Socioeconomic Differences in Cervical Cancer: Two Case–Control Studies in Colombia and Spain

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ABSTRACT

Objectives. This study examined the causes of socioeconomic differences in invasive cervical cancer in two countries that differ substantially in cervical cancer incidence and economic development.

Methods. Data were derived from two case–control studies carried out in Spain and Colombia; there were 373 case subjects, 387 control subjects, and 425 husbands interviewed with a structured questionnaire. Exfoliated cells were obtained from cervical or penile scrapes and tested for human papillomavirus (HPV) DNA.

Results. Relative to better educated women, women with low educational levels in both countries reported fewer Pap smears and had a higher prevalence of HPV DNA. The prevalence ratio of HPV DNA across educational strata was twofold in Spain and fourfold in Colombia. In both countries, husbands of poorly educated women reported higher use of prostitutes than husbands of better educated women. In Colombia, 30% of husbands of poorly educated women harbored HPV DNA, compared with 10% of husbands of better educated women.

Conclusions. Socioeconomic differences in invasive cervical cancer could be partly explained by differences in the prevalence of HPV DNA and by a lower use of preventive care. (*Am J Public Health.* 1996; 86:1532–1538)

Introduction

Invasive cervical cancer is characterized in most populations by a higher incidence among the socially less privileged.[1–3] Several attempts to explain this association have shown contradictory results. In the United Kingdom and in France, women with low socioeconomic status were younger at first sexual intercourse but had a lower number of partners than women with higher socioeconomic status.[4–6]

Infection by certain types of human papillomavirus (HPV) is now accepted as the major cause of cervical cancer, and proxy measures of sexual behavior, such as number of sexual partners or age at first sexual intercourse, are largely considered surrogates of HPV infection.[7–9] Recent studies indicate that randomly selected women with normal cervical cytology living in countries with high incidence of cervical cancer have higher prevalence of HPV DNA in cervical cells compared with women living in low-risk countries.[9,10] It is still unclear whether the higher rates of the disease among the poor at the community or the individual level can be fully explained by a higher prevalence of HPV infections in these social groups.

Bosch et al.[9] in two case–control studies carried out in Spain and Colombia reported an elevated risk of cervical cancer associated with no school attendance (odds ratios of 2.4 and 3.3 respectively), even after adjusting for HPV DNA status and other risk factors for the disease. Using the data of this study, we present an analysis of the prevalence of established risk factors for cervical cancer among women with normal cervical cells by socioeconomic strata and a detailed analysis of the association of socioeconomic characteristics and invasive cervical cancer. The study is presented for Spain and Colombia, two social contexts characterized by extreme differences in the incidence of cervical cancer and substantially different in the level of economic development.

Methods

The study has been described in detail.[10] The fieldwork was conducted in Spain from June 1985 to December 1987 and in Colombia from June 1985 to December 1988. The studies included all

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incident, histologically confirmed, invasive squamous cell carcinomas of the cervix identified among residents in the city of Cali, Colombia, in eight provinces of Spain (Alava, Gerona, Guipuzcoa, Murcia, Navarra, Salamanca, Seville, and Vizcaya), and in the city of Zaragoza, Spain. Control subjects, one per case subject, were a 5-year age-stratified random sample selected from the general population that generated the case subjects. Case subjects were actively identified by periodic visits to all hospitals, pathology laboratories, and screening clinics of each area. Eligible husbands were defined as men who had had regular sexual intercourse with the index women for at least 6 months. Individuals identified as control subjects who were ineligible or untraceable were replaced, but those who refused to participate were not. Study subjects and their husbands were interviewed with a structured questionnaire, which included questions on sociodemographic characteristics, reproduction, sexual behavior, smoking habits, oral contraception use, frequency of Pap smears, and history of common sexually transmitted diseases. Interviews took place in nearby facilities and only rarely at home. Interviewers were preferentially recruited among non–health-related professionals and were specially trained for the project. The average time to complete the interview was 45 minutes. A total of 760 women (373 case subjects and 387 control subjects) and 425 husbands were included; these represent 80% of the incident carcinoma cases, 74% of the eligible control subjects, and 55% of the eligible husbands (82.3% if women with a current partner were considered).

