

## Etiology of cervical cancer (C53) in Central and South America

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### Human papillomavirus

Persistent infection of the cervix with high-risk types of human papillomavirus (HPV) has been established as a necessary (but not sufficient) cause for the development of cervical cancer [1]. Evidence suggests that HPV infection precedes the development of cervical cancer by several decades and that persistent infection with HPV is necessary for the development and progression of pre-cancerous lesions of the cervix, either to higher grades of pre-cancerous disease or to invasive cancer – a process that can take 10–30 years [2].

HPV is a very common sexually transmitted infection that is usually acquired soon after the initiation of sexual activity. Most HPV infections clear spontaneously within 1–2 years, but persistent infections with high-risk types of HPV (particularly HPV16 and HPV18) may progress to precursors of and ultimately to invasive cervical cancer [3]. High-risk types of HPV are identified in nearly all cancers of the cervix, and the expression of HPV oncoproteins is necessary to maintain the cancer phenotype. The International Agency for Research on Cancer evaluated the following 12 HPV types as carcinogenic to humans: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV16 and HPV18 are responsible for about 70% of cervical cancer cases worldwide [4]. Little geographical variation has been found in the prevalence of the predominant HPV types associated with cervical cancer, but the proportion of cancers associated with types other than 16 and 18 is higher in high-risk areas [4].

A study that evaluated HPV infection in 10 575 histologically confirmed cases of invasive cancer from 38 countries in Asia, Europe, Latin America and the Caribbean, North America, Oceania, and Sub-Saharan Africa over a 60-year period – using paraffin-embedded samples – revealed that 85% ( $n = 8977$ ) of the cases were positive for HPV DNA [5]. The eight most common types of HPV detected were 16, 18, 31, 33, 35, 45, 52, and 58; their combined contribution to the 8977 positive cases was 91%. HPV types 16, 18, and 45 were the three most common types in each histological form of cervical cancer (squamous cell, adenocarcinoma, and adenosquamous carcinoma), accounting for 61%, 10%, and 6%, respectively.

### HPV infection in Central and South America

Several reports have shown considerable variability in the prevalence of HPV in Latin America and the Caribbean; however, the results of these surveys should be

interpreted carefully because of differences in methodologies, biological specimens, and the genotyping techniques used. In particular, because the prevalence of HPV is strongly associated with age, the age distribution of the women included in a given sample can create spurious data.

According to the Institut Català d'Oncologia (ICO) Information Centre on HPV and Cancer, the prevalence of HPV reported from different studies among women with normal cytology has ranged between 3.8% in Peru (women aged 18–65 years) and 49.9% in Argentina (women aged 18–69 years) [6]. As expected, the prevalence increased consistently with the severity of the lesions, especially for certain HPV types such as HPV16 and HPV18, as has been similarly observed in other regions in the world. The prevalence of these two HPV types was 4.5% in women with normal cytology and 69.5% in women with invasive cervical cancer (Figure 1).

HPV16 and HPV18 are globally the most prevalent types in invasive cancer [7], indicating that approximately 70% of cervical cancer cases in the region could potentially be prevented by the HPV vaccines currently in use. However, the available data at the ICO HPV information centre show some variability in the prevalence of HPV16 and HPV18 across Central and South American countries, ranging from 38.3% in Bolivia to 85.2% in Chile for invasive cancer and from 37.8% in Cuba to 71.0% in Chile for high-grade lesions (HSIL) (Figure 2). These variations could influence the cost-effectiveness of HPV vaccine programmes, as well as the performance of HPV-genotyping-based screening strategies; however, limitations in the quality of the data should be reviewed.

Countries in the region with the lowest incidence rates have been reported to have a higher prevalence of these two HPV types in invasive cancer and vice versa (i.e. a cancer incidence of 13.9 per 100 000 and HPV16/18 cancer prevalence of 85.8% in Chile but a cancer incidence of 22.2 per 100 000 and HPV16/18 cancer prevalence of 38.3% in Bolivia). This may be related to both a greater participation of other HPV types in the spectrum of the disease and a greater frequency of multiple infections. Similar findings have been described in analyses of HPV prevalence worldwide [8].

