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# Risk Factors for Invasive Carcinoma of the Uterine Cervix in Latin America<sup>1</sup>

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*A study of 759 cervical cancer patients, 1,430 controls, and 689 sex partners in four Latin American countries has made it possible to assess the influence of multiple factors upon the risk of invasive cervical cancer. The principal risk factors identified were the woman's age at first coitus, the number of her steady sex partners, her number of live births, the presence of DNA from human papillomavirus (HPV) types 16 or 18, a history of venereal disease, nonparticipation in early detection programs, and low socioeconomic status. There is good reason to believe that extensive detection programs directed mainly at high-risk groups in the Americas can reduce the high incidence of cervical cancer in this Region.*

Cancer of the uterine cervix causes more than 30,000 deaths per year among women in the Americas (1), despite the fact that a large number of the deaths from this disease can be avoided by early detection (2). Indeed, the incidence in Latin America continues to be several times higher than that observed in developed countries, and the highest levels in the world have been observed in

Latin American cities (1). A series of circumstances—relating to culture, education, and access to health services—that affect vast sectors of these populations expose many women to certain high-risk etiologic factors and probably explain the persistently high incidence of this disease within the Region.

Cancer of the uterine cervix is considered a sexually transmitted disease (3, 4),

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as evidenced by its absence among virgins and its high incidence among women who start having sexual relations young or who report having a large number of sex partners (5). Recently, the human papillomaviruses have been recognized as possible transmissible carcinogenic agents (6). However, these viruses are not found in all tumorous lesions and are often found in healthy women, which suggests that their presence is neither necessary nor sufficient for tumor development. Also, their exact means of transmission is not known, and it is probable that they interact in as yet undefined ways with other factors such as hormones and tobacco byproducts. However, laboratory techniques for studying these viruses are still in the developmental stage, and none of those currently available can be considered ideal.

Other identified risk factors include a woman's number of pregnancies (7, 8), low socioeconomic status (9), smoking practices (10, 11), use of oral contraceptives (12), and lack of certain nutrients (13, 14). Certain characteristics of sex partners, mainly with regard to their role as possible carriers of an etiologic agent, are also considered probable determinants of risk (15, 16). In sum, many factors are involved in the etiology of this neoplasm; and even though a great deal of research has revealed valuable information about several of these factors, the specific manner in which they interact is still unknown.

To help define the specific risk factors (including the "male factor") responsible for the high incidence of invasive cervical cancer in Latin America, and to clarify interactions among the different factors, our group carried out a study of cases and controls in four different areas. This study obtained detailed information about the study subjects' demographic, sexual, reproductive, medical, and dietary histories as well as about their hy-

gienic practices, tobacco consumption, and participation in early cervical cancer detection programs. Similar information was obtained from the partners of women who said they had had only one sex partner, and biological samples were obtained from all the study subjects to determine whether or not DNA from human papillomaviruses was present in their genitals. This article summarizes the findings of that research, a more detailed account of which may be found in other publications (17-22).

## MATERIALS AND METHODS

### Cases

Patients with a recent diagnosis of invasive carcinoma of the uterine cervix were identified before they received treatment in four geographic areas of Latin America—Mexico City, Mexico; Costa Rica (the entire country); Panama (the entire country); and Bogotá, Colombia—during the period January 1986-June 1987. Patients under 70 years old who had lived in one of the study areas for at least six months were considered eligible for inclusion in the study. Their cases were detected by medical personnel at the main hospitals for cancer patients in each study region, these being (1) the Hospital Nacional de Oncología in Mexico City, (2) the Hospital San Juan de Dios, the Hospital México, and the Hospital Calderón Guardia in Costa Rica, (3) the Instituto Nacional de Oncología in Panama, and (4) the Instituto Nacional de Oncología in Bogotá.

### Controls

For each case, two controls were selected. In Bogotá and Mexico City these controls were both hospital patients, while in Costa Rica and Panama one was

a hospital patient and one was a member of the study subjects' community. The control subjects were matched to cases by age group, within a five-year range. Replacements were found for potential controls with a previous history of cancer or hysterectomy.

Hospital controls were selected at random from lists of inpatients at hospitals located in the areas where the study subjects resided, excluding those with neoplastic, endocrinologic, nutritional, psychiatric, circulatory, gynecologic, or smoking-related disorders.

The geographic and organizational characteristics of health services in Costa Rica and Panama made it possible to use community controls. These were randomly selected from the census list applicable to each study subject's area of residence.

Hospital and community controls who refused to be interviewed were not replaced.

### Data Collection

A personal interview was conducted with each participant. In addition to obtaining detailed demographic, sexual, reproductive, medical, and socioeconomic data, the interview gathered specific information on the subject's employment history and her dietary, contraceptive, and hygienic practices. The average duration of the interview was one hour. All the interviewers were given the same training and carried out their interviews in private areas under strict national and international supervision.

A total of 766 eligible cases were identified during the study period, and interviews were conducted with 759 of these patients (99.1%). Out of 1,532 eligible hospital controls, 1,467 (95.8%) were interviewed. Failure to obtain information from study subjects and controls was due to death (0.4% among cases versus 0%

among controls), refusal to participate (0% versus 2.7%), hearing and speech problems (0.3% versus 0.7%), mental incompetence (0.1% versus 0.5%), and change of residence (0.1% versus 0.5%). In order to adjust both for age at first sexual contact and number of sex partners, virgins were excluded from the analysis, 37 controls being excluded for this reason. Overall, therefore, 759 cases and 1,430 controls were included in the analysis.

Information on the histology of the tumorous lesion was obtained from 728 (95.9%) of the study subjects. This information indicated that 92% of the lesions were epidermoid carcinomas and 8% were adenocarcinomas.

