THE MALE FACTOR IN THE ETIOLOGY OF CERVICAL CANCER AMONG SEXUALLY MONOGAMOUS WOMEN

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To address the hypothesis that male sexual behavior may affect the etiology of invasive cervical cancer, a case-control study was undertaken in Panama, Costa Rica, Colombia and Mexico. The study enrolled husbands of those women with invasive cervical cancer and of those age-matched controls who reported only one lifetime sexual partner. A total of 204 case and 485 control husbands (78% and 72%, respectively, of identified husbands) were interviewed, clinically examined, and had penile swabs taken for papillomavirus assays. Risk increased significantly ($p = 0.005$) with the number of sexual partners reported by the husband (RR = 2.0 for 26+ vs. <6 partners). Low educational status of the husband was also an important predictor of risk, possibly indicating the role of unmeasured aspects of sexual behavior. Visits to prostitutes, circumcision status and sexually transmitted disease histories were not important predictors of risk, but evidence from clinical examination indicated that poor genital hygiene may be involved. Human papillomavirus (HPV) expression as defined by filter *in situ* hybridization was detected in 20–23% of subjects and, except in the small group with both HPV types 6/11 and 16/18, was not related to risk. This may reflect sampling problems in the male or the importance of host factors which enhance viral carcinogenicity in the female.

Although the importance of a sexually transmitted agent in the etiology of cervical cancer is well recognized (Brinton and Fraumeni, 1986), most studies have focused on the sexual behavior of females, with little attention given to the contribution of their male sex partners. Indications that the male may play an important role derived initially from studies showing geographic clustering of cervical and penile cancer (Cartwright *et al.*, 1980; Li *et al.*, 1982; MacGregor and Innes, 1980) and elevated rates of cervical cancer among wives of penile cancer patients (Graham *et al.*, 1979; Martinez, 1969; Smith *et al.*, 1980). A follow-up study of the wives of men previously married to women with cervical cancer showed that the incidence of cervical abnormalities among these subsequent wives was greater than among control wives (Kessler, 1977). More recently, two studies have directly assessed the contribution of the male by comparing sexual behavior of the husbands of cervical cancer cases and of their controls. Buckley and others (1981) focused on the husbands of subjects who reported only one sexual partner, enabling assessment of the effects of male behavior independent of well-recognized female characteristics. Notably, husbands of cases more often reported multiple sexual partners, earlier ages at first intercourse, extramarital affairs and histories of sexually transmitted diseases. In a study among Hispanic immigrants to the San Francisco Bay Area (Zunzunegui *et al.*, 1986), a similar pattern of risk was observed, with husbands of cases being 5.3 times more likely than husbands of controls to report 20 or more sexual partners.

Skegg and others (1982) have proposed that the relative importance of the male factor will depend on the pattern of sexual behavior in society as a whole, and that the high incidence rates of cervical cancer in Latin America may relate to certain behaviors, including sexual relationships outside of marriage and visits to prostitutes. To address this hypothesis and to clarify "male factor" relationships suggested by previous studies, we undertook a large case-control study in four Latin American countries, including for study husbands of invasive cervical cancer patients and controls who reported only one lifetime sexual partner.

SUBJECTS AND METHODS

This study focused on the husbands of women who, in a case-control study of cervical cancer in Panama; Costa Rica; Bogota, Colombia; and Mexico City, reported only one lifetime sexual partner. Female cases consisted of women diagnosed with incident invasive cervical cancer during the period January 1, 1986 to June 30, 1987 at the Panamanian National Oncology Institute; three government referral centers in San Jose, Costa Rica; the Colombian National Cancer Institute in Bogota; and the Oncology Hospital of the Mexican Social Security System in Mexico City. All cancers were histopathologically confirmed and clinically staged. Cases who had received prior treatment, who were older than 69 years or who had not been residents of the defined study areas for at least 6 months were not enrolled in the study.

