Importance of Human Papillomavirus Endemicity in the Incidence of Cervical Cancer: An Extension of the Hypothesis on Sexual Behavior[1]

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Abstract

The risk of cervical cancer for a woman depends largely on the probability of being infected with some specific types of Human Papillomavirus (HPV). In the control groups of four case-control studies in Colombia and Spain we have shown a strong correlation between the number of sexual partners of males and females and HPV DNA prevalence in the genital tract. Our results suggest that the lifetime number of sexual partners in both sexes are surrogates of the probability of HPV infection and, as such, insufficiently explain the geographical variation in the incidence of cervical cancer. It is proposed that the high rates of cervical cancer in Latin America are linked to the largely unknown characteristics of the HPV endemicity in the population and to the absence of widespread screening for cervical neoplasia. Reliable surveys on the HPV prevalences in selected social groups (*i.e.,* young males and prostitutes) as well as in populations in countries at different risk of cervical cancer are required.

Introduction

In 1982 a model of cervical cancer etiology was proposed whereby the geographical variation in incidence, including the high rates in Latin America, and the downward trend in mortality over time could be largely explained by the sexual behavior of the male population (1) and its role in transmitting what was then an unidentified infectious agent.

According to the model, low risk for cervical cancer would be seen in countries in which both men and women were predominantly monogamous, designated type A. High risk countries, defined as type B, would be characterized by a high level of promiscuity (through sexual contact with prostitutes) among men, with monogamy (or smaller number of sexual partners) among women. A third pattern was proposed for "permissive" societies, type C, in which men and women had similar numbers of partners and the practice of prostitution was limited. Although not specifically stated, the implication of the paper was that the incidence of cervical cancer in the latter would be intermediate.

At the time there were no reliable data sets in which to test this hypothesis. Since 1982, several surveys on sexual habits have been reported from countries at high and low risk for cervical cancers. Furthermore, a specific etiological agent, HPV,[3] has been identified, and the association between the presence of HPV DNA in the genital tract and sexual behavior of both men and women can be investigated directly.

We examined different aspects of the sexual behavior in samples of the female and male population in Spain, a country at low risk for cervical cancer (age-adjusted incidence rates, 5–8/100,000/year) and in the city of Cali in Colombia, a country at a 6–8-fold higher risk (age-adjusted incidence rates, >45/100,000/year) (2). We conducted four concurrent case control studies on cervical neoplasia including the husbands or current male partners of the participant women. We report now on the sexual habits and on the correlation between the number of sexual partners and HPV DNA prevalence in the four control groups. Polymerase chain reaction-based hybridization methods have been used to detect HPV DNA.

Materials and Methods

Four case-control studies of cervical neoplasia were carried out in Spain and Colombia to identify risk factors and to explain the large difference in the incidence between the two countries. The study subjects were enrolled from June 1985 to December 1988 from nine provinces in Spain and the city of Cali in Colombia.

Cases were all women newly diagnosed with invasive squamous cell cancer or CIN III, resident in the study areas. In each country, controls for the invasive cases were women randomly sampled from the general population. Most of the CIN III cases were asymptomatic and identified through screening or family planning clinics; therefore, their controls were selected among women attending the

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[2] The abbreviations used are: HPV, human papillomavirus, STD, sexually transmitted disease.

Table 1 Mean age and sexual behavior among females and males in Spain and Colombia

	Spain		Colombia	
	Men	Women	Men	Women
Total number	323	480	253	448
Age, mean (SD)	45.5 (12.7)	44.1 (13.3)	46.2 (13.2)	42.1 (12.3)
No. of sexual partners (%)				
0	0	8 (1.7)	0	2 (0.4)
1	91 (28.4)	406 (84.6)	1 (0.4)	264 (58.9)
2–5	109 (34.1)	57 (11.9)	14 (5.9)	166 (37.1)
6–10	35 (10.9)	6 (1.3)	22 (9.2)	2 (0.5)
11–20	36 (11.3)	2 (0.4)	64 (26.8)	0
21–50	32 (10.0)	0	67 (28.0)	0
51–100	11 (3.4)	0	36 (15.1)	0
>100	6 (1.9)	1 (0.2)	35 (14.6)	14 (3.1)
Unknown	3		14	
Mean (SD)	12.2 (20.3)	1.6 (4.7)	39.5 (33.3)	5.1 (5.0)
Men contacts with prostitutes (%)				
None	153 (48.0)		51 (21.3)	
1	34 (10.7)		18 (7.5)	
2–5	58 (18.2)		40 (16.7)	
6–10	16 (5.0)		39 (16.3)	
11–20	26 (8.2)		23 (9.6)	
21–50	19 (6.0)		35 (14.6)	
51+	13 (4.1)		33 (13.8)	
Unknown	4		14	
Mean (SD)	8.0 (18.5)		20.1 (29.5)	
Women practice of prostitution (%)				
Ever		1 (0.2)		14 (3.1)
Never		479 (99.8)		434 (96.7)