### Sex Partners

In order to analyze the "male factor" and isolate it from the effect of the woman's sexual behavior, the study included sex partners of those participants who said they had had only one sex partner (40% of the cancer patients and 52.8% of the controls). Forty-four monogamous patients and 102 monogamous controls said they were widows. Interviews were conducted with 204 partners of patients (corresponding to 78.5% of the living subjects), and 485 were conducted with partners of controls (71.1% of the living subjects). Failure to obtain information was due to refusal (involving 4.2% of the patients' partners versus 11.7% of the controls' partners), inability to locate individuals (14.2% versus 12.9%), communication problems (1.2% versus 1.8%), and other reasons (1.9% versus 1.9%).

The interviewers, most of them male physicians, conducted an interview with each male participant to obtain information on sociodemographic factors, sexual and medical history, genital hygiene, and family history of cancer, after which they performed a physical examination with

emphasis on the genital area in order to assess hygiene, circumcision, and signs of venereal disease. The interviews lasted an average of 25 minutes.

### **Detection of Human Papillomavirus (HPV)**

To determine the presence of HPV, at the time of the interview a swab of the tumorous lesion was obtained from each cancer patient and an endocervical swab was obtained from each control. In all, 99.6% of the interviewed patients and 95.4% of the interviewed controls agreed to have these samples taken. In the case of male participants, a cotton tip applicator was used to obtain a smear from the coronal sulcus and another from the distal urethra.

Samples were obtained from 97.5% of the patients' husbands and 95.2% of the controls' husbands. These samples were preserved in phosphate-buffered saline (PBS), frozen as soon as possible, and maintained at  $-20^{\circ}\text{C}$  until they could be tested in the laboratory. The tests were conducted using filter in situ hybridization, modified as described in another publication (18). This procedure detects specific sequences of viral DNA, permitting the identification of viral types. In our tests, DNA segments from HPV types 16 and 18 or HPV types 6 and 11 were used. The tests were carried out under stringent hybridization conditions, and results were recorded as marginally positive (+/-) or definitely positive.

### **Statistical Analysis**

In order to estimate the risk associated with different factors, odds ratios were calculated as approximations of relative risk (RR) (23). An RR of 1.5 indicates that the incidence of the disease is 1.5 times greater in the group exposed to the factor

than in the unexposed group; in other words, the risk is increased 50%.

Unconditional logistic regression was used to adjust for possible confounding variables (variables simultaneously related to the factor under study and to the disease), and estimates of maximum RR probability were obtained with 95% confidence intervals (24). Trend tests were carried out as part of these logistic regression analyses, categorizing the variable under study and treating it as a continuous variable. In addition, logistic regression was used to test the statistical significance of interactions on a multiplicative scale.

## **RESULTS**

Community and hospital controls were combined for the analysis, since no significant differences were found between the two types of controls with regard to the prevalence of diverse risk factors.

Table 1 shows certain basic demographic characteristics of the participants (their basic geographic distribution, age distribution, and religious affiliations). The average age of both the patients and the controls was 46.5 years.

The relative risks shown later (in Tables 2, 3, 4, 6, and 7) are first adjusted solely for age, to show the effect before the inclusion of the confounding variables, and are then presented adjusted for confounding variables—the latter RRs being generally smaller than the former and showing the effect of the variable under study independent of the other factors.

### **Sexual Behavior**

The average age at first coitus was 17.4 years for the patients and 18.8 for the controls. As shown in Table 2, early initiation of sexual relations was associated with risk of cancer of the uterine cervix.

**Table 1.** Basic demographic characteristics of the cervical cancer patients and control subjects.

Variables	Cases		Controls	
	No.	%	No.	%
<i>Location:</i>				
Bogotá	214	28.2	416	29.1
Costa Rica	192	25.3	372	26.0
Mexico	155	20.4	294	20.6
Panama	198	26.1	348	24.3
<i>Age:</i>				
<35	128	16.9	237	16.6
35–44	217	28.6	424	29.6
45–54	200	26.4	364	25.5
≥55	214	28.2	405	28.3
<i>Religion:</i>				
Catholic	661	87.1	1,278	89.4
Other	86	11.3	135	9.4
None	12	1.6	17	1.2

The group at greatest risk consisted of women who said they had had their first coitus at age 14 or 15 (adjusted RR = 1.8, 95% CI = 1.3–2.4), as compared to those who said they had it at age 20 or older. Among the women who started to have sexual relations before the age of 14, no increased risk was observed after adjustment for major variables. Restricting the analysis to monogamous women and adjusting the estimated risk for the number of sex partners of the husbands yielded the same associations between cervical cancer risk and age at first coitus.

Having multiple sex partners was also associated with increased risk. Women who reported having six or more partners had an adjusted relative risk of 1.7 in comparison to monogamous women. This risk clearly rose as the number of steady sex partners (in relationships lasting three months or longer) increased, and the trend was significant ( $p < 0.0001$ ). On the other hand, no association whatever was found with the number of nonsteady partners. Anal sexual relations were related with an RR of 1.5

for women who reported having this experience once in their lives and an RR of 1.9 for those who reported having it more than once.

### Reproductive Factors

The average number of pregnancies was 6.8 among the patients versus 5.5 among the controls. In general, study participants with a larger number of pregnancies started to have sexual relations earlier, but they also had a more frequent history of cervical cytology. Because of this, when adjusted estimates were made for these factors as well as for other variables, the result was only minor reductions in risk estimates. Overall, a linear trend of increasing risk was observed as the number of pregnancies rose ( $p < 0.001$ ), to a point where women with 14 or more pregnancies had an RR of 5.1 (95% CI = 2.7–9.7) in comparison with those reporting 0–1 pregnancies. These relative risk estimates were essentially unchanged when nulliparous women were excluded.

