Invasive Cervical Cancer and Smoking in Latin America

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A case-control study of 667 patients with invasive squamous cell carcinoma of the cervix and 1,430 controls from four Latin American countries showed an age-adjusted relative risk (RR) of 1.2 [95% confidence interval (CI) = 1.0–1.4] for women who had ever smoked, with risk rising to 1.7 (95% CI, 0.8–3.6) for women who smoked ≥ 30 cigarettes per day. The associations were practically eliminated after adjustment for the number of sexual partners and alcohol consumption, probably a surrogate for an unidentified life-style risk factor. Some excess risk persisted among women who smoked for extended periods (RR = 1.5 for ≥40 yr), as well as those who began smoking at older ages (RR = 1.7 for >30 yr), which suggests a late-stage effect. In addition, among women who tested positive for human papillomavirus (HPV) type 16 or 18 by filter in situ hybridization, there was an increased risk for women who had ever smoked and a dose-response relationship with the number of cigarettes smoked (adjusted RRs compared with HPV-negative nonsmokers = 5.0 for HPV-positive nonsmokers, 5.5 for < 10 cigarettes/day, and 8.4 for ≥ 10 cigarettes/day). In contrast, HPV-negative women had no increased risk associated with smoking. These results, from a high-incidence area where intensive smoking among women is still relatively rare, suggest that smoking has a limited effect on cervical cancer risk, possibly only among women with specific types of HPV. [J Natl Cancer Inst 1989;81:205–211]

In 1966, Naguib et al. (*1*) reported an increased risk of cervical neoplasia among women who smoked. Since this initial report, > 20 studies have been conducted that attempted to demonstrate a causal association. Most investigations have found varying degrees of excess risk among smokers, for both invasive and preinvasive cervical neoplasia. Some have detected dose-response relationships with intensity (*2–5*), duration (*3,4*), or combined measures of smoking (*6–8*). Sexual behavior has been shown to be associated with both smoking and cervical disease (*2,4,9,10*), and most studies that have adjusted for its confounding effect have detected reduced but persistent excess risks for smokers (*4,6,11–14*). Very few negative studies have been published (*15–17*), yet no consensus exists on a cause-effect relationship.

A recent report of an International Agency for Research on Cancer (IARC) expert committee (*18*) judged the current evidence supporting a causal role for cigarette smoking in cervical neoplasia to be insufficient. The report emphasized that smoking is correlated with sexual behavior and suggested the need to identify and consider the effects of specific causal agents, which are probably infectious.

Most of the previous smoking and cervical cancer studies have been conducted in areas of low risk for the disease, and a relatively high prevalence of tobacco exposure (*19*). In contrast, the incidence rates of cervical cancer in Latin America are among the highest in the world (*20*), while smoking prevalence is generally low among women (*21,22*).

To assess the role of smoking and other risk factors including human papillomavirus (HPV) in this population, a case-control study was conducted in four areas of Latin America. Detailed interviews with a large number of female subjects, as well as cervical cell samples that enabled the detection of HPV DNA, provided extensive information to

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evaluate the effect of smoking in relation to other biologic risk factors for the disease.

Materials and Methods

Between January 1986 and June 1987, incident cases of invasive cervical cancer were ascertained in four study sites in Latin America: Bogota, Colombia; Costa Rica; Mexico City, Mexico; and Panama. Patients were considered eligible for study if they were not previously treated for cervical cancer, were <70 years old, and had lived in the study areas for at least 6 months prior to diagnosis. Gynecologic oncologists detected and staged the cases in the study hospitals, which included: (*a*) the Ministry of Health cancer referral center in Bogota, Colombia, which treats most lower- and lower-middle-class cancer patients in that city; (*b*) three Social Security hospitals in San Jose, Costa Rica, which are the major referral centers for all neoplastic diseases in the country; (*c*) the Social Security's Oncology Hospital in Mexico City, Mexico, which provides care for the majority of salaried employees in the area; and (*d*) the National Oncology Institute in Panama, which is the major referral center for oncologic treatment and treats at least 90% of patients with cervical cancers who are diagnosed in Panama (*23*).

