UNCIRCUMCISED AND CIRCUMCISED MEN ACCORDING TO VARIOUS CHARACTERISTICS.*

CHARACTERISTIC	UNCIRCUMCISED MEN		CIRCUMCISED MEN		P VALUE†
	NO. TESTED	NO. POSITIVE FOR HPV (%)	NO. TESTED	NO. POSITIVE FOR HPV (%)	
Overall	847	166 (19.6)	292	16 (5.5)	<0.001
Study location					
Brazil	103	40 (38.8)	6	1 (16.7)	0.41
Colombia	236	52 (22.0)	4	0	0.58
Thailand	171	35 (20.5)	12	2 (16.7)	1.0
Philippines	22	2 (9.1)	233	12 (5.2)	0.34
Spain	315	37 (11.7)	37	1 (2.7)	0.16
Age					
≤37 yr	225	42 (18.7)	69	4 (5.8)	0.008
38–46 yr	212	39 (18.4)	88	6 (6.8)	0.01
47–56 yr	200	38 (19.0)	69	4 (5.8)	0.007
≥57 yr	210	47 (22.4)	66	2 (3.0)	<0.001
Level of education					
Never attended school	104	21 (20.2)	3	0	
Primary school	449	87 (19.4)	88	2 (2.3)	<0.001
Secondary school or higher	293	57 (19.5)	201	14 (7.0)	<0.001
Unknown	1	1 (100.0)	0	0	
Age at first sexual intercourse					
≤16 yr	315	72 (22.9)	48	2 (4.2)	0.002
17–18 yr	229	43 (18.8)	69	5 (7.2)	0.02
≥19 yr	301	51 (16.9)	175	9 (5.1)	<0.001
Unknown	2	0	0	0	
Lifetime number of sexual partners					
1–5	263	33 (12.5)	145	4 (2.8)	0.001
6–20	275	49 (17.8)	93	9 (9.7)	0.07
≥21	301	81 (26.9)	52	3 (5.8)	<0.001
Unknown	8	3 (37.5)	2	0	
Sexual intercourse with prostitutes					
No	274	49 (17.9)	138	4 (2.9)	<0.001
Yes	570	116 (20.4)	154	12 (7.8)	<0.001
Unknown	3	1 (33.3)	0	0	
Genital washing after intercourse					
Always	342	64 (18.7)	39	5 (12.8)	0.51
Never or occasionally	504	101 (20.0)	253	11 (4.3)	<0.001
Unknown	1	1 (100.0)	0	0	
Physician's assessment of genital hygiene‡					
Good	160	38 (23.8)	175	13 (7.4)	<0.001
Fair or poor	133	37 (27.8)	76	2 (2.6)	<0.001
Unknown	3	2 (66.7)	0	0	
Condom use with regular partner‡					
No	255	64 (25.1)	173	10 (5.8)	<0.001
Yes	41	13 (31.7)	77	5 (6.5)	0.001
Unknown	0	0	1	0	
Condom use with prostitutes§					
Never or occasionally	380	65 (17.1)	33	4 (12.1)	0.63
Usually or always	189	51 (27.0)	120	8 (6.7)	<0.001
Unknown	1	0	1	0	
Current partner's lifetime number of sexual partners					
1	611	105 (17.2)	241	13 (5.4)	<0.001
2–3	207	53 (25.6)	44	3 (6.8)	0.005
≥4	28	8 (28.6)	7	0	0.17
Unknown	1	0	0	0	

*Because of rounding, percentages may not total 100.

†Fisher's exact test was used to assess the association between penile HPV and circumcision status.

‡Subjects from Colombia and Spain were excluded.

§The analysis is limited to men who had had sex with prostitutes.

risk factor that was significantly associated with the risk of penile HPV infection was the number of sexual partners the men had had; as compared with men who had five or fewer partners, those who had had six or more partners had an odds ratio of 2.0 (95 percent confidence interval, 1.3 to 3.2).

The odds ratio for HPV infection among circumcised men, as compared with uncircumcised men, was similar after the exclusion of men from Spain and Colombia; these men did not undergo a medical examination of the penis (odds ratio, 0.56; 95 percent confidence interval, 0.20 to 1.56). The odds ratio was also not changed significantly by the exclusion of men from the Philippines, who represented 65.4 percent of all circumcised men in the study (odds ratio, 0.32; 95 percent confidence interval, 0.11 to 0.93).

Circumcision and Cervical Cancer

Male circumcision was associated with a moderate, but nonsignificant, decrease in the risk of cervical cancer in the men's female partners (odds ratio for self-reported circumcision, 0.72; 95 percent confidence interval, 0.49 to 1.04; odds ratio for clinician-confirmed circumcision, 0.69; 95 percent confidence interval, 0.43 to 1.11). There was no evidence of heterogeneity with respect to the location of the study ($P=0.41$), and the inverse association was not substantially altered by any of the characteristics of the wom-

TABLE 3. RISK OF CERVICAL CANCER IN FEMALE PARTNERS OF CIRCUMCISED MEN, AS COMPARED WITH THOSE OF UNCIRCUMCISED MEN, ACCORDING TO SELECTED CHARACTERISTICS OF THE WOMEN.