**Table 2.** Relative risks of invasive cervical cancer associated with sexual behavior.

	Cases	Controls	RR <sup>1</sup>	RR <sup>2</sup>	95% CI
<i>Age at first sexual contact:</i>					
≥ 20	170	521	1.0	1.0	
18–19	139	284	1.5	1.2	0.9–1.7
16–17	189	303	1.9	1.3	1.0–1.8
14–15	217	233	2.9	1.8	1.3–2.4
< 14	42	84	1.5	1.1	0.7–1.7
p for trend			<0.0001	0.0007	
<i>Total number of sex partners:</i>					
1	303	783	1.0	1.0	
2–3	340	489	1.8	1.6	1.3–2.0
4–5	65	92	1.8	1.4	1.0–2.1
≥ 6	51	64	2.1	1.7	1.1–2.5
p for trend			<0.0001	0.0009	
<i>Number of steady sex partners:<sup>3</sup></i>					
0–1	416	1,015	1.0	1.0 <sup>4</sup>	
2	203	270	1.8	1.5	1.2–2.0
3	90	93	2.3	2.0	1.4–2.9
4	30	27	2.7	1.8	1.0–3.3
> 4	19	19	2.4	2.0	1.0–4.3
p for trend			<0.0001	<0.0001	
<i>Number of nonsteady sex partners:</i>					
0	561	1,068	1.0	1.0 <sup>5</sup>	
1	101	181	1.1	1.1	0.8–1.5
2	35	71	0.9	1.0	0.6–1.6
3–4	26	57	0.9	0.9	0.5–1.5
≥ 5	35	47	1.4	1.1	0.7–1.9
p for trend			0.45	0.85	
<i>Frequency of anal sexual relations:<sup>6</sup></i>					
Never	631	1,248	1.0	1.0	
Once	35	44	1.6	1.5	0.9–2.6
More than once	88	103	1.7	1.9	1.3–2.6
p for trend			0.0002	0.0003	

<sup>1</sup> Adjusted for age, unknowns excluded.

<sup>2</sup> Adjusted for age, number of sexual partners, age at first sexual contact, presence of HPV DNA, time elapsed since last Pap smear, number of pregnancies, and socioeconomic status.

<sup>3</sup> In relationships lasting 3 months or more.

<sup>4</sup> RR<sup>2</sup> also adjusted for number of nonsteady sex partners.

<sup>5</sup> RR<sup>2</sup> also adjusted for number of steady sex partners.

<sup>6</sup> Including only women with at least one steady sex partner.

The chief determinant of this high risk was the number of live births. Accordingly, as can be seen in Table 3, women with 12 or more live births had an RR of 3.7 (95% CI = 2.0–6.7) in comparison to those with 0–1 live births. On the other hand, no relationship was found between relative risk and the number of stillbirths, spontaneous abortions, or induced abortions.

A history of cesarean section was associated with reduced risk. Although we did not have information on the number of cesarean sections, it was noted that among women with only one term pregnancy (18 patients, 86 controls) none of the patients had a history of cesarean section, as compared with 27% of the controls.

A history of prenatal care was also as-

sociated with reduced risk (RR = 0.8, 95% CI = 0.6–1.0). However, no such reduced risk was found to be associated with use of vitamins or home remedies during pregnancy. We did not find any indication that continuation of sexual relations up to the third trimester or resumption in the first or second month after delivery had any effect on risk. All associations observed with reproductive factors were independent of the detec-

tion of DNA from human papillomavirus and the other factors related to sexual activity.

### Detection of Human Papillomavirus

DNA from HPV types 16 or 18 was detected in 62% of the patients and 32% of the controls. Table 4 shows that the risk of cervical cancer was significantly associated with a positive response to the test

**Table 3.** Relative risks of invasive cervical cancer associated with reproductive history.<sup>1</sup>

	Cases	Controls	RR <sup>2</sup>	RR <sup>3</sup>	95% CI
<i>No. of live births:</i>					
0–1	39	146	1.0	1.0 <sup>4</sup>	
2–3	152	387	1.5	1.8	1.2–2.8
4–5	180	334	2.1	2.2	1.4–3.5
6–7	148	211	2.9	2.8	1.8–4.5
8–9	99	145	3.0	2.6	1.6–4.4
10–11	70	101	3.2	2.2	1.3–3.8
≥ 12	57	53	5.0	3.7	2.0–6.7
p for trend			<0.0001	0.0001	
<i>No. of stillbirths:</i>					
0	672	1,257	1.0	1.0 <sup>5</sup>	
1	64	101	1.2	1.1	0.8–1.6
≥ 2	9	19	0.9	0.7	0.3–1.7
<i>No. of spontaneous abortions:</i>					
0	456	896	1.0	1.0 <sup>6</sup>	
1	159	284	1.1	1.2	0.9–1.5
2	77	116	1.3	1.3	0.9–1.9
≥ 3	53	81	1.3	1.3	0.8–1.9
<i>No. of induced abortions:</i>					
0	704	1,306	1.0	1.0 <sup>7</sup>	
1	22	47	0.9	0.9	0.5–1.5
≥ 2	19	24	1.5	1.5	0.8–2.9
<i>History of cesarean section:</i>					
No	668	1,164	1.0	1.0 <sup>8</sup>	
Yes	74	197	0.6	0.7	0.5–1.0
<i>History of prenatal care:</i>					
No	284	398	1.0	1.0 <sup>8</sup>	
Yes	461	979	0.6	0.8	0.6–1.0

<sup>1</sup> Including only women who reported having been pregnant.