For each case, two controls were selected. In Bogota and Mexico City, two hospital controls were chosen, while in Costa Rica and Panama, one hospital and one community control were selected. Controls were matched to cases by 5-year age groups; potential controls with a previous hysterectomy or history of cancer were excluded. Hospital controls were selected randomly from hospital admission lists. Women with neoplastic, endocrine, nutritional, psychiatric, selected circulatory, gynecologic, or smoking-related diseases were excluded. In Costa Rica and Panama, hospital controls were selected from inpatients at the primary referral hospitals that served the area of residence of the cases, whether or not the actual primary detection had been made at those centers. In Bogota they were chosen from eight tertiary level government hospitals, and in Mexico City they were chosen from three Social Security hospitals that served the population from which the cases derived. Most diagnoses of hospital controls included: digestive diseases (21%), injuries (15%), diseases of the nervous system and sense organs (14%), varicose veins (11%), skin diseases (9%), and respiratory diseases (8%). Community controls were selected randomly from current census listings of the corresponding case's county of residence. The few eligible controls who refused to participate (*see* below) were not replaced.

A personal interview was conducted with each participant to obtain detailed information on demographic, socioeconomic, reproductive, occupational, and medical history, as well as dietary, sexual, hygienic, and contraceptive practices. Standardly trained interviewers collected the information under strict national and international supervision. The average length of the interviews was 1 hour. The information collected on smoking included whether the women had ever smoked cigarettes, cigars, or pipes; usual daily amount of the specific product; years of smoking; age when started; age when stopped; inhalation into the chest; type of tobacco; and use of filters.

During the 18-month study period, 766 eligible cases were detected. Interviews were obtained from 759 patients (99.1%) and 755 cervical swabs were taken (99.6% of those interviewed). Of 1,532 eligible hospital controls, 1,467 were interviewed (95.8%) and 1,325 cervical samples were collected (95.4% of those interviewed). Nonresponse among patients versus controls was due to death (three patients vs. zero controls), refusal (zero vs. 41), language and hearing problems (two vs. 10), mental incompetence (one vs. eight), and change of residence (one vs. six). Response rates were similar for hospital and community controls.

Histologic information was available for 95.9% of the cases ($n = 728$), of whom 91.6% had squamous or related histologies [International Classification of Diseases for Oncology (ICD-O) 8010-8130]. All analyses presented in this article are based on information from pathologically confirmed cases of papillary and squamous cell carcinomas ($n = 649$), epithelial neoplasms, not otherwise specified ($n = 17$), and basaloid carcinoma ($n = 1$). In order to adjust simultaneously for the effects of the number of sexual partners and age at first intercourse, virgins were excluded from the analysis, leaving a final group of 667 cases, 1,064 hospital controls (74.4% of total controls) and 366 community controls (25.6%).

To assess the presence of HPV, a cervical swab was obtained, at the time of interview, from the neoplastic lesion of the patients and from the cervical os of the controls, preserved in phosphate-buffered saline, and frozen as soon as possible at −20 °C until tested. Assays were conducted by the filter in situ hybridization method (*24,25*), modified as detailed elsewhere (*26,27*). Cells from each sample were filtered onto three separate nitrocellulose filters. DNA-DNA hybridization was carried out at 42 °C in 50% formamide (Tm −17 °C) using pBR plasmid alone, or with inserts of HPV 16 and 18 or HPV 6 and 11 DNA. The probes were labeled with ^{32}P deoxycytosine triphosphate (dCTP) to a specific activity of $>1 \times 10^8$ cpm/μg using a commercial nick translation system (Bethesda Research Laboratories, Gaithersburg, MD). After hybridization, the filters were washed four times for 1 hour at 65 °C (Tm −15 °C) and then exposed at −70 °C for 1–3 days to x-ray film, using a Kodak intensifying screen. All autoradiographs were examined independently by three observers who were blinded as to case-control status. Those specimens recorded as positive by at least two observers were considered positive. Specimens that reacted positively in the pBR assay (3% of cases, 5% of controls) were considered as a separate category in analyses.

To estimate the risk of invasive cervical cancer associated with the different factors, odds ratios were calculated as approximations of relative risks (RR). Unconditional logistic regression was used to adjust for potential confounding variables (*28*), which derived maximum likelihood estimates of RRs and 95% confidence intervals (CI). Tests for trends in the logistic analyses were obtained by categorizing the exposure variable, and treating the scored variable as continuous. This continuous variable was then tested for significance

(Wald test) using the same model (same covariates) as when the categorical variable was evaluated. Logistic regression was also used to test the statistical significance of interactions on a multiplicative scale. Since the results of conditional logistic regression (29) were similar to the unmatched analyses, the latter have been chosen for presentation.