For each case, two age-matched (by 5-year age groups) female controls were randomly selected. In Panama and Costa Rica, one community and one hospital control were selected, while in Bogota and Mexico both controls were from hospitals. Hospital controls were selected in Panama and Costa Rica from inpatients at the primary referral hospital serving the area of residence of the cases; in Bogota from 8 tertiary level government hospitals; and in Mexico from 3 social security hospitals serving the population from which cases derived. Hospital controls were randomly selected from women admitted with non-gynecologic conditions; women with a previous diagnosis of cancer, who had undergone hysterectomy, or who were admitted with endocrine or smoking-related diseases were not eligible as controls. Community controls from Panama and Costa Rica were randomly selected from computerized census listings, which are updated every several years. An age-matched control was selected from a random censal segment in the same district of residence of each case. A short questionnaire was administered to all selected subjects and those found to have had a hysterectomy were replaced with another randomly selected woman.

Of the 766 patients and 1,532 controls eligible for study, 759 (99.1%) and 1,467 (95.8%) agreed to be interviewed. A total of 40.0% of the cases and 53.0% of the controls reported one lifetime sexual partner; monogamy rates among controls varied

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from 39.3% in Panama to 67.3% in Mexico. Forty-four monogamous cases and 102 monogamous controls were widows. Interviews were successfully completed with 204 (78.5%) identified case husbands and 485 (71.7%) control husbands. Non-response was accounted for by refusal (4.2% of cases vs. 11.7% of controls), inability to locate (14.2% vs. 12.9%), communication problems (1.2% vs. 1.8%), and other miscellaneous reasons (1.9% vs. 1.9%). Case vs. control husbands from each study area consisted of 53 vs. 104 from Bogota, 58 vs. 160 from Costa Rica, 45 vs. 123 from Mexico, and 48 vs. 98 from Panama.

Trained interviewers (usually male physicians) conducted a standard personal interview in a private setting in conjunction with a physical examination, usually at the subject's home or work place (mean interview time = 25 minutes). Interviews focused on socio-demographic factors, residential patterns, sexual behavior, genital hygiene, medical history, and family history of cancer. The physical examination included assessment of hygiene, circumcision status and stigmata of genital disease.

Material for human papillomavirus (HPV) DNA assays was collected using a cotton-tipped swab to gently scrape the coronal sulcus and another swab inserted into the urethral meatus. Both swabs were suspended in phosphate-buffered saline and stored at $-20°C$ until tested. HPV DNA was detected by the filter in situ hybridization method (Durst et al., 1983; Schneider et al., 1985) modified as detailed elsewhere (Caussy et al., 1988; Reeves et al., 1987). Cells from each sample were filtered onto 3 separate nitrocellulose papers. DNA-DNA hybridization was carried out at $42°C$ in 50% formamide ($Tm-17°C$) using pBR plasmid alone or with inserts of HPV-16 and 18 or HPV-6 and 11 DNA. The probes were labelled with ^{32}P dCTP to a specific activity of more than 1×10^8 cpm/g using a commercial nick-translation system (Bethesda Research, Gaithersburg, MD). After hybridization, the filters were washed 4 times for 1 hr at $65°C$ ($Tm-15°C$) and then exposed at $-70°C$ for 1 to 3 days to X-ray film, in a Kodak intensifying screen. All autoradiographs were examined independently by 3 observers and those specimens recorded as positive by at least 2 observers were considered positive. Specimens which reacted positively in the pBR322 assay (less than 2%) were considered separately in analyses.

To estimate the risk of cervical cancer associated with characteristics of husbands, odds ratios, as approximators of relative risks (RR), were calculated. Multivariate logistic regression was used to adjust for potential confounding variables (Breslow and Day, 1980), deriving maximum likelihood estimates of combined RRs and 95% confidence intervals (CI). Tests for trend in the logistic analyses were obtained by categorizing the exposure variable, and treating the scored variable as continuous. Conditional logistic regression was also undertaken (Lubin, 1981), but since this necessitated elimination of all unmatched elements and resulted in considerable loss of power, unmatched results have been chosen for presentation. Separate analyses were undertaken using only hospital or community controls, but since results were similar the 2 control groups were pooled.

