Short Communication

Population-Based Prevalence and Age Distribution of Human Papillomavirus Among Women in Santiago, Chile

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Abstract

More than 18 types of human papillomavirus (HPV) are associated with cervical cancer, the relative importance of the HPV types may vary in different populations.

Objective: **To investigate the types of HPV, age distribution, and risk factors for HPV infection in women from Santiago, Chile.**

Methods: **We interviewed and obtained two cervical specimens from a population-based random sample of 1,038 sexually active women (age range, 15-69 years). Specimens were tested for the presence of HPV DNA using a GP5+/6+ primer-mediated PCR and for cervical cytologic abnormalities by Papanicolaou smears.**

Results: **122 women tested positive for HPV DNA, 87 with high risk types (HR), and 35 with low risks (LR) only. Standardized prevalence of HPV DNA was 14.0% [95% confidence interval (95% CI), 11.5-16.4]. HR HPV by age showed a J reverse curve, whereas LR HPV showed a U curve, both statistically significant in comparison with no effect or with a linear effect. We found 34 HPV types (13 HR and 21 LR); HPV 16, 56, 31, 58, 59, 18, and 52 accounted for 75.4% of HR infections. Thirty-four (3.6%) women had cytologic lesions. Main risk factor for HPV and for cytologic abnormalities was number of lifetime sexual partners, odds ratios for ≥3 versus 1 were 2.8 (95% CI, 1.6-5.0) and 3.8 (95% CI, 1.3-11.4), respectively.**

Conclusions: **LR HPV presented a clear bimodal age pattern; HR HPV presented a J reverse curve. HPV prevalence was similar to that described in most Latin American countries.** (Cancer Epidemiol Biomarkers Prev 2004;13(12):2271–6)

Introduction

HPV prevalence and HPV types vary widely throughout the world (1). Here, we report the prevalence of HPV infection, the HPV types, and its associated risk factors in women from the general population of Chile. This is part of the IARC-coordinated multicenter study, with centralized HPV DNA detection. Field work was conducted from June 2000 to May 2001.

Materials and Methods

Study Population and Enrollment. We used a three-stage random sampling to select an age-stratified sample of 1,100 women (100 women in each of 11 age groups) living in the area served by El Roble Health Center, with a population of 32,085 inhabitants, in Santiago, Chile. We enumerated the 430 blocks in the area and, in each block, numbered all household units, before selecting one of every three houses. The interviewer classified by age all women living in the selected house and consulted a chart that indicated which of the eleven 5-year age groups (between 15 to 19 years of age and ≥65 years) should be obtained from that household. If there were more than one woman in the age group, the one with the age closest to the mean age of the group was selected. If there was no eligible woman in the desired age category, the interviewer moved to the next household to the right. If

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Written informed consent obtained from patients; study protocols were approved by the IARC Ethical Review Committee and the Hospital Sótero del Rio Human Research Committee.

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eligible women were absent, the interviewer revisited the house up to five times, at different hours and days, before eliminating the candidate. Eliminated candidates were not replaced. Women were eligible if they were older than 15 years and covered by the national health insurance system. The national health insurance system attends most (70%) of the Chilean population; the remainder, the population with higher incomes is covered by a private health insurance system. Women, who had had a hysterectomy, were pregnant, or had mental disabilities, were not eligible. Women with no history of sexual intercourse were interviewed but did not undergo pelvic examination. Eligible women, who accepted to participate, signed a consent form. The ethical committees of the Ministry of Health's South-Eastern Health Service and of IARC cleared the study protocol.

The study goal was 1,100 women, but we searched a larger number to compensate for noneligible candidates and refusals. A total of 1,567 women were contacted, 1,393 were eligible (noneligible were 137 who were not covered by national health insurance system, 31 who were pregnant, and 6 who had mental disabilities). A total of 1,221 women (87.6% of the eligible candidates; age range, 15-86 years) agreed to participate and were interviewed in their homes, using a structured questionnaire that explored in detail their sexual and reproductive histories and consumption of tobacco. They were scheduled to visit the El Roble Health Center for a pelvic examination. The supervision of the field work included verification of the selection procedures and repetition of 5% of the questionnaires.