### **Risk factors for HPV infection**

HPV is a common sexually transmitted infection and both men and women can carry, transmit, and suffer the health effects of the infection [9]. Therefore, the risk factors associated with HPV infection are related to the sexual behaviour of individuals. Immaturity, low production of mucus, and ectopy of the cervix have been described as biological conditions that favour the acquisition of HPV in young women [10].

### **Age at first sexual intercourse**

Multiple studies have indicated that an early age at the time of first intercourse is a risk factor for HPV infection and for invasive cervical cancer [11]. A widespread belief is that the age at which cervical cancer occurs is decreasing and the number of cervical cancer cases in young women is increasing, and a decline in the age at first intercourse has been proposed as the reason for this phenomenon [12]. Consequently, several countries in Central and South America plan their screening

programmes according to the median age at first sexual intercourse (see the section on screening programmes).

A report by the World Health Organization based on population-based cross-sectional surveys showed slightly increased sexual activity among young Latin American women with a consequent decline in the median age at the time of the sexual debut [12]. Moreover, one study showed an association between poverty and lower age for beginning sexual activity in Latin America [13]; indeed, the percentage of women aged 15–19 years who report having ever had sexual intercourse in the USA is slightly lower than that in Colombia (43% and 50%, respectively, in 2010) [14, 15], the latter having one of the lowest median ages at sexual debut in the region (Figure 3). However, other countries with a lower per capita gross domestic product, such as Honduras or Bolivia, have a lower percentage of younger women who report having had sexual intercourse (36% and 27%, respectively) [13]. A young median age at the time of the sexual debut is frequently presented as the main reason for promoting the screening of adolescents because it is interpreted as a higher risk for cervical cancer despite the almost absent incidence of the disease under the age of 25 years. According to the available information, a slight decline in the median age at the sexual debut has been observed, but differences among countries are small and have no correlation with the risk of cervical cancer (Figure 3).

### Number of sexual partners

As expected for a sexually transmitted infection, the main risk factor for HPV infection is the number of sexual partners of the women and the number of sexual partners of their partners. However, only limited information is available on the number of sexual partners in Latin American countries. A review of epidemiological studies showed a variation in the percentage of people having more than one sexual partner in the previous year from 20% in Colombia to 49% in Peru [16]; however, this evidence does not correspond to population-based data making its interpretation difficult. Recent reports from the Joint United Nations Programme on HIV/AIDS based on population surveys showed a high frequency of multiple sexual partnerships in the previous year for some of the countries with the lowest incidence rates of cervical cancer in Central and South America (Chile, 9.2%; Uruguay, 16.5%; Costa Rica, 16.9%; Panama, 45.1%; and Brazil, 66.1%) [17]. These data indicate a low correlation between the number of sexual partners and the risk of cervical cancer at the population level, probably pointing to a role of the sexual behaviour of men but also due to the effect of screening programmes on the incidence of cervical cancer.

Despite the possibility of reporting bias, data published by the World Health Organization showed a greater number of sexual partners among men than women in developing countries, while the proportion of multiple sexual partners was similar between men and women in Australia, Europe, and North America [12]. In addition, differences in the number of sexual partners between sexes observed in developing countries were found in all age groups.

## Co-factors for the progression of HPV infection

HPV infection alone may not be sufficient for the development of cervical cancer; therefore other factors may also be involved in the progression of this malignancy [18].

High parity (more than 6 full-term pregnancies) is associated with the risk of cervical carcinoma among women with high-risk HPV, and fertility has been suggested to have played a relevant role in the decline in the incidence of cervical cancer in Latin America [16]. Total fertility rates (number of children per woman in the whole population) have decreased dramatically in all countries in Central and South America (period 2010–2015 in Figure 4). For the year 2013 (period 2010–2015 in Figure 4), no rates above four were observed; Bolivia and Guatemala had the highest rates (3.8 and 3.2 per woman, respectively) while Brazil, Chile, Costa Rica, and Cuba had the lowest rates (ranging from 1.7 to 1.9 per woman). Most countries in the region had total fertility rates between 2.0 and 2.8 per woman (period 2010–2015 in Figure 4). In addition, projections of the trends for total fertility rates for 2050 suggest that differences between countries for this indicator will disappear (Figure 4); consequently, variations in the incidence of and mortality from cervical cancer among Latin American countries are unlikely to be explained by this factor.

