3

Human Papillomavirus Worldwide Distribution in Women Without Cervical Cancer

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1. Introduction

Infection by certain types of Human Papillomavirus (HPV) is closely related to the corresponding risk of cervical cancer (Trottier and Franco, 2006). Cervical cancer represents the third most common malignancy in women, and the seventh overall, with an estimate 529.000 new cases in 2008 (Ferlay et al., 2010). More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancer (Ferlay et al., 2010).

HPV subtypes have been associated with the development of cervical, vulvar, anal, penile and oropharyngeal cancer in 2002 (Parkin, 2006), representing 5.2% of all cancers worldwide. It has also been estimated, on basis of cross-sectional observations (Clifford et al., 2005, de Sanjose et al., 2007) that approximately 10% of women worldwide with normal cytological findings carry a detectable cervical HPV infection. Therefore, HPV can be considered as the most common known sexually transmitted agent worldwide (de Sanjose et al., 2007).

HPV vaccines hold great promise to reduce the global burden of HPV infection as well as cervical cancer development. In June 2006, the quadrivalent HPV vaccine types 6, 11, 16, and 18 (GARDASIL™, manufactured by Merck and Co., Inc., Whitehouse Station, New Jersey) was licensed for use among females aged 9-26 years for prevention of vaccine HPV-type-related cervical cancer (Markowitz et al., 2007). On October 2009, the Food and Drug Administration (FDA) licensed bivalent HPV vaccine (Cervarix, GlaxoSmithKline) for use in females aged 10 through 25 years. Cervarix is the second HPV vaccine licensed for use in females in the United States (F.D.A., 2010). Both vaccines might provide protection against some other HPV-related cancers in addition to cervical cancer, although there are currently only data sufficient to recommend Gardasil™ for protection against vulvar and vaginal cancers and precancers. Gardsil™ is also recommended for prevention of genital warts.

The well established knowledge for HPV type distribution worldwide is a key feature for the rational design of future vaccination, that would include a broadest spectrum, and for the development of new HPV screening tests (Clifford et al., 2005). To contribute for this effort, we hereby present a worldwide description of HPV type distribution in women without cervical abnormalities.

2. Population data

To describe HPV type distribution, the geographical definition of the regions was based on Globocan, a project of the International Agency for Research on Cancer, that presents incidence, prevalence and mortality estimates of 27 major cancer for all countries in the world (Ferlay et al., 2010). The geographical areas include four regions in Africa (Northern, Southern, Eastern and Western), three regions in the Americas (central, south and northern), four regions in Europe (Northern, Southern, Eastern and Western), and four regions in Asia (Eastern, Southeastern, Southern and Western).

3. Worldwide HPV type distribution in women with normal cytology

3.1 Africa

Africa has a population of 274.49 millions women ages 15 years and older who are at risk of developing cervical cancer (WHO/ICO, 2007a). Current estimates indicate that every year 80419 women are diagnosed with cervical cancer and 53334 die from the disease (WHO/ICO, 2007a). Cervical cancer ranks as the second most frequent cancer among women between 15 and 44 years of age (WHO/ICO, 2007a). The prevalence of HPV is higher in African women with normal cytology than in women from other world regions and about 24.9% of women in the general population are estimated to harbor cervical HPV infection at a given time. Furthermore, HPV16 infections are found most commonly than infections caused by other HR types in regions of the world apart from Sub-Saharan Africa, where infections by other oncogenic HPV types, most significantly, HPV35, may dominate.

3.1.1 Northern Africa

In the Northern Africa, there are available studies from Tunisia, Morocco, Egypt and Algeria that describe the HPV distribution in women with normal cytological findings.

Tunisia has a population of 3.68 millions women and every year, 314 of them are diagnosed with cervical cancer, the third most common cancer in female, and 148 die from the disease (WHO/ICO, 2007a). About 14.6% of women in the general population are estimated to harbor cervical HPV infection at a given time (WHO/ICO, 2007a). A pilot study was carried out in 2006 by De Marco et al to identify the HPV prevalence in the country (De Marco et al., 2006). HPV prevalence among healthy women was 45% and HPV16 and HPV58 were the most common high risk (HR) types with a prevalence rate of 38% and 27% respectively (Table 1). HPV82 ranked third with 15% prevalence and types 31, 33 and 35 had 4% prevalence while there were no cases of HPV18. HPV72 and HPV83 were the only low risk (LR) types with 4% each. Overall prevalence appear to be within the expected range and well in agreement with the 39% already reported in Hassen et al cohort (Hassen et al., 2003).

Region	Total tested	HPV positive (%)	n	Spectrum[a]	Common type	Single HPV[b] (%)	Multiple HPV[c] (%)	HR HPV[d] (%)	LR HPV[e] (%)	Age[f]	Method[g]
Asia											
China	1701	205	8.7	High / low	16 / 52	9.4	2.6	8.6	3.9	15 - 59	GP5+/6+PCR, DNA chip
India	3061	367	12	High / low	16 / 18	9.7	2.4	8.5	0.8	-	GP5+/6+PCR, MY09/11
Iran	400	22	5.5	High	16 / 18	-	-	5.5	-	20 - 72	GP5+/6+ PCR
Japan	1328	288	21.7	High / low	52 / 16	20.7	13.5	18	7	17 - 73	Reverse ibridization, Hybrid capture
South Korea	821	70	8.5	High / low	70 / 33	6.9	1.6	4.4	4.1	15 - 69	GP5+/6+ PCR
Thailand	1673	80	4.7	High / low	72 / 16	3.6	1.2	2.9	1.8	15 - 65	GP5+/6+ PCR
Vietnam	1878	98	5.2	High / low	16 / 52	3.2	2.0	-	-	15 - 69	GP5+/6+ PCR
America											
Brazil	2512	532	21.1	High / low	16 / 72	-	6.3	5.3	0.5	>10 - 84	GP5+/6+PCR, MY09/11PCR
Chile	921	103	11.2	High / low	16 / 56	75	28	7.7	3.5	15 - 65	GP5+/6+ PCR
Columbia	1845	275	14.9	High / low	16 / 58	10	4.4	11.4	3.2	<20 - >55	GP5+/6+ PCR
Argentina	839	130	15.4	High / low	16 / 6	8.9	3.3	56	22	17 - 69	GP5+/6+ PCR
Mexico	1340	194	14.5	High / low	16 / 53	80.4	19.6	11	19	<25 - >65	Reverse ibridization
Costa Rica	7459	1670	22.4	High / low	71 / 16	16.6	5.8	9.9	12.5	<25 - >65	MY09/11 PCR
Unites States	2356	603	25.6	High / low	16 / 52	-	-	20.9	7.4	14 - 60	MY09/11 PCR
Canada	489	124	25.4	High / low	16 / 31	16	5.9	17	14.3	15 - 69	MY09/11 PCR
Africa											
Tunisia	64	28	45	High / low	16 / 58	-	-	-	-	≤25 - ≥35	PCR
Morocco	785	124	15.9	High	16 / 18	-	-	-	-	17 - 80	MY09/11 PCR
Algeria	732	33	5.3	High / low	31 / 16	4.5	0.82	2.9	2.7	15 - 65	GP5+/6+ PCR
South Africa	848	173	20.4	High / low	83 / 53	16.3	8.8	9.7	4.9	21 - 59	Reverse line blot assay
Zimbabwe	1987	487	24.5	High / low	58 / 16	-	-	-	-	-	MY09/11 PCR
Mozambique	195	148	75.9	High / low	51 / 35	38	38	-	-	-	Reverse ibridization
Kenya	454	183	40.3	High / low	58 / 16	20.9	32.5	27.3	26.2	<25 - ≥35	GP60/GP124