Specimen Collection. Women (n = 1,038; 74.5% of eligible candidates) attended the health center where a midwife did a pelvic examination, obtained exfoliated cervical cells using an Ayre spatula for the ectocervix and a cytobrush for the endocervix, to prepare a cervical Papanicolaou (Pap) smear and took another cervical sample with a second Ayre spatula and placed it in tubes with PBS; the spatula and brush used for the Pap were also washed in the same PBS tube. A sample of 10 mL of blood was collected for serologic studies. Samples were kept at 4°C until processing in the central laboratory, where they arrived within 24 hours of collection.

The samples of exfoliated cervical cells were centrifuged at 3,000 g per 10 minutes, the resulting pellet diluted in saline solution, and poured into labeled tubes. Tubes were stored at −30°C until shipment to Amsterdam for HPV testing.

Pap smears were stained and read by trained cytopathologists in Chile, were supervised by a senior pathologist (R.P.), and were classified according to the Bethesda classification. All abnormal smears and a 10% random sample of the negatives were reexamined. Women who had an inadequate cytologic result were excluded from the analysis.

Women with abnormal cytology were followed, according to the guidelines of the National Cancer Program of Chile. HPV results were not taken into consideration for the clinical management of women.

HPV DNA Detection Techniques. HPV DNA testing was done on exfoliated cell samples in the pathology laboratory of Vrije University, Amsterdam. To analyze the quality of target DNA, β-globin gene-specific primers were used, and only β-globin positive samples were included. Fifty (4.8%) of the 1,038 were β-globin negative, 8 women did not have an HPV test, 3 women had no Pap smear, and in 22 the Pap smear was reported as inadequate. Thus, adequate DNA for HPV testing and Pap smears were available for 955 women, who are the subject of our present report.

HPV DNA positivity was assessed using a general primer-mediated GP5+/6+ PCR. PCR positivity was assessed by hybridization of PCR products in an enzyme immune assay, using two HPV oligoprobe cocktails that together detect the following 44 HPV types: 6, 11, 16, 18, 26, 30 to 35, 39, 40, 42 to 45, 51 to 59, 61, 64, 66 to 69, 70, 71 (equivalent to CP8061); 72, 73, 81 (equivalent to CP8304); 82 (IS39 and MM4 subtypes); 83 (equivalent to MM7); 84 (equivalent to MM8); cond85, 86, JC9710 and CP6108 (2). The sensitivity and specificity of enzyme immune assay detection were previously determined using dilution lines of cloned HPVs or cervical smears in which these types were identified in earlier studies (3). In addition, HPV positivity was assessed by low stringency Southern blot analysis of PCR products with a cocktail probe of HPV-specific DNA fragments (4). Subsequently, GP5+/6+ PCR was repeated on positive samples in triplicate to generate sufficient products for further typing. After pooling these PCR products, typing was done using enzyme immune assay and HPV type-specific oligoprobes for the HPV types listed above (5). Samples that were GP5+/6+ positive by low-stringency Southern blot analyses but could not be identified by enzyme immune assay were considered to be uncharacterized HPV types. Special precautions were taken to minimize false positive results of PCR, as described in detail elsewhere (4).

HPV types considered high risk (HR) for this analysis included all those described by Muñoz et al. (6): 6, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68.73, 82; but in the final analysis, the HR group types 26, 53, and 66 were left out. Low-risk (LR) types included all other HPV tested. Infection with more than one HPV type was considered to be HR if any HPV detected was a HR type.

