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Burden of Human Papillomavirus Infection in Latin America

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1. Introduction

Human papillomavirus (HPV)-associated disease is an important public health problem worldwide. HPV is not only associated with 530,000 new cases of cervical cancer and 275,000 cervical cancer deaths worldwide each year but also causes vulvar, vaginal, anal, and penile cancers as well as cervical and vulvar/vaginal precancerous lesions, genital warts, and respiratory papillomatosis. Most individuals are not aware that they are infected with HPV because of its subclinical or asymptomatic presentation, and thus, the virus can be spread easily and unknowingly during sexual foreplay or sexual intercourse [1].

Cervical HPV infection is the most prevalent sexually transmitted disease [2]. HPV is so common that more than half of all sexually active adults will be infected in their lifetime, although young, sexually active women bear the brunt of both infection and clinical complications. The Centers for Disease Control estimates that at least half of all sexually active individuals will acquire HPV at some point in their lives, and at least 80% of women will acquire an HPV infection by age 50 [3]. At least 50% of men will acquire a genital HPV infection during their lifetime [1].

In 1995, the International Agency for Research on Cancer (IARC) first classified HPV types 16 and 18 as carcinogenic to humans, but based on more recent evidence, the list of carcinogenic HPV types has been expanded to include a total of 13 genital mucosotropic HPV types as being definite or probable carcinogens (grade 1 or 2a) based on their frequent association with invasive cervical cancer (ICC) (4). The causal role of HPV in all cancers of the uterine cervix has been firmly established biologically and epidemiologically. The proteins of the early genes E6 and E7 of the high-risk HPV types act as oncoproteins and play a key role in

carcinogenesis [5]. HPV-16 and -18 account for approximately 70% of cancers of the cervix, vagina, and anus and approximately 30–40% of cancers of the vulva, penis, and oropharynx. Other cancers that are causally linked to HPV include non-melanoma skin cancer and cancer of the conjunctiva. Although HR-HPV infection is a necessary cause of cervical cancer, it is not a sufficient cause [6].

For the vast majority of people, these infections will be asymptomatic and will clear within 1–2 years [7-12]; however, a substantial increase in the risk for cervical cancer exists for women who develop persistent infection with HR-HPV [13-16]. Infection with low oncogenic risk HPV types (LR-HPV) is also responsible for considerable morbidity associated with benign lesions known as condyloma acuminata (genital warts) and a proportion of low-grade squamous intraepithelial cervical lesions [17-19].

Because cervical cancer affects relatively young women, it represents the single biggest cause of years of life lost (YLL) from cancer in the developing world, contributing more to this burden of disease measure than tuberculosis, maternal conditions or acquired immunodeficiency syndrome (AIDS). In developed countries, Papanicolaou (PAP) smear test screening has decreased the incidence of cervical cancer by approximately 70% in recent decades; however, cervical cancer still represents a major public health issue in Latin America because of the failure of prevention programs [20].

Cervical cancer is the third most common malignancy in women worldwide and the second most common malignancy in women living in developing countries. More than 85% of the global burden occurs in developing countries. Cervical cancer accounts for 13% of all female cancers, and South America is a high-risk region (2.5%); approximately 88% of deaths occur in developing countries. These differences between countries are believed to reflect protection through screening, differences in exposure to HPV and other cofactors. HPV is associated with 68,220 new cases of cervical cancer and 31,712 associated cervical cancer deaths in Latin America each year [21]. Cervical cancer is a major public health problem in Latin America, which has some of the highest incidence and mortality rates worldwide. Information on HPV prevalence and type distribution in several countries in Latin America is crucial to predict the future impact of HPV16/18 vaccines and screening programs and to establish appropriate post-vaccine virological surveillance.

The discovery of HPV infection as a necessary cause of cervical cancer has created many new paths for prevention. The most promising strategies include screening for infection with HR-HPV types and immunization to prevent infection with HR-HPV types. Unfortunately, many developing countries that have invested in screening programs have yet to witness a substantial reduction in cervical cancer [22]. HPV DNA testing has been suggested as an alternative to primary screening; HPV DNA testing is less dependent on the quality of personnel training [23-26]. Prophylactic HPV vaccination, which currently protects against the most common LR-HPV types (HPVs 6 and 11) and HR-HPV types (HPVs 16 and 18), offers the greatest potential to reduce the burden of ICC and other HPV-related diseases [1]. In many of the nations where the burden of HPV and cervical cancer is the highest, vaccination and HPV testing remain too expensive.