RESULTS

Table I presents risks according to educational status and sexual behavior of the husbands. Education was significantly inversely related to risk, with the RR (adjusted for other factors) rising to 2.0 for those with 1–3 years of education compared to 10 or more years (p for trend = 0.02). After adjustment for education, there was a significant trend of increasing risk with number of sexual partners (p = 0.005), the reporting of more than 25 partners being associated with a risk of 2.0 (95% CI 1.2–3.4) compared to 5 or fewer partners. Risk in-

TABLE I – RELATIVE RISKS OF CERVICAL CANCER ACCORDING TO EDUCATION AND SEXUAL BEHAVIOR OF HUSBANDS

	Husbands		RR	(95% CI)
	Cases	Controls		
Education (years)				
10 +	26	92	1.00[1]	
7–9	27	53	1.81	(0.9–3.4)
4–6	76	182	1.62	(0.9–2.7)
1–3	56	118	2.03	(1.1–3.6)
None	19	40	2.24	(1.0–4.8)
Number of sexual partners				
1–5	39	128	1.00[2]	
6–10	53	128	1.40	(0.9–2.3)
11–25	54	125	1.54	(0.9–2.5)
26 +	58	104	2.04	(1.2–3.4)
Age at first sexual intercourse				
18 +	57	151	1.00[3]	
16–17	50	137	0.83	(0.5–1.3)
14–15	69	133	1.07	(0.7–1.7)
<14	28	64	0.87	(0.5–1.5)

[1]Adjusted for age (mean ages: cases = 49.2 years, controls = 49.6 years) and number of sexual partners.–[2]Adjusted for age and years of education.–[3]Adjusted for age, years of education, and number of sexual partners.

creased with number of partners in Bogota (RR = 2.7 for 26 + partners), Mexico (RR = 5.1), and Panama (RR = 2.3), although the relationship was not present in Costa Rica (RR = 1.1). When the reference group was changed to those with only 1 partner (5 cases, 22 controls), the trend became slightly stronger, the RR associated with more than 25 partners increasing to 2.8 (95% CI 1.0–8.0). Although there was a slight trend toward increasing risk with earlier ages at first intercourse, this was not significant and disappeared after adjustment for number of sexual partners.

Further analyses considered other measures of sexual activity, including frequency of intercourse, visits to prostitutes, and other specific sexual practices. There was no relationship of risk with usual frequency of sexual activity (Table II), or with frequency early in life or maximum frequency within any 10-year period (results not shown). Although a substantial proportion (61.0%) of subjects reported ever having visited a prostitute, this did not relate to risk (RR = 1.0). Neither total lifetime visits nor frequency of visits at various times were important predictors. There was some suggestion of decreasing risk with use of condoms (RR = 0.5 for frequent vs. no use), but frequent use was uncommon. Neither anal intercourse nor sexual relations with animals was associated with risk.

Table III presents risks associated with a variety of genital disorders. Although many of these were commonly reported, including genital warts (RR = 0.8), genital lice (1.4), gonorrhea (1.0) and syphilis (1.2), none of the specific conditions was associated with significant risk. In addition, vague symptoms such as lymphadenopathy, penile secretions, soreness when urinating, or genital ulcers/sores, were not predictive of risk. Bathing practices, including times of bathing per week, type of facilities, and frequency of washing the genitals, did not generally relate to risk, although frequent use of a bathtub was associated with a low risk (RR = 0.2, 95% CI 0.1–1.0) (Table IV). A problem with suspension of the foreskin was associated with a non-significantly increased risk (1.6, 95% CI 0.5–4.5), although based on small numbers.