<sup>2</sup> Adjusted for age, unknowns excluded.

<sup>3</sup> Adjusted for age, number of sexual partners, age at first sexual contact, presence of HPV (16 or 18) DNA, time elapsed since last Pap smear, and socioeconomic status.

<sup>4</sup> Also adjusted for number of stillbirths, spontaneous abortions, and induced abortions.

<sup>5</sup> Also adjusted for number of live births, spontaneous abortions, and induced abortions.

<sup>6</sup> Also adjusted for number of live births, stillbirths, and induced abortions.

<sup>7</sup> Also adjusted for number of live births, stillbirths, and spontaneous abortions.

<sup>8</sup> Also adjusted for number of pregnancies.

**Table 4.** Relative risks of invasive cervical cancer associated with marginally positive (+/-) and definitely positive DNA hybridization from HPV types 16/18 and 6/11 in female study participants.<sup>1</sup>

	Cases	Controls	RR <sup>2</sup>	RR <sup>3</sup>	95% CI
<i>HPV types 16/18:</i>					
Negative	273	833	1.0	1.0	
+/-	109	173	1.9	2.2	1.6-2.9
Positive	339	219	4.8	5.2	4.1-6.6
<i>HPV types 6/11:</i>					
Negative	595	1,143	1.0	1.0	
+/-	77	59	2.5	2.1	1.5-3.1
Positive	49	23	4.1	4.2	2.4-7.2

<sup>1</sup> Thirty-eight cases and 205 controls were eliminated because they did not provide samples or those provided were technically inadequate.

<sup>2</sup> Adjusted for age.

<sup>3</sup> Adjusted for age, number of sexual partners, age at first sexual contact, number of pregnancies, time elapsed since last Pap smear, and socioeconomic status.

for DNA from HPV types 16 or 18—the relative risk being 2.2 for a marginally positive (+/-) response and 5.2 for a clearly positive response.

DNA from HPV types 6 or 11 was detected in far lower percentages of study participants (17% of the patients and 7% of the controls), but it likewise was associated with increased risk (RR = 4.2 for clearly positive responses, 95% CI = 2.4-7.2).

As can be seen in Table 5, no association was found between other risk factors and detection of the virus—that is, the virus was detected, among controls, with roughly the same frequency regardless of education, number of sex partners, age at first coitus, or number of live births. Rates of positivity increased only slightly with age. Significant interactions were not observed between presence of the virus and the number of sex partners, age at first coitus, previous use of oral contraceptives, or smoking, although the smoking data suggest that those who smoked 10 or more cigarettes per day and tested positively for HPV (types 16 or 18) were at high risk of cervical cancer (see below).

**Table 5.** The percentages of controls in various risk categories testing positively for HPV 16/18. The percentages (adjusted for the controls' age and excluding unknowns) include both marginally and definitely positive results.

Risk factors	% of controls positive for HPV 16/18
<i>Age:</i>	
< 40	29.7
40-49	28.5
50-59	34.6
≥ 60	39.1
<i>Education:</i>	
≥ 7 years	31.1
1-6 years	32.0
None	31.6
<i>Number of sexual partners:</i>	
1	34.3
2	32.3
3	26.0
≥ 4	27.3
<i>Age at first sexual contact:</i>	
≥ 20 years	33.6
18-19 years	35.1
16-17 years	30.8
< 16 years	26.4
<i>Number of live births:</i>	
0-3	32.9
4-7	29.9
≥ 8	34.4



## Smoking

Smoking was more common among younger women and people who reported early initiation of sexual activity, several sexual partners, alcohol consumption, or a history of venereal disease. Eighteen percent of the patients and 16% of the controls said they were smokers at the time of the interview.

Smaller percentages said they smoked more than 20 cigarettes a day or had smoked for more than 20 years.

After adjustment for the confounding factors, it was found that risk of cancer of the uterine cervix was not significantly associated with most measures of smoking (Table 6). An RR of 1.7 was observed (95% CI = 1.1-2.6) among women who said they acquired the smoking habit af-

**Table 6.** Relative risks of invasive cervical cancer associated with various factors.

	Cases	Controls	RR <sup>1</sup>	RR <sup>2</sup>	95% CI
<i>Smoking:</i>					
Never	523	1,028	1.0	1.0	
Former smoker	102	168	1.2	1.1	0.8-1.4
Smoker	134	234	1.1	1.1	0.8-1.4
<i>Cigarettes per day:</i>					
Nonsmoker	523	1,028	1.0	1.0	
< 20	183	329	1.1	1.1	0.8-1.3
≥ 20	53	73	1.4	1.1	0.7-1.7
p for trend			0.06	0.55	
<i>Years of education:</i>					
≥ 10	62	230	1.0	1.0	
7-9	65	140	1.7	1.2	0.8-1.9
4-6	252	483	2.1	1.1	0.7-1.6
1-3	230	353	2.7	1.1	0.7-1.7
None	149	223	2.8	1.0	0.6-1.6
<i>No. of listed facilities<sup>3</sup> in the home:</i>					
6	220	654	1.0	1.0	
4-5	322	511	1.9	1.5	1.2-1.9
≤ 3	217	265	2.4	1.6	1.2-2.0
<i>Length of oral contraceptive use:<sup>4</sup></i>					
None	568	1,072	1.0	1.0	
< 5 years	101	204	0.9	1.1	0.8-1.5
5-9 years	61	101	1.1	1.4	1.0-2.1
≥ 10 years	27	51	1.0	1.3	0.8-2.3
p for trend			0.76	0.50	
<i>Time elapsed since last Pap smear:<sup>5</sup></i>					
< 2 years	123	384	1.0	1.0	
2-3 years	109	345	1.0	0.9	0.7-1.3
4-5 years	45	84	1.7	1.6	1.0-2.5
≥ 6 years	66	139	1.6	1.5	1.0-2.2
Never done	372	409	3.0	3.0	2.3-4.0
Not known	44	69			

<sup>1</sup> Adjusted for age, excluding unknowns.