Results

The distribution of cases and controls was fairly equal by study site, with a slightly larger group from Bogota and a slightly smaller group from Mexico City (table 1). The mean age was 46.5 years for both patients and controls. Nearly 65% of the participants were mestizos (mixed European and American Indian ancestry), while 30% were white and 5% were black, Indian, or other races. Patients and controls were composed of groups similar in racial origin. Nearly 90% of the patients and controls were Catholic. Separate analysis by race or country did not alter our estimates for most variables. No major differences were detected by calculating the RRs with the use of only hospital or community controls; therefore, both types of controls were combined in the analyses.

The risk factors identified in the present study included the following: number of sexual partners (adjusted RR = 1.5 for ≥4 vs. 1), age at first sexual intercourse (RR = 1.9 for < 16 yr of age vs. ≥20 yr of age), grams of ethanol per week (RR = 2.1 for occasional drinking, RR = 1.6 for ≤48.6 g per wk, RR = 1.1 for > 48.6 g per wk vs. nondrinking), history of venereal disease (RR = 1.7), reaction with HPV 16/18 DNA probes (RR = 4.7 for positive signal, RR = 10.2 for strong positive signal vs. negative signal), number of pregnancies (RR = 3.2 for ≥10 vs. 0-1), interval since last Pap smear (RR = 2.4 for never vs. one in the last 24 mo), and number of household facilities (i.e., electricity, toilet inside the house, stove, refrigerator, radio, and television) (RR = 1.7 for ≤1 vs. 6), the socioeconomic measure most strongly related to risk.

The percent of controls who were smokers in each risk factor category is shown in table 2. Smoking among controls was associated inversely with age and with age at first sexual intercourse and was correlated positively with number of sexual partners, grams of ethanol consumed per week, and history of venereal disease. The percent of smokers did

Table 1. Demographic characteristics of cases and controls

Variables	Cases		Controls	
	No.	%	No.	%
Site				
Bogota, Colombia	202	30.3	416	29.1
Costa Rica	173	25.9	372	26.0
Mexico	124	18.6	294	20.6
Panama	168	25.2	348	24.3
Age (yr)				
<35	112	16.8	237	16.6
35-44	190	28.5	424	29.6
45-54	177	26.5	364	25.5
≥55	188	28.2	405	28.3
Race				
Mestizo	435	65.2	928	64.9
White	206	30.9	426	29.8
Black	20	3.0	40	2.8
Mulatto	1	0.1	19	1.3
Indian	2	0.3	7	0.5
Other	3	0.5	10	0.7
Religion				
Catholic	582	87.3	1,278	89.4
Other	74	11.1	135	9.4
None	11	1.6	17	1.2

Table 2. Prevalence of smoking (women who ever smoked for ≥6 mo) among controls according to age and cervical cancer risk factors identified in this study

Risk factors	Percent of smokers among controls*
Age (yr)	
<35	39
35-44	27
45-54	28
≥55	23
No. of sexual partners	
1	23
2	27
3	32
≥4	36
Age (yr) at first sexual intercourse	
≥20	25
18-19	27
16-17	29
<16	32
Grams of ethanol per wk	
Nondrinker	22
Occasional	38
≤48.6 g/wk	44
>48.6 g/wk	48
History of venereal disease	
No	25
Yes	37
Reaction with HPV 16/18 DNA probes	
Negative	28
Minimal signal	28
Positive signal	25
Strong positive signal	28
Unknown or pBR +	25
No. of pregnancies	
0-1	28
2-3	28
4-5	34
6-7	26
8-9	29
≥10	22
Interval since last Pap smear (yr)	
<2	27
2-3	26
4-5	32
≥6	31
Never	27
Unknown	20
No. of household facilities†	
≥6	29
5	26
4	25
2-3	26
≤1	25

*Adjusted for age.
†Includes electricity, toilet inside the house, stove, refrigerator, radio, and television.

not vary substantially with respect to the other risk factors (i.e., HPV-DNA positivity, number of pregnancies, interval since last Pap smear, number of household facilities). In assessing risk associated with smoking, the two variables that exerted some confounding effects were the number of sexual partners and alcohol consumption. These variables, along with age, were included in all subsequent analyses of risk associated with smoking. Further adjustment for all of the above-mentioned risk factors plus race, religion, use of oral contraceptives (not significantly related to risk in this study), dietary factors, and years of education did not significantly alter the risks associated with smoking.