HPV DNA sequences were sought in cytological specimens obtained by cervical scraping or in males by scraping of the distal urethra and the coronal sulcus of the glands. A polymerase chain reaction amplification using HPV L1 consensus primers was carried out for 60% of the study subjects.[11] The amplification products were hybridized sequentially with probes to HPV 6, 11, 16, 18, 31, 33, and 35 and β-globin under high-stringency conditions. Subsequently the filters were screened with a generic probe that contained a mixture of amplimers of HPV 16 and 18.

Antibodies to *Chlamydia trachomatis,* to *Neisseria gonorrhoeae,* to *Treponema pallidum* and to herpes simplex virus type 2 were detected as previously reported.[12] Briefly, antibodies to *C trachomatis* were detected by indirect immunofluorescence using as antigen purified elementary bodies of L2 serovar. Antibodies to *N gonorrhoeae* were examined by indirect hemagluttination. Antibodies to syphilis were tested by an enzyme-limited immunosorbent assay (ELISA) for Immunoglobin G (IgG) and Immunoglobin M (IgM) against the Veneral Disease Research Laboratory antigen and by an ELISA assay for IgG antibodies against the *Treponema flagellum.* Antibodies to herpes simplex virus type 2 were detected by using an enzyme immunoassay that reacts against glycoproteins C (gC) that are type-specific antigens for herpes simplex virus type 2 (gC-2) and for herpes simplex virus type 1 (gC-1) and a type of common antigen. The absorbance value obtained for each tested serum with herpes simplex virus type 1 antigen was divided by that for the herpes simplex virus type 2. The ratio of herpes simplex virus type 1 to herpes simplex virus type 2 absorbance in ELISA had to be lower than 0.8 to define herpes simplex virus type 2 serological reactivity in the presence of antibodies to herpes simplex virus type 1.

Socioeconomic Indicators

The following information on socioeconomic status was requested in the questionnaires: education of the women, of their husbands, and of the women's parents; ability to write and read; monthly income salary; and availability of five different in-home amenities (radio, television, videocassette recorder, water, heating). Educational level was selected as the socioeconomic indicator to evaluate behavioral differences. Education has been extensively used in other health-related settings either separately or in combination with occupational status to discriminate social groups within a given community. The majority of women were housewives; this limited the possibility of an analysis using women's occupation as a social indicator.

Household monthly income salary was converted into US dollars and divided by the number of dependents (a dependent was defined as any individual living from the global household income). In Colombia 1 US dollar was, on average, equivalent in 1985 to 145 pesos (during the study period, Colombia experienced significant devaluation in terms of the US dollar). In Spain 1 US dollar was equivalent to 174 pesetas in 1985.

Statistical Analysis

The risk of cervical cancer associated with the different socioeconomic indicators was evaluated by the use of logistic regression analysis to obtain maximum likelihood estimates of odds ratios and their 95% confidence intervals while the confounding factors detected in each study group were controlled for.[13] Odds ratios for different socioeconomic indicators were estimated on the basis of case subjects with available information on HPV status. This led to the exclusion of 457 women (55%) from the original sample. Untested samples for HPV DNA were more common among case subjects than among control subjects (for unknown HPV status, the odds ratio [OR] = 4.0; 95% confidence interval [CI] = 2.7, 5.6); however, the proportions of untested samples for HPV status for case subjects and control subjects in both countries were not associated with educational level.

The prevalence of exposure to cervical cancer risk factors was calculated as the percentage of a given risk factor across educational categories among control women in the population. When appropriate, tests for linear trend across socioeconomic strata or chi-squared test for heterogeneity were calculated.