Nigeria	844	209	24.8	High / low	42 / 16	16.7	8.1	18.3	6.5	<2
Guinea	831	360	47.9	High / low	16 / 45	29	37.9	29.3	29.1	1
Senegal	1639	178	13	High / low	16 / 54	6.2	1.2	6	2.9	≤3
Cote d'Ivoire	120	37	31.1	High	16 / 18	-	-	31.1	-	2
Europe										
United Kingdom	23775	2226	11.3	High	16 / 18	-	-	11.3	-	2
Denmark	11918	2501	22.9	High / low	16 / 31	9.3	12.1	19.2	7.4	1
Sweden	282	70	24.8	High / low	16 / 18 / 42	8.8	6	23.4	3.2	2
Ireland	886	101	11.4	High / low	16 / 18	-	-	-	-	1
Norway	736	78	10.6	High / low	-	-	-	-	-	
Spain	-	298	-	High	16 / 31	-	-	-	-	
Italy	3151	307	9.7	High / low	16 / 31	9.8	2.1	6.2	2.7	2
Greece	1029	185	18	High / low	33 / 6	7.7	0.5	-	-	≤2
Croatia	205	73	35.6	High	16 / 31	32.6	2.9	35.6	-	2
Portugal	275	30	10.9	High / low	31 / 16	9.4	1.4	6.1	1.8	1
France	980	128	13	High / low	16 / 53	-	3	8.2	3.5	≤2
Belgium	581	155	26.7	High	-	-	-	17.9	8.8	1
Germany	7833	341	4.4	High / low	16 / 31	3.1	1.2	3.7	1.3	3(
Netherlands	1437	75	5.2	High / low	-	-	-	3.7	1.5	4
Switzerland	680	117	17.2	High / low	16 / 31	10.9	6.3	8.1	2.7	≤2
Poland	42	9	21.4	High / low	51 / 52	9.5	9.5	21.4	4.7	2
Hungary	1018	60	5.9	High	-	-	-	-	-	
Russia	309	90	29	High / low	16 / 31	25	1.6	53	26	2
Belarus	3187	929	27.5	High	16 / 31	15.1	24.9	31.2	-	≤2
Latvia	3187	929	26.2	High	16 / 31	15.1	24.9	31.2	-	≤2
Romania	285	123	43.5	High / low	16 / 18	-	-	22.8	5.6	≤2

[a] Spectrum of HPV types tested for: [b] Single infection; [c] Multiple infection; [d] High risk HPV types; [e] Low risk HPV types; [f] Age of enrolled women; [g] Main HPV testing method

Table 1. HPV prevalence in women without cervical cancer by world region.

In Morocco, statistical data showed that cervical cancer represents a serious health problem, with 500 new cases annually registered in the National Institute of Oncology, Rabat (Amrani et al., 2003). A study conducted by Alhamany et al determined the prevalence of the most oncogenic HPV in the Moroccan population (Alhamany et al., 2010). The cervix samples were collected from healthy women between 17 and 80 years of age. HPV DNA detection/typing was acquired by PCR with MY09/MY11 primers with specific probes for HPV16, 18, 31, 33, 35 and 45. HPV DNA was identified in 15.9% of women: 13.7% had HPV16, 8.9%had HPV18, 3.2% cases had HPV31, 0.8% had HPV33, 2.4% case had HPV35, 1.6% of HPV45 and 69.4% had an unknown HPV type infection (Table 1). The HPV prevalence in Moroccan women was in concordance with the overall world distribution of HPV in asymptomatic women. HPV16 was the predominant infectious type and, once again in concordance with the worldwide tendency (Figure 1).

A population-based study identified the HPV type distribution and prevalence in Algerian women (Hammouda et al., 2011), where cervical cancer is the second most common cancer. From the 11.51 millions women at risk of developing the disease, 1398 will be diagnosed per year and 797 will die (WHO/ICO, 2007a). HPV prevalence among women with normal cytology was 5.3% with 33 single infections and 6 multiple infections (Table 1). Prevalence of HR and LR types was 2.9% and 2.7% respectively, and HPV31 was the most common type (1.1%) followed by HPV16 (0.5%). Regarding LR types, HPV6 and HPV66 were the most common – 0.5%. This study is the first population-based HPV survey carried out in Northern Africa, and revealed a rather low burden of HPV infection. In addition, the prevalence of HR HPV in Algeria can be directly compared with women attending cervical screening in Europe and Canada (Figure 1).

3.1.2 Southern Africa (Sub-Saharan Africa)

In South Africa, despite the high prevalence of cervical cancer, few studies have been performed to describe the HPV type distribution in the country. A study enrolling 848 women with normal cytological findings was reported by Allan et al in 2008. The median age of the women was 44 years, ranging from 21 to 59 years. The specimens were HPV typed by a reverse line blot assay (Roche). The most prevalent types were LR HPV83 (2.6%), followed by HR HPV53 (2.2%) and HPV16 (2.0%). The prevalence of HPV16 and HPV18 was 3.3% while the HPV prevalence (20.4%) was high when compared with that reported in studies of populations elsewhere in the world (Table 1, Figure 1).

3.1.3 Eastern Africa (Sub-Saharan Africa)

A study carried out during the second phase of a cervical cancer screening project in Zimbabwe analyzed 1579 women classified as normal cytology (Womack et al., 2000). 35% of women had an HPV infection detected by HCII. Fukuchi et al performed serial HPV testing in a cohort of human immunodeficiency virus (HIV)-negative women to assess the HPV incidence and prevalence (Fukuchi et al., 2009). Testing was performed using MY09/MY11 consensus HPV L1 primers and specimens that tested positive were further studied to determine the specific HPV type. HPV prevalence at enrollment was based on a total of 1987 healthy women. The overall HPV prevalence was 24.5% and the HR HPV infection rate corresponded to 16.1% (Table 1).