Similarly, oral contraception has been associated with increased risk of cervical cancer (RR, 1.9; 95% CI, 1.69–2.13) and dose–response analyses have shown higher risks with longer durations of use [16]. However, the available population-based data reveal no correlation between the prevalence of contraceptive use among married women aged 15–49 years and the incidence of cervical cancer. In fact, the prevalence of oral contraception was similar among countries with a differential incidence of cervical cancer for the period 2010–12 (i.e. Argentina, 78.9%; Brazil, 80.3%; Colombia, 79.1%; Costa Rica, 76.2%; Nicaragua, 80.4%; Paraguay, 79.4%; and Peru, 75.5%) [19].

Despite the significant increase in the risk of cervical cancer for current smokers (RR, 1.50; 95% CI, 1.35–1.66) and the reduction in risk observed after smoking cessation, the association between cervical cancer and tobacco consumption is limited to squamous cell carcinoma, and the data on a dose–response are still controversial [16].

The evidence from observational studies has consistently found an association between HPV and other sexually transmitted infections, particularly *Chlamydia trachomatis*, herpes simplex virus type 2, and HIV; in addition, *Chlamydia trachomatis* and herpes simplex virus type 2 have been associated with an increased risk of cervical cancer (odds ratio [OR], 1.8 for *Chlamydia trachomatis*; OR, 2.2 for herpes simplex virus type 2) (16). For HIV, the available information shows a clear association of the co-infection with a higher risk of cervical intra-epithelial neoplasia, but less consistent data have been reported regarding invasive cervical cancer, partially due to the high prevalence of both diseases in high-risk countries for HIV [20]. All of the above-mentioned infections are related given their shared dynamic of exposure and transmission as well as their common social determinants. However, as with other risk factors described previously, no major differences in HIV-AIDS prevalence are observed among Latin American countries; consequently, no

association between HIV-AIDS and cervical cancer could be assumed at the population level in the region (prevalence range for 2012, 0.1–0.3% for people aged 15–29 years; except for Costa Rica with a prevalence of < 0.1%) [17].

### Socioeconomic determinants

As with many other infectious diseases, poverty is the strongest determinant of the incidence of and mortality from cervical cancer around the world [21], with developing countries showing the highest incidence and mortality rates (15.7 and 8.3 vs 9.9 and 3.3 for the less developed and the most developed regions, respectively). The human development index and poverty rates have shown a clear association (inverse and direct, respectively) with incidence and mortality, thus explaining about 52% of variability in cervical cancer globally [22, 23].

With the exception of Venezuela, the top 10 countries with the highest mortality rates in the region correspond to those with the lowest per capita gross domestic product. Among countries with the lowest mortality rates (below 10 per 100 000), Colombia and Cuba occupy unique positions: both have lower per capita gross domestic products than other countries, suggesting that factors other than poverty might also play a relevant role as social determinants in mortality from cervical cancer in areas where the development of health systems and health services may be the most influential.

Because poverty is a strong determinant of such social indicators as level of education, access to health care, and birth or fertility rates, elucidating the contribution of these factors on the incidence of and mortality from diseases is particularly challenging. Disparities in mortality from cervical cancer by level of education have consistently been described worldwide, where illiteracy and primary education were associated with higher rates than secondary or higher education; concordantly, the level of education is related to screening and sexual and reproductive health practices associated with invasive cancer [21, 24]. In this respect, in Brazil, 7 or fewer years of schooling was associated with a higher risk of advanced disease at diagnosis than more than 7 years of education (OR, 1.4; 95% CI, 1.3–1.5) [25]. In Colombia, cervical cancer accounts for the highest mortality from cancer among those with primary or lower education (RR, 5.75 compared with college and university education) [26]. In Mexico, women living in rural areas had higher mortality rates than those in urban areas (RR, 3.07); however, no linear association was observed when mortality rates were examined according to the level of urbanization among Mexican states [27].