CHARACTERISTICS OF THE WOMEN	WOMEN WITH CERVICAL CANCER		CONTROL WOMEN		ODDS RATIO (95% CI)*
	CIRCUMCISED PARTNER	UNCIRCUMCISED PARTNER	CIRCUMCISED PARTNER	UNCIRCUMCISED PARTNER	
Overall	194	783	176	760	0.72 (0.49–1.04)
Study location†					
Brazil	3	69	6	70	0.41 (0.08–2.08)
Colombia	1	217	6	247	0.32 (0.04–2.88)
Thailand	22	205	18	156	1.04 (0.51–2.12)
Philippines	139	16	103	8	0.60 (0.22–1.65)
Spain	29	276	43	279	0.69 (0.38–1.25)
Age					
≤36 yr	59	249	53	259	1.25 (0.68–2.28)
37–48 yr	69	282	66	239	0.36 (0.18–0.73)
≥49 yr	66	252	57	262	0.63 (0.31–1.27)
Level of education					
Secondary school or higher	94	156	101	210	0.59 (0.30–1.16)
Primary school or less	100	625	75	549	0.82 (0.52–1.28)
Unknown	0	2	0	1	
Age at first sexual intercourse					
≥19 yr	142	509	153	596	0.84 (0.55–1.28)
≤18 yr	52	273	23	163	0.57 (0.27–1.19)
Unknown	0	1	0	1	
Lifetime number of sexual partners					
1	146	515	156	603	0.75 (0.49–1.14)
≥2	48	267	20	157	0.55 (0.24–1.24)
Unknown	0	1	0	0	
Condom use					
Yes	22	159	33	175	0.83 (0.37–1.87)
No	172	624	143	585	0.67 (0.44–1.02)

*In this analysis, the men's self-reported circumcision status was used. For all analyses the reference group is current stable female partners of uncircumcised men within the stratum. Models were adjusted for the study location, age of male and female subjects, male subjects' level of education, male subjects' age at first sexual intercourse, male subjects' frequency of genital washing after sex, male subjects' lifetime number of sexual partners, female subjects' lifetime number of sexual partners, and female subjects' age at first intercourse. None of the interaction terms between risk factors and circumcision status were statistically significant. CI denotes confidence interval.

†P for heterogeneity=0.41.

en that we assessed (Table 3). Results were similar after the exclusion of men from Spain and Colombia (odds ratio, 0.79; 95 percent confidence interval, 0.47 to 1.33) and after the exclusion of men from the Philippines (odds ratio, 0.76; 95 percent confidence interval, 0.51 to 1.15).

To minimize confounding as a result of the women's having had male partners other than the current partner, we restricted the analysis to the 1420 men whose female partner reported having had only one sexual partner. We also stratified this analysis according to several variables related to the male partner's sexual behavior in order to test the hypothesis that the reduction in the risk of cervical cancer would be greater among women whose male partners were at higher risk for HPV infection. As one measure of risk, we computed an index based on a man's age when he first had sexual intercourse and his total number of sexual partners. Men who had had six or more sexual partners and who had first had intercourse before the age of 17 years were considered to be at high risk; men who had had five or fewer sexual partners and who were at least 17 years of age when they first had intercourse were considered to be at low risk; and the remaining men were classified as being at intermediate risk.

The inverse relation between circumcision and the risk of cervical cancer was stronger and was significant in the case of women whose partners had a high risk index and who engaged in sexual practices known to increase the risk of exposure to HPV, such as having had intercourse before the age of 17 years, having had six or more sexual partners, and having a history of contact with prostitutes (Table 4). Tests for an interaction between circumcision status and the male part-

TABLE 4. RISK OF CERVICAL CANCER IN THE MONOGAMOUS FEMALE PARTNERS OF CIRCUMCISED MEN, AS COMPARED WITH THOSE OF UNCIRCUMCISED MEN, ACCORDING TO SELECTED CHARACTERISTICS OF THE MEN.*

CHARACTERISTICS OF THE MEN	MONOGAMOUS WOMEN WITH CERVICAL CANCER		MONOGAMOUS CONTROL WOMEN		ODDS RATIO (95% CI)†
	CIRCUMCISED PARTNER	UNCIRCUMCISED PARTNER	CIRCUMCISED PARTNER	UNCIRCUMCISED PARTNER	
Overall	146	515	156	603	0.75 (0.49–1.14)
Age at first sexual intercourse					
≥17 yr	121	315	132	424	0.89 (0.56–1.40)
≤16 yr	25	199	24	178	0.30 (0.09–1.06)
Unknown	0	1	0	1	
Test for interaction					P=0.27
Lifetime number of sexual partners					
1–5	70	127	90	272	1.40 (0.76–2.57)
≥6	74	377	65	325	0.42 (0.23–0.79)
Unknown	2	11	1	6	
Test for interaction					P=0.03
Sexual intercourse with prostitutes					
No	66	132	85	237	1.39 (0.70–2.74)
Yes	80	380	71	365	0.53 (0.30–0.94)
Unknown	0	3	0	1	
Test for interaction					P=0.32
Sexual-behavior risk index‡					
Low	66	111	82	255	1.61 (0.86–3.02)
Intermediate	58	213	57	183	0.50 (0.27–0.94)
High	20	179	16	159	0.18 (0.04–0.89)
Unknown	2	12	1	6	
Test for interaction					P=0.02
Test for trend					P<0.05

*Monogamous women were women who reported having had only one male partner.