Results

In Spain 22.7% of control women had not attended school, and the average income level per person was $96 per month. The corresponding figures for Colombia were 6% and $46. Case subjects in both countries were less educated and had a lower income than their age-stratified control subjects. The age-adjusted odds ratios for cervical cancer by different socioeconomic indicators are shown in Table 1 together with odds ratios adjusted for age, number of sexual partners, age at first sexual intercourse, history of Pap smears, HPV DNA status, husband's contact with prostitutes, and area of recruitment (in Spain). Cervical cancer was associated with a low level of education in both countries. After adjustment for sexual and reproductive behavior, history of Pap smears, and HPV prevalence, the association between women's education and cervical cancer was considerably reduced. Of all variables introduced in the logistic model, history of Pap smears and HPV status were the variables that most confounded the risk for cervical cancer due to low educational level in Colombia. Adjustment for history of Pap smears reduced the odds ratio for low education from 5.3 to 4.6; adjustment

TABLE 1—Odds Ratios of Invasive Cervical Cancer Associated with Different Socioeconomic Indicators among Spanish and Colombian Women

	Spain			Colombia		
	Case/Control Subjects (n = 142/130)	OR[a]	OR[b] (95% CI)	Case/Control Subjects (n = 87/98)	OR[a]	OR[b] (95% CI)
Education						
Secondary and higher	11/23	1	1	13/26	1	1
Primary	85/81	2.0	1.5 (0.5, 4.5)	59/65	2.1	0.8 (0.3, 2.3)
No schooling	46/26	3.3*	2.9 (0.9, 9.7)	15/7	5.3*	2.8 (0.6, 12.6)
Ability to read						
Yes	121/116	1	1	73/93	1	1
No	21/14	1.3	1.3 (0.5, 3.6)	14/5	5.9*	2.9 (0.8, 10.4)
Ability to write						
Yes	117/114	1	1	71/90	1	1
No	25/16	1.4	1.1 (0.4, 3.0)	16/8	2.7*	2.7 (0.8, 9.0)
Income[c]						
Average income	144/196			35/46		
Highest quartile	34/35	1	1	11/21	1	1
2nd and 3rd quartile	60/60	1.1	1.6 (0.7, 3.8)	32/40	1.4	0.9 (0.3, 3.0)
Lowest quartile	48/35	1.6	1.9 (0.7, 5.1)	44/37	2.2	1.0 (0.3, 3.1)
No. house amenities						
4–5	129/122	1	1	6/8	1	1
1–3	98/97	1.3	1.4 (0.3, 5.8)	76/88	4.1	4.3 (0.7, 25.3)
Father attended school[c]						
Yes	73/89	1	1	28/56	1	1
No	67/41	2.0*	2.8 (1.1, 7.3)	16/12	2.8*	2.6 (0.8, 8.1)
Mother attended school[c]						
Yes	63/76	1	1	31/58	1	1
No	77/54	1.6*	2.0 (0.8, 4.6)	27/17	3.2*	1.0 (0.4, 2.9)
Husband attended school[c]						
Yes	57/73	1	1	29/42	1	1
No	22/12	2.2*	2.8 (0.9, 8.7)	5/4	2.2	1.8 (0.3, 11.3)

Note. OR = odds ratio; CI = confidence interval.
[a]OR adjusted for age.
[b]OR adjusted for age, number of sexual partners, age at first sexual intercourse, history of Pap smears, presence of HPV DNA, area of recruitment (only in Spain), and husband's contacts with prostitutes.
[c]In US dollars. Totals do not add up because of missing values.
*Indicates that 95% confidence limits do not include 1.

for HPV DNA reduced the odds ratio from 5.2 to 3.3. The fully adjusted odds ratio in Colombia was 2.8. In Spain, the strongest confounder of the association of cervical cancer risk with low education was history of Pap smears. Adjustment for history of Pap smears reduced the odds ratio from 3.3 to 2.9. The fully adjusted odds ratio was 2.9. When only HPV-positive women from Spain and Colombia were considered (to reduce potential misclassification of HPV status), the adjusted odds ratio for cervical cancer risk in relation to low educational level was 2.2 (95% CI = 0.2, 21.5).