same clinics and who had a normal Papanicolaou smear within the same week of the case. Controls were age and health center matched to the cases. Women with previous hysterectomy were excluded. Husbands or current sexual partners of cases and controls were also invited to participate. An interviewer-administered questionnaire was used to collect information on risk factors for cervical cancer, including sexual history, and among men, history of sexual contacts with prostitutes.

HPV DNA was detected in cervical scrapes and in cells collected from the distal urethra and the surface of the glans in men. The methods used to detect HPV DNA have been described (3). In brief polymerase chain reaction amplification was done using a mixture of HPV L1 consensus primers and β globin primers. Amplification was performed for 35 cycles. The amplification products were hybridized sequentially with probes for HPV 6, 11, 16, 18, 31, 33, 35 and β globin under high stringency conditions. Subsequently, the filters were screened with a generic probe which contained a mixture of amplimers of HPV 16 and 18. The primers for preparation of amplimers were kindly supplied by Dr. M. Manos.

Tests for linear trend across strata were calculated to asses the significance of the increasing HPV DNA prevalence with the categories of the variable of interest.

Results

Among women who participated as controls in the four studies and who had a husband at the time of the interview, the participation rate of the men was 67.4% in Spain and 71.9% in Colombia. Overall, 480 women and 323 male partners were included in the control groups in Spain, and 448 women and 253 male partners in Colombia.

Table 1 shows the mean age, distribution of the number of sexual partners, and prostitution experience of the control subjects by sex. In both countries, most women reported fewer sexual partners than their husbands. Lifetime female monogamy was predominant in Spain. The proportion of women reporting having ever practiced prostitution was 0.2% in Spain and 3.1% in Colombia ($P < 0.0001$). Men in Colombia reported a higher number of both sexual partners and contacts with prostitutes than men in Spain. Never sexual contacts with prostitutes was reported by 48.0% of Spanish male participants *versus* 21.3% in Colombia ($P < 0.0001$), and the average number of prostitute contacts was 2.5-fold higher in Colombia (Spain, 8.0 *versus* Colombia, 20.1; $P = 0.07$).

Fig. 1 shows the distribution of the reported number of partners among men and women in each country according to the format suggested by Skegg *et al.* (1).

Table 2 shows the prevalence of HPV DNA in cytological specimens from the genital tract by sexual history. The prevalence of HPV DNA in cervical scrapes was about 5% in Spain and 13% in Colombia ($P = 0.0003$). After combining the data from both countries, the HPV prevalence among women reporting ever practicing prostitution (based on 12 individuals) was 50.0% as compared to 8% among those who never practiced ($P = 0.0001$). Among men, the HPV prevalences were 3.6% in Spain and 18.7% in Colombia ($P = 0.00005$). In both sexes there is a significant correlation between number of partners and the prevalence of HPV DNA (tests for trend, $P < 0.01$). However,

