Chapter 20
Human Papillomavirus Research in Latin America

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1 Introduction

Papillomaviruses are 8000-base-pair (8000-bp), double-stranded, circular DNA viruses that can cause warty and neoplastic changes in epithelia from many host species. Their genome consists of double-stranded DNA and encodes sequences for six early (E1, E2, E4, E5, E6, E7) and two late (L1, L2) proteins involved in capsid formation [30, 79]. Viral types are defined as a viral genome with an L1 late gene sequence that is at least 10% different from that of any other type. Interestingly, differing from most other viruses, papillomavirus infection is determined by DNA detection and not viral isolation.

Of the nearly 200 human papillomavirus (HPV) types identified, approximately 40 can infect human mucosa, particularly the anogenital and aerodigestive tracts [8], albeit cervical HPV infections are best understood.

The International Agency for Research on Cancer (IARC) has classified 12 HPV types as group 1 carcinogens; they are called "high-risk HPVs" (hr-HPVs) and include the following types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [12]. Among the hr-HPVs, HPV16 is by far the most carcinogenic in terms of numbers of cervical cancer (CC) cases and its precursors [11, 52]. HPV16 also causes most HPV-related cancers in other anogenital epithelia and the oropharynx. HPV18 is classified second in terms of etiological importance but accounts for a high proportion of adenocarcinomas [52].

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The varying carcinogenicity of HPV types partly relates to the expression of two early genes, the E6 and E7 oncogenes. Among other functions, E6 and E7 oncoproteins interfere with the functions of tumor suppressor proteins p53 and pRb, respectively. During the carcinogenic process, the HPV genome may integrate into the epithelial cell genome, and, during integration, parts of the HPV genome can be lost [76, 79]. However, the continued presence and expression of E6 and E7 gene regions are needed to sustain cancers and cancer cell lines.

Latin America (LA) has one of the highest incidence and mortality rates from CC in the world, with age-adjusted incidence rates ranging from 10 to 80 per 100,000 women/year [26, 32]. Overall, mortality rates are extremely high despite cytological screening in place in several countries. On the other hand, little is known about the rates of other HPV-associated tumors such as vulvar, vaginal, anal, penile, and oropharyngeal cancers. HPV DNA prevalence and type distribution are well known in many LA countries [15]. Moreover, data on the natural history of HPV infections and risk of disease development are available from large cohort studies and serve to propose new primary and secondary prevention modalities that include prophylactic HPV vaccination and HPV testing, respectively. The HPV vaccine was introduced in several LA national immunization programs, and multiple screening experiences using HPV testing were introduced in the region [45, 77]. Although promising, challenges to control HPV-related tumors are significant, mainly because as a comprehensive strategy it should include both components: vaccination and virological screening. Furthermore, information on HPV prevalence and type distribution in several LA countries is key both to measure the impact of HPV prophylactic vaccines and to establish appropriate post-vaccine epidemiological surveillance, with virological and disease endpoints.

2 HPV Natural History and Cervical Carcinogenicity

The cervix provides the best model of HPV and anogenital neoplasia natural history. The major stages in cervical carcinogenesis include infection of the cervical transformation zone metaplastic epithelium with one or more hr-HPV types, viral persistence, clonal progression of the persistently infected epithelium to cervical pre-cancer, and invasion.

Several epidemiological studies conducted in LA have contributed to establish these fundamental stages and to shed light on the factors that influence each of these transitions. Table 20.1 summarizes the main LA studies, pointing out their most relevant findings. The following findings should be highlighted: the cohort studies of the case-control studies conducted by IARC in Colombia, Paraguay, Brazil, and Peru; the cohort studies of Proyecto Guanacaste (Costa Rica) and Ludwig-McGill cohort (Brazil); and the HPV prevalence studies by IARC in Colombia, Mexico, Argentina, and Chile.

The great majority of sexually active women and men have been infected with HPV at least once in their lifetime [16]. HPV is the most common sexually

Table 20.1 Summary of major contributions of HPV epidemiological studies carried out in Latin American populations

Countries	Main contributions	References (first author, journal, year, vol:pages)
Colombia, Costa Rica, Mexico, and Panama (NCI case-control study)	First to show an association of HPV infection and CC [r1] Studied associations between CC and other risk factors (cervical screening, education, number of sexual partners, age at first sexual intercourse, male sexual behavior, and parity) [r2–r5]	r1 Reeves, *N Engl J Med* 1989;320:1437–1441 r2 Brinton, *Int J Cancer* 1989;44:199–203 r3 Herrero, *Bull Pan Am Health Organ* 1990;24:263–283 r4 Herrero, *Cancer* 1990;65:380–386 r5 Herrero, *Int J Epidemiol* 1992;21:1050–1056
Pooled analyses of these studies have established the current evidence on carcinogenic risks (IARC monographs), leading to the launch of HPV vaccine programs		
Colombia and Spain (IARC case-control studies)	First to show the higher sensitivity and specificity of PCR assays for HPV DNA detection, compared to other hybridization assays [r6] First to report a strong association between HPVs 16,18,31,33,35, and CIN3/CIS [r7] and of HPVs 16,18,31,33,35, and CC [r8] Evaluated the association of different risk factors and CIN3/CIS [r9] and CC [r10] and concluded that HPV infection could have a causal association with CC Comparison of risk factors' distribution in women of LAC and Europe [r11] Studied the husbands' risk factors, reported prevalence of penile HPV infection and its association with the risk of CC in their wives [r12, r13]	r6 Guerrero, *J Clin Microbiol* 1992;30:2951–2959 r7 Bosch, *Cancer Epidemiol Biomarkers Prev* 1993;2:415–422 r8 Muñoz, *Int J Cancer* 1992;52:743–749 r9 Muñoz, *Cancer Epidemiol Biomarkers Prev* 1993;2:423–431 r10 Bosch, *Int J Cancer* 1992;52:750–758 r11 de Sanjose, *Am J Public Health* 1996;86:1532–158 r12 Muñoz, *J Natl Cancer Inst* 1996;88:1068–1075 r13 Castellsague, *J Infect Dis* 1997;176:353–361
Paraguay (IARC case-control studies)	Strong association of HPV infection (types 16,18,31,33,45,58) and of other risk factors (education, lifetime number of sexual partners and screening history) with increased risk of CC	r14 Rolon, *Int J Cancer* 2000;85:486–491
Brazil (IARC case-control studies)	Strong association of HPV infection (types 16,18,31,33) and high parity with an increased risk of CC and history of previous cervical smears with reduced risk of CC [r15] A pooled analysis with the case-control studies in Colombia and Spain reported risk factors for HPV infection in middle-aged women and HPV distribution by age [r16]	r15 Eluf-Neto, *Br J Cancer* 1994;69:114–119 r16 Munoz, *Sex Transm Dis* 1996;23:504–510
Peru (IARC case-control studies)	HPV infection, long-term use of oral contraceptives, and smoking associated with increased risk of CC	r17 Santos, *Br J Cancer* 2001;85:966–971
Honduras	Prevalence of HPV types by histological grade (CIN1-CC); association of HPV16 and HPV18 infection and other high-risk types and risk of CC [r18] A sub-analysis reported the association between other cofactors and CC [r19]	r18 Ferrera, *Int J Cancer* 1999; 82:799–803 r19 Ferrera, *Int J Epidemiol* 2000;29:817–825