In Spain, the risk of cervical cancer was also related to the father's educational level even in the adjusted models. The effect of parental education on a woman's risk for developing cervical cancer was further evaluated among women who had a parent with no school education. For both Spanish and Colombian women, women who had not gone to school and whose mothers had not gone to school had a 65% increase in risk for cervical cancer (OR = 1.65; 95% CI = 1.0, 2.7) compared with women who had gone to school but whose mothers had not. Similarly, an increase of 80% in the risk of cervical cancer was observed when the effect of father's education was considered (OR = 1.80; 95% CI = 0.96, 3.37).

There was no statistically significant association of reported family income with cervical cancer in either of the two countries.

The prevalence of established risk factors for cervical cancer among control women by educational level is summarized in Table 2. In Spain, the prevalence of ever having had a Pap test, ever having used oral contraceptives, and ever having had a smoking habit increased with educational level. The number of sexual partners also increased with educational level. Use of prostitutes was four times more likely to be reported by husbands of less educated women than by husbands of women with higher education (OR = 4.4; 95% CI = 1.6, 11.9). Similarly, these husbands were more likely to have had more than five sexual partners, but the difference was not statistically significant.

The overall HPV DNA prevalence was 4.6% in Spain and 13.3% in Cali. Among those who were HPV positive, for both countries, the distribution of HPV types was as follows: 67.7% HPV 16; 6.7% HPV 18; 12.8% HPV 31, 33, and 35; and 12.8% HPV of unknown types (specimens positive only with the generic probe). The highest prevalence of antibodies to four sexually transmitted diseases and of HPV DNA were observed among women with no school education. Women in the lower

TABLE 2—Characteristics of Spanish and Colombian Control Women, by the Women's Education

	Spanish Women				Colombian Women		
	No Schooling	Primary Schooling	Further Schooling	*P*	No Schooling and Primary Schooling	Further Schooling	*P*
Women							
No. women	54	142	40		110	39	
Age, mean	**59**	**53**	**42**	**.0001**	**50**	**41**	**.001**
History of PAP smear, %	**20.4**	**26.1**	**45.2**	**.009**	**63.6**	**92.3**	**.001**
First intercourse < 18 y, %	5.6	6.3	5.0	.942	46.4	35.9	.257
Sexual partners > 1, %	**3.7**	**6.3**	**22.5**	**.002**	43.6	35.9	.400
Ever use oral contraceptives, %	**7.4**	**25.3**	**52.5**	**.000**	**28.2**	**58.9**	**.001**
No. children > 4, %	25.9	21.8	10.0	.150	**61.8**	**30.8**	**.001**
Ever smoking, %	**3.7**	**12.7**	**35.0**	**.000**	32.7	25.6	.410
Antibodies to 4 STDs,[a] %	25.9	19.7	16.7	.250	69.1	64.1	.566
HPV DNA+,[b] %	7.6	3.8	4.0	.450	16.7	3.8	.098
Husbands							
No. husbands	26	89	24		53	19	
Sexual partners > 5, %	46.2	46.1	39.1	.636	95.8	88.9	.29
Use of prostitutes, %	**61.5**	**64.0**	**29.2**	**.025**	**92.4**	**73.7**	**.03**
HPV DNA+,[c] %	0	5.3	0	.941	31.0	10.0	.188

Note. Bold characters indicate that the test for trend was statistically significant.
[a]*N gonorrhoeae, C trachomatis, T pallidum,* and herpes virus type II.
[b]Owing to untested samples, denominators for the 5 columns are 26, 79, 25, 72, and 26, respectively.
[c]Owing to untested samples, denominators for the 5 columns are 17, 27, 18, 29, and 10, respectively.

educational levels, although reporting fewer number of sexual partners, were 1.9 times more likely to harbor HPV DNA than women in the higher educational levels. The differences between the strata, however, were not statistically significant.