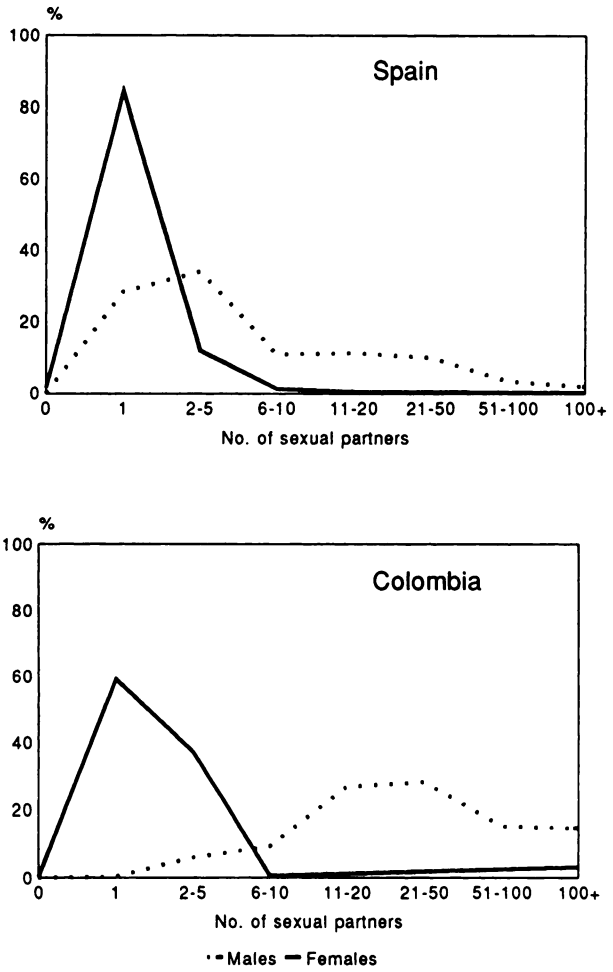

Fig. 1. Lifetime number of sexual partners (%) in Colombia and Spain.

among men, the number of HPV-positive individuals is small, and the statistical test is not significant when broken down by country.

Table 3 shows the correlation between number of partners of the husband and the HPV prevalence in the cervix of their wives. HPV DNA prevalence tended to increase with male sexual promiscuity in all subsets. The association is stronger and statistically significant when the analyses are restricted to self-reported monogamous women. In contrast, there is not clear association between HPV prevalence in women and the number of their husband's partners who were prostitutes.

Discussion

The major advance in the understanding of the epidemiology of cervical neoplasia has been the recent demonstration that a few HPV types play a key etiological role (4, 5, 6, 7). The number of sexual partners of men and women is associated with cervical cancer largely as a surrogate measure of HPV infection (8, 9). In this report we used data collected in four studies in Spain and Colombia to estimate the strength of the correlation between the HPV prevalence and the number of sexual partners and to test to what extent male

Table 2 HPV DNA prevalence by number of sexual partners and sex[a]

	Spain HPV+/tested (+%)[b]	Colombia HPV+/tested (+%)	Total HPV+/tested (+%)
Women			
No. of partners			
1	12/278 (4.3)	21/179 (11.7)	33/457 (7.2)
2–5	2/45 (4.4)	13/115 (11.3)	15/160 (9.3)
6+	2/4 (50.0)	6/14 (42.9)	8/18 (44.4)
Total	16/327 (4.9)	40/308 (13.0)	56/635 (8.8)
	$P = 0.003$	$P = 0.09$	$P = 0.0002$
Prostitution			
Never	16/327 (4.9)	34/296 (11.5)	50/623 (8.0)
Ever	0/0	6/12 (50.0)	6/12 (50.0)
		$P = 0.002$	$P < 0.001$
Men			
No. of partners			
1	1/52 (1.9)	0/1 (0.0)	1/53 (1.9)
2–10	2/76 (2.6)	5/18 (27.8)	7/94 (7.4)
11+	3/39 (7.7)	18/98 (18.4)	21/137 (15.3)
Unknown	0/1	1/11	1/12
Total	6/168 (3.6)	24/128 (18.7)	30/296 (10.1)
	$P = 0.16$	$P = 0.53$	$P = 0.003$
No. of contacts with prostitutes			
0	2/88 (2.3)	7/27 (25.9)	9/115 (7.8)
1–5	1/44 (2.3)	6/32 (18.7)	7/76 (9.2)
6+	3/35 (8.6)	11/60 (18.3)	14/95 (14.7)
Unknown	0/1	0/9	0/10
Total	6/168 (3.6)	24/128 (18.7)	30/296 (10.1)
	$P = 0.13$	$P = 0.46$	$P = 0.11$

[a] *P*-values correspond to a χ^2 test for heterogeneity between two categories or to a test for trend across categories.
[b] HPV+, HPV positive.

sexual behavior can predict the high incidence rates of cervical cancer in some populations in Latin America.

Of concern was the possibility that self-reported number of partners was exaggerated or underreported. We had the opportunity to test serum specimens from all study participants for antibodies against common STDs and there was a significant correlation between the seroprevalence of any single antibody and the reported number of partners. The correlation was consistent among men and women and was interpreted as an indirect confirmation of the accuracy of the questionnaires (10).