In this chapter, we will discuss HPV infection and provide data on HPV prevalence and genotype distribution, risk factors for HPV infection, co-factors associated with HSIL or ICC progression, the burden of cervical cancer and prevention strategies. All of these topics will be discussed in the context of Latin America. We hope that this chapter will provide researchers with important up-to-date information concerning the problem of HPV infection and HPV-associated cancers in Latin America.

2. HPV prevalence and genotype distribution

The establishment of the etiologic role of HPV on cervical cancer and the development of proposals for preventive and clinical applications have prompted considerable interest in exploring the epidemiological characteristics of HPV infection in different populations.

Worldwide, there are important variations in the prevalence of HPV in different age groups. Although in the United States, Europe, and some Asian countries, HPV prevalence declines with age [27-30], in Latin American countries, the majority of studies with age-specific HPV prevalence data have shown a slight U-shaped curve [31]. Overall, HPV prevalence in the Latin American and Caribbean (LAC) population has been found to be 2-fold higher than the average worldwide prevalence [32]. Different studies from countries in Latin America have assessed the prevalence of HPV infection and types in healthy women [33] and patients with pre-neoplastic and neoplastic cervical lesions (HSIL, ICC) [20]. These studies showed prevalence rates of HPV infection of 16.1%, 82% and 89% in NC, HSIL and ICC, respectively. The most prevalent HPV types were the following: NC (HPV-16, 31, 18, 58, and 6), HSIL (HPV-16, 18, 58, 31, and 33), and ICC (HPV-16, 18, 31, 45, and 33). See Tables 1 and 2.

Country	More prevalent HPV types	Cyto-histological diagnosis	HPV prevalence (%)	References
Argentina	16,18,6,11,31,58	NC	26 - 43	[34 - 39]
		LSIL	33.1 - 96	
		HSIL	71.4 - 100	
		ICC	100	
Bolivia	6,11,26, 52,66,39	NC	5.9	[40]
		LSIL	NR	
		HSIL	NR	
		ICC	NR	

Country	More prevalent HPV types	Cyto-histological diagnosis	HPV prevalence (%)	References
Brazil	16,18,33,6,11,58	NC	12 - 25	[41 - 50]
		LSIL	26.4 - 90.4	
		HSIL	57 - 100	
		ICC	41.8 - 93	
Chile	16,18,31,33,45,52	NC	11.2 - 40	[51 - 58]
		LSIL	61.2 - 100	
		HSIL	55.9 - 100	
		ICC	71 - 95	
Colombia	16,18,31,58,33,45	NC	10.5 - 39.1	[10, 59 - 64]
		LSIL	46.9 - 83.9	
		HSIL	53.8 - 91.8	
		ICC	70 - 100	
Ecuador	16,31,18,6,52,56	NC	20 - 20.6	[65 - 68]
		LSIL	44.8 - 76.9	
		HSIL	50 - 100	
		ICC	81	
Paraguay	16,18,33,31,45, 52	NC	25	[69 - 71]
		LSIL	68	
		HSIL	78	
		ICC	97	
Perú	16,18,31,35,45,52	NC	13.4 - 17.7	[72, 73]
		LSIL	NR	
		HSIL	NR	
		ICC	92 - 95.3	
Venezuela	16,18,33,45,52,58	NC	NR	[74, 75]
		LSIL	68	
		HSIL	92.8 - 95.3	
		ICC	98.7 - 98.9	

Table 1. HPV prevalence and more frequent HPV types in South America.

Country	More prevalent HPV types	Cyto-histological diagnosis	HPV prevalence (%)	References
Costa Rica	16,18,58,31,33	NC	11 - 22.4	[76, 77]
		LSIL	73 - 80.9	
		HSIL	87.5 - 89	
		ICC	88 - 97.1	
Cuba	16,31,52,66,18	NC	NR	[78]
		LSIL	33.3	
		HSIL	55.6	
		ICC	NR	
Guatemala	16,18,56,66,35	NC	33.6 - 59	[79]
		LSIL	NR	
		HSIL	NR	
		ICC	82.6 - 95.2	
Honduras	16,18,31,58,45,11,51	NC	39.5 - 51	[80 - 83]
		LSIL	47.7 - 81	
		HSIL	66.7 - 97	
		ICC	80 - 93	
Mexico	16,18,31,58,45,59	NC	8.8 - 40.9	[28, 84 - 91]
		LSIL	24 - 94.5	
		HSIL	29.4 - 93.7	
		ICC	84.6 - 100	
Nicaragua	16,58,31,52,51	NC	48.1	[92]
		LSIL	67.5	
		HSIL	86.8	
		ICC	94.7	
Panama	16 ^a	NC	NR	[93]
		LSIL	NR	
		HSIL	NR	
		ICC	70	

Table 2. HPV prevalence and more frequent HPV types in Central America and Mexico.