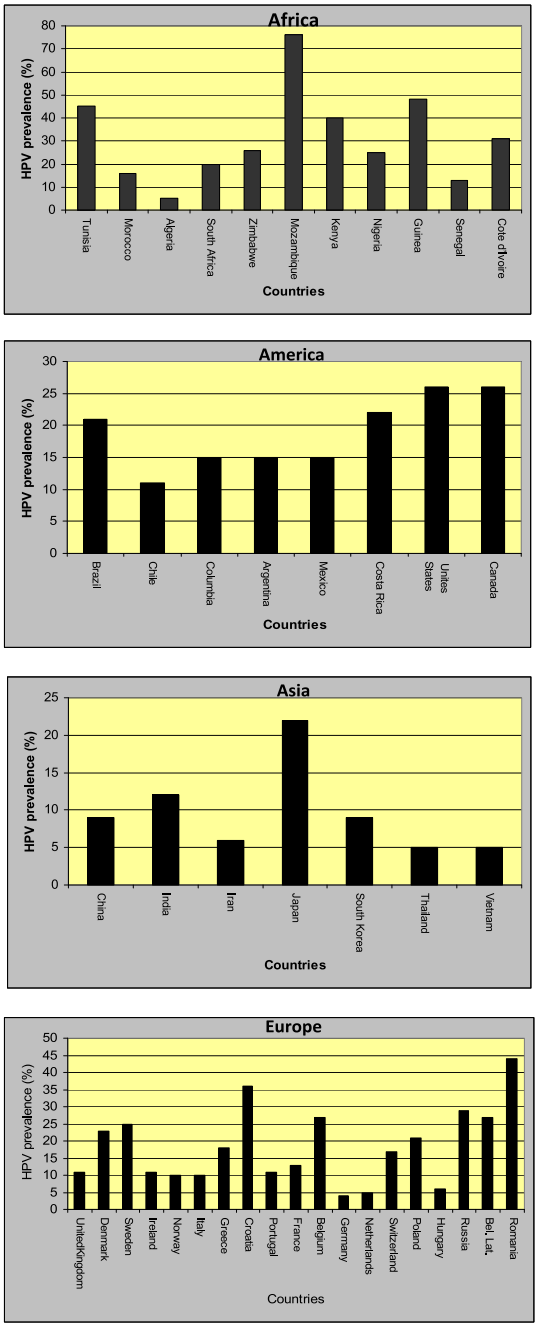

Fig. 1. HPV prevalence in women without cervical cancer

Among the prevalent infections, HPV58 was the most common HR type with 5% of women testing positive, followed by HPV16 and HPV18 with 4.7% and 2.3%, respectively. HPV70 was the most common LR type with 2,4%. HPV6 and HPV11 were rare in this cohort with 0,7% and 0,2% of women testing positive, respectively. The most common HPV types found in multiple infections were HPV types 58, 16, 70, 18, 53 and 33. The frequency of HPV58 is relatively high when compared with North America and Europe and it is associated with 3.3% of cervical cancer globally and 1.5% of cancer in Africa (WHO/ICO, 2007b).

In Mozambique, Castellsagué et al evaluated the HPV distribution in 196 women with normal Papanicolaou (Pap) smears. They used PGMY09/PGMY11 primer system in a reverse line-blot strip-based assay (Castellsague et al., 2001). The overall HPV DNA prevalence was 32%. In addition to the high prevalence of HPV infections, the most striking features in the epidemiology of HPV infection in this population were the high frequency of multiple simultaneous infections and the unexpected singularity of the type-specific HPV distribution. In 2008 Castellsagué et al reported a second study on HPV genotypes distribution in Mozambique. They collected cervical samples from 195 women without cervical abnormalities and tested them for HPV genotyping by SPF_{10}-$LIPA_{25}$ PCR system (Castellsague et al., 2008). HPV prevalence was 75.9%, the highest reported in the present work (Table 1, Figure 1). In descending order of frequency, the most frequent types were: HPV51 (23.6%), HPV35 (19.6%), HPV18 (14.2%), HPV31 (13.5%) and HPV52 (12.8%).

In Kenya, there are 10.32 million women in the general population, 2454 will be diagnosed with cervical cancer and 1676 will die from the disease (WHO/ICO, 2007a). In 1992, HPV prevalence was 19.5% among women with normal cytology (Czegledy et al., 1992). HPV16 was the most common type, followed by HPV18. To improve the epidemiological knowledge in Kenya, another HPV prevalence survey was developed in 2010 (De Vuyst et al., 2010). Among 454 women with normal cytological findings, 40.3% had a HPV DNA positive result (Table 1). The most common types were HPV58 with 9.9% prevalence, followed by HPV16 (7.5%) and HPV53 (6.6%). This study shows a high prevalence of HPV, similar to that found in other Sub-Saharan African populations. Not surprisingly for sub-Saharan Africa, half of HPV-positive women were infected with multiple types (Figure 1).

3.1.4 Western Africa (Sub-Saharan Africa)

Nigeria is the most populous country in Sub-Saharan Africa, with approximately 117 million inhabitants and an incidence of cervical cancer in Ibadan (1998-1999) of 19.9 per 100 000 (Cancer, 2003). To investigate the prevalence of cervical infection with HPV in the country, women with a sexually active life were tested (Thomas et al., 2004). HPV positivity was assessed by general primer-mediated GP5+/6+ PCR and by hybridization with an enzyme immunoassay (EIA). Among 844 women with normal cytology findings, the HPV prevalence was 24.8% with 18.3% of HR infections and 6.5% of LR infections (Table 1). The most commonly found HPV types, in either single or multiple infections, were HPV42 (4,4%), HPV16 and HPV35 (3%), HPV81 (2.7%), and HPV31 (2.6%). Other study on HPV infection in women without cervical cancer in Nigeria evaluated 844 women with normal cervical findings (Okolo et al., 2010). About 26.3% women were HPV positive. The prevalence of HPV16 and HPV35 were equally frequent (12.2%) followed by HPV 31 (11%).

Low risk and multiple HPV infections were also common with 44.9% and 27.8% respectively. The prevalence of HPV of 24.8% to 26.3% found in Nigeria studies is consistent with previous reports of the elevated prevalence of HPV in women of Sub-Saharan Africa.

To investigate HPV infection in Guinea, 831 healthy women aged 18-64 years from the general population were investigated (Keita et al., 2009). The overall presence of HPV DNA was determined by performing a general primer GP5+/6+ mediated PCR and HPV positivity was assessed by hybridization of PCR products in an EIA. HPV prevalence was 47.9% (Table 1). Prevalence of HR and LR types (29.3%, 29.1%, respectively) was similar. The commonest HR HPV types were HPV16 (6.7%), HPV45 (4.7%), HPV52 (4.0%), and HPV18, HPV35 and HPV58 (3.2% each). HPV66, HPV42 and HPV81 were the most commonly detected LR types. Totally, 29% of women had single type infection and 37.9% had multiple type infections.

In Senegal, Xi et al (2003) conducted a study among previously unscreened women to determine the prevalence of specific HPV types. HPV detection and typing analyses were carried out using a PCR-based reverse-line blot strip test (Xi et al., 2003). HPV DNA was detected in 13% women with normal cytology results, where 6.2% had a single type infection and 1.2% had a multiple type infection (Table 1). The most commonly detected types were HPV16 (1.0%), HPV54 (1.0%) and HPV18 (0.9%).

In a case-control study in the Cote d'Ivoire, the relationship between HIV infection and invasive cervical cancer was tested in 120 women with normal cytology. HPV DNA was detected by means of L1 consensus PCR assay (PGMY09/PGMY11 primer system), followed by typing in the Roche linear probe assay (Adjorlolo-Johnson et al., 2010). The prevalence of HPV infection was 31.1% and the most common types were HPV16, HPV18, HPV45, HPV35 and HPV31 (Table 1).

3.2 America

America has 336 millions of women older than 15 years which are at risk of developing cervical cancer (WHO/ICO, 2010a). Annually, 81000 of cervical cancer cases were diagnosed and 36000 of women died with the disease (WHO/ICO, 2010a). Cervical cancer ranks as the fourth most frequent cancer in women in America and the second most frequent among women between 15 and 44 years of age.