The controls included in these studies were recruited from two different sources as described in "Materials and Methods." Controls in the studies of invasive cancer were a sample of the underlying population that generated the cases, whereas the controls of the CIN III studies were recruited among participants in screening or family planning clinics. Separate analyses were initially conducted and yielded identical results; therefore, we merged the two data sets (of about equal size) in each country and we present here the combined results by country.

Patterns of Sexual Behavior in Spain and Colombia. Men in Colombia report higher numbers of partners and greater frequency of contacts with prostitutes than Spanish men. These results are consistent with the hypothesis that male promiscuity in Latin America plays a crucial role in cervical cancer etiology. However, women in Colombia also reported more partners than Spanish women and in both countries, the average number of partners of the males was 7–8-fold higher than the average number of partners of the women. The most obvious difference between the

Table 3 Number of partners of the husband and HPV DNA prevalence of the wives[a]

Husbands sexual behavior	Spain HPV positive/all (%)	Colombia HPV positive/all (%)	Total HPV positive/all (%)
No. of sexual partners			
1	2/68 (2.9)	0/1 (0.0)	2/68 (2.9)
2–10	5/109 (4.6)	1/22 (4.5)	6/131 (4.6)
11+	3/59 (5.1)	13/136 (9.6)	16/195 (8.2)
All	8/236 (3.3)	14/159 (8.8)	24/394 (6.1)
P	0.55	0.9	0.08
No. of sexual partners (only monogamous wives)			
1	2/66 (3.0)	0/1 (0.0)	2/67 (3.0)
2–10	4/93 (4.3)	0/16 (0.0)	4/109 (3.7)
11+	3/49 (6.5)	11/92 (11.9)	14/141 (9.9)
All	9/208 (4.3)	11/109 (10.1)	20/317 (6.3)
P	0.4		0.029
No. of sexual partners being prostitutes			
0	4/113 (3.5)	3/35 (8.6)	7/148 (4.7)
1	1/27 (3.7)	2/9 (22.2)	3/36 (8.3)
2–10	3/55 (5.4)	3/55 (5.5)	6/110 (5.4)
11+	2/41 (4.9)	6/60 (10.0)	8/101 (7.9)
All	10/236 (4.2)	14/159 (8.8)	24/395 (6.1)
P	0.7	0.9	0.4

[a] *P*-values correspond to a χ^2 test for trend.

two countries is that in Colombia, the number of partners of both sexes are 3-fold higher on average. The curves in Fig. 1 suggest a shift to the right in the Colombian distributions rather than a different pattern. These results indicate that a high rate of sexual contacts with new partners is of relevance in explaining the 6–8-fold higher incidence of cervical cancer in Colombia as compared to Spain.

In our studies, the sexual behavior pattern in Spain seems to be broadly similar to the pattern in Colombia and both are closest to model B under the hypothesis of Skegg *et al.* (1). Under Skegg's model the population of Spain, a country with one of the lowest incidence rates of cervical cancer, should behave as a type A country with a low number of partners among men and a ratio to the female number of partners close to one. In contrast, we observed among men a much higher number of sexual partners (average 12.2; SD, 20.3) and a 6–7-fold ratio to the number of sexual partners of women. In Spain, about 70% of the women recruited from the general population reported never having had a screening test (8); therefore, the low rates in the incidence of cervical cancer cannot be attributed to high rates of screening coverage.

The lifetime number of partners thus appears to have limitations in predicting cervical cancer incidence, as other surveys have also revealed. The mean number of partners reported in France was 11.0 for men and 3.3 for women (ratio, 3.3) (11). In Britain, corresponding figures were 9.9 and 3.4 (ratio, 2.9), (12) and in Denmark 13.5 and 6.1 (ratio, 2.2) (13). Despite having similar average number of partners among males, lower averages in females, and male:female ratios in the number of partners lower than Spain, the age-adjusted incidence rate of cervical cancer in these countries are consistently higher than the Spanish rates (France, 12.3–16.2; Britain, 11.7; Denmark, 18.5; Spain, 5.7–7.7) (2).

Number of Sexual Partners and HPV Prevalence. To the extent that the number of sexual partners is a surrogate for the probability of HPV infection, the strength of the association between the number of partners and the incidence of cervical cancer will depend on the underlying correlation between number of partners and HPV prevalence.

Within populations, it seems clear both in this and other case control studies (9) that the number of partners is a key determinant of HPV prevalence among females and a good surrogate in predicting incidence of cervical cancer.