<sup>2</sup> Adjusted for age, number of sexual partners, presence of DNA from HPV types 16/18, time elapsed since last Pap smear, number of pregnancies, and socioeconomic status.

<sup>3</sup> Including electricity, indoor sanitary facilities, kitchen, refrigerator, radio, and television.

<sup>4</sup> Excluding cases and controls for whom the duration of use was unknown.

<sup>5</sup> Excluding cytology done in the year immediately preceding the diagnosis or interview.

ter age 30. Among women who tested positive for HPV 16 or 18, smokers of 10 or more cigarettes per day were at increased risk (RR = 1.7) when compared to nonsmokers, while no associations of intensity of smoking with risk of cervical cancer were observed among HPV negative women (RR = 0.8). The interaction term, however, was not significant. This effect was also restricted to women who started to smoke after age 30.

### Other Risk Factors

Table 6 also shows that higher risks were found among women with relatively lower levels of education, and that those reporting no school attendance had an RR of 2.8 in comparison to those who received 10 or more years of education. However, when the adjustment was made for the various confounding variables, this association was no longer evident.

Another variable was developed that took into account a series of socioeconomic indicators—including access to indoor sanitation, electricity, a kitchen, a refrigerator, radio, and television. Access to a smaller number of such facilities was significantly associated with higher risk, even after the estimates were adjusted for confounding variables.

A total of 191 patients (25.2%) and 357 controls (25.0%) said they had used oral contraceptives at some time. Despite the fact that a slight increase in risk was observed among persons using oral contraceptives for prolonged periods, no significant trend was observed relative to the duration of oral contraceptive use. In the group of patients with adenocarcinomas, a history of oral contraceptive use was related to higher risk (RR = 2.2, 95% CI = 1.2–4.2), but the duration of oral contraceptive use was not associated with increased risk.

The use of condoms was not associated with the risk of invasive cervical cancer, and a slight protective effect (data not shown) disappeared when adjustments were made for confounding factors.

A history of sexually transmitted disease of some kind (including gonorrhea, syphilis, herpes, genital warts, crab lice, and "other" ailments) was associated with an adjusted RR of 1.8 (95% CI = 1.2–2.5).

Fifty percent of the controls reported having had a cervical cytology, versus only 28% of the patients, yielding a crude RR of 2.5 (95% CI = 2.1–3.0). A history of Pap smears was more frequent among younger, more educated women, and among women who used contraceptives or had a history of pregnancy or venereal disease. However, risk estimates for variables related to a history of no previous cervical cytology did not change when adjustments were made for the effects of other factors. As compared with women who reported having had cytology done between one and two years before the diagnosis or interview, those who reported having had it done two or three years before the interview did not exhibit greater risk. However, women who reported having had their last test four or more years previously showed an increased risk on the order of 50%, while those who reported never having had a smear exhibited a relative risk of 3.0 (a 200% increase).

### The Male Factor

Table 7 shows estimates of relative risk relating to the education and sexual behavior of the partners of monogamous women. A significant inverse relationship was found between the partner's education and risk, the adjusted RR being 2.0 for women whose partners said they had one to three years of education

**Table 7.** Relative risks of invasive cervical cancer associated with monogamous women's male partners—in terms of the male partners' education, sexual behavior, and physical examination results.

	Partners of patients	Partners of controls	RR	95% CI
<i>Education:</i>				
≥ 10 years	26	92	1.0 <sup>1</sup>	
7–9 years	27	53	1.8	0.9–3.4
4–6 years	76	182	1.6	0.9–2.7
1–3 years	56	118	2.0	1.1–3.6
None	19	40	2.2	1.0–4.8
<i>No. of sex partners:</i>				
1–5	39	128	1.0 <sup>2</sup>	
6–10	53	128	1.4	0.9–2.3
11–25	54	125	1.5	0.9–2.5
≥ 26	58	104	2.0	1.2–3.4
p for trend			0.005	
<i>Age at first sexual contact:</i>				
≥ 18	57	151	1.0 <sup>3</sup>	
16–17	50	137	0.8	0.5–1.3
14–15	69	133	1.1	0.7–1.7
< 14	28	64	0.9	0.5–1.5
<i>No. of visits to prostitutes:</i>				
None	63	156	1.0	
< 50	50	97	1.3	0.8–2.0
50–249	23	67	0.7	0.4–1.3
≥ 250	55	128	0.8	0.5–1.3
Unknown	13	37	1.0	0.5–2.0
<i>Circumcised (data from physical examination):</i>				
No	157	362	1.0	
Yes	47	123	0.9	0.6–1.3
<i>Presence of smegma:</i>				
No	150	381	1.0	
Yes	48	79	1.5	1.0–2.3
Unknown	6	25	0.6	0.2–1.6

<sup>1</sup> Adjusted for age (mean age of patients' partners = 49.2 years and of controls' partners = 49.6 years) and number of sex partners.

<sup>2</sup> Adjusted for age and years of education.

<sup>3</sup> Adjusted for age, years of education, and number of sex partners.

as compared to women whose partners said they had 10 years or more (p for trend = 0.02).