^a Only HPV 16 was detected.

3. Risk factors for HPV infection and co-factors associated with HSIL or ICC progression

Epidemiological studies investigating risk factors for HPV infection have clearly and consistently shown that sexual behavior patterns influence the acquisition of HPV because

the primary mode of transmission of HPV is sexual. Sexual behavior patterns include early age at first sexual intercourse, the number of sexual partners, and the sexual behavior of male partners [32].

Almost all cases of cervical cancer are attributable to persistent HPV infections, leading to the conclusion that HPV infection is a necessary cause of the disease [94]. Follow-up studies of women with and without cervical abnormalities have indicated that the continuous presence of HR-HPV is necessary for the development, maintenance and progression of cervical intraepithelial neoplasia (CIN) [9-13]. However, only a small fraction of women with cervical HPV infection develop ICC, suggesting that other co-factors in addition to HPV are necessary to cause cancer progression. High parity, the long-term use of oral contraceptives, cigarette smoking, and co-infection with human immunodeficiency virus (HIV) have been described [32].

Tables 3 and 4 describe the co-factors associated with HPV infection and co-factors associated with HSIL or ICC progression in several studies from Central and South America, respectively.

Country	Co-factors	Reference
Argentina	Number of sexual partners, <i>C. trachomatis</i> infection or history of previous sexually transmitted diseases, early age at first intercourse, early age at first pregnancy.	[35, 36, 38, 95]
Brazil	Marital status, age under 30, number of sexual partners, sexually transmitted diseases, alcohol abuse, sexual behavior.	[49,96]
Colombia	Number of sexual partners, indigenous ethnicity, no history of previous pregnancies, nulliparity, early age at first intercourse, <i>C. trachomatis</i> infection, high parity.	[97 - 99]
Costa Rica	High vaginal pH, <i>C. trachomatis</i> infection, number of sexual partners.	[77, 100]
Cuba	Parity, early age at first sexual intercourse.	[78]
Ecuador	Number of sexual partners.	[66]
Guatemala	Occasional partner during the last 6 months and smoking habit.	[79]
Honduras	Sexual behavior, smoking, exposure to wood smoke and low socioeconomic status, single female.	[82, 83, 101, 102]
Mexico	Age, marital status, number of sexual partners, infection with <i>C. trachomatis</i> , progesterone-based contraceptives, history of sexually transmitted diseases and use of emergency contraceptive pill.	[28, 103, 104]
Peru	Early age at first sexual intercourse and number of sexual partners.	[105]

Table 3. Co-factors associated with HPV infection in Latin America.

Country	Co-factors	Reference
Brazil	Age ^a , ethnicity ^b , early age at first sexual intercourse ^c , number of sexual partners ^d , history of sexually transmitted diseases or concurrent sexually transmitted disease ^e , smoking habit ^f , <i>C. trachomatis</i> infection ^g .	[41, 44, 106, 107]
Colombia	Parity ^h , exposure to wood smoke ⁱ , viral load ^l .	[61, 108]
Costa Rica	Number of live births ^k , use of oral contraceptives ^l and smoking habit ^f .	[109]
Honduras	Number of sexual partners ^d , parity ^h , early age at first sexual intercourse ^c , exposure to wood smoke ⁱ , low socioeconomic status ^m , absence of Pap smear screening ⁿ .	[80, 82]
Mexico	Age ^a , early age at first sexual intercourse ^c , number of sexual partners, parity ^h , viral load ^l .	[84, 88, 110]
Panama	Early age at first sexual intercourse ^c , parity ^h , absence of Pap smear controls ⁿ , smoking habit ^f .	[93]
Paraguay	Parity ^h , early age at first intercourse ^c , no schooling ^o , number of sexual partner ^d and absence of Pap smear screening ⁿ .	[69]
Peru	Parity ^h , age ^a , no schooling ^o , lack of good-quality screening and of adequate follow-up care ^p , long-term use of oral contraceptives ^q and smoking habit ^f .	[72, 105]

Measures of risk (OR or RR) and their corresponding 95% CI and reference.

^a OR 231 [25,48-2108,63] Ref 41; OR 2,1 [1,1-4,1] Ref 110.

^b OR 5,77 [2,76-12,09] Ref 41.

^c OR 6,83 [1,46-32,02] Ref 41; OR 1,26 [0,76-2,08] Ref 82; OR 2,11 [1,2-3,6] Ref 110; OR 8,5 [4,4-16,8] Ref 84; OR 1,91 [1,2-3] Ref 93; OR 7,8 [3,4-17,7] Ref 69.