In Colombia, the percentages of women who had ever had a PAP test and had ever used oral contraceptives were higher among the more educated. Women who had not attended school or who had reached only a primary level were significantly more likely to have higher parity than better educated women. Husbands of less educated women reported a higher use of prostitutes than did husbands of more educated women (OR = 4.2; 95% CI = 1.7, 10.6). Less educated women had a prevalence of HPV DNA 4.3 times higher than women with a higher educational level, although the differences did not reach statistical significance (95% CI = 0.5, 37.9). Their husbands were also more likely to harbor HPV DNA.

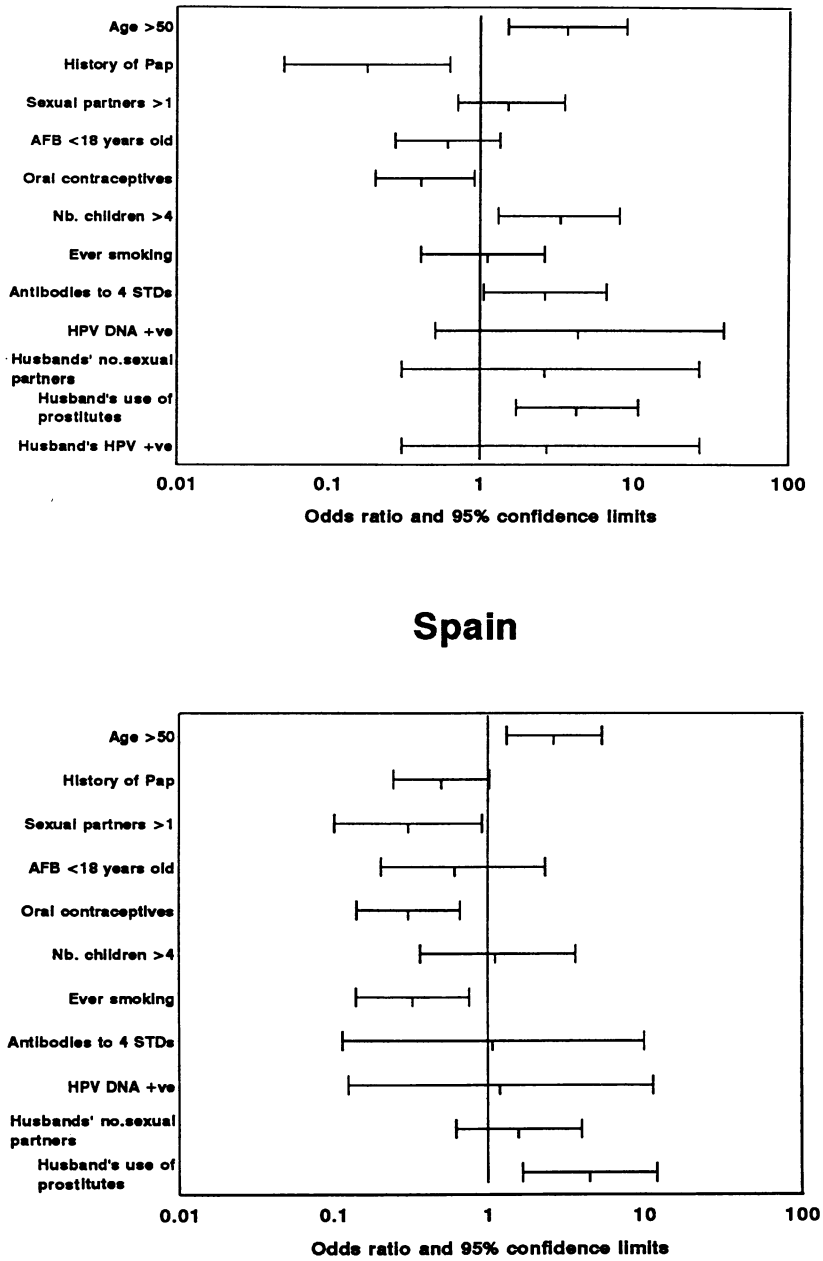
The characteristics associated with low educational attainment (defined as no schooling or primary schooling) in Colombia and Spain are shown in Figure 1. Results are presented as odds ratios where the risk among women with low educational level (no schooling or primary school) for each potential risk factor for cervical cancer is compared with that of better educated women (secondary schooling or higher). Odds ratios are adjusted for age and history of Pap smears. However, controlling for age and history of Pap smears did not modify the association between the risk of invasive cervical cancer and sexual behavior, oral contraceptive use, and smoking habit shown in Table 2.