Statistical Methods. We calculated crude and age-adjusted prevalence of HPV infection, using the Chilean population and the world standard population as the reference. Odds ratio (OR) for HPV DNA detection and corresponding 95% confidence interval (95% CI) were computed by means of unconditional logistic regression models. Age-adjusted (in six age groups: <25, 25-34, 35-44, 45-54, and 55-64) ORs are presented. Tests for the linear trend of the ORs were done, giving an increasing score for each level of the categorized variable and fitting them in the model as a continuous variable. All tests were two tailed. When analyzing LR or HR only types the reference were the HPV negative women. Age prevalence of HR and LR HPV were analyzed with a logistic regression model in which the linear predictor was explained by a smooth function of the age covariate (7). The smooth term was represented using a penalized cubic regression spline with smoothing parameter selected with the generalized cross validation criterion (8). The generalized cross validation score approximates the weighed sum of prediction errors resulting from leaving out each observation in turn and predicting its

value form the other $n - 1$ observations. The significance of the smooth term was tested based on the change in the residual deviance with respect to the null model and to the linear model.

Results

We found a total of 164 HPV infections (among 122 women infected); HR HPV types were more frequent than LR types (106 versus 58 infections). Ninety (54.9%) of HPV infections involved a single type. The most common HR types, by frequency, were HPV 16, 56, 31, 58, 59, 18, and 52, which accounted for 82.8% (48 of 58) of single HR infections and 75.5% (80 of 106) of total HR infections (Table 1).

Overall, 122 women were infected with HPV (87 with HR HPV and 35 with LR HPV only) for a crude prevalence of 12.8% (95% CI, 6.9-18.7). HPV prevalence standardized by the world population was 14.0% (95% CI, 11.5-16.4). The prevalence by age showed a bimodal curve, statistically significant compared with no effect or with linear effect (i.e., high prevalence in young and old ages with a nadir in middle age) for both HR ($P = 0.007$) and LR HPV ($P = 0.006$). For HR HPV, the larger branch of the U curve was in the younger ages, constituting a reverse J curve; the LR HPV had a U-shaped curve with a slightly larger branch in the older groups (Fig. 1). The HR/LR HPV ratio peaked at ages 15 to 19 (4.3 and thereafter decreased to 1.7 at 60-64 years of age); LR was less frequent in young women.

Table 1. HPV infections by HPV type, multiplicity of infection, and cytological findings among 955 women (Chile, 2000-2001)