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Table 20.1 (continued)

Countries	Main contributions	References (first author, journal, year, vol:pages)
Costa Rica (the Guanacaste project, funded by the US NCI)	Risk factors associated with HSIL and CC and with the progression of HPV infection [r20-r22] First study to observe the second peak of HPV infection in women older than 65 in LA [r23] First to show that HPV testing (hc2) and liquid base cytology are more sensitive than conventional cytology in LA. Several screening strategies have been evaluated [r24] The incidence, persistence, and clearance of HPV infection in women aged 18–26 years [r25] Highest risk of CIN2+ among women younger than 30 years with HPV16 infections that persisted for at least 12 months; importance of not single-time HPV detection [r26] The rate of new infections declines with age, and new infections typically do not progress to CIN 2 or worse disease in older women [r27]	r20 Herrero R, *Rev. Panam Salud Publica* 1997;1:362–375 r21 Herrero R, *J Infect Dis* 2005;191:1796–1807 r22 Hildesheim A, *Br J Cancer* 2001;84:1219–1226 r23 Herrero R, *J Natl Cancer Inst* 2000;92:464–474 r24 Ferreccio C, *Cancer Epidemiol Biomarkers Prev* 2003;12:815–823 r25 Rodriguez AC, *Sex Transm Dis* 2007;34:494–502 r26 Rodriguez AC, *J Natl Cancer Inst* 2008;100:513–517 r27 Rodriguez AC, *J Natl Cancer Inst* 2010; 102:315–324
Brazil (the Ludwig-McGill cohort) Colombia (The Bogota cohort)	Strong associations of persistence of HPV16/18 infections with subsequent risk of cervical lesions [r28] Estimation of incidence and duration of infections by type and lesion sojourn time [r29, r30] Bimodal age distribution of hr-HPV types. Type-specific HPV prevalence [r31, r32] Characterization of the hazard rate of cumulative incidence of HPV infection [r29, r30] No difference in the likelihood of clearance by HPV type or woman's age, but lower clearance for HPV16 infection. Viral load inversely associated with clearance [r33]	r28 Trottier, Cancer *Epidemiol Biomarkers Prev* 2006;15:1274–1280 r29 Schlecht, *J Natl Cancer Inst* 2003;95:1336–1343 r30 Schlecht, *Am J Epidemiol* 2003;158:878–886 r31 Mendez, *J Infect Dis* 2005;192:1158–1165 r32 Muñoz, *J Infect Dis* 2004;190:2077–2087 r33 Muñoz N, *Br J Cancer* 2009; 100:1184–1190
Brazil and Argentina (The Latin American Screening Study - LAMS)	Comparisons of screening techniques; highest sensitivity of hc2 to detect either CIN2 or CIN3 and the overall increased sensitivity of different combinations of pair of tests with a corresponding loss of specificity [r34] Description of risk factors [r35, r36]	r34 Sarian, *J Med Screen* 2005;12:142–149 r35 Syrjanen, *Anticancer Res* 2005;25:3469–3480 r36 Gontijo, *Eur J Obstet Gynecol Reprod Biol* 2007;133:239–246

These studies have contributed to the description of age-specific and type-specific prevalence of HPV infection by country/region, giving the baseline information for the implementation of HPV vaccination programs in the world		
Colombia (IARC HPV prevalence survey)	Most common HPV types in negative cytology; bimodal age curve of HPV infection. Number of sexual partners and use of oral contraceptives as risk factors for HPV infection	r37 Molano, *Br J Cancer* 2002;87:324–33
Mexico (IARC HPV prevalence survey)	Most common HPV types in women with negative cytology. Main determinant of infection with high- and low-risk HPV types: number of sexual partners	r38 Lazcano-Ponce, *Int J Cancer* 2001;91:412–20
Argentina (IARC HPV prevalence survey)	HPV types in general population. Main factors for HPV infection: lifetime number of sexual partners and vaginal discharge. Decreasing trend of HPV infection with age	r39 Matos, *Sex Transm Dis* 2003;30:593–599
Chile (IARC HPV prevalence study)	HPV 16, 56, 31, 38, 39, 18, and 52 accounted for 75% of high-risk HPV infections. Main risk factor for abnormal cytology and HPV infection: lifetime number of sexual partners	r40 Ferreccio, *Cancer Epidemiol Biomarkers Prev* 2004;13:2271-6
Mexico and USA	Prevalence of HPV infection by both hc2 and PCR (low- and high-risk types) [r41] Risk factors for HPV infection by country. Mean viral load by the same risk factors, by different types of HPV infection, and by cytological lesions in the same population [r42]	r41 Giuliano, *Rev. Panam Salud Publica* 2001;9:172–81 r42 Flores, *Int J Cancer* 2006;118:1187–1193
Mexico (Morelos HPV study)	Sensitivity of conventional cytology and HPV testing (hc2) (both of self-collected and clinician-collected samples). Potential HPV testing role in primary screening. Risk factors in the general population	r43 Salmeron, *Cancer Causes Control* 2003;14:505–12
Mexico (Male factor studies)	Overall and type-specific prevalence of male genital HPV infection. Anal intercourse with males was positive associated with HPV acquisition, and being circumcised gave protection against persistent HPV infection [r44] HPV type-specific prevalence. Lifetime number of sexual partners was associated with HPV positivity. Condom use with both regular and sex worker partners and circumcision were protective against HPV prevalence [r45]	r44 Lajous, *Cancer Epidemiol Biomarkers Prev* 2005;14:1710–1716 r45 Vaccarella, *Int J Cancer* 2006;119:1934–1939