Thirty-two percent of the patients reported ever having smoked cigarettes for ≥ 6 months, compared to 28% of controls, which resulted in a nonsignificant RR of 1.2 (table 3). Adjustment for confounding variables produced a RR of 1.0. Current smokers and ex-smokers showed the same adjusted RR of 1.0. Crude risks increased with the number of cigarettes smoked per day up to 1.7 for ≥ 30 cigarettes; this yielded a significant trend (P for trend = .05), but adjustment eliminated the increased risks. No consistent trend was noted for number of years of smoking, but a nonsignificant risk of 1.5 persisted among women who had smoked for ≥ 40 years after adjustment. It is to be noted that the number of individuals in these high exposure levels was low in this study population.

No differences were noted in the risk estimates for use of filter cigarettes, type of tobacco (light vs. dark), or intermittency of the habit (table 4). The only significantly elevated risks that persisted after adjustment were for women who reported not inhaling into the chest, with an adjusted RR of 1.3 (95% CI = 1.0–1.7), and for women who started smoking after age 30 (RR = 1.7, 95% CI = 1.1–2.6). Among these late starters, the risk was increased mostly for the more intense smokers (RR = 3.2 for smokers of ≥ 10 cigarettes, 95% CI = 1.3–8.3), with a significant dose-response relationship after adjustment (P for trend = .005). Very few of these women had smoked for > 20 years, and no increase in risk was noted with duration of the habit among the late starters. The effects of late starting and noninhalation were not modified by adjusting one by the other.

By analyzing the data according to HPV 16 and 18 status, it was evident that the risk associated with smoking was higher for women who tested HPV positive, while practically no increased risk for any smoking measure was observed among HPV-negative women (table 5). The fact that they had ever smoked, the number of cigarettes per day, and duration of the habit were not associated with increased risks among HPV-negative women, while for HPV-positive women, risks were higher for smokers (adjusted RRs = 5.0 for nonsmokers, 6.3 for smokers), increased clearly with number of cigarettes (adjusted RRs = 5.0 for nonsmokers, 5.5 for smokers of <10 cigarettes, and 8.4 for smokers of ≥10 cigarettes), and were affected slightly by duration of smoking. The test for multiplicative interaction, however, was nonsignificant (P = .13). The risk among HPV-positive women was particularly high for women who started smoking at age >30 years (RR = 13.1, 95% CI = 5.7–29.9), while no difference was noted between HPV-positive nonsmokers and smokers starting at ≤30 years of age. The test for multiplicative interaction between HPV positivity and late age at start of smoking resulted in a P value of .07.

Analysis of the data among drinkers and nondrinkers revealed the same risk estimates for ever smoking and the daily

Table 3. Relative risks of invasive squamous cell cervical cancer by smoking habits

	Cases	Controls	RR*	RR†	95% CI
Smoking status					
Never smoked for ≥6 mo	455	1,025	1.0‡	1.0	—
Ex-smoker	90	168	1.2	1.0	(0.8–1.3)
Current	121	234	1.2	1.0	(0.7–1.2)
Unknown	1	3			
Cigarettes per day					
<10	141	283	1.1	1.0	(0.8–1.2)
10–19	25	46	1.2	1.0	(0.6–1.7)
20–29	34	58	1.3	1.0	(0.6–1.5)
≥30	11	15	1.7	1.1	(0.5–2.5)
P for trend			.05	.8	
Yr of smoking					
<10	64	118	1.2	1.0	(0.7–1.4)
10–19	67	122	1.2	1.0	(0.7–1.4)
20–29	37	64	1.3	1.1	(0.7–1.7)
30–39	22	65	0.8	0.6	(0.4–1.1)
≥40	17	23	1.6	1.5	(0.8–2.8)
Unknown	4	10			
P for trend			.3	.8	

* Adjusted for age.
† Adjusted for age, No. of sexual partners, and alcohol consumption.
‡ Referent group.