After adjustment for education, there was a significant trend toward increased risk according to the number of sex partners reported (p = 0.005), and women whose partners reported having over 25 sex partners had an RR of 2.0 when com-

pared with those whose partners reported having five sex partners or less.

This risk associated with the man's number of sex partners did not change when further adjustments were made for a series of risk factors involving the female patients and controls, but the association with education was no longer evident (data not shown). No relationship

was found between risk and the male partner's frequency of sexual relations, visits to prostitutes, anal sexual relations, sexual relations with animals, or age at which sexual relations began. A history of circumcision was as frequent among the male partners of the patients as among those of the controls, and no significant differences were found between the two groups regarding the presence of phimosis, hygienic practices, or prior histories of venereal disease, alcoholism, or smoking.

About a fifth of the husbands of monogamous women (22.9% of the patients' husbands and 19.8% of the controls' husbands) tested positively<sup>11</sup> for some type of HPV. No significant relationship was found between positive test findings and the risk of cancer among their partners, nor was any association found between positive test results in male participants and positive test results in their female partners.

## DISCUSSION

### Early Sexual Activity

Early initiation of sexual relations was associated with increased risk of invasive cervical cancer regardless of the number of sex partners and other confounding factors, including the male factor. During adolescence the squamocolumnar junction moves toward the endocervix through a process of epithelial metaplasia (in which the cylindrical epithelium is replaced by flat stratified epithelium) comprising what is called the transformation zone, which is where most neoplasms of the uterine cervix originate. Most epidemiologic studies show an increased risk of neoplasms of the uterine cervix in

women who started sexual relations during adolescence (25–28), and the theory has been advanced that during adolescence the uterine cervix is particularly susceptible to carcinogens associated with coitus (29, 30).

Areas of atypical metaplasia have been observed more frequently in the uterine cervix of sexually active adolescents than in virgins (31), and it has recently been suggested that the rapid proliferation of cells infected with papillomavirus during this period of great regenerative activity could lead to the lateral expansion of cells carrying the viral genome (32). The research reported here provides evidence supporting the existence of a vulnerable period, suggesting that early sexual relations is probably one of the factors determining the high incidences of uterine cervical cancer observed in Latin America.

Although the highest risks were observed among women who said they started coitus at 14–15 years of age, those who started earlier did not appear to be at high risk. The average age of onset of menstruation was 13.5 years for the cases and likewise 13.5 years for the controls. The lack of unusually high risk experienced by those who started sexual relations prior to age 14 could relate to a possible need for hormonal factors to be present in order for a carcinogenic effect to be produced—or it could reflect other sociocultural characteristics of this group.

### Number of Sex Partners

The number of sex partners was also related to increased risk. Women who said they had six or more partners had an RR of 1.7 in comparison to monogamous women, and the observed risk was similarly high for those with two or three partners (see Table 2). This finding is consistent with previous research (33–36)

<sup>11</sup> These figures include both marginally (+/-) and definitely positive results.

and is interpreted as pointing to the existence of a sexually transmitted agent.

Within this context, it is interesting to note that the number of steady sex partners (in relationships lasting three months or more) was more directly associated with risk than the number of nonsteady partners. This could be explained by a possible need for repeated or prolonged exposure to a partner carrying an infectious agent in order to produce disease. Alternatively, the risk might be diminished by adoption of measures (such as the use of condoms) intended to prevent impregnation or transmission of venereal diseases by nonsteady partners—as has been seen recently in the case of human immunodeficiency virus transmission (37). Although the explanation of this phenomenon is not obvious, another recent study also found no association between risk of invasive cervical cancer and the number of nonsteady sex partners (8).

The frequency of sexual relations has been studied by a number of investigators, most of whom have concluded that this factor is not related to risk of cervical cancer (8, 26, 28, 38). In both the present study and one by other authors (39), the frequency of sexual relations has been associated with increased risk only among women who reported having sexual relations on a comparatively frequent basis before the age of 20 (RR = 1.5, 95% CI = 1.2–2.2 for seven or more times a week versus once a week or less), which again supports the theory of a vulnerable period.

### The Role of Coitus

Various carcinogenic mechanisms have been proposed to explain the association between coitus and the risk of cervical cancer. The most accepted theory is that an infectious agent, probably HPV, is transmitted from an infected male to his

partner. However, if transmission occurred with one single exposure, we should not expect the number of steady sex partners to be more significant than the total number of partners. An alternative explanation is that the infectious agent is not always transmissible, and because it has a cyclic pattern of infectivity, it is generally transmitted only after repeated exposures.

Other theories relating to the role of coitus take into account possible carcinogenic effects of human semen. It has been observed that basic proteins in human semen can alter epithelial and subepithelial cells and induce neoplastic changes (40). In this regard, a recent study has shown that protamine from human and animal semen can produce transformations of epithelial cells from the human uterine cervix *in vitro* (41). However, support for this notion is weakened by a general lack of evidence linking the frequency of sexual relations to increased risk.

The finding of somewhat elevated risk associated with the practice of anal sexual relations could simply reflect other factors related to the sexual behavior or hygienic practices of the women and male partners involved.

### Parity

Most previous studies have ruled out parity as a risk factor in cervical cancer, attributing the associations observed to aspects related to sexual activity (42–45). Only recently has consideration been given to the interrelation of these variables (and of vaginal cytology) with reproductive factors.

In the present study, after adjustments were made for multiple confounding factors, a strong linear relationship was found between risk and the number of births. Indeed, it was found that women reporting 10 or more live births had a risk

of developing the disease that was four times greater than the risk of those reporting only one or no live births.