3.2.1 South and Central America

Latin America continues to be an important burden of cervical cancer (Murillo et al., 2008). South and Central America, along with Sub-Saharan Africa and Southeast Asia, exhibited some of the highest incidence rates worldwide (Gage et al., 2003). The incidence of cervical cancer is highest among poor women with few years of schooling, who tend to be diagnosed at advanced stages of the disease (Murillo et al., 2008). Even when these women are screened or diagnosed, less than one fourth of them receive adequate follow-up and care (Gage et al., 2003). Numerous countries in the region have attempted to implement cytology-based screening programs but without success, even in countries where cytology has been available for many years and where organized health care systems exist. While the lack of impact is frequently attributed to problems associated with program performance,

new screening technology and prophylactic HPV vaccines emerge as promising alternatives for cervical cancer control (Murillo et al., 2008). Nevertheless, to ensure success of these technological advances, public health programs will still need to be organized and structured to maximize the benefits that could be obtained with the adoption and implementation of novel methods to control cervical cancer (Murillo et al., 2008). Latin America has a high HPV prevalence among women with normal cytology (Table 1) but the incidence of this disease varies between rich and poor countries, even between regions within a country (Figure 1). Age–specific prevalence ranges from 30% among women younger than 25 to 11% among women aged 45-54 (Figure 2). It is very high among teen-agers and then it slowly declined until 45-54 years of age to increase again significantly among women more than 55 years (20%). HPV16 was the most prevalent type among women with normal cervical histology but other common HPV genotypes are HPV18, HPV52, HPV31, and HPV6.

In Mexico cervical cancer is the most common cancer among women and its incidence rate is the highest world-wide. Mexico has a population of 37.45 million women aged 15 years and older who are at risk of developing cervical cancer (WHO/ICO, 2010k). Annually 10000 women are diagnosed with cervical cancer and 5000 die from the disease (WHO/ICO, 2010k). In countries like Mexico, cervical cancer early detection programs have had a minimal impact on the incidence and death rates (Lazcano-Ponce et al., 1999, Lazcano-Ponce et al., 2003, Ogedegbe et al., 2005). In addition, in poor regions, Pap smears have generally proven to be ineffective (Chu et al., 2007), frequently due to inadequate sampling of the specimen (Raab et al., 2008), poor fixation, and lack of competencies (Tworek et al., 2007). The consequence is a very high number of false-negative results (DeMay, 1996). The HPV prevalence among women with normal cervical cytology in Mexico was 14.5% (Table 1). As in Chile, Columbia, and Costa Rica, the age standardized–HPV prevalence among healthy women follows a bimodal distribution. HPV DNA was detected in 16.7% among women less than 25 years, with the prevalence declining rapidly to 3.7% between 45 and 54 years (12.3%), and increasing again to a maximum of 23% among women with 65 years of age. The HR HPV types were predominant in the first peak while LR HPV types were more frequent among women over 65 years of age. The most common genotype was HPV16, followed by HPV53 and HPV31.

Cervical cancer and breast cancer are leading causes of cancer-related morbidity and mortality in Costa Rica. In a population where every year 1.5 million of teenagers are at risk for cervical cancer, 403000 cervical cancer cases were diagnosed and 158000 women older than 15 years died with the disease (WHO/ICO, 2010h). HPV prevalence among women with normal cervical histology was high (22.4) (Table 1). Infection with a single type occurred in 16.6%, and 5.8% of women were infected with at least two HPV genotypes. The LR HPV types were predominant compared with HR HPV types, infecting 12.5 and 9.9% of women, respectively. HPV71 was the most frequent genotype. The prevalence of type HPV16 was relatively low, while the HR HPV58, HPV51, and HPV52 were relatively frequent. This finding placed Costa Rica close to African and Asian countries, where the HPV58 and HPV52 were the most frequent. As in the areas of Latin America where a high HPV prevalence was detected, the age-specific prevalence followed a bimodal distribution with the highest peaks at the extremes of ages. HR HPV genotypes were more common in women younger than 25 years old, with a decrease in prevalence in the intermediate age

group, and a minor peak in the older women. On the contrary, LR HPV genotypes showed an initial peak in prevalence among young women, a decreasing in the middle age group of women, and a highest peak among women over 60 years.

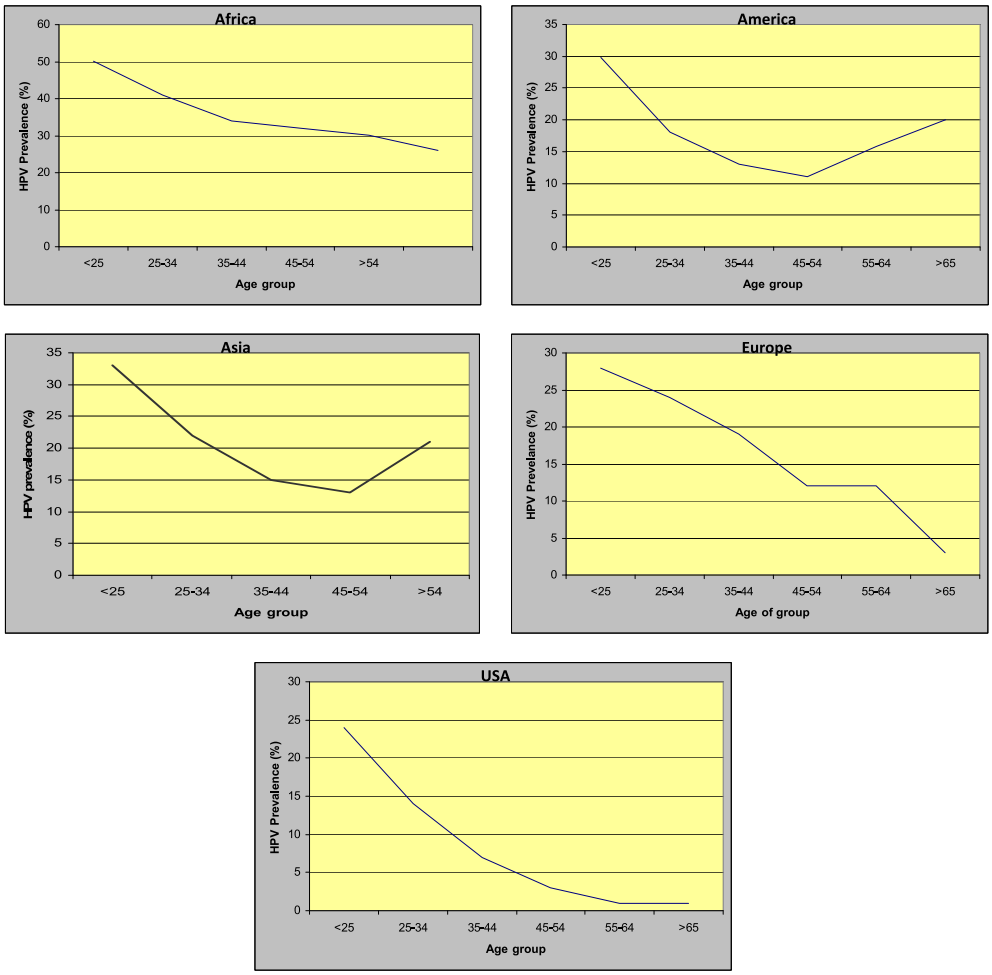

Fig. 2. HPV age-specific distribution in women without cervical cancer

In Brazil cervical cancer incidence remains among the highest in Latin America. North and Northeast regions have a higher mortality than Eastern and Southern states. Annually, 20000 cervical cancer cases were diagnosed and 8000 of Brazilian women in the general population died with the disease (WHO/ICO, 2010d). Cervical cancer is the second most frequent cancer in women in Brazil. Approximately 70 millions of women older than 15 years are at risk of developing cervical cancer (WHO/ICO, 2010d). The prevalence of HPV infection among women with normal cervical cytology was 21.1%