Discussion

The study investigated the variation in sexual behavior and in the prevalence of several sexually transmitted diseases, including HPV, across socioeconomic strata in Spain and Colombia. The purpose was to understand why the socially less privileged are at high risk of cervical cancer.

It is well accepted that the major cause of cervical cancer is the persistence of certain types of HPV infections.[10] In trying to explain socioeconomic differences in the disease rates, we expected a higher HPV DNA prevalence, a higher number of sexual partners, or an earlier age at first sexual intercourse among the socially less privileged. In our data in both countries, HPV DNA prevalence decreased with increasing education. In Spain, women with lower educational level reported a lower number of sexual partners, but their partners were more likely to have ever used prostitutes. In Colombia, the prevalence of sexually related risk factors for cervical cancer was higher than in Spain and was higher for the less educated women. In both countries, husbands of less educated women more often reported ever having used prostitutes. Taken together, these results indicate that the explanation of social differences in cervical cancer is at least partially mediated by differences in HPV DNA prevalence and that sexual contacts with prostitutes by the husband may be a more important source of HPV infections than the woman's lifetime number of sexual partners. This qualitative difference is in agreement with our previous observation of a higher rate of preneoplastic lesions among prostitutes relative to nonprostitutes[14] and of other studies[15] indicating that prostitutes may be an important reservoir of HPV infection.

In addition to HPV, other factors contributed to explain the higher rates of cervical cancer among women in the low socioeconomic strata. Among these, not having regular Pap smears appeared to be of special importance. In both countries, women in the low socioeconomic strata had a lower record of ever having had a Pap smear than better educated women. In Colombia, a history of Pap smears was high in all social strata, and almost all women with a high educational level have had a Pap smear at least once. The high



Note. Risks are relative to those among women of high educational attainment (secondary levels and higher). Odds ratios are adjusted for age and history of Pap smears.

FIGURE 1—Odds ratios and 95% confidence intervals for potential risk factors for cervical cancer among Colombian and Spanish women of low educational attainment.

rate of Pap smears reported in Colombia, even among the less educated women (63.6%), compared with a much lower rate of screening practices in Spain (20.4% to 45.2%), is not surprising. Colombia has one of the highest incidence rates of cervical cancer in the world (age standardized incidence rate = 42.2 per 100 000 women), and Spain has one of the lowest (age standardized incidence rate = 7.7 per 100 000 women). In Cali, there exists an organized cervical cancer screening program,[16] and about 30% of the women report an annual screening.

Smoking and oral contraceptive use have been reported as possible risk factors for cervical cancer. We had previously reported no association between smoking habits and cervical cancer and a positive association between ever using oral contraceptives and cervical cancer among women who were positive for HPV DNA.[9] Better educated women were more likely to have ever used oral contraceptives and, in Spain, also to be smokers. This inverse relationship between smoking and oral contraceptives with socioeconomic status may well be limited to the age-cohort under study, particularly for smoking. In many societies, the smoking habit was first accepted by those in the higher social scale. Later, people with higher socioeconomic status tend to be the first to give up the habit when public health actions take place.[17] Data from National Health Surveys for Spain show that smoking among women increased during the period 1987 through 1993 and was higher among the better educated. However, social differences in smoking are disminishing.[18]

To understand the almost threefold increase in the risk estimates related to social class in our study (Table 1), the reader should consider two major sources of measurement error: the classification of socioeconomic status and the underdetection of HPV. We will discuss these in turn.