^d OR 5,43 [2,58-11,40] Ref 41; OR 2,25 [1,32-3,82] Ref 82; OR 7,4 [3,8-14,5] Ref 69.

^e OR 13 [1,9-56,3] Ref 44, 106.

^f OR 11,24 [5,09-24,83] Ref 41; RR 2,7 [1,1-6,7] Ref 109; OR 1,86 [1,1-3,1] Ref 93.

^g OR 2,1 [1,1-4] Ref 107.

^h OR 4,1 [1,6-10,6] Ref 108; OR 6,3 [1,36-2,98] Ref 80; OR 10,9 [2,6-46,5] Ref 84; OR 1,87 [1,2-3] Ref 93; OR 9,3 [3,6-23,9] Ref 69; OR 8,3 [1-65,6] Ref 105; OR 6,5 [1,1-6,93] Ref 72.

ⁱ OR 7,3 [3-19,4] Ref 108; OR 4,89 [0,51-47,1] Ref 80.

^j OR 13,4 [2,4-74] Ref 61; OR 3,51 [2,2-5,6] Ref 110; OR 365,8 [94,7-1412] Ref 88.

^k RR 3,7 [1,8-7,4] Ref 109.

^l RR 1,6 [0,89-2,9] Ref 109.

^m OR 1,8 [1,2-2,5] Ref 82.

ⁿ OR 2,31 [1,16-4,63] Ref 82; OR 2,88 [1,8-4,5] Ref 93; OR 23,9 [10,4-54,9] Ref 69.

^o OR 27,7 [9,6-79,9] Ref 69; OR 3,2 [1,3-8,3] Ref 105.

^p OR 29,4 [3,6-240,1] Ref 105.

^q OR 2,6 [0,9-7,6] Ref 72.

Table 4. Co-factors associated with HSIL or ICC progression in Latin America.

4. Burden of cervical cancer

After breast and colorectal cancer, cervical cancer is the third leading cancer site worldwide, and it is second among women. The incidence of cervical cancer in Latin America is among the highest in the world. Cervical cancer incidence and mortality are a significant public health problem. In total, 85% of the global burden of cervical cancer occurs in developing countries, where it accounts for 13% of all female cancers. South America is a region of high risk. In 2008, cervical cancer was responsible for 275,000 deaths, 31,400 in Latin America and the Caribbean [21].

In Latin American countries, the incidence and mortality of ICC ranges from 14.4 to 39.9 and 6.8 to 20.6 cases per 100,000 women, respectively, with the highest incidence and mortality rates in Nicaragua (39.9 and 20.6, respectively, Table 5). The data were taken from Globocan (<http://globocan.iarc.fr/factsheets/cancers/cervix.asp>). These differences between countries are most likely a reflection of screening programs and differences in exposure to HPV and other cofactors.

5. Prevention strategies

Cervical cancer caused by HPV is a major public health problem that can be prevented with cervical cancer screening programs. Public health programs for cervical cancer screening with cytology and the effective treatment of early pre-cancers and cancers have resulted in a major reduction in mortality from cervical cancer. Unfortunately, cervical cancer screening programs have not yet been successful in most developing countries [111], despite the highest burden of cervical cancer in these countries [21].

In Colombia, supply problems are found in cervical cancer in terms of structure, processes and results [112]. The follow-up for women with abnormal cytology has not been carried

out, information systems are insufficient, and problems in the quality of cytology readings have been reported ([112, 113]. These deficiencies explain, in part, the low impact that screening has had on cervical cancer in Colombia, and the national screening and diagnostic services offered are not organized into a structured program [112].

Country	Incidence rate (per 100,000 women)	Mortality rate (per 100,000 women)
Argentina	17.5	7.4
Bolivia	36.4	16.7
Brazil	24.5	10.9
Chile	14.4	6.6
Colombia	21.5	10.0
Costa Rica	17.5	6.7
Cuba	23.1	8.9
Ecuador	27.1	13.3
Guatemala	30.5	15.2
Honduras	37.8	19.7
Nicaragua	39.9	20.6
Panama	25.3	12.6
Paraguay	35.0	16.6
Peru	34.5	16.3
Uruguay	16.5	6.8
Venezuela	31.4	14.4

Table 5. Incidence and mortality rates for ICC in Latin America.

To screen successfully in LAC, the screening programs must follow the requirements of low-resource settings: screening, diagnosis and treatment provided on-site or in clinics accessible to the majority of at-risk women; a low-cost, low-technology screening test that can lead to the immediate treatment of abnormalities; wide coverage of at-risk women; appropriate ed-

educational programs directed toward health workers and women to ensure correct implementation and high participation; and a built-in mechanism for evaluation of the screening program [22].