Table 4. Relative risks of invasive squamous cell cervical cancer by smoking habits

	Cases	Controls	RR*	RR†	95% CI
Nonsmoker	455	1,025	1.0‡	1.0	—
Filtration					
Filter	170	332	1.2	1.0	(0.8–1.2)
No filter	40	70	1.3	1.0	(0.7–1.6)
Unknown	1				
Type of tobacco					
Light	175	313	1.3	1.1	(0.8–1.3)
Dark	34	87	0.9	0.7	(0.5–1.1)
Unknown	2	2			
Intermittency					
Intermittent	49	122	0.9	0.8	(0.6–1.2)
Continuous	162	279	1.3	1.0	(0.8–1.3)
Unknown		1			
Inhalation					
Noninhaler	89	133	1.5	1.3	(1.0–1.7)
Inhaler	121	269	1.0	0.8	(0.6–1.1)
Unknown	1				
Age when started smoking					
>30	43	50	1.9	1.7	(1.1–2.6)
21–30	50	99	1.1	0.9	(0.7–1.4)
16–20	72	172	0.9	0.8	(0.6–1.1)
<16	45	79	1.3	1.1	(0.7–1.6)
Unknown	1	2			

* Relative risk adjusted for age.
† Adjusted for age, No. of sexual partners, and alcohol consumption.
‡ Referent group.

Table 5. Relative risks associated with combined measures of smoking and HPV 16/18 status

	HPV negative				HPV positive*			
	Cases	Controls	RR†	95% CI	Cases	Controls	RR†	95% CI
Nonsmokers	159	586	1.0‡	—	202	165	5.0	(3.8-6.6)
Ever smoked								
Yes	76	247	0.9	(0.7-1.3)	103	54	6.3	(4.3-9.2)
Cigarettes/day								
<10	55	170	1.0	(0.7-1.5)	65	40	5.5	(3.5-8.3)
≥10	21	77	0.8	(0.5-1.3)	38	14	8.4	(4.4-16.2)
Yr of smoking								
<10	22	70	1.0	(0.6-1.7)	31	18	5.7	(3.0-10.6)
10-19	27	77	1.0	(0.6-1.6)	32	16	5.9	(3.1-11.1)
≥20	27	95	0.9	(0.6-1.5)	36	19	6.6	(3.6-12.1)
Age started smoking								
≤30	64	218	0.9	(0.6-1.2)	76	46	5.1	(3.4-7.8)
>30	12	27	1.4	(0.7-2.9)	26	8	13.1	(5.7-29.9)

*HPV positive includes those with positive and strong positive signals.
†Adjusted for age, No. of sexual partners, and alcohol consumption.
‡Referent group for all RRs; unknowns excluded from analysis.

number of cigarettes. Similarly, no interaction was noted with the number of sexual partners, since risks for smoking variables among monogamous women were similar to those among women with several partners.

Ever having smoked cigars was associated with a nonsignificant RR of 1.5 (95% CI = 0.9-2.4), which was reduced to 1.1 after adjustment for their number of partners, for ever drinking alcohol, and for their socioeconomic status (number of household facilities). Pipe smoking was associated with an adjusted RR of 2.0 (95% CI = 0.8-4.8), with very few women exposed (12 cases and 10 controls).

Discussion

In this high-incidence area for cervical cancer, where smoking prevalence among women is relatively low, smoking appears to have only a minimal etiologic role. Although originally we detected excess risks associated with a variety of smoking variables, the relationships were considerably confounded by other identified risk factors. Similar to others, we found a strong correlation between smoking and the number of sexual partners. In addition, alcohol consumption exerted a strong confounding influence. Drinking alcohol was associated with a significantly increased risk of invasive cervical cancer, independent of all other risk factors, but it was higher for women who reported occasional consumption than for those who drank in a more consistent pattern, showing an "inverse dose response." This contradicts a biologic effect of ethanol as a carcinogen and supports an indirect effect of drinking through its association with other factors, probably sexual behavior.

Thus, after adjustment for relevant confounders, no increased risk was detected for women who had ever smoked. Current and ex-smokers were found to be at the same risk of disease as nonsmokers. Filtration habits, intermittency, and type of tobacco were not associated with increased relative risks. Contrary to the findings of other investigators (*4*), women who reported inhalation of smoke into the chest were at lower risk than nonsmokers, while noninhalers were at a marginally significantly increased risk. We consider this finding biologically implausible and probably due to chance or confounding by unidentified factors.