(Table 1). It was close to Canada and USA with 25.4% and 25.6%, respectively (Roteli-Martins et al., 2011). A decline in the HPV prevalence was found with increasing age. The most frequent HPV genotypes among healthy women were HPV16 and HPV72. The prevalence of HR types (16 ,18, 31, 33) was 5.3%, while the prevalence of LR types (72, 54, 6) was 10 fold lower (0.5%). The prevalence of HPV infection was linked to sexual behavior. HPV DNA increased with increasing number of regular partners. Women with two or more sexual partners had a higher prevalence of HPV DNA, but this finding was not statistically significant.

In Chile, cervical cancer is the sixth cause of death from malignant tumors and it represents a major public health problem (Chilean Ministry, 2005). Every year, 1500 cervical cancer cases are diagnosed in Chile and 721000 Chilean women in the general population died (WHO/ICO, 2010f). These deaths represents a major social and economic impact, because this type of cancer affects relatively young women in their reproductive age (Chilean Ministry, 2005). In fact 6.25 millions of women older than 15 years are at risk of developing cervical cancer (WHO/ICO, 2010f). The level of HPV infection (11.2%) among Chilean women with normal cytology is similar to the prevalence found in other Latin American countries, such as Mexico (14.5%), Columbia (14.9%) but higher than in many parts of Europe and Asia (Table 1). Seventy-six (73.6%) HPV infections involved a single genotype while 28 (27.1%) involved multiple types. The most common HPV genotypes were HPV16 and HPV56, followed by HPV70, HPV52, HPV58, and HPV59. The prevalence by age showed a bimodal curve with the two picks at the young and old ages and with a nadir in the middle age. For HR HPV infections the highest peak was represented by younger ages while for LR HPV by older groups. Consequently, among healthy women among 15 and 19 years of ages HR HPV was more frequent and LR HPV was less frequent. The new LR HPV increase after age 70 might be a result of the selective elimination of HR HPV by treatments. Similarly in Columbia and Costa Rica the second peak is mostly due to LR HPV while in Mexico the increase is caused by both HR and LR. Interesting, single widowed and divorced women had higher HPV infection, compared with married women. Moreover the number of partners was correlated with HPV infection. Women who reported their husbands had extramarital sexual relationships had high prevalence of HPV, but this did not reach statistical significance.

In Columbia cervical cancer is the principal cause of cancer mortality among women. Annually, 4700 cervical cancer cases are diagnosed and 2000 Colombian women in the general population died with the disease (WHO/ICO, 2010g). Approximately, 15 millions of women older than 15 years are at risk of developing cervical cancer (WHO/ICO, 2010g). The overall HPV DNA prevalence rate among healthy women was 14.9% (Table 1) which is similar to that reported in other high-risk populations. Of the HPV-positive women, 11.4% were infected with HR types and 3.2% with LR types. Similarly to Chile, the HPV age-standardized prevalence among women with normal cytological findings showed a bimodal curve, with a highest peak (26%) among women below age 20 and a lower peak among women over 55 (13.2%). HPV prevalence among women aged 45-54 was very low (2.3%). HR HPV infections were more prevalent then LR HPV infections except among women aged over 55. Mexico and Costa Rica presented some increase in HPV infection among woman in peri-and post-menopause as well. But while in Costa Rica the predominance was LR HPV, in Mexico the predominance was HR HPV with an increasing of LR HPV in

younger women. This could due to a reactivation of HPV infection by decreased immune response or by hormonal changes (Ginaldi et al., 1999). The most common genotype found was HPV16 followed by HPV58. Although HPV16 is the predominant type detected worldwide, HPV58 was noted with high prevalence as well. Multiple infections were detected in 29.7% of HPV-positive women, with a high frequency among women less than 25.

Cervical cancer ranks as the second most frequent cancer in women in Argentina, and the second most frequent cancer among women between 15 and 44 years of age. Argentina has a population of 14.74 million women ages 15 years and older who are at risk of developing cervical cancer (WHO/ICO, 2010b). Current estimates indicate that every year 4000 women in the general population are diagnosed with cervical cancer and 1809 die from the disease (WHO/ICO, 2010b). The disease was not homogeneous in all the country, developed provinces of Argentina, in the northwest, had an incidence of cervical cancer nearly four times higher than Buenos Aires. The main problem is due to lack of prevention and control. For decades poor women with low education levels and less access to information were often brought into the hospital in a state of abnormal vaginal bleeding and advanced cervical cancer. In the last years, a vaccine has been developed to prevent HPV for girls from 10 to 11 years in areas at high risk. The HPV prevalence among women without cervical abnormities was 15.4% (Table 1). This value was slightly high compared with other part of the country and other geographical regions of the world (range 7.7-13.9%) (Clifford et al., 2005). Among all HPV-positive women 8.9% had an infection with a single HPV type, while 3.3% had multiple HPV types detected. The HR HPV genotypes were predominant compared to LR HPV. The most common HPV genotype was the HR HPV16, followed by LR HPV6. Differently from the other Latin American countries, the prevalence decreased consistently with the age, reaching the lowest point among women over 65 years of age.

3.2.2 North America

The incidence of cervical cancer in the United States and Canada has declined for some time until to be relatively low (Dailard, 2003). The major reason the rates are so low, despite high rates of HPV infection, is the widespread availability of Pap tests (Dailard, 2003). Pap-test can detect not only early-stage cervical cancer, but also cervical dysplasia. Since the Pap test was introduced, cases of cervical cancer in the United States have decreased dramatically (74%) between 1955 and 1992 (Dailard, 2003). HPV prevalence among healthy women in North America was high in the United States and Canada (Table 1, Figure 1). Age–specific prevalence among women with normal cytology ranged from 30% among women younger than 25 to 1% among women aged 45-54. It was very high among teen-agers and then it slowly declined until 45-54 years of age for significantly increase again among women more than 55 years (20%) (Figure 2). Only Unites States showed a significant decreasing with age (Figure 2). HPV16 was the most prevalent type among women with normal cervical cytology.

HPV was estimated to be the most common sexually transmitted infection in the United States (Winer et al., 2003, Tarkowski et al., 2004, Revzina and Diclemente, 2005, Manhart et al., 2006, Trottier and Franco, 2006). An estimated over 122 millions of women in the general population, showed that approximately 40% of the population are currently HPV-infected

(WHO/ICO, 2010l). Each year in the United States, 11000 cases of cervical cancer were diagnosed and 4000 women died with the disease (WHO/ICO, 2010l). Almost half of the infections were among women 15-25 years old. The prevalence of HPV infection among women with normal histology was 25.6% (Table 1), including 20.9% with an HR HPV type and 7.4% with an LR HPV genotype. HPV16, the most common cervical infection worldwide, was the most common prevalent type, followed by HPV52 and HPV53. It is notable that HPV18 and HPV31 were not found as commonly as in other areas of America or Asia. Similar to other studies in Europe, the prevalence of HPV increased from 14 years to 24 years, and then decreased significantly with the age. There was a 20-fold variation in the prevalence of HPV infection between young women and women over 55.