With the advent of newer technology, such as HPV vaccines and HPV tests, followed by simple well-known techniques, such as Pap, VIA and cryotherapy, cervical cancer rates may start to decrease worldwide. Prophylactic HPV vaccines containing oncogenic types HPV-16 and 18 can prevent up to 65–70% of cervical cancer deaths. However, they have yet to become accessible to poorer countries, where the greatest burden of disease exists. The price per dose is expensive for use in most countries in LAC. This situation is extremely disappointing because the experience of resource-poor countries in LAC has demonstrated that vaccination programs have been very effective. The results from different countries in Latin America have indicated that HPV testing has a greater sensitivity to detect CIN 2/3 and ICC than the Pap test [114-116], and HPV typing is an inexpensive and effective method for identifying cervical neoplasia and women at risk of developing cervical neoplasia; HPV typing improves quality control for both false-negative and false-positive cytology results [117].

The screening guidelines of the American College of Obstetricians and Gynecologists indicate that if HPV testing is used in combination with Pap smears, women who are negative for both tests should return to be tested in three years [35]. This strategy minimizes unnecessary follow-up visits and invasive procedures without compromising the detection of disease. This scheme is more appropriate for communities with limited access to public health services, such as countries in Latin America.

Different studies in countries in Latin America have described recommendations for successful screening programs, such as greater HPV education of the public and health care practitioners [118]; educational interventions for physicians in screening and management norms [119]; the implementation of sex education in schools and the promotion of condom use and an organized screening program to prevent cervical cancer in young women [120]; a screening program with high follow-up rates, not only high coverage [121]; and behavioral measures, including delaying sexual intercourse and the regular use of latex condoms [66]. HPV information is complex, and many women remain confused after reading educational materials; thus, it is important to ensure that HPV information is accessible to people at all levels [23].

The Regional Strategy for Comprehensive Cervical Cancer Prevention and Control proposes to improve country capacity for the sustained implementation of comprehensive cervical cancer prevention and control programs, with the goal of reducing incidence and mortality. It promotes an integrated package of services for health information and education; screening of asymptomatic women and pre-cancer treatment (improving the quality of screening tests; considering introducing HPV DNA testing to triage HPV-positive women for further testing; increasing the screening coverage of women in the at-risk age group (>30 years); and increasing the proportion of timely and appropriate follow-up care for women with abnormal screening test results); invasive cervical cancer treatment and palliative care; and evidence-based policy decisions on whether and how to introduce HPV vaccines [122].

6. Conclusion

Cervical HPV infection is the most prevalent sexually transmitted disease. HPV is so common that more than half of all sexually active adults will be infected in their lifetime, although young, sexually active women bear the brunt of both infection and clinical complications. The Centers for Disease Control estimates that at least half of all sexually active individuals will acquire HPV at some point in their lives, whereas at least 80% of women will acquire an HPV infection by age 50. At least 50% of men will acquire a genital HPV infection during their lifetime. In developed countries, PAP smear test screening has decreased the incidence of cervical cancer by approximately 70% in recent decades; however, cervical cancer still represents a major public health issue in Latin America and the Caribbean because of the failure of prevention programs.

Cervical cancer is a major public health problem in Latin America, which has some of the highest incidence and mortality rates worldwide. Information on HPV prevalence and type distribution in several countries in Latin America is crucial to predict the future impact of HPV16/18 vaccines and screening programs and to establish appropriate post-vaccine virological surveillance, primarily with the information obtained from high-grade cervical lesions and invasive cervical cancer.

Ultimately, the integration of screening with prophylactic HPV vaccination, which currently protects against the most common LR-HPV types (HPVs 6 and 11) and HR-HPV types (HPVs 16 and 18), offers the greatest potential to reduce the burden of ICC and other HPV-related diseases. Unfortunately, for many of the nations where the burden of HPV and cervical cancer is the highest, vaccination and HPV testing remain too expensive. Fortunately, the Pan American Health Organization Revolving Fund for vaccine purchase will allow vaccine prices to be reduced, and the vaccine would be available for free in most Latin American countries. The implementation of HPV vaccination will have a great impact on the reduction of the incidence and mortality of HPV-associated cancers.

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Nomenclature

CIN - Cervical intraepithelial neoplasia.

LSIL- Low-grade intraepithelial lesions.

HSIL – High-grade intraepithelial lesions.

NC- Normal cytology.

ICC Invasive cancer cervical

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