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Table 20.1 (continued)

Countries	Main contributions	References (first author, journal, year, vol:pages)
Nicaragua (Rivas screening project)	HPV type-specific prevalence by cytological grade and their association with CC [r46] Found better performance on VIA over cytology and difficulties of using VIA [r47] HPV type-specific prevalence by histological grade [r48]	r46 Claeys P, *Sex Transm Infect* 2002;78:204–207 r47 Claeys P, *Trop Med Int Health* 2003;8:704–709 r48 Hindryckx P, *Sex Transm Infect* 2006;82:334-336
Uruguay	HPV types 16, 18, and 45 have a very high prevalence in CC [r49] HPV infections increased from 16% in women with normal cytology to 96% in HSIL [r50] Type-specific HPV prevalence in samples from cervical screening [r51]	r49 Berois, *Int J Gynecol Cancer* 2013;23:527–532. r50 Ramas, *J Med Virol* 2013;85:845–851 r51 Berois, *J Med Virol* 2014;86:647–652
Peru (The TATI project)	A sub-analysis compared VIA, conventional cytology, LBC, and HPV testing (hc2). HPV testing had the highest sensitivity of all, and conventional cytology and VIA had low sensitivity but better specificity. Description of risk factors [r52] Effectiveness of cryotherapy treatment for CIN in this setting [r53]	r52 Almonte, *Int J Cancer* 2007;121:796–802 r53 Luciani, *Int J Gynaecol Obstet* 2008;101:172–177
Brazil, Mexico, and the USA (HPV Infection in Men: the HIM Study)	Incidence and clearance of oral HPV infection in men (r54) Broad HPV distribution in the genital region of men(r55) High genital prevalence of cutaneous HPVs on male genital skin (r56) Long-term persistence of oral HPV16 infection in men (r57) Data about the natural history of genital HPV among HIV-negative men having sex with men and men having sex with women (r58)	r54 Kreimer AR, *Lancet*, 2013;382:877–887 r55 Sichero L, *Virology*, 2013; 443:214–2170 r56 Sichero L, *BMC Infect Dis*, 2014; 9:14–16 r57 Pierce Campbell CM, *Cancer Prev Res (Phila)* 2015; 8:190–196 r58 Nyitray AG, *J Infect Dis*, 2015; 212:202–212
Argentina, Brazil, Chile, Colombia, Guatemala, Honduras, Mexico, Paraguay, Peru, and Venezuela (the ICO study)	HPV type-specific distribution in CC. HPV types 16, 18, 31, 33, 35, 45, 52, and 58 should be given priority when the cross-protective effects of current vaccines are assessed and for formulation of recommendations for the use of second-generation polyvalent HPV vaccines (r59) Stability on the HPV type distribution in a large series of CC over 70 years before vaccination (r60)	r59 de Sanjose, *Lancet Oncol* 2010; 11:1048–1056 r60 Alemany, *Int J Cancer* 2014; 135:88–95

Adapted from Almonte et al. [1]

CC invasive cervical cancer, *CIS* carcinoma in situ, *CIN* cervical intraepithelial neoplasia, *IARC* International Agency for Research on Cancer, *ICO* Instituto Catalán de Oncología, *NCI* National Cancer Institute (USA)

transmitted infection; thus, HPV prevalence peaks around the sexual debut age, when exposure is high. Infections become undetectable within 2 years in more than 90% of individuals. Approximately 60% of these infections will prompt type-specific seroconversion, and if cervical samples are collected during productive viral infection, they may be associated with mild cervical abnormalities [i.e., low-grade squamous intraepithelial lesions (LSILs) or cervical intraepithelial neoplasia 1 (CIN1)]. Most of them are "transient" infections (cleared by the immune system) and do not result in clinical complications. Genital warts are other benign and common clinical sequelae in low-risk cases of HPV infection [66]. On the other hand, the hr-HPV infections that "persist" are more likely to progress to true cervical cancer (CC) precursor lesions, that is, high-grade squamous intraepithelial lesions (HSIL) or CIN3; progression to cervical cancer may take several years if left untreated.

It is well known that cervical HPV infection is age dependent; an inverse relationship between age and HPV prevalence has been reported. HPV prevalence peaks below age 25 and declines with age. Using data from the Guanacaste cohort [39] and the TATI project (that only tested for 13 hr-HPVs) [2], the overall HPV prevalence was 26% in women younger than 25, dropping to 12% in those aged 35–44 and climbing again to 22% in those older than 54 (Table 20.1) [20]. This U-shaped age-specific curve of hr-HPV prevalence was previously shown by independent reports in Costa Rica [41], Mexico [49], Chile [34], Brazil (see r29, Table 20.1), and Colombia [57]. In Argentina, the curve peaked below age 25 and then dropped and plateaued around 30 to 35 years, reaching its minimum at 65 years of age or older [55]; this pattern resembles more those of Europe and North America.