HPV type	Normal cytology			Abnormal cytology			Total		
	Single	Multiple	Total (%)	Single	Multiple	Total (%)	Single	Multiple	Total (%)
HPV−			818			15			833
HPV+	75	28	103 (11.2)	15	4	19 (55.9)	90	32	122 (12.8)
HR HPV+	46	25	71 (7.7)	12	4	16 (47.1)	58	29	87 (9.1)
LR HPV+	29	3	32 (3.5)	3	0	3 (8.8)	32	3	35 (3.7)
HR infections									
16	14	6	20 (2.2)	5	0	5 (14.7)	19	6	25 (2.6)
18	4	0	4 (0.4)	0	1	1 (2.9)	4	1	5 (0.5)
31	1	4	5 (0.5)	4*	0	4 (11.8)	5	4	9 (0.9)
33	1	0	1 (0.1)	1	0	1 (2.9)	2	0	2 (0.2)
35	1	2	3 (0.3)	0	0	0	1	2	3 (0.3)
39	2	4	6 (0.7)	0	1	1 (2.9)	2	5	7 (0.7)
45	2	4	6 (0.7)	0	0	0	2	4	6 (0.6)
51	1	5	6 (0.7)	0	0	0	1	5	6 (0.6)
52	4	3	7 (0.8)	0	1	1 (2.9)	4	4	8 (0.8)
56	6	6	12 (1.3)	0	2†	2 (5.9)	6	8	14 (1.5)
58	4	5	9 (1.0)	1	0	1 (2.9)	5	5	10 (1.0)
59	4	4	8 (0.9)	1†	0	1 (2.9)	5	4	9 (0.9)
73	2	0	2 (0.2)	0	0	0	2	0	2 (0.2)
Subtotal	46	43	89	12	5	17	58	48	106
LR infections									
6	0	2	2 (0.2)	0	0	0	0	2	2 (0.2)
11	2	2	4 (0.4)	0	0	0	2	2	4 (0.4)
30	0	0	0	0	1†	1 (2.9)	0	1	1 (0.1)
32	0	1	1 (0.1)	0	0	0	0	1	1 (0.1)
40	1	1	2 (0.2)	0	0	0	1	1	2 (0.2)
42	4	3	7 (0.8)	0	0	0	4	3	7 (0.7)
43	1	2	3 (0.3)	0	0	0	1	2	3 (0.3)
53	1	1	2 (0.2)	1	0	1 (2.9)	2	1	3 (0.3)
54	1	0	1 (0.1)	0	0	0	1	0	1 (0.1)
55	1	0	1 (0.1)	0	0	0	1	0	1 (0.1)
64	2	0	2 (0.2)	0	0	0	2	0	2 (0.2)
66	3	1	4 (0.4)	0	1	1 (2.9)	3	2	5 (0.5)
67	2	3	5 (0.5)	1	0	1 (2.9)	3	3	6 (0.6)
70	5	0	5 (0.5)	1	1	2 (5.9)	6	1	7 (0.7)
72	0	1	1 (0.1)	0	0	0	0	1	1 (0.1)
81	3	2	5 (0.5)	0	0	0	3	2	5 (0.5)
83	1	1	2 (0.2)	0	0	0	1	1	2 (0.2)
85	1	0	1 (0.1)	0	0	0	1	0	1 (0.1)
86	1	0	1 (0.1)	0	0	0	1	0	1 (0.1)
CP6108	0	2	2 (0.2)	0	0	0	0	2	2 (0.2)
JC9710	0	1	1 (0.1)	0	0	0	0	1	1 (0.1)
Subtotal	29	23	52	3	3	6	32	26	58
Total	75	66	141	15	8	23	90	74	164

*Includes two HSIL or worse.
†Includes one HSIL or worse.

History of a previous cytology was reported by 79% of women; those who never had a Pap had a significant higher risk of HPV infection compared with those who had a Pap (OR, 1.6; 95% CI, 1.02-2.51). Nine hundred twenty-one women (96.4%) had normal Pap and 34 (3,6%) had cytologic lesions; HPV was isolated in 11.2% and 55.9% of women with normal and abnormal cytology, respectively.

Univariate analysis, age-adjusted, showed a tendency among less educated women to have higher HPV prevalence, but this risk trend was of borderline statistical significance (Table 2). Women who smoked at some time were at increased risk of HPV infection, but risk did not change with number of cigarettes. Single, widowed, or divorced women had higher HPV infection, compared with those that were married, but with borderline statistical significance (Table 2). Parity and age at menarche were not associated with HPV infection (data not presented). There was a trend of higher prevalence of HPV with younger age at first intercourse, but did not reach statistical significance (Table 2).

Number of sexual partners was the strongest risk factor for HPV infection, with a significant linear trend in risk. Women who reported their husbands had extramarital sexual relationships had a higher prevalence of HPV, but this did not reach statistical significance (Table 2). There was a slightly higher risk of HPV among users of oral and injectable contraceptives, but neither reached statistical significance. The OR for short-term oral contraceptive users was higher than for long-term oral contraceptive users (Table 2).

We evaluated the combined effect of significant risk factors for any HPV infection for women <35 and >35 years of age; and for HR, LR, single and multiple infections (data not presented). Among women <35 years of age, being single, and having had >3 sexual partners were significant risk factors for any HPV infection. Whereas among women ages ≥35, the only significant risk factor was having had >3 sexual partners. The only significant risk factor for LR HPV was being single. Risk factors for HR HPV were being <25 years of age and the number of sexual partners.