It should be noted that several recent studies have detected increased risk associated with multiparity after adjusting for multiple factors (8, 46). The potential for detecting an association of this type is clearly greater in a population—such as the Latin American population—experiencing a relatively large number of births per subject. Thus, the failure of previous studies to detect increased risk associated with multiparity might be due to the small number of women with multiple pregnancies in their study samples.

Cervical neoplasms occur most frequently on the anterior lip of the cervix, which is the site of most obstetric trauma (47), and the reduction of risk associated with a history of cesarean section, although possibly reflecting social status, also suggests an effect resulting from the trauma associated with vaginal delivery. In animal models it has been observed that wounds act as agents that stimulate carcinogenesis (48). Such wounds might also favor access of infectious agents, such as papillomaviruses, to the basal layers of the epithelium; ensuing scarring might encourage viral multiplication by increasing local blood flow (49).

In addition, pregnancy has been associated with a state of immunosuppression (50) that may increase susceptibility to infectious agents. Pregnant women have high detection rates in papillomavirus tests (51, 52), mainly during the third trimester (52), and although this study did not find an association between the number of births and detection of HPV types 16 or 18 DNA, our data do not rule out the possibility of a synergistic effect between the persistence of HPV DNA and pregnancy, since the women studied were not pregnant when the tested tissue sample was taken.

Another explanation for these findings might be that pregnancy has an adverse effect through hormonal mechanisms. Although cervical cancer is not usually recognized as a hormone-dependent tumor, hormone receptors have been found in both normal and cancerous tissue of the uterine cervix (53, 54), and several recent studies suggest an association between prolonged use of oral contraceptives and the risk of cervical cancer (55–57). These hormonal factors might also be responsible for the increased detection of HPV during pregnancy. In the present study, even though use of oral contraceptives was neither frequent nor significantly associated with risk, the subject's number of pregnancies was associated with greater risk among oral contraceptive users than among nonusers. Moreover, the risk effect from the number of pregnancies was greater among premenopausal women (who have higher hormone levels) than it was among postmenopausal women.

Finally, the associations between risk and parity might be explained by dietary factors, particularly the folate depletion that occurs with each pregnancy (58). Megaloblastic characteristics in epithelial cells of the uterine cervix, as well as low levels of serum folate, have been observed among oral contraceptive users, and supplementation of folates has led to improvement of cervical dysplasias (59, 60). However, a relationship between folate deficiency and risk of neoplasms among nonusers of oral contraceptives has not been demonstrated.

The strong influences of high parity demonstrated in this study point up a need to reexamine effects of reproductive factors on cervical cancer risk, especially among populations where multiple births are common and other risk factors do not sufficiently explain the high cancer incidences observed.

## Human Papillomavirus

A heterogeneous group of papillomavirus strains has been strongly implicated in the etiology of preneoplastic lesions of the uterine cervix, vulva, and penis. DNA from HPV is commonly detected in malignant tumors of these organs, and some of these agents have a recognized ability to transform cells *in vitro*. For this reason, HPV is considered a probable etiologic agent for cancer of the uterine cervix (6). However, the technology for studying HPV strains is still in the developmental stage, and many aspects of the interaction of the virus with the human host and other risk factors remain unknown.

To date, the study reported here is the largest case-control study that has included detection of viral DNA. Our tests detected HPV DNA types 16 or 18 in 448 (62%) of the cancer patients studied, a proportion reasonably similar to those found by studies using biopsy material that were carried out in Brazil (35%), Panama (60%), and Peru (73%) (61-63).

Viral genetic material from HPV types 16 or 18 was also detected in 392 (32%) of the controls. This percentage is higher than the percentages of normal women yielding positive responses in population studies using the same laboratory methodology, notably in Germany (2%-13%) (64) and Denmark and Greenland (6%-13%) (65), but lower than the 84% of normal women recently yielding positive responses in England—who were tested using a new laboratory method (66). These variations may reflect different prevalences of HPV infection, or they may simply reflect the use of different laboratories and methods.

Despite the high rate of HPV detection in our healthy controls, detection of HPV types 16 and 18 was strongly associated with increased risk of cervical cancer. The

possibility that the virus is more easily detectable in actively proliferating epithelia might account for these findings, or perhaps the viral infection is a necessary but not sufficient condition for the development of neoplasias (32).

As stated earlier, sexual behavior was a risk factor for cervical cancer but not for detection of HPV DNA—contrary to the assumption that this infectious agent is transmitted in a manner similar to other venereal disease agents. In this regard, it is interesting to point out that other investigators recently failed to find any association between sexual behavior and HPV (67). It is probable that transmission occurs through coitus, but other aspects of coitus need to be studied in order to understand the mechanisms involved.

In addition, it is possible that the presence of HPV DNA, detected by means of the technique employed here, does not reflect all the infections present but merely those latent or persistent infections being expressed at the time of the test. In addition, the degree to which the HPV genome's state of expression may affect the results of the various hybridization tests is unknown.

The hybridization tests used in our study also detected papillomavirus types 6 and 11 in a certain percentage of the participants, and the presence of these viral types was also associated with higher risk of cervical cancer. This finding is difficult to interpret, since the specificity of the tests used is unknown. Thus, in order to define the role of these viruses in the etiology of cervical cancer, a more sensitive and specific test needs to be utilized. The potential offered by the polymerase chain reaction (PCR) technique, which is capable of amplifying specific DNA sequences, has not yet been established despite initial reports attributing greater sensitivity and specificity to it than to the tests currently available (68).

## Smoking

A series of studies have demonstrated an association between smoking and cervical cancer or its precursor lesions, mainly among women who smoke heavily or for extended periods (69-72). However, smoking among women is also associated with other risk factors, primarily those related to sexual behavior, making it difficult to separate the two effects. Several recent studies that have taken these other factors into account have found a persistent risk remaining among smokers (72, 73).