CC risk is largely, and almost exclusively, defined by HPV natural history. Among HPV-infected women, the most important determinants of carcinogenic risk are persistence of infection and viral genotype, HPV16 being the most prominently carcinogenic [67].

Although hr-HPV DNA is detected in almost all CC cases, HPV infection alone is not sufficient to drive full carcinogenesis. A substantial part of the evidence of risk factors for HPV infection and progression to cervical cancer comes from studies conducted in LA. The lifetime number of male sexual partners and their sexual behavior are associated with an increased risk of HPV infection. High parity, long-term oral contraceptive use, and smoking are associated with an increased risk of HPV infection progression to CC; the role of chronic inflammation, especially from coinfection with *Chlamydia trachomatis*, and certain dietary deficiencies have also been reported [1, 29].

Immunity is obviously an important risk factor; an effective cell-mediated response to the early proteins is necessary for lesion regression. Host genetics and other influences on host immunity might affect the immune response to HPV infection; weak associations of HLA with risk of CIN3+ have been noted [31, 54]. Coinfection with HIV is important because HIV-induced immunosuppression impairs cell-mediated immune control of HPV infections [1].

3 HPV Prevalence and Type Distribution in Normal Cytology and Cervical Lesions in LA

The genotype distribution in normal cytology and LSIL reveals a wide spectrum of HPV types, both low- and high-risk types; as the severity of the cervical lesion increases, hr-HPVs become the most frequent types, being the only types in CC, with HPV16 and HPV18 accounting for about 70% of cases.

In one of the largest meta-analyses, including 48,171 women with normal cytology from studies in Trinidad and Tobago, Costa Rica, Honduras, Guatemala, Belize, Mexico, Argentina, Brazil, Chile, Colombia, Paraguay, and Peru, the prevalence of HPV (any type) was 16.1%. The vaccine-targeted HPV types (16 and/or 18) were identified in 4.3% of normal samples [15].

In LSIL, the most common viral types identified in samples from the LA region were HPV16 (26%), HPV33 (13%), HPV6 (11%), HPV58 (8%), and HPV31 (7%) [24].

In the regional meta-analyses including 2446 cases of HSIL and 5540 of CC, 46.5% of HSIL cases harbored HPV16 and 8.9% HPV18; in CC, 53.2% of cases harbored HPV16 and 13.2% HPV18, the next five most common types, in decreasing frequency, being HPV31, HPV58, HPV33, HPV45, and HPV52 [23].

The more recent worldwide meta-analysis of cross-sectional HPV-type distribution in HPV-positive women of all types of clinical status (from normal cytology to CC) included 35,895 samples from South and Central America studies, in which genotyping was performed by polymerase chain reaction (PCR)-based methods [36]. Overall HPV prevalence increased with growing severity of cervical disease from 24% in normal cytology (substantially higher than worldwide prevalence estimates) up to 90% in CC. HPV16 was the most frequently detected type in every grade. HPV16 positivity varied slightly across normal cytology (16.1%) and LSIL (25.1%), but increased substantially in HSIL (53.5%), to reach 59.5% in CC.

4 HPV Genetic Variability

Comparative nucleotide sequence analysis of these viruses has elucidated some features of their phylogenetic relationship and pathogenesis implications.

HPV genomes have been classified into *molecular variants* when they present more than 98% similarity to the prototype in the L1 gene sequence [27]. Nevertheless, more recently, the comparison of the complete nucleotide sequence of HPV16 isolates from different phylogenetic branches showed that 4% of the full genome may vary in the eight genes and that 9.9% of amino acid positions are variable [22].

The most extensive worldwide studies concerning HPV intratypic nucleotide heterogeneity by far have been conducted for HPV16 because of its global predominance, followed by HPV18 and HPV45, HPV6 and HPV11, HPV5 and HPV8, and, more recently, HPV58, HPV31, HPV33, HPV35, and HPV52 [17]. Table 20.2 presents a selection of the main studies on HPV variability performed in LA.

Table 20.2 Summary of selected HPV variants studies in Latin America

Country	Viral type and technique	Main findings	References (first author, journal, year, volume: pages)
Argentina	HPV16. Cross-sectional studies in aboriginal women PCR-based hybridization of L1 and E6 genes; sequencing of a LCR fragment	Ninety percent of the specimens from *Quechua* women had E variants. Only about 10% had non-E variants (AA, As, and NA-1); 87% of normal smears had EP, whereas non-EP were detected mainly in SIL and CC. A new variant was identified in the AA branch, with nucleotide substitutions adjacent to or within transcription factor binding sites Cervical samples from *Guarani* women with different clinical categories (normal cytology, LSIL, and HSIL) were identified: 51% EP, 32% E-350G, 9% Af1-a, 4% E-6862C, 3% Af2-a, and 1% AA-a Cervical samples from *Pilaga* women with normal cytology; 68.2% were E and 31.8% AA	Picconi MA, *J Med Virol* 2003; 69:546–552 Tonon SA, *Int J Infect Dis* 2007; 11:76–81 Deluca GD, *Medicina (B Aires)*, 2012; 72:461–466
Brazil (Ludwig-McGill cohort)	HPV16 and HPV18 Cohort study LCR sequencing and dot-blot hybridization of the E6 and L1 genes of HPV16 Sequencing of HPV18 LCR fragment	E variants were the most prevalent and diverse group. The same variant was detected in specimens of different visits. Non-E variants tended to persist more frequently than E variants. Women with non-E variants had higher risk for HSIL compared to those with E variants Persistent infections with HPV-18 associated with E variants; however, risk for simultaneous detection of HSIL and HPV DNA higher for non-E HPV16 variants. Same was observed with HSIL during follow-up, confirming the association between non-E variants and risk of CC	Villa LL, *J Gen Virol* 2000; 81:2959–2968 Sichero L, *Int J Cancer* 2007; 120:1763–1768
Costa Rica (Guanacaste cohort)	HPV16 Nested case-control study. Sequencing of HPV16 LCR HPV types: 31, 33, 35, 52, 58, 67, 73, 18, 39, 45, 70, 68, 51, 69, 53, 56, 66. Sequencing of a fragment of LCR/E6 genes	Non-E variants were seen in 5.8% of normal cytology, 14.3% of HSILs, and 43.7% of cancers. Women with non-E variants had a RR of 2.7 for HSIL and 11 for CC For HPV16, non-E variants were significantly more likely than E variants to cause persistence and CIN3+. HPV35 and HPV51 variant lineages also predicted CIN3+. A continued evolution of HPV types has led to even finer genetic discrimination linked to HPV natural history and cervical cancer risk	Hildesheim A, *J Natl Cancer Inst* 2001; 93:315–318 Schiffman M, *Cancer Res* 2010; 70:3159–3169
Honduras	HPV16. Cross-sectional study PCR–reverse hybridization assay for E6/E7 variants.	Most infections in all clinical groups (CIN I, II, and II and normal cytology) belong to the E6-E variants, suggesting that HPV-16 non-E variants do not represent an additional factor associated with increased occurrence of CC in this population. Mixed variants were detected mostly in normal cytology	Tabora N, *Int J Gynecol Cancer*, 2010; 20:323–328