### Acknowledgements

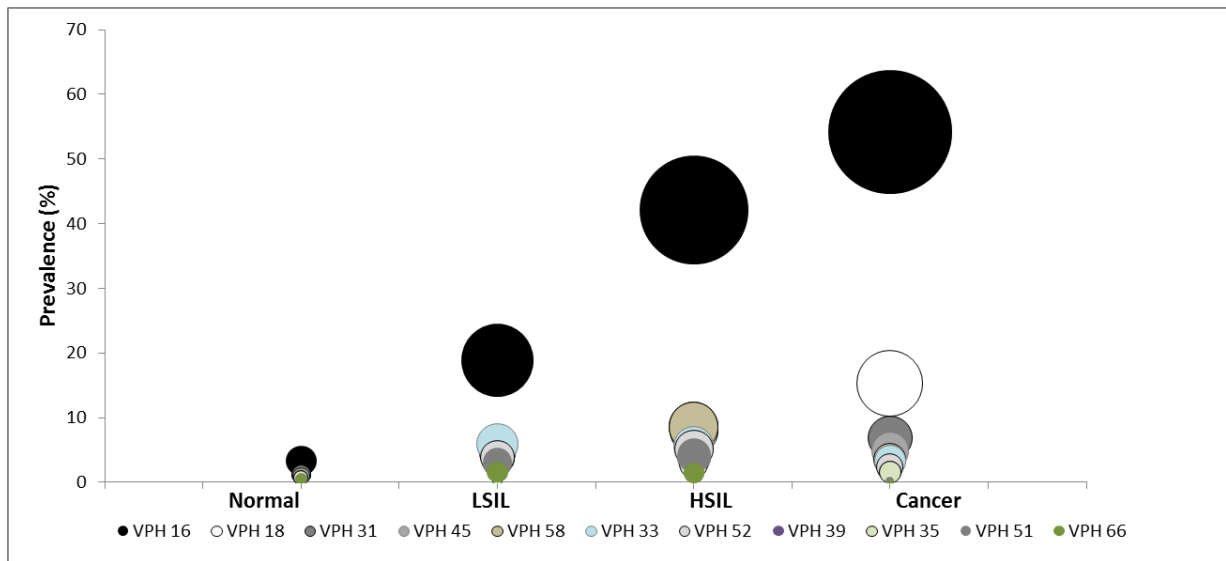
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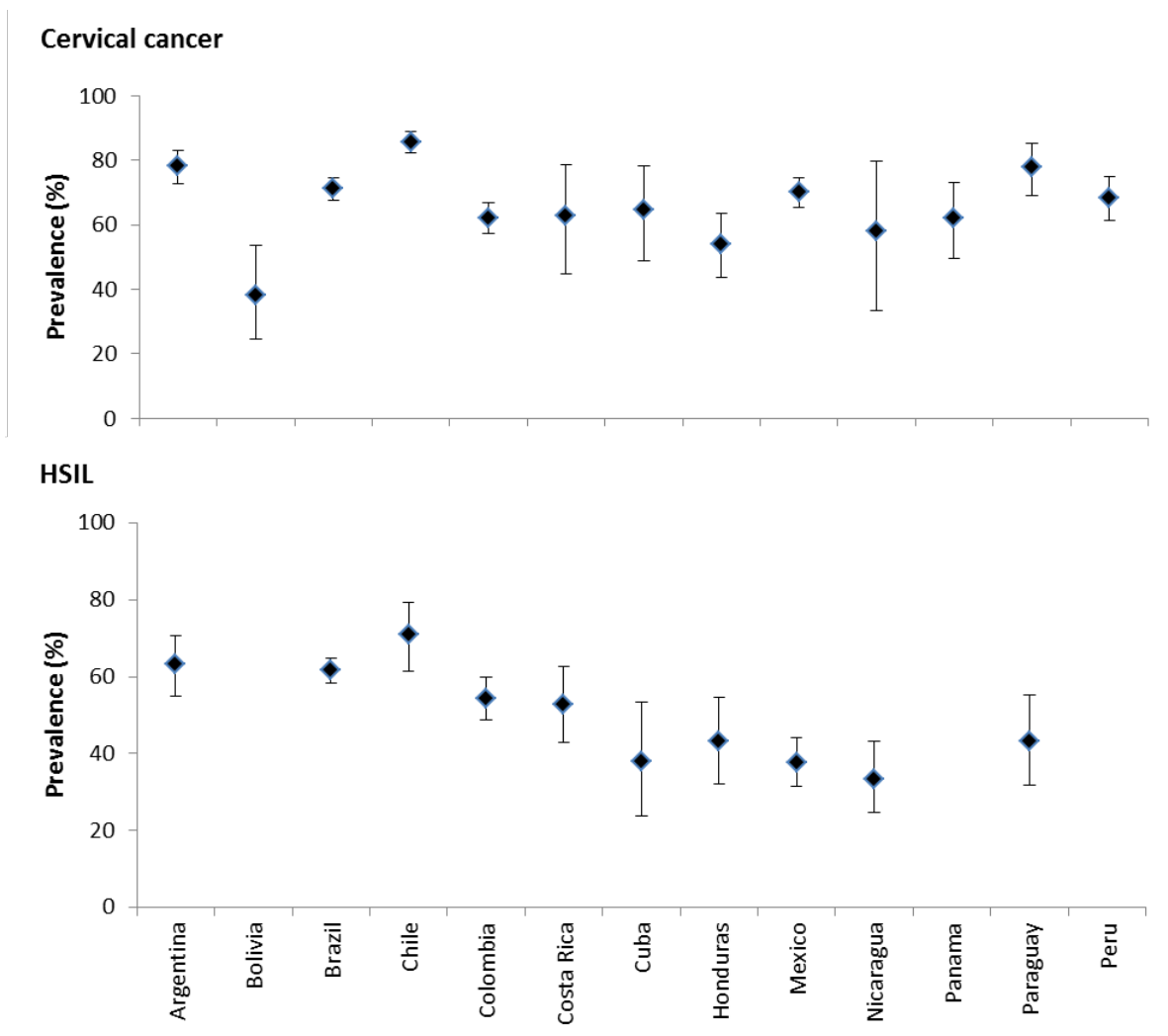
**Figure 1. Prevalence of the most frequent high risk HPV types in Latin American women according to level of cervical lesion.**