HPV is among the most common sexual transmitted disease (STD) in Canada (Public health, 2007). HPV infection affects about 550 000 Canadians in the general population annually, and at some point in their lives 80% of sexually active women will be infected by one or more of the 100 HPV types (WHO/ICO, 2010e). Of those infected, approximately 1400 women were diagnosed with cervical cancer and 544 women died with the disease (WHO/ICO, 2010e). Cervical cancer ranks as the 11th most frequent cancer among women in Canada, and the second most frequent cancer among women between 15 and 44. In September 2009, a school-based HPV vaccine program was commenced in all 14 provinces and territories of Canada (Ogilvie et al., 2010). The vaccine has the potential to change the demographics of cervical cancer among young women (Kaplan-Myrth and Dollin, 2007). The HPV prevalence among Canadian women with normal cytology was 25.4% (Table 1). The HR HPV infections were more frequent than LR HPV. The most common HPV type among HR and LR infections was HPV16 that was detected in 4.6% of the population under investigation, while HPV18 was detected only in 1.6% of the population. Similarly to Latin American countries, the HPV age-specific prevalence in healthy Canadian women showed a bimodal distribution, with about 20% of prevalence in younger and older women and a decrease among 40-49 years old. HR HPV types were common in single infections among women younger than 40 years of age but made a smaller contribution to single infections in older women.

3.3 Asia

Cervical cancer is a significant problem in developing countries and resource-insufficient areas such as Asia (Behbakht et al., 2004). This is partially related to poor availability of health care, which is induced by social and cultural barriers that decrease patient compliance and interrupt physician education (Cooper et al., 2005). It is also related to the fact that HPV vaccines will be first introduced into industrialized countries and only later in developing countries. Asia has more than 1000 million women who are at risk of developing cervical cancer (WHO/ICO, 2010c). About 313,000 cases of cervical cancer are diagnosed each year, with 160.000 women in the general population dying from the disease (WHO/ICO, 2010c). It is the second most common female cancer in the region, where a woman dies of cervical cancer every 4 minutes, often in the prime of her life. The statistics consider almost half of the world's cervical cancer cases are diagnosed in Asia, but the distribution is heterogeneous, presumably because of the ample geographical and cultural diversities of Asian population (Figure 1) (Clifford et al., 2005). For example HPV prevalence in woman with normal cytology was high in Japan and Russia but not in China

or India, where the prevalence was only intermediate, or in Thailand or Vietnam, where the number of infections was the lowest (Table 1). Those data are not in agreement with historical cervical cancer incidence that showed rates of cervical cancer low for China and high for India (Parkin, 2002). The discrepancies might reflect a more liberal sexual behaviour developed in recent decades, forming new HPV epidemiology in Asian countries (Li et al., 2006). This finding could predict a rising cervical cancer epidemic in the world with a so fast growing to match the HIV epidemic. HPV prevalence tended to be lower than in other regions of the world, with the exception of Russia and Japan. Age–specific prevalence among healthy women ranged from 33% among women younger than 25 to 13% among women aged 45-54 (Figure 2). It was very high among teen-agers and then it slowly declined until 45-54 years of age for significantly raising again to 21% among women more than 55 years (Figure 2). HPV16 was the most prevalent type among women with normal cervical histology but other common HPV genotypes were HPV52, HPV58, HPV31, and HPV32. It is noteworthy that Eastern Asia (South Korea, Japan, and Thailand) had the lowest contribution of HPV16 compared with the other Asian regions. In South Korea the most frequent HPV types were HPV70 and HPV33 with 1.34% and 0.85% against 0.24% of HPV16. In Japan and in Thailand the most frequent HPV types were HPV52 and HPV72 with 6.4% and 0.78%, respectively, against 4.1% and 0.48% of HPV16. Moreover only 0.6% of woman with normal cervical histology tested positive for HPV18, which is very common in western countries.

3.3.1 Eastern Asia

In China the age standardized–HPV prevalence was similar to those areas with high incidence rates of cervical cancer like Latin America and India but lower than in the high-risk regions in Asia and South Africa (Dai et al., 2006). It was homogeneous in all the country, in urban populations in North- and South-east of China (Li et al., 2006) as well as in the rural population in Central China (Dai et al., 2006). The highest HPV prevalence in the general population was found among middle aged women even if a peak was seen among women younger than 25 years. Castle et al. suggested HPV persistence in over 45 years old women than acquisition of new infection (Castle et al., 2005). Thus, a high prevalence might indicate a reactivation of HPV infection. Furthermore, China is a conservative society, especially the central area, so it is likely that middle aged women are more frequently exposed to the HPV than young women (Dai et al., 2006). One of the limitations of HPV prevalence studies in China is the difficulty to obtain specimens from unmarried women (Dai et al., 2006). Indeed in some studies the age-specific pattern of HPV infection for the tertiary sector workers was different with a gentle decline with increasing age (Winer et al., 2003). The prevalence of HR HPV infections (8.7%) in healthy women was similar to the global average (9.2%) (Clifford et al., 2005) while the infection with LR HPV genotypes was lower (Sun et al., 2010) (Table 1). The most common identified HPV type was HPV16 but HPV52 was predominant as well, more than in non-Asian populations (Clifford et al., 2005). Only 1.80% of healthy women in China were diagnosed with HPV18 infection. The prevalence of single-type HPV infection was 9.4% while the prevalence of multiple-type HPV infection was 2.6%.

HPV infection is the most prevalent but also the least known STD in Japan. (Garland et al., 2008). Cervical cancer ranks 7th in women overall and 2nd in women aged 15-44 years (Clifford et al., 2005, WHO/ICO, 2010j). Fifteen thousand women in the general population

are diagnosed with cervical cancer yearly, leading to 3500 deaths (JMH, Castellsague et al., 2007). Prevalence of HPV infection in the Japanese population has been usually conducted in small geographic areas, and little information regarding nationwide HPV prevalence was available. The proportion of HPV-positive cases among woman with normal cytology was 21.7% and decreased with aging (Table 1). Women aged 20-25 years with normal cytology and HPV infection were relatively high compared with other women from the Asian Pacific region, with the exception of Australian women (Garland et al., 2008). Although the studies were not based in the same geographic region and used different primer systems HPV DNA positivity appears to be very high in Japanese women (Onuki et al., 2009). In the most recent studies, the HPV prevalence in Japan resulted increased. The high prevalence might reflect a more liberal sexual behaviour developed in recent decades or could be due to differences in the detection methods (Onuki et al., 2009). New PCR primers used in recent studies have a higher sensitivity. Among the high-risk types, HPV52 was the most prevalent among healthy women in Japanese population, while HPV16 was more closely associated with cervical abnormalities (Konno et al., 2008). HPV16 and HPV51 were the second and the third most prevalent HPV types. The numbers of single and multiple-HPV infections were high (20.7% and 13.5%, respectively) (Table1). Several women were positive for five HPV types (0.6%).