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Table 20.2 (continued)

Country	Viral type and technique	Main findings	References (first author, journal, year, volume: pages)
Mexico	HPV16. Case-control study Sequencing of E6 and L1 regions HPV18. Site-directed mutagenesis and immunofluorescence analysis HPV16. Cross-sectional study Sequencing of E6 region	AA and E variants were found in 23.2% and 27.1% of cases and in 1.1% and 10% of controls. The frequency of AA variants was 21 times higher in CC than in controls, being the OR for CC associated with AA variants significantly higher than that of E variants Sequence variations in E1 and LCR affect ori function, particularly for Af and AA HPV18 variants Most of variants (82.12%) belonged to the E lineage, 17.58% to AA1, and 0.3% to Af2 sublineages, and eight new E6 variants were identified. AA-a variants showed the greatest risk of leading to the development of CC was AA-a, followed by E-A176/G350, AA-c, E-G350, and E-C188/G350	Berumen J, *J Natl Cancer Inst* 2001; 93:1325–1330 Amador-Molina A, *J Gen Virol* 2013; 94:393–402 Ortiz-Ortiz J, *Virol J* 2015; 22(12):29
Paraguay	HPV16 Cross-sectional study LCR sequencing	Most HPV-16 variants belonged to the E branch (82%) in all clinical groups (normal cytology, LSIL, HSIL, and CC). Two new E variants were characterized. Non-E variants, such as Af1 (1.5%) and AA (16.5%), were detected only among women with cervical lesions	Mendoza LP, *Int J Gynaecol Obstet* 2013; 122:44–47
Worldwide study[a]	HPV16 PCR-based hybridization of E6/L1	In CC, E variants were found in 76.4% of the samples, AA in 19.7%, Af1 in 2.2%, Af2 in 1.3%, and NA1 in 0.43%	Yamada, *J Virol* 1997; 71:2463–72
Worldwide IARC study[b]	HPV16 Complete sequencing of E6 /LCR	Two new sublineages within each of the lineages Af1 and Af2 were characterized. Improved classification system for HPV16 genomes based on phylogenetically distinguishing positions in E6 and the LCR, that distinguish nine HPV16 variant sublineages	Cornet I., *J Virol* 2012; 86:6855–6861
Worldwide IARC study[b]	HPV18 Complete sequencing of E6/LCR	No significant differences in the distribution of HPV18 variant lineages between CC and controls. Findings do not support the role of HPV18 (sub)lineages for discriminating cancer risk or explaining why HPV18 is more strongly linked with adenocarcinoma than squamous carcinoma	Chen AA, *J Virol*, 2015; 89:10680–10687
Worldwide study[c]	HPV 58 Sequencing of concatenated E6-E7-E2-E5-L1-LCR fragments	HPV-58 can be classified into four lineages that show some degree of ethnogeographic predilection in distribution. Lineage A was the most prevalent lineage across all regions	Chan PKS, *Int J Cancer* 2013; 132:2528–2536 Chan PKS, *J Infect Dis* 2011; 203:1565–1573

Phylogenetic branches: *E* European, *EP* European prototype, *AA* Asian-American, *As* Asian, *Af1* African 1, *Af2* African 2, *NA1* North American
Some authors grouped the variants in European (E) (including E branch) and non-European (non-E) (including AA, As, Af1, and Af2 branches)
CC cervical cancer, *LSIL* low-grade squamous intraepithelial lesions, *HSIL* high-grade squamous intraepithelial lesions
[a]Included samples from Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Panama, and Paraguay
[b]Included samples from Argentina Bolivia, Brazil, Chile, Colombia, Cuba, Panama, Paraguay, and Peru
[c]Included samples from Argentina, Brazil, Honduras, and Mexico

Investigations of HPV type diversity have identified different phylogenetic branches (variants); particularly for HPV16, there are six branches: European (E), Asian (As), African-1 (Af-1), African-2 (Af-2), Asian-American (AA), and North American (NA) [17]. Different HPV16 variants exhibit differences in their biological and biochemical properties.

The prevalence of HPV variants and their association with cervical cancer has been reported in three case-control studies [9, 42, 69] and five cross-sectional studies in LA women with different grades of cervical lesions [18, 47, 56, 62, 78]. Follow-up studies have reported the role of HPV variants in the persistence of infection and disease progression [69, 74]. Overall, studies conducted in Argentina, Brazil, Costa Rica, Honduras, Mexico, and Paraguay have shown a large diversity of variants, with a higher frequency of E variants compared to other phylogenetic branches (Table 20.2). Interestingly, a high prevalence (>80%) of E variants was also observed in indigenous groups from Argentina [28, 62, 71]. These studies also suggested that the colonization of the American continent by Europeans and Africans is reflected in the composition of its variants.