A total of 47 case and 123 control husbands reported being circumcised (RR = 0.9). Limited concordance was found between self-reported circumcision status and clinical evidence, with the latter being associated with a RR of 1.1 (Table V). With the clinical examination as the standard, sensitivity of the interview information was 92% in the cases vs. 88% in the controls, while the specificity was lower (86% vs. 82%), i.e.,

TABLE II – RELATIVE RISKS OF CERVICAL CANCER ACCORDING TO SELECTED SEXUAL CHARACTERISTICS OF HUSBANDS

| | Husbands | | RR[1] | (95% CI) |
	Cases	Controls		
Average weekly frequency of sexual intercourse				
1	26	80	1.00	
2	54	105	1.56	(0.9–2.7)
3	56	144	1.11	(0.6–1.9)
4	31	75	1.14	(0.6–2.1)
5+	34	58	1.57	(0.8–3.0)
Unknown	3	23	0.36	(0.1–1.3)
Ever visit a prostitute				
No	63	156	1.00	
Yes	128	292	0.95	(0.6–1.4)
Unknown	13	37	0.98	(0.5–2.0)
Lifetime visits to prostitutes				
None	63	156	1.00	
<50	50	97	1.25	(0.8–2.0)
50–249	23	67	0.73	(0.4–1.3)
250+	55	128	0.78	(0.5–1.3)
Unknown	13	37	0.99	(0.5–2.0)
Anal intercourse				
Never	154	385	1.00	
Sometimes	50	100	1.11	(0.7–1.7)
With wife	24	46	1.19	(0.7–2.0)
Not with wife	26	54	1.04	(0.6–1.8)
Use of condoms				
Never	130	297	1.00	
Rarely	34	77	0.95	(0.6–1.5)
Sometimes	32	78	0.93	(0.6–1.5)
Frequently/always	7	30	0.52	(0.2–1.3)
Unknown	1	3	0.82	(0.1–8.1)
Sex with an animal				
No	181	442	1.00	
Yes	23	43	1.13	(0.6–2.0)

[1]Adjusted for age, years of education, and number of sexual partners.

TABLE III – RELATIVE RISKS OF CERVICAL CANCER ACCORDING TO HISTORIES OF GENITAL DISORDERS AMONG HUSBANDS

| | Husbands | | RR[1] | (95% CI) |
	Cases	Controls		
Genital warts				
No	195	459	1.00	
Yes	9	26	0.75	(0.3–1.6)
Genital lice				
No	169	424	1.00	
Yes	35	61	1.36	(0.8–2.2)
Gonorrhea				
No	152	374	1.00	
Yes	50	111	0.98	(0.6–1.5)
Unknown	2	0		
Syphilis				
No	196	469	1.00	
Yes	8	16	1.17	(0.5–2.8)
Lymphadenopathy				
No	163	403	1.00	
Yes	41	81	1.20	(0.8–1.8)
Unknown	0	1		
Penile secretions				
No	181	439	1.00	
Yes	23	46	1.22	(0.7–2.1)
Soreness when urinating				
No	139	355	1.00	
Yes	65	130	1.26	(0.9–1.8)
Genital ulcers or sores				
No	195	464	1.00	
Yes	9	20	1.02	(0.4–2.3)
Unknown	0	1		

[1]Adjusted for age, years of education, and number of sexual partners.

a significant relationship between risk of cervical cancer and sexual behavior of the male partner. By restricting our study to the husbands of those female subjects who reported only one lifetime sexual partner, we were able to assess risk in relation to male behavior unencumbered by the well-recognized effects of female sexual characteristics. A noteworthy finding was a