In our study, relatively few of our female subjects were smokers, and no significant association was found between a history of smoking and risk of cervical cancer. Nevertheless, it is worth noting that in women testing positively for HPV types 16 or 18 an association was found between increased risk of squamous carcinoma and the number of cigarettes smoked per day, suggesting a synergistic interaction between papillomavirus and tobacco use, as has been suggested elsewhere (74).

## The Male Factor

Our results with respect to the "male factor" provide some evidence of a link between the sexual behavior of the partners of monogamous women and those women's risk of cervical cancer, but the association was not nearly as strong as that presumed at the beginning of this study and documented by previous authors (15, 75). This difference could reflect a greater stability of our estimates due to the larger size of the sample, or it could reflect the fact that our investigation of this matter was limited to the partners of monogamous women, men who in turn may have been "low-risk" partners. Nevertheless, persistence of the associations between risk and the men's

number of female sex partners, even after adjustment for the risk factors of their wives, suggests that male sexual behavior has an effect on the risk of cervical cancer, albeit to a lesser extent than suggested previously (16).

Despite the fact that more than 60% of our male participants said they had visited a prostitute at some time, we did not detect any cervical cancer risk associated with this factor, unlike previous studies (15, 75). A possible explanation may be that we do not have detailed information about the types of prostitutes visited, a distinction that might be a factor in the transmission of sexually transmitted diseases according to a study done in Panama (76).

Also, we found no evidence of increased risk of cervical cancer associated with a history of venereal disease in the women's partners. This finding could have been influenced by the interview subjects' low levels of education and their limited understanding of medical events in general. However, some evidence obtained during the physical examination suggests that hygienic aspects could be related to risk (RR of 1.5 for the presence of smegma under the prepuce).

Although we found that the male factor contributed somewhat to the risk of cervical cancer, it appears that this factor might not be specifically associated with the presence of papillomavirus, principally types 16 or 18. Several studies have been consistent in finding an association between papillomavirus infection and the presence of intraepithelial neoplasia in male sex partners (77-80). Therefore, we had expected more positive tests for HPV in the partners of the patients or controls who tested positive for HPV. The result observed could reflect difficulties in obtaining proper samples from male participants, problems with the validity of the hybridization tests con-



ducted, or the influence of host factors in women upon their susceptibility to the virus or its persistence.

Circumcision was difficult to define, and there were also differences between circumcision declared and circumcision observed during the physical examination, as has been reported elsewhere (81). However, circumcision, as cited by participants and identified during the physical examination, was not associated with increased risk of cervical cancer. Within the context of this study, which was limited to patients with a single sex partner, circumcision does not appear to play any role in the risk of cervical cancer.

## CONCLUDING REMARKS

Overall, this study found that early initiation of sexual relations and the number of a woman's stable sex partners were significantly associated with the risk of cervical cancer in the study population. In addition, a woman's number of live births was found to be an independent risk factor that had not been clearly recognized earlier—one that calls for attention from the point of view of program planning.

A positive test for HPV DNA was associated with an increased risk of cervical cancer but not with sexual activity. The precise role of this virus in the etiology of cervical cancer has not been resolved, and laboratory methods available for its study are still in the experimental stage. Certain evidence of interaction has been found between smoking and the presence of papillomavirus, although in general smoking was not found to be associated with increased risk.

It is also possible that some dietary factors play a role in the risk of cervical cancer. As part of our investigation, a dietary interview was conducted and blood samples were taken to determine micronutrients present in the blood of the cases and

controls. The results of this analysis will be the subject of a subsequent publication.

The number of sex partners reported by a woman's male partner was found related to risk in monogamous women, but only after 25 or more partners, and no relationship was found between visits to prostitutes or other aspects of male sexual behavior.

A history of a previous Pap smear was found to protect against invasive cervical cancer at any age and in any subgroup exposed to risk, presumably through the resulting elimination of precursor lesions. The results indicate that women who have never had vaginal cytology are in greatest danger and should probably be given priority in detection programs. Although many risk factors of this disease have roots in sociocultural conditions, the transformation of which is a relatively slow and complex process, broad health education and early detection programs aimed at covering the entire female population, particularly the groups at greatest risk, could significantly reduce the incidence of cancer of the uterine cervix in Latin America.

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### *Fellowships for Research on Tropical Diseases*

The Social Research Laboratory of the Central University of Venezuela, with support from the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR), is developing a fellowship program to promote research. Grants of up to US\$5,000 will be given to investigators studying the social and economic aspects of the transmission and control of six diseases included in the TDR program: malaria, filariasis, leishmaniasis, leprosy, schistosomiasis, and Chagas' disease. The research is to be carried out in the country of residence of the investigator, generally within a one-year period.

Priority will be given to proposals that address priority problems in a country, promote community participation, and seek to coordinate biomedical and social science knowledge. Institutional contacts with the governmental agencies responsible for disease control should be maintained. The fellowships are particularly intended for graduate students and young researchers affiliated with recognized academic institutions, as well as personnel engaged in research in public health agencies and nongovernmental organizations. Exceptionally, undergraduate students working under qualified mentors may be considered.

Evaluation of proposals will take place in May and November each year. Proposals may be presented in English, French, Portuguese, or Spanish, but correspondence must be in Spanish. For more detailed information on the presentation of proposals, contact Dr. Roberto Briceño-León, Laboratorio de Investigaciones Sociales, Universidad Central de Venezuela, Apartado Postal 47795, Caracas 1040-A, Venezuela; telephone (02) 622-6970.

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