Studies carried out in Mexico, Costa Rica, and Brazil have shown that non-E HPV16 variants, mostly AA variants, are associated with a higher risk of viral persistence and/or HSIL and CC [9, 18, 42, 68, 69, 74]. These studies with a large number of samples provide enough study power to detect associations between low-prevalence variants and persistent infections or disease risk [1].

In vitro functional assays show that several HPV variants differ in their ability to induce p53 degradation, Bax degradation, activation of mitogen-activated protein kinase (MAPK) signaling, E2-related transcription, and immortalization activity. Specific studies with non-E variants have shown enhanced transcription and replication efficiency in HPV16 and HPV18 AA variants compared to E variants [17]. This information may explain the increased oncogenic potential reported for these variants and their contribution for the high incidence of CC.

HPV vaccines are based on virus-like particles (VLPs) composed of L1 protein, the viral capsid main component. So far, serological studies of different HPV16 variants have shown that the humoral immune response to HPV16 does not seem to discriminate between different molecular variants [60]. The cross-protection between variants was confirmed by the near 100% prophylactic efficacy of vaccines in multicenter studies [1].

Although the coevolution of human populations and HPV16 and HPV18 variants is well supported, the geographic association for variants of other types remains unresolved. Global studies of HPV variant lineages from worldwide populations are needed to better understand the relationship between HPV and the recent and past evolution and dispersion of their human hosts, as well as the genetic basis of the pathogenesis of specific HPVs, viral–host interactions, and host evolution, among other applications and scientific inquiries. Multicenter studies and/or meta-analyses will be useful to validate the nucleotide level of pathogenesis and provide insights into the molecular basis of HPV-associated disease [17].

5 Epidemiology of HPV-Related Neoplasias

About 1.1 million new cancer cases and 600,000 cancer deaths per year are estimated in Latin America and the Caribbean [32]. Estimates indicate a 72% increase in the incidence of cancer and 78% increase in mortality between 2012 and 2030 [26]. Cancer rates vary considerably within LA: although breast cancer remains the leading cause of death for women worldwide, CC is the main cause of death from cancer in Bolivia, Honduras, and Nicaragua. Also, cervical cancer incidence rates vary considerably in the region, ranging from 11.4 cases per 100,000 in Costa Rica to 47.7 cases per 100,000 in Bolivia [59].

Decades of Papanicolaou-based screening to detect precancerous cervical lesions have not had a major impact in reducing CC incidence and mortality rates, which are still high in the region (Fig. 20.1). Despite efforts to reorganize screening programs in a few countries of the region, only a slight reduction in cervical cancer mortality has been noted [59]. Among the difficulties to control the burden of cancer in the region are the uneven allocation of resources, variable infrastructure and ser-

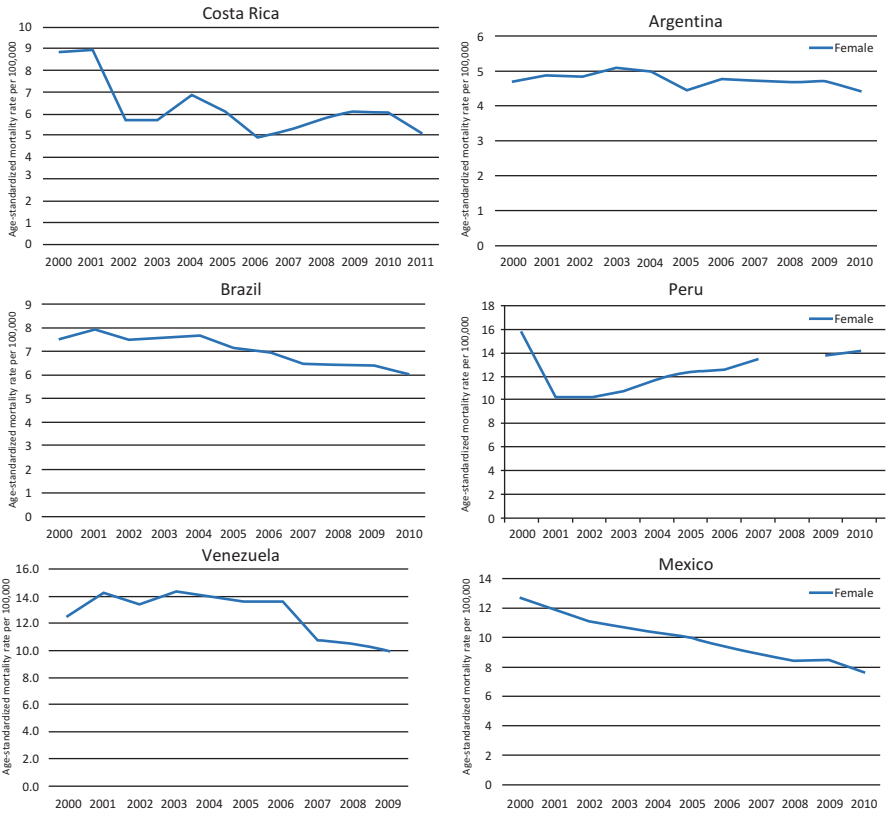

Fig. 20.1 Cervical cancer mortality rates for selected countries in Latin America. (Adapted from Pan American Health Organization [59])

vice availability, limited number of population-based cancer registries, and scarce distribution of public health posts, which is more evident in rural areas, distant from the large urban centers. These difficulties result in a scenario of disproportionate care provided to individuals affected by cancer.