The only significant risk factor for cytologic abnormality was lifetime number of sexual partners; OR for ≥3 versus 1 was 3.8 (95% CI, 1.3-11.6). Cytologic abnormalities showed a similar age distribution to HPV positivity. Marital status, smoking, and oral contraceptive use were not associated with cytologic abnormalities (data not presented).

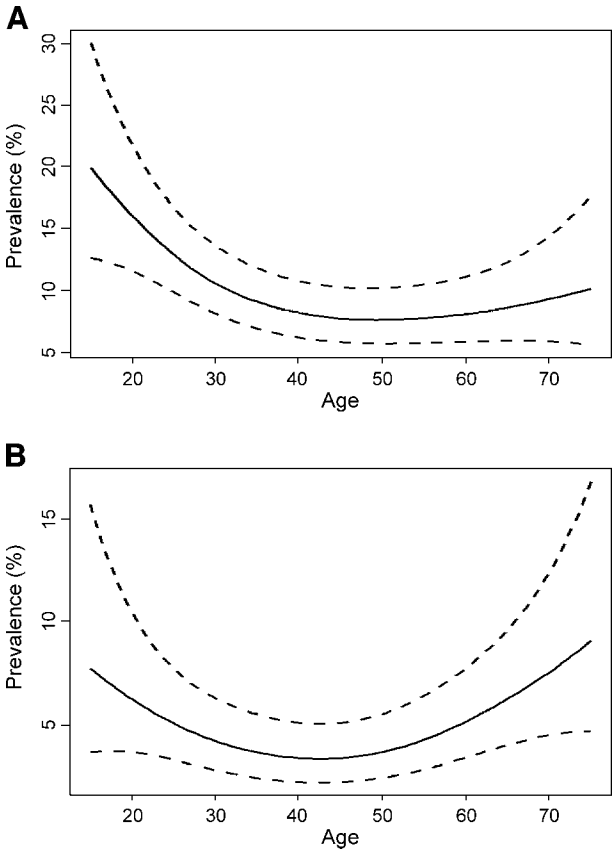

Figure 1. A. Prevalence of HR HPV by age groups among 955 women (Chile, 2000). Nonparametric regression and 95% CIs. **B.** Prevalence of LR HPV by age groups among 955 women (Chile, 2000). Nonparametric regression and 95% CIs.

Discussion

The level of HPV infection (14.0%) among Chilean women is similar to the prevalence described in other Latin American countries: Mexico, 14.5%; Costa Rica, 16.0%; and Colombia, 14.8% (9-11), but higher than in many parts of Europe (2, 12) and Asia (13, 14).

We found 15 HR HPV types, most of the HPV types associated to invasive cervical cancer worldwide (6, 15). We did not find HPV types 26, 68, and 82, or any unclassified type. HPV types in our study are comparable with the findings from other Latin American countries.

The main risk factor for HPV infection was number of sexual partners, in agreement with most previous work in different parts of the world (16-18). As described by other authors (19), number of sexual partners was a stronger risk factor for HR HPV than for LR HPV.

This is the first study to explore the age distribution with nonparametrical models. For HR HPV, the curve was a reverse J, indicating that the risk peaked at younger ages then steadily fell to flatten around 40 years old. After age 70, there was an indication of a new increase, but its confidence interval was too wide (Fig. 1). For LR HPV, the age curve had a U shape: with a first peak <25 years and a second and even larger peak >60 years of age, its nadir was at 40 years of age (Fig. 1B). Similar LR HPV distribution was described in the Netherlands (2). The increase of LR HPV could be the result of the selective elimination of HR HPV by treatment (2), but it does not explain the absolute increase in the LR HPV prevalence to reach a second peak, even higher than that at younger ages. Similarly to our findings in Chile, in Colombia and Costa Rica, the second wave is mostly due to LR HPV, whereas in Mexico, the increase is caused by both HR and LR; the persistence and increase of HR HPV in Mexico