The incidence of cervical cancer in Korea has steadily increased over the past 10 years and with a pattern of a developing country because of the increase in incidence and mortality related with cervical cancer. HPV prevalence in Korean women has been found to be diverse according to age groups, areas, socioeconomic status, and methods for detection of HPV DNA. However, most reports have shown that the prevalence of HPV infection among women with normal cervical histology was 10-15% with an average of 8.5%, in agreement with intermediate-risk developing countries (Table 1). The incidence of HPV infection was significantly higher in females between 20 and 30 years than in older women. Then it declined at age 50-59 years and increased again above 60. DNA from HR HPV types was predominant over LR HPV types below age 35, whereas LR HPV types were as equally frequent as HR HPV types in women aged 35 and older. The most common HPV genotype in either single or multiple infections was HPV70 followed by HPV33 and HPV16. Together they infected half of HPV DNA positive women. Single infections (9.8%) were more frequent than multiple infections (1.75).

3.3.2 South-eastern Asia

Vietnam is one of the poor, developing countries. Malnutrition and infectious diseases are still major health problems. Cervical cancer ranks in a relatively modest position of priority and the geographical distribution is not homogenous within the country. It used to be frequent in both the North and South but there is a gender difference between two regions: it was higher in the South than in the North. In the North the HPV detection in women without cervical abnormalities was very rare (2%); in the South the HPV detections among healthy women (10.9%) were 5-fold higher than in the North. The overall HPV prevalence was very low (5.2%), lower than worldwide average (Table 1). Infections with multiple HPV types were 9-fold more common in the South (4.5%) than in the North (0.4%). In Vietnam the most frequent HPV genotype was HPV16, followed by HPV52. A peak in the HPV prevalence among women younger than 25 years was found only in the South that then

significantly decline with age. In North no clear age-pattern emerged, but the highest prevalence was found among women 35-44 years of age group. The differences between the regions cannot be due to technical reason, as women were randomly chosen in the same way and the samples were examinated in parallel. It may rather be due to the greater isolation between North and South during many decades of socialist economy.

Cervical cancer is the leading cancer in Thailand. Despite that, the prevalence of HPV infection was relatively low (4.7%) among women with normal cervical history, suggesting the spread of the infection to be relatively limited (Table 1). The vast majority of women tested reported having only one sexual partner in their lifetimes. Women who reported more than 2 sexual partners appeared to be at an increased risk of HPV detection, but only borderline statistical significance was estimated. HPV prevalence among healthy women was higher in the North area of Thailand than in South regions. This does not appear to be explained by differences in sexual habits or in HPV detection methods, as all samples were analyzed in parallel and in the same laboratory. The majority of HPV-positive women had infections with HR HPV type (61%) and the most common genotypes were HPV72 and HPV16. Multiple infections were found in 1.5% of HPV-positive women. The age-standardized prevalence among women with normal cytological findings was two fold higher in population from North Thailand than in South Thailand. In both cases, HPV DNA positivity was higher among women younger than 25 years of age and then formed a plateau among women older than 35 years of age. The prevalence of HR HPV types reached the highest value (6.5%) among women aged 25-34 years while the highest LR HPV prevalence (5.1%) was found among women younger than 25 years of age. The representativeness of HPV DNA prevalence among women younger than 25 is limited, because young women in Thailand generally were not willing to undergo a pelvic examination.

3.3.3 Western Asia

Iran is a country with a low prevalence of HPV. The incident of HPV infection among women with normal cytology in Iran was only 5,5% lower than the worldwide average but similar to that in low-prevalence areas (Table 1). Age–specific prevalence among healthy women was 4.5% among women aged between 20-40 years and gradually increased to 20% in 50-59 years old women. The prevalence of high-risk HPV was around 2% among younger women and decreased to zero in the older age group. The decreased occurrence with increasing age may suggest that the HPV infection at a young age is transient and it is eradicated by the immune-system. For the same reason not all HPV-infected women develop cervical abnomarlities (Centurioni et al., 2005, Onuki et al., 2009). The most common HPV genotype in either single or multiple infections was HPV16 followed by HPV18.

3.3.4 Southern Asia

In India the incidence of cervical cancer is high and the majority of Indian women had difficulties to access appropriate screening facilities. The country is exploring various strategies for preventing the disease and the vaccination is one of the solutions (Ghim et al., 2002, Das et al., 2008). The vaccine was found to be safe and highly immunogenic and possibly able to protect women already exposed to natural infection as well as HPV-naïve

women (Swarz, 2007, Keam and Harper, 2008). In India the HPV prevalence among women with normal cervical histology was 12% which was similar to other geographical regions of the world (range 7.7-13.9%) (Clifford et al., 2005) (Table 1). Bao et al found a higher HPV infection in healthy women from hospital-based studies (25%) than from population based studies (10.9%) (Bao et al., 2008). HPV16 was the predominant type found in Indiam women without cervical abnomarlities and it was more common than HPV18 in perfectly accordance with other analysis from Asia (Clifford et al., 2005, Clifford et al., 2006). The HPV16/18–positive fraction was 32% with some variations between North and South India, with North more significant than South. After these, HPV33, HPV56, and HPV52 accounted for additional 16%. The prevalence of single-type HPV infection was 9.7% while the prevalence of multiple-type HPV infection was 2.4%. A limitation of HPV prevalence studies among women without cervical neoplastic desease in India was a reduced number of studies that fulfilled all the inclusion criteria. The few existing were not representative of each region; the Western and the central areas were not well documented.

3.4 Europe

In 2007, Europe had a population of 321.8 million and each year 59931 women are diagnosed with cervical cancer and 29812 die from the disease (WHO/ICO, 2007b). In this continent, cervical cancer is ranked as the 7th most common cancer in women, and as the second most frequent cancer among women between 15 and 44 years of age. About 6.6% of women in general population are estimated to harbor cervical HPV infection at a given time, and 73.3% of invasive cervical cancer are attributed to HPV16 and 18 (WHO/ICO, 2007b).

3.4.1 Northern Europe

The effectiveness of HPV testing in primary cervical cancer was evaluated in the United Kingdom (Kitchener et al., 2006). The HPV detection was performed on 42647 healthy women (20-64 years) by HC2 and typing through Roche reverse line blot assay. The age-specific prevalence pattern was 7.3% in the 20-29 years old group, 25.9% between 30-49 years, 11.6% in the 50-64 years of age and 44.8% in the oldest group, with ages among 50-64. Regarding HPV types, there was a 2.2% prevalence of HPV16 and HPV18 together and 8.2% of other HR HPV types, meaning that 11.3% of normal cytology samples were infected with a HR type (Table 1). In 2010, another study evaluated prevalence of type-specific HPV infections in the country (Howell-Jones et al., 2010). The Roche Linear Array test was used and the six most common HPV infections in women with normal cytology were HPV16, 61, 62, 53, CP6108 and 54, in descending order; HPV18 was only the nineteenth most common type. Infection with HR HPV was identified in 12.2% of participants.