The global burden of HPV infections and related diseases is significant [35]. HPV was associated with 83,195 new cases of cervical cancer and 35,673 associated CC deaths in LA in 2012 [14]. Most of the cases are associated with HPV16 and HPV18, followed by five additional hr types (HPVs 31, 33, 45, 52, 58), which together account for about 90% of CC cases worldwide.

Information concerning HPV-related tumors outside the uterine cervix in LA countries is scarce [14, 32]. A recent systematic review of the presence of HPV in noncervical sites suggests a high HPV prevalence and higher clearance rates than in the uterine cervix [70]. Anal cancer incidence rates vary from as low as 0.2 × 100,000/year to 1.4 × 100,000/year in the northeast of Brazil and some areas of Argentina [26]. Estimates for other LA are limited or nonexistent. Similarly to high-income countries, anal cancer incidence is increasing with time in both women and men. This neoplasia is associated with hr-HPV types, particularly HPV16. In fact, most HPV-positive neoplasias outside the cervix are related to HPV16 [70].

Vulvar and vaginal cancers are relatively rare tumors with incidence rates less than 1 × 100,000/year [59]. Information is very limited in LA. Regional data show that HPV16 is the most prevalent type and is found in 75% to 100% of the basaloid/warty vulvar cancers that are more common in young women. About two thirds of vaginal cancers are linked to HPV, in particular HPV16 [14].

In some LA countries, the incidence of penile cancer is significantly higher than in more developed parts of the world: the central region of Brazil and some areas in Colombia and Paraguay account for about 2.0 × 100,000/year as compared to other countries with incidence rates around 0.4 × 100,000/year [26, 73]. Studies performed in LA show HPV DNA positivity in 30% and 50% of penile cancers [10, 70].

In the head and neck anatomical sites, some cancers are linked to HPV, although in variable frequencies, being more HPV associated in the base of the tongue and tonsils [19]. The most common HPV type found is HPV16 worldwide and in series of cases from LA [19, 46, 64, 70]. Notwithstanding, there have been reports of lower HPV positivity in oropharyngeal cancers from LA countries as compared to other countries in the Northern Hemisphere [37, 53, 65]. Further studies are warranted to better understand the basis for such differences and the impact on cancer patient management.

6 Control of HPV Infections and Related Diseases

6.1 Primary Prevention: HPV Vaccines

Since 2006, two vaccines composed of HPV L1 proteins self-assembled into virus-like particles (VLP) have been approved in LA: one containing VLPs of HPV types 6, 11, 16, and 18 (Merck & Co.) and one composed of HPV 16 and 18 VLPs (GlaxoSmithKline). Large phase II and III clinical trials to assess prophylactic

efficacy have been conducted in which both HPV infection and cervical disease endpoints were evaluated, particularly HSIL (CIN2 or CIN3) as well as vulvar and vaginal intraepithelial neoplasias (VIN and VaIN, respectively) and genital warts for the quadrivalent vaccine [75]. Very high efficacy rates were noted in different populations that included young women between 16 and 26 years and older (up to 55 years). The quadrivalent HPV vaccine has also proven to be efficacious in men to prevent genital and anal infection and disease caused by the types included in the vaccine [13, 40]. Importantly, several clinical trials of HPV prophylactic vaccines conducted in LA clearly demonstrated the safety, immunogenicity, and efficacy of such recombinant vaccines among Latin Americans [61]. Furthermore, data collected in these clinical trials concerning the incidence and prevalence of genital HPV-associated infection and disease have provided important insights on the burden of genital HPV in the region [40, 61]. Moreover, seminal demonstration studies and surveys have shown that the HPV vaccine acceptability is very high in the region [3, 6, 50].

Most LA countries have a well-developed public immunization infrastructure including adolescent vaccination, which has facilitated the introduction of national immunization programs in the region (Fig. 20.2). Organizations such as the United Nations Children's Emergency Fund (UNICEF), Global Alliance for Vaccines and Immunization (GAVI), and the PAHO revolving fund have enhanced HPV vaccine introduction in LA. After an initial phase, most countries are adopting the two-dose program supported by WHO [77] and are vaccinating girls aged 9 to 13 years at 0 and 6 months. Moreover, in several countries of the region, the HPV vaccine is offered to HIV-positive women up to 26 years of age.

Interestingly, a broad evaluation of the programs is driving a revision of the entire CC control strategies adopted by each country, which includes HPV vaccination for female adolescents and cytology/HPV testing for adult women [72]. Implementation of effective vaccine programs might seem straightforward and obvious in light of the vaccine efficacy and lack of serious adverse events to date; nonetheless, significant challenges remain. These problems include the cost of the program, covering two doses of vaccine and extending the vaccination to boys and other populations at risk including HIV-positive individuals. Equally important is to monitor the impact of this intervention that requires tools and strategies unavailable in many countries of the region. Introduction of cost-effective measures such as HPV vaccination only or vaccination supplemented with screening, with good coverage rates, will reduce HPV-related tumors in LA, as is happening in several countries of the world [13].

6.2 Secondary Prevention: HPV Testing as Primary Screening

For more than 50 years, cervical cytology [the Papanicolaou (Pap) smear) has been the standard of care for CC screening. Cytology-based mass screening programs have been successful in reducing incidence and mortality in developed countries (such as the U.S. and European countries). Unfortunately, most LA countries tried unsuccessfully to replicate these results, evidencing, however, after decades of efforts, high incidence and mortality rates, with little impact on the disease burden [58].