The lack of general association with smoking in this study is most likely due to the low prevalence among Latin American women of heavy and prolonged cigarette use, measures that have most often been linked with an increased risk of cervical cancer. Although we found a slightly increased risk (1.5) among those smoking for ≥40 years, no excess risk was associated with smoking ≥30 cigarettes per day, which is not a surprising finding given the limited power to detect such an association. It is, however, noteworthy that a significant risk of 1.7 was found for women who reported that they started smoking after the age of 30, with even higher risks for late starters who smoked ≥ 30 cigarettes per day. An enhanced risk among women who started smoking at late ages has been observed by other investigators (*4*), who suggested that smoking may represent a late-stage carcinogenic influence. To support this hypothesis, current, long-term smokers should also be at increased risk, unless a modification of the carcinogenic potential of tobacco products occurs over time.

Despite the consistency of findings regarding a relationship of extended measures of smoking and elevated cervical cancer risk, a biologic mechanism remains unclear. The biologic plausibility of the smoking-cervical cancer association is based on the fact that carcinogens absorbed through the lung reach the bloodstream and can be detected in the urine (*30-32*). Tobacco products, like cotinine, a nicotine derivative, have been detected in the breast fluid of nonlactating women (*33*) and in the cervical mucus of smokers (*34*), where it can be considered a reliable biochemical marker for smoking (*35*); however, controversy remains about the presence of mutagens in the mucus (*36,37*).

To expand on possible biologic mechanisms, we were interested particularly in assessing whether smoking effects might be differential according to the presence of human papillomaviruses, which are candidate etiologic agents for cervical abnormalities. When the data in different subgroups were analyzed, it became evident that among women who tested negative for the presence of HPV 16/18 DNA, no risk was associated with smoking practices, while among HPV-positive women, the risk was elevated for women who smoked, with evidence of a dose-response relationship with intensity of smoking and a slight increase in risk with years of smoking. Interestingly, this effect was limited to late starters, while HPV-positive early smokers were at the same risk as nonsmokers. One explanation for these findings is that smoking increases the shedding of occult papillomaviruses, especially in the early years after the habit commences. Alternatively, these findings are consistent with a synergistic interaction model proposed by zur Hausen (*38*), in which infection with papillomavirus leads to proliferation, with subsequent transformation into a malignant lesion depending on other carcinogenic insults, in this case, smoking. Other examples of synergistic carcinogenic interactions with papillomaviruses are the malignant transformation of HPV 5/8 warts in sun-exposed areas of patients with epidermodysplasia verruciformis (*39*); the increased conversion to squamous carcinomas of cottontail rabbit papillomas when exposed to methylcholanthrene or tar (*40*); the interaction of bracken fern, a radiomimetic carcinogen, with papillomas of the alimentary tract in cattle to produce bovine alimentary tract carcinomas (*41*); and, in humans, the observation of increased incidence of laryngeal squamous cell carcinomas in juvenile patients with laryngeal papillomatosis who smoke or receive x-ray therapy (*42*).

In assessing the methodologic strengths and limitations of this study, it is noteworthy that the participation rates were close to 95% for both cases and controls. The use of hospital controls, excluding smoking-related diseases, might tend to overestimate risk in our study, but limiting the analysis to community controls did not produce different estimates. A potential recall bias exists regarding sexual behavior; patients may be more reliable reporters than controls, which could cause overestimation of the risk associated with sexual behavior. However, this bias could be offset by the higher education of the controls. It is unlikely that smoking practices would be reported differently by patients and controls, since subjects as well as interviewers were generally unaware of the hypotheses being tested. Interviewers knew the case-control status of the participant because this is difficult to conceal in the hospital and community setting. To avoid bias derived from this, detailed instructions and supervision on the method of interview were stressed. Laboratory tests for detection of HPV-DNA constitute a new and evolving field, and the sensitivity and specificity of the different hybridization techniques are still unknown, as well as the interlaboratory (*43*) and intertest reproducibility (*44,45*). Although Southern blot hybridization and filter in situ hybridization were found to be comparable in a recent limited survey (*27*), the exact meaning of a positive test result is still unclear.

In summary, our results provide evidence for a limited role of smoking in the etiology of cervical cancer, at least in this high-risk area, and are suggestive only of a cocarcinogenic effect of smoking in cervical cells with evidence of HPV type 16 or 18. More accurate means to detect HPV or other biologic agents, pharmacologic assessment of the metabolic pathways of tobacco-related carcinogens and their detection in specific anatomic sites, as well as carefully designed prospective studies are necesssary to better assess the separate role of each factor involved in the etiology of this fatal disease.

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