Education, occupation, and income are indicators that have been widely used in public health studies and have proved to be useful in identifying groups of people at higher risk for specific diseases. In Spain and Colombia, such studies are scarce, and the best possible indicators of socioeconomic status easily available in epidemiological studies are not yet well established. In Spain the majority of health-related studies used an adaptation of the British social class classification based principally on occupation.[19] In Cali, Cuello et al.[20] used census tract information based on family income, housing, and educational level in a study to evaluate socioeconomic differences in cancer incidence. A strong negative trend with socioeconomic status was observed with cervical cancer incidence rates. In Brazil, household facilities as well as education have been used in different studies to predict cervical cancer risk.[21,22] In our study, the number of household amenities was not related to cervical cancer. The valid use of this indicator probably re-

quires thorough research on identifying the items that differ within social groups.

In our study, income level was not a good indicator of sexual and reproductive behavior, nor was it related to cervical cancer. Particularly in Colombia, the correlation between educational levels and income was very poor (correlation coefficient = 0.27). Income level may be more likely to be misreported. We explored the distribution of risk factors for cervical cancer by three income strata (data not shown). A decreasing parity with increasing income among Colombian women was the only statistically significant association observed (parity higher than 4 = 79.3% among the lowest income quartile vs 38.9% among those in the highest quartile, $P < .001$).

The determinants of education may vary in Spain and Colombia. Thus, the analysis was limited to a within-country comparison. In Colombia, the study population was predominately urban, and 90% had attended school at some time in their life. In Spain the study included both rural and urban populations, and a high percentage reported illiteracy. A geographical analysis within the Spanish study areas showed that in two of the nine areas, about 50% of women were illiterate (data not shown). These two areas, situated in the south of Spain, are among the three poorest areas included in the study and have an important percentage of rural residents whose access to school in the years 1930 through 1950 was clearly difficult.

The second potential source of classification error is underdetection of HPV infection. In our study, HPV testing by polymerase chain reaction was completed for only 60% of the study subjects. Cervical cells had previously been used to detect HPV DNA with less sensitive techniques (i.e., ViraPap and Southern Blot), and in a relative high proportion of these women, further testing was not allowed. For both case subjects and control subjects, no differences were observed in the distribution of risk factors for cervical cancer in relation to knowledge of HPV status. However, lack of knowledge of HPV status appeared to induce misclassification, as the association between cervical cancer and socioeconomic status was considerably reduced when these subjects were excluded from the analysis. The analysis restricted to women positive for HPV DNA provided an odds ratio similar to the one for all subjects with known HPV status.

We have reported that even with the use of a highly sensitive polymerase chain reaction technique, HPV DNA among case subjects was underdetected when cervical scrapes rather than tissue samples were used.[23] Furthermore, the polymerase chain reaction method initially described by Manos et al.[24] has been considerably improved, notably in its sensitivity to detect the less prevalent HPV types.[25]

Finally we recognize that other factors acting through socioeconomic strata have not been investigated in our study. For example, diets vary across social strata and some studies have suggested that dietary factors are associated with cervical cancer.[26-27]

In the short term, there is only one way to prevent invasive cervical cancer: regular screening. In Spain and Colombia, less educated women have a risk of invasive cervical cancer at least three times higher than that of the better educated women. This risk could be reduced by increasing the use of preventive medical care services among the less educated. The risk of cervical cancer is, however, mediated by persistent HPV infections, which is often determined by a husband's use of prostitutes. At this stage it is uncertain that the use of condoms leads to a reduction in HPV infections; therefore, health education remains a pivotal issue in the prevention of cervical cancer. □

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