TABLE IV – RELATIVE RISKS OF CERVICAL CANCER ACCORDING TO GENITAL HYGIENE OF HUSBANDS

| | Husbands | | RR[1] | (95% CI) |
	Cases	Controls		
Times of bathing/week				
<3	24	53	1.00	
3–6	46	115	0.88	(0.5–1.6)
7–9	106	257	0.96	(0.5–1.7)
10+	28	60	1.06	(0.5–2.1)
Place of bathing				
Shower in home	139	351	1.00	
Shower outside	26	45	1.41	(0.8–2.4)
Bathtub in home	2	20	0.24	(0.1–1.0)
Spigot, well	14	24	1.34	(0.6–2.7)
Lake, river, stream	19	45	1.00	(0.5–1.8)
Other	4	0		
Wash genitals when bathing				
No	154	374	1.00	
Yes	50	109	1.14	(0.8–1.7)
Unknown	0	2		
Problems in suspending foreskin[2]				
No	149	345	1.00	
Yes	6	10	1.56	(0.5–4.5)
Unknown	2	7	0.59	(0.1–2.9)
Circumcised				
No	157	362	1.00	
Yes	47	123	0.88	(0.6–1.3)

[1]Adjusted for age, years of education, and number of sexual partners.
[2]Circumcised men excluded.

more individuals reported themselves circumcised than were found on examination. Clinical examination failed to find differences between case and control husbands with respect to evidence of phimosis. However, the detection of smegma under the foreskin was associated with a significantly elevated adjusted risk (1.5, 95% CI 1.0–2.3). The examination also assessed evidence of genital swelling, ulcers, chancres, warts, herpes, monilia, or discharge. These conditions were rarely found and were equally common among case and control husbands. When questioned about past infections, more case than control husbands reported a history of ulcers or chancres, although the association was not statistically significant (RR = 2.0, 95% CI 0.9–4.4).

DNA hybridization assays revealed evidence of positivity to HPV types 6/11 or 16/18 in 22.9% of the cases vs. 19.8% of the controls for whom valid results were available. Presence of HPV 6/11 or 16/18 DNA alone was not associated with elevated risk (RRs = 1.2 and 0.9, respectively), but a relationship was seen among the small number of husbands with both viral types (RR = 2.6, 95% CI 0.9–6.9). Further analyses, which considered associations according to degree of positivity (amount of signal) as well as the presence of other risk factors (e.g., number of sexual partners, educational level) did not reveal any further enhancements of risk.

Smoking and drinking on the part of the husbands were not related to risk of disease in the wives, even when the heaviest use was considered.

DISCUSSION

This study supports previous investigations in demonstrating

TABLE V – RELATIVE RISKS OF CERVICAL CANCER ACCORDING TO RESULTS OF THE PHYSICAL EXAMINATIONS OF HUSBANDS

	Husbands		RR[1]	(95% CI)
	Cases	Controls		
Circumcised				
No	174	409	1.00	
Yes	24	52	1.14	(0.7–1.9)
Unknown	6	24	0.66	(0.3–1.6)
Smegma				
No	150	381	1.00	
Yes	48	79	1.51	(1.0–2.3)
Unknown	6	25	0.63	(0.2–1.6)
Infection with HPV				
None	111	292	1.00	
Types 6/11 alone	11	24	1.25	(0.6–2.7)
Types 16/18 alone	14	39	0.91	(0.5–1.8)
Types 6/11 and 16/18	8	9	2.55	(0.9–6.9)
pBR +	3	10	0.83	(0.2–3.1)
No specimen	57	111	1.34	(0.9–2.0)

[1]Adjusted for age, years of education, and number of sexual partners.

significant increase in risk of cervical cancer with the number of sexual partners reported by the husband, more than 25 partners in a lifetime being associated with a 2-fold increase in risk when compared to 5 or fewer partners and a 3-fold increase in risk when compared to 1 partner. In contrast, no association of risk was noted with age at first sexual intercourse after number of partners was taken into account.