†For all analyses the reference group is current stable female partners of uncircumcised men within the stratum. Models were adjusted for the study location, age of the male and female subjects, male subjects' level of education, male subjects' age at first sexual intercourse, male subjects' frequency of genital washing after sex, male subjects' lifetime number of sexual partners, and female subjects' age at first intercourse. CI denotes confidence interval.

‡High-risk men were those who had had six or more sexual partners and who had first had intercourse before the age of 17 years. Low-risk men were those who had had five or fewer sexual partners and who were at least 17 years of age when they first had intercourse. The remaining men were classified as being at intermediate risk.

ner's number of sexual partners and between circumcision status and the risk index were significant (P= 0.03 and P=0.02, respectively).

DISCUSSION

In our study, male circumcision was associated with a reduced risk of penile HPV infection in men. We also found an inverse association between circumcision and the risk of cervical cancer was significant among women whose male partners engaged in sexual practices known to increase the risk of infection with HPV, such as having had multiple sexual partners.

The assessment of the reliability and validity of self-reported circumcision status has yielded inconsistent results,[8,28-30] and potential misclassification of circumcision status with the use of this method has been a major concern in previous studies. One strength of our study is the high rate of accuracy of self-reported circumcision status. Medical examination of the penis, performed in 43 percent of the men, confirmed the self-reported circumcision status in 95 percent of those examined. Inverse associations with the risks of penile HPV infection and cervical cancer were similar when circumcision status was classified according to self-report or medical examination. Likewise, the exclusion of subjects who had not undergone a penile examination (men from Spain and Colombia) did not materially affect the findings.

A potential concern with respect to our study was the fact that 65 percent of the circumcised men were from the Philippines. This result was not unexpected, since mass circumcision sessions are regularly conducted by many organizations in that country and most boys are circumcised before puberty. We performed a secondary analysis excluding men from this study site and found that results were virtually unchanged.

Some studies have reported that genital warts are more common among uncircumcised men than among circumcised men,[4,5,30-33] but other studies have not confirmed these associations.[2,34-37] Epidemiologic evidence suggests that the absence of circumcision at birth and the presence of phimosis, poor genital hygiene, genital warts, and HPV infection are risk factors for penile cancer.[3,10,11,38,39] Other data have suggested that the risk of cervical cancer is reduced among the female partners of circumcised men, but these studies were limited by the small number of circumcised men or the low sensitivity of the methods used to detect HPV DNA.[40-42]

Little is known about the mechanisms by which removal of the foreskin may protect against HPV infection. Our data suggest that, even though circumcision increases the probability of maintaining good penile hygiene, there are other ways in which circumcision reduces the risk of penile HPV infection.

The penile shaft and the outer surface of the foreskin are covered by a keratinized stratified squamous epithelium that provides a protective barrier against HPV infection. In contrast, the mucosal lining of the prepuce is not keratinized and may be more vulnerable to the virus.[43] Since during intercourse the foreskin is pulled back, the inner mucosal surface of the prepuce is wholly exposed to vaginal secretions. HPV might be afforded access to the basal cells through minute ulcers or small epithelial abrasions.[44] Removal of the foreskin could minimize the probability of viral entry by markedly decreasing both the size of the surface area vulnerable to HPV and the likelihood of mucosal trauma during intercourse. The glans of a circumcised penis has a thicker, cornified epithelium, making it more resistant to abrasions and less susceptible to the entry of HPV. The only mucosal epithelium in a circumcised penis is in the distal urethra, a site known to contain comparatively few HPV-related lesions.[33]

Our finding that male circumcision may reduce the risk of cervical cancer in female sex partners is highly plausible for several reasons. First, circumcision is associated with a significant decrease in the risk of penile HPV infection. Second, and as indicated in further analyses of the same data, penile HPV infection is associated with a fourfold increase in the risk of cervical HPV infection in the female partner (data not shown). Third, cervical HPV infection is associated with a 77-fold increase in the risk of cervical cancer (data not shown).

In conclusion, our study has provided epidemiologic evidence that male circumcision is associated with a reduced risk of genital HPV infection in men and with a reduced risk of cervical cancer in women with high-risk sexual partners. Thus, circumcision can be considered an important cofactor in the natural history of HPV infection, since it may influence the risks of the acquisition and transmission of HPV as well as of cervical cancer. These findings are consistent with those of other studies that male circumcision is associated with a reduced risk of HIV infection,[7-9] penile cancer,[2,3] and a number of other common sexually transmitted diseases.[4,5] Given the worldwide effect of these diseases on public health, further study is needed to determine whether routine circumcision can reduce the risks of HIV and HPV infections and other sexually transmitted diseases.

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APPENDIX

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