Source: ICO, Bruni, Gonzalez M, Casas-Beltrán JP. Adjusted prevalence by population at risk, prevalence of preneoplastic lesions, and number of cancer cases in Central America, South America, and the Caribbean

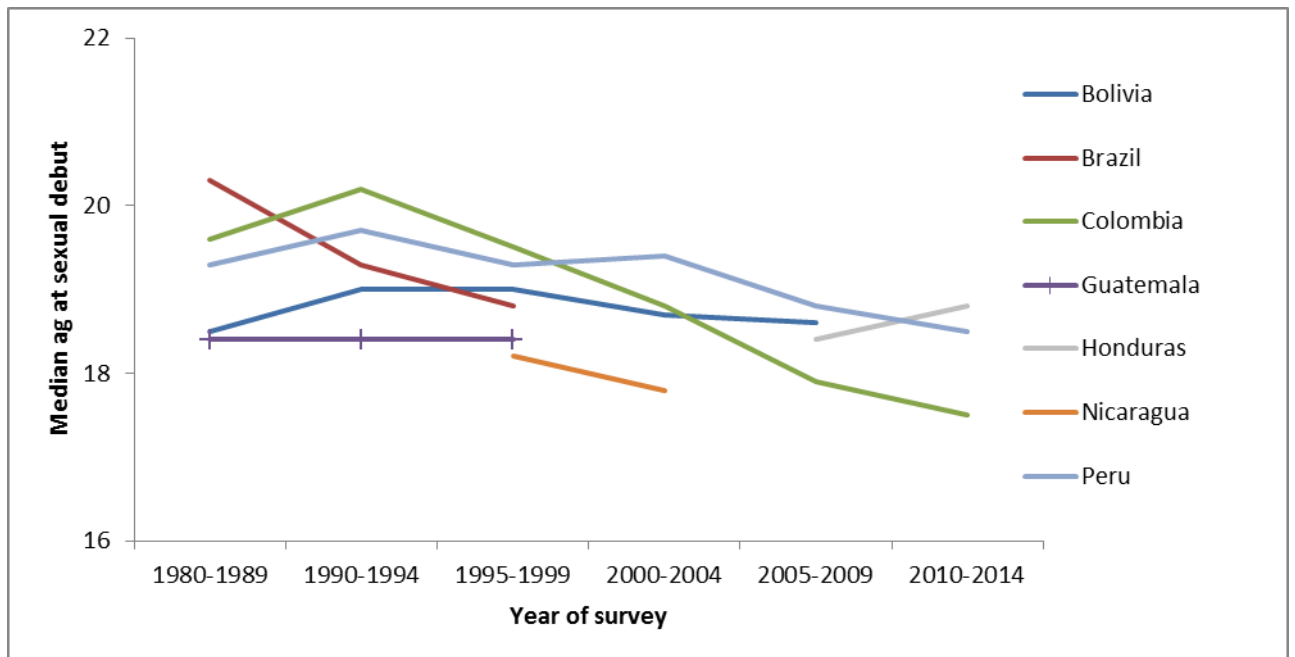


**Figure 2. Prevalence of HPV 16/18 in invasive cervical cancer and High Grade Lesions (HSIL) for selected countries in Central and South America.**



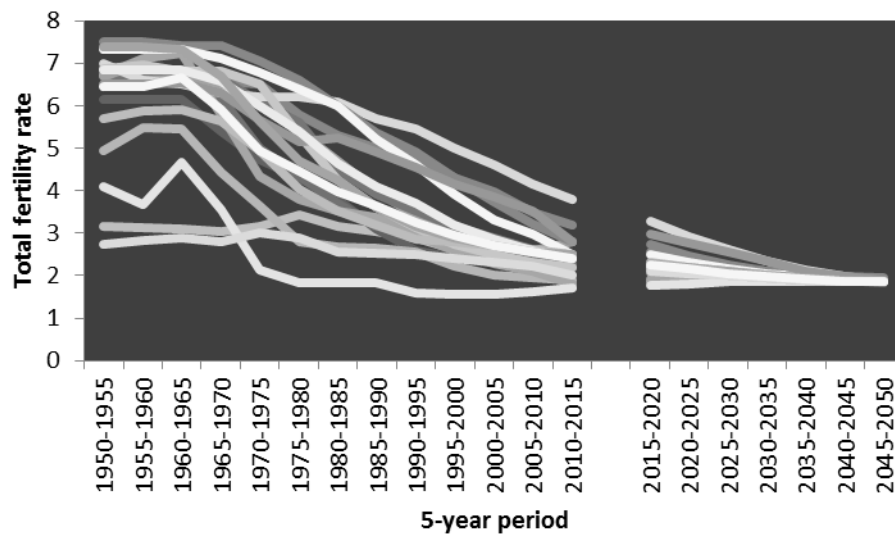
Source: ICO HPV Information Center

**Figure 3. Trends in median age at sexual debut in selected Central and South American countries.**



Source: USAID. STAT Compiler: The DHS Program. <http://www.statcompiler.com>. Data correspond to those reported for the lowest five-year age interval in every country. Only the most recent survey was included when more than one available for the same quinquennium. All countries with available information were included.

**Figure 4. Schematic representation of observed and estimated trends for fertility rates in Latin American countries.**



Source: *Observatorio demográfico América Latina y el Caribe CEPAL*. [Demographic Report for Latin America and the Caribbean] Data for the period 2010-2015 correspond to observed rates in 2013 (PRB). Fertility rates correspond to the number of children per women