Our findings are in general agreement with those reported by Buckley *et al.* (1981) and Zunzunegui *et al.* (1986), although the strength of our association with number of partners is considerably less than in their studies. This difference may reflect a greater stability of our estimates, since the studies of Buckley and Zunzunegui included only 31 and 39 case husbands, respectively. In addition, our study enrolled incident invasive cervical cancer cases from defined high-risk populations, whereas the other studies included husbands of patients with both pre-invasive and invasive disease from less well-defined populations. Our estimates may, however, reflect misclassified reporting for the extreme categories of sexual partners (either high or low), resulting in a diminution of true risks. Alternatively, the risks could have been over-estimated, if female cases had incorrectly reported themselves as sexually monogamous, and if sexual behavior of the husbands and wives was correlated. Because we interviewed only the husbands of those women who reported one lifetime partner, we were unable to evaluate this possibility, but neither the study of Buckley nor that of Zunzunegui found support for such a bias. Thus, it would appear that our data support a contribution of male sexual behavior in the etiology of disease among their wives, although to a lesser extent than previously hypothesized (Skegg *et al.*, 1982).

In addition, risk of cervical cancer was found to relate to low educational status of the husband, and the relationship persisted after adjustment for a variety of factors, particularly specific sexual practices. Although this effect may represent a bias due to differential non-response, it is possible that low education is a surrogate for an unidentified aspect of sexual behavior. However, since we are unable to determine the extent of misclassification of number of sexual partners by educational status, the exact reasons for the elevated risk of cervical cancer among women with poorly educated husbands remains unresolved.

We were unable to relate risk to specific aspects of sexual behavior, such as visits to prostitutes, an association noted elsewhere (Buckley *et al.*, 1981; Zunzunegui *et al.*, 1986). This may reflect our inability to examine the number of different prostitutes or types of prostitutes visited (*i.e.*, streetwalkers, house prostitutes, cabaret entertainers), an important determinant of the prevalence of sexually transmitted diseases in Latin America (Reeves and Quiroz, 1987). Moreover, we did not find that risk related significantly to a history of sexually transmitted diseases, as reported by Buckley, which probably reflects the low educational status of our subjects and their lack of knowledge of general medical events. However, there was a suggestion, particularly from the physical examination, that poor hygiene might be involved, notably, a significantly increased risk related to presence of smegma under the foreskin (RR = 1.5). Other non-significant associations were histories of ulcers or chancres reported at the time of examination (but not at interview) and reported problems in suspending the foreskin while bathing.

Although an effect of male sexual behavior on cervical cancer risk was apparent in this study, it was disappointing that it could not be definitely related to HPV positivity, especially to types 16/18, putative agents for invasive cervical cancer. The only suggestion of a relationship was among the small subgroup of husbands with both HPV types 6/11 and 16/18. This could reflect a biologic effect of HPV types 6/11 on the expression of types 16/18, misclassification of types 16/18 as types 6/11, or merely chance. Given studies that have demonstrated a concordance of papillomaviral infection and intraepithelial neoplasia among sexual partners (Barrasso *et al.*, 1987; Campion *et al.*, 1985; Levine *et al.*, 1984), we would have expected higher rates of HPV positivity in general among our case husbands. However, HPV infection rates in our male subjects were considerably lower than those in women during a pilot phase of this study (Reeves and Quiroz, 1987). This may indicate either difficulties in obtaining appropriate samples from males, problems with the validity of the assay utilized, or the influence of host factors among females on viral susceptibility or persistence. Of specific interest among females are promotional effects of both herpesviruses and smoking on the carcinogenicity of papillomaviruses (zur Hausen, 1982).

Finally, in concordance with a previous investigation (Lilienfeld and Graham, 1954), circumcision status was difficult to define, because of variability in information obtained from subjects and clinical examinations, in the amount of foreskin present, and in the amount of foreskin removed at surgery. Circumcision status, however, did not appear to affect risk, either when we considered the information obtained from subjects or from clinical examinations. Although difficulties in assessing circumcision status as a risk factor were encountered in this study, we did not have the problem of many previous studies in considering circumcision status of multiple partners, since our focus was on women who presumably had had only one sexual partner. Thus, our data do not support the contention that circumcision affects the risk of cervical cancer.

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