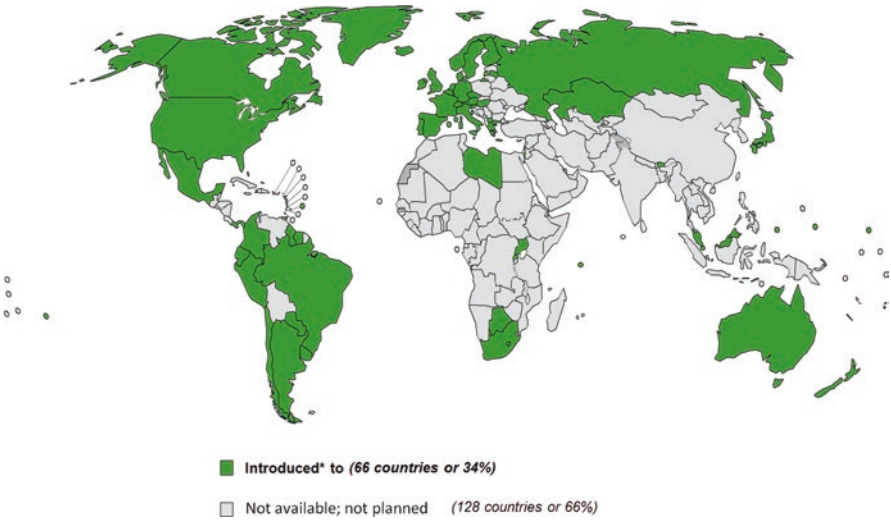

Fig. 20.2 Countries with prophylactic HPV vaccine in their immunization programs, 2016. Countries with partial introduction are not included. (Adapted from a WHO Immunization, Vaccines and Biologicals image 61, using data from the WHO Immunization, Vaccines and Biologicals database (accessed May 2016))

The limitations inherent in cervical cytology prompted the development of new screening technologies: tests to detect the presence of hr-HPV DNA, which should be clinically validated for this purpose. HPV testing offers numerous potential advantages compared to cytology-based screening, such as greater sensitivity, high negative predictive value (which allows to extend the screening intervals in HPV-negative women), and automation [21]. However, even among women over 30 years of age, the cancer to transient infection ratio is low, and HPV assays must overcome the intrinsic problem of low positive predictive value. This lower specificity of HPV testing requires an additional test ("triage") in women who are HPV DNA positive in the primary screening to identify those who are at risk of having a cervical cancer precursor and to reassure those who only have transient or low-risk infections. Triage includes visual inspection methods, cytology, and molecular biomarkers (high-risk HPV E6/E7 mRNA, high-risk HPV E6 proteins, p16, among others). Locally adapted algorithms employing primary screening with HPV testing are being developed in different settings [63]. The initial HPV tests were very expensive and unaffordable for several LA countries, but in recent years, more HPV tests became available and the prices have started to drop, making them more affordable.

During the past decade, there have been multiple experiences with HPV testing in LA, some as part of research studies and others to pilot the implementation of HPV tests in the public system and, more recently, the implementation of HPV testing as part of the public programs provided by the ministries of health [45]. Pilot studies that took place in Argentina [4, 5], Chile [33, 51], Colombia [58], El Salvador [25], Mexico [38, 48], and Nicaragua [7, 44] were highly efficacious to detect precancerous cervical lesions and good feasibility and acceptance of self-sampling.

Similarly, in 2011 Argentina was the first country in the region to implement HPV DNA testing for primary screening within its public system for all women aged 30 or older. In recent years, Mexico has expanded the implementation of HPV DNA testing to 17 sites across the country, applying its extensive knowledge in this field. El Salvador, Guatemala, Honduras, and Nicaragua are beginning to institutionalize HPV testing at population level [45].

The need to develop a comprehensive quality assurance program associated with the specific HPV test to be implemented should also be considered to guarantee reliable test results in real-world settings. Despite the fact that most tests have their own internal quality control, quality control procedures should be put in place to ensure proper transportation and storage of reagents and samples, correct sample labeling and processing, suitable monitoring of positivity rates, and other test characteristics to rule out contamination [45, 63].

LA is slowly shifting toward HPV testing for cervical cancer screening, with the endorsement of several regional experiences that have resulted in increased coverage and better detection of pre-cancer lesions using HPV tests. In line with this, the ESTAMPA study, recently launched in LA countries by the International Agency for Cancer Research, will contribute valuable information about the performance of emerging CC screening and triage techniques and the feasibility of different approaches to implement organized HPV-based screening programs in the region [43].

Finally, it is important to emphasize that the screening test is important, but it is only one component of many other aspects of population-based programs that should be implemented to effectively impact CC cancer incidence and mortality.

7 Conclusions and Perspectives

The prevalence and incidence of HPV-related infection and disease in LA underscore the importance of supporting CC prevention strategies in the region. CC is one of the leading killers among women in LA, a region where many countries have not been successful in implementing population-level cytology-based screening programs. Hence, a more comprehensive CC control approach is required, wherein primary and secondary prevention strategies are implemented with both high coverage and sustainability.

Although regional data seem to indicate a favorable trend in prevention, significant challenges still remain. In primary prevention these include the cost of the program, covering two doses of vaccine, and extending the vaccination to boys and other populations at risk, including HIV-positive individuals. Equally important is to monitor the impact of this intervention that requires tools and strategies unavailable in many countries of the region.

In secondary prevention, it is crucial to change the paradigm by implementing HPV testing as primary screening in the most appropriate way. Among several challenges for its implementation, it should take into account the need to update screen-

ing guidelines, strengthen treatment capacity, and develop a comprehensive quality assurance plan for HPV testing.

Finally, gaps still exist in the knowledge and the future lines of research, policy, and advocacy for noncervical HPV cancer prevention, mainly anal and oropharyngeal cancers and precancers; further studies are warranted to better understand their pathogenesis and the impact on cancer patient management. Public health commitment and research to implement HPV-based preventive strategies, together with stronger and common advocacy to counter barriers affecting the adoption of these strategies, are likely to yield major benefits in reducing the burden of HPV-associated diseases in LA.

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We wish to dedicate this chapter to the memories of Dr. Angélica R. Teyssié (1922–2015), a prestigious Argentine virologist, a pioneer in the research of viral oncogenesis, particularly HPV, and in the training human resources, and to Dr. Xavier Castellsagué (1959–2016), one of the most productive and influential epidemiologists in the field of HPV-related neoplasias.

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