Table 2. OR and 95% CI of HPV infection by selected characteristics among 955 women (Chile, 2000-2001)

Selected characteristics		HPV Neg	HPV Pos	% Pos	OR* (95% CI)
Age (y); χ^2 per trend, 1.65; $P = 0.20$	<25†	104	30	22.4	1
	25-34	163	22	11.9	**0.5 (0.3-0.9)**
	35-44	197	18	8.4	**0.3 (0.2-0.6)**
	45-54	151	17	10.1	**0.4 (0.2-0.7)**
	55-64	137	20	12.7	**0.5 (0.3-0.9)**
	> 65	81	15	15.6	0.6 (0.3-1.3)
Education (years in school); χ^2 per trend 3.67; $P = 0.06$	> 12†	178	24	11.9	1
	8-11	306	42	12.1	1.2 (0.7-2.0)
	4-7	216	33	13.3	1.4 (0.8-2.6)
	<3	133	23	14.7	1.6 (0.8-3.4)
Smoking; χ^2 per trend 7.12; $P = 0.01$	Never†	378	38	9.1	1
	Former	131	20	13.3	1.5 (0.8-2.6)
	Current				
	< 5 cigarette/d	165	35	17.5	**2.1 (1.2-3.5)**
	> 5 cigarette/d	155	29	15.8	**2.0 (1.2-3.5)**
	Ever	451	84	15.7	**1.8 (1.2-2.8)**
Marital status	Married†	644	78	10.8	1
	Single	73	20	21.5	1.6 (0.9-3.0)
	Separated/divorced/widowed	116	24	17.1	**1.8 (1.0-3.3)**
Age at first sexual intercourse; χ^2 per trend: 1.78; $P = 0.18$	> 21†	190	20	9.5	1
	19-20	135	17	11.2	1.2 (0.6-2.4)
	17-18	252	37	12.8	1.3 (0.7-2.3)
	<17	247	47	16.0	1.5 (0.8-2.7)
No. lifetime sexual partners; χ^2 per trend: 15.55; $P < 0.001$	1†	532	57	9.7	1
	2	223	43	16.2	**1.8 (1.2-2.8)**
	> 3	71	21	22.8	**2.8 (1.6-5.0)**
Husband extramarital sexual relations	No†	331	45	12.0	1
	Uncertain	92	9	8.9	0.7 (0.3-1.6)
	Yes	403	67	14.3	1.3 (0.9-2.0)
Condom use	Never†	698	106	13.2	1
	Ever	127	15	10.6	0.8 (0.4-1.2)
Intrauterine device use	Never†	232	45	16.3	1
	Ever	601	77	11.4	0.8 (0.5-1.2)
Injectable contraceptive use	Never used hormonal contraceptive†	491	64	11.5	1
	Ever	48	9	15.8	1.8 (0.8-4.0)
Oral contraceptive use	Never†	502	69	12.1	1
	Ever	322	52	13.9	1.3 (0.8-1.9)
	Current	81	16	16.5	1.4 (0.7-2.6)
	Former	242	36	13.0	1.2 (0.8-1.9)
Duration oral contraceptives; χ^2 per trend: 0.02; $P = 0.89$	<3	140	36	20.5	**1.9 (1.2-3.0)**
	≥3	183	16	8.0	0.7 (0.4-1.3)

NOTE: Some strata do not add up to the total because of missing values.
Abbreviations: neg, negative; pos, positive.
*Adjusted by age ($P < 0.05$, in bold).
†Reference category.

may reflect the historical lack of impact of its cancer prevention program. A bimodal age curve for HPV infection was also suggested by the data in Spain (12). In Thailand, an increase in LR HPV with age was found, reaching statistical significance when comparing women over 65 with those ages 35 to 44 (14). In Vietnam, in Ho Chi Minh, but not in Hanoi, a slight increase in HPV prevalence after age 54 was found (13). This bimodal curve has not been seen in South Korea, where HPV prevalence steadily decreases at older ages (20).

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