The predictions based on the number of partners are less good between the two countries in our study. Table 2 shows that only 15% of males reporting more than 11 sexual partners are HPV positive (thus potential vectors of HPV) and that 50% of the prostitutes are HPV positive. It is conceivable that a small number of male partners in a country (or population group) where HPV is common might represent the same risk of infection for a woman as a greater number of partners from countries (or populations) with lower HPV endemicity. Other studies have also indicated that the number of partners of the husbands is a crude measure of the risk of cervical neoplasia because of the different risk conveyed by existing sub populations of "high risk" males (14). If HPV prevalence varies across populations independently of the number of partners, the models proposed by Skegg et al. (1) will not fully explain the geographical variation in the incidence of cervical cancer. Our data show that this is true especially in the proposed role of male contacts with prostitutes. As shown in Table 3, the number of the husbands' partners who were prostitutes did not influence the HPV DNA prevalence in their wives.

Among women without cervical cancer and their husbands, HPV DNA prevalence was 2.7- and 5.2-fold times more common in Colombia than in Spain, respectively. These prevalences, although they correlate well with the differences between the two countries in incidence of cervical cancer, are difficult to interpret. They may represent transient HPV infections (particularly among the young), reactivation of latent infections, or chronic viral persistence. We know little about the dynamics of the HPV infection in men and women. The role of variables like age at infection, number of episodes or intensity of the HPV infection, the duration of infectivity after exposure, or the risk factors for HPV cronification are largely ignored. To these biological sources of variability we should add the complexity of the sexual behavior patterns in the community, which may lead to differences in the prevalence of HPV by age and social groups. Some of these variables might be as relevant as the number of partners to predict the risk of cervical cancer in a given population.

The Decreasing Trend in Cervical Cancer Mortality. In European countries, there has been a steady decrease in both incidence and mortality from cervical cancer for the last 50 years, although recent increases in mortality among young women have been reported (15, 16). Time trends in cervical cancer mortality are difficult to interpret in etiological terms without considering concurrent changes in sexual behavior and on screening and treatment practices.

From descriptive statistics we could predict that socioeconomic development is linked to cervical cancer mortality, since declines in the latter have only been confirmed in developed countries. Increased screening and better treatment might offer a reasonable explanation for mortality reduction, at least in the recent third of the century. Surveys on sexual behavior over time tend to indicate that prostitution patronage has decreased in Europe (17, 18). However,

the hypothesis linking reduced prostitution activity to the pronounced decreasing trend in cervical cancer mortality remains difficult to test. There is no documented evidence as to the evolution over time of the prevalence of HPV genital infections.

The Role of Other Risk Factors for Cervical Cancer. The prevalence of risk factors for cervical cancer other than HPV is strikingly different between populations and may represent important determinants of the geographical variation in the incidence of cervical cancer. Early age at first intercourse and at first birth, multiparity, and the prevalence of several STDs are all more common in developing countries which are in turn at higher risk for cervical cancer than developed countries (19). Other factors, such as sexual hygiene, gynecological care of infectious diseases, screening, and nutrition status might contribute to the low rates of cervical cancer in developed countries. In our case-control studies, we collected information on the prevalence of all established risk factors for cervical cancer (7, 20). A comparison between the two control groups indicated that the significant differences were related to measures of sexual behavior (number of partners of the women, early age at first intercourse, and higher prevalence of seropositivity to common STDs). These were all more common in Colombia and the differences were statistically significant. The prevalence of smoking was inconsistent across generations. Controls of invasive cancer were more often smokers in Colombia (39.6% in Colombia *versus* 16.8% in Spain; $P < 0.0001$) and the opposite was true among controls of CIN III (34.4% in Colombia *versus* 43.4% in Spain; $P = 0.03$).

The role of most of these factors is difficult to assess from studies conducted in developed countries where the majority of the population has access to fresh foods, high levels of genital hygiene, and medical care. In contrast, studies from China (21) and Africa (22) have reported associations of cervical cancer with poor hygiene and with increased number of genital infections even after consideration is given to HPV status.

In summary, the variation in the number of sexual partners does not fully explain the geographical and temporal variations in the incidence of cervical cancer. The characteristics of the HPV endemicity such as the age, sex and social group distribution, and perhaps its HPV type-specific variation, as well as the background level of exposure to other risk factors, might also be important predictors of the geographical variation in cervical cancer incidence.

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