In 1997, a population-based prospective cohort study evaluated the HPV infection in 1000 randomly chosen young Danish women (Kjaer et al., 1997). The participants were healthy women distributed over the age range (20-29 years); 30, 32 and 38% were 20-23 years old, 24-26 and 27-29 years old. Overall HPV DNA was detected in 15.4% women, 73.8% women had HR HPV types. LR HPV6, 11 was found in 30% of the women. Of the positive samples, approximately 10% contained more than one HPV type (only 3% harbored both HR and LR HPV types). Prevalence of any HPV type was associated with age: 19.4% of group age 20-23, 14.1% of 24-26 and 13.1% of 27 to 29 years old. In 2008, a study assessed the type-specific

HPV prevalence to estimate the preventive potential of an HPV 16/18 VLP vaccine in preventing cervical cancer (Kjaer et al., 2008). 11918 women with normal cytology and a mean age of 36.3 years old were tested by HC2. The HPV prevalence was 22.9%, 19.2% infected with HR HPV types and 7.4% with LR HPV types (Table 1). Multiple HPV infections (12.1%) were more prevalent than single HPV infections (9.3%). The most common HPV type was HPV16 (4.8%) followed by HPV31, 52 and 51 (3.8-3.6%).

In Sweden, Dahlstrom et al. (2010) evaluated the HPV distribution and the risk of cervical adenocarcinoma using 282 women with normal smears. The HPV prevalence was 24.8% (Table 1). Among all HPV-positive women 8.8% had an infection with a single HPV type, while 6% had multiple HPV types detected. The HR HPV genotypes were predominant compared to LR HPV. The most common HPV genotype was the HR HPV16, followed by HR HPV31 and LR HPV 42.

Keegan et al. (2007) reported an analysis of the cytological and HPV status of Irish women undergoing opportunistic cervical cancer screening. Detection of HPV was performed using MY09/MY11 consensus primers and then samples were sequenced to genotype the virus. 886 women with normal cytology were analyzed. HPV DNA was detected in 11.4% of the samples tested (Table 1). Regarding age distribution, the study samples ranged from 16 to 72 years. There were 27 HPV positive cases in women bellow 25 years, 48 cases between 25-30 and 26 cases in women with more than 35 years. The samples with normal cytological findings had HPV16 and HPV18 as the most common HPV types.

In Norway, a study investigated the cross-sectional positivity for HPV in 736 women with normal cytological findings (Trope et al., 2009). 30 years or older women were recruited from 4 Norwegian hospitals and were attending routinely administered clinical services with normal Pap smear cytology, normal cytological results from the preceding 2 years and no previous history of treatment of cervical neoplasia. A total of 10.6% women with normal cytology tested positive for HR HPV using Amplicor HPV test (Roche) (Table 1).

3.4.2 Southern Europe

Dutra et al (2008) characterized the HPV genotype distribution in 275 Portuguese women with normal cytology findings. The samples aged from 16 to 81 years old. HPV DNA was detected and typed using the commercially available Papillomavirus Clinical Arrays kit. The virus was detected in 30 women (10.9%) and it was more prevalent in age groups ranging from 25 to 34 years old and from 40 to 54 years old (Table 1). There were 1.8% cases of LR HPV infection, 6.1% cases of HR HPV and 2.5% cases of undetermined risk infection. The most common types were HPV31 (26.67%) and HPV16 (10%).

In 2011, the prevalence and distribution of HR HPV genotypes in Spanish women was studied (Lindemann et al., 2010). HC2 was carried out and all positive samples were further studied with Linear Array HPV Genotyping test (Roche). The author found 298 healthy women infected. The most prevalent type was HPV16 (17.8%) followed by HPV31 (12.8%) and HPV52 (12.4%). In total, 17 HR HPV types were identified.

Agarossi et al. (2009) studied the prevalence and the distribution of oncogenic HPV genotypes in Italy. HPVs were detected using HC2. Positive samples were genotyped by PCR. HPV 16 or 18 were present in 4% of healthy women and both were detected

simultaneously in only 14 women. A study conducted by Rossi et al, analyzed the distribution of high and low risk HPV types in Italy (Giorgi Rossi et al., 2011). The presence of HR and LR types was investigated through HC2 in 3151 women with normal cytology aging from 25 to 64. The HC2 positive specimens were amplified and typed with "consensus high risk HPV genotyping test". HPV prevalence was 9.7% (Table 1). A HR HPV infection was found in 6.2% of women and LR HPV infection in 2.7%. The most common types were HPV16 found in 67 samples (2.1%) and HPV31 (0.8%).

In Greece, two molecular methods of HPV detection were used in a large sample of women (Tsiodras et al., 2010). The two methods were: commercially available HC2 and an in house PCR using consensus primers GP5+/6+. During the 4 years period, 1029 women with normal cytology were evaluated (mean age: 34,2 ± 12,1 years old). HC2 detected HPV infection in 10.2% and the PCR methodology identified 18% of infected women (Table 1). It was also possible to genotype HPV by PCR, and 2.7% multiple HPV cases were detected. The most common types were HPV33 and HPV6 with 10 cases each, HPV6 with one case and HPVX (undetermined) was identified in 159 cases. There was not any case of HPV16, 18 or 11.

Grahovac et al investigated the prevalence of HPV among Croatian women attending a regular gynecological visit (Grahovac et al., 2007). 205 women (21-37 years old) without obvious cervical changes were analyzed. HPV DNA detection and genotyping was performed by HC2 assay and additionally by consensus and type-specific primers directed PCR. The overall prevalence of HR HPV in the group of women was 35.6% with HPV16 found in 43.8% cases followed by HPV31 (17.8%), HPV33 (9.5%) and HPV18 (6.8%) (Table 1). The prevalence of HPV of undetermined type was 13.7% and 6 were the cases with multiple HPV infections (8.2%).

3.4.3 Eastern Europe

Not many studies were developed on HPV prevalence in Russia, although some reports have been released until now. In many related socio-medical aspects, Russia seem to be similar to European countries. But the sexual attitudes were long considered "inappropriate". Decades of poor knowledge on the reproductive hygiene and ignorance of the risks of STD might have been affected the distribution of HPV. The HPV prevalence among healthy women in Russia was one of the highest revealed in this study. HPV was detected in 29% of the women with normal cervical cytology (Table 1, Figure 1). The largest proportion of HPV-positive cases was regarding women on reproductive age and no significant decline of the infection was observed in older women. HPV16 was the most prevalent type being present in 21% of the infected women alone and in 5% in combinations with other HPV types. Other common types were HPV31, HPV66, and HPV39. A strong correlation between excessive number of contraceptive abortions and the presence of HPV was observed among young Russian women (Popov, 1991)

The HPV prevalence was also investigated among 3187 healthy women in the two new independent states of former Soviet Union (Kulmala et al., 2007). HPV detection, type distribution and viral load analysis in DNA samples from cervical scrapes were done with real-time PCR-based assay. The overall HPV prevalence in Belarus and Latvia were 27.5%

and 26.2% respectively and HPV16 was the most prevalent type followed by HPV31 and HPV33 in Belarus and HPV39 in Latvia (Table 1).

In 2008 the relationship between the distribution of HPV types and the outcome of cytological examination was investigated in Poland (Szostek et al., 2008). Forty-two women with normal cytology were analyzed. HPV DNA amplification and genotyping was performed with the SPF10 primer set and reverse hybridization line probe assay (INNO-LiPA). The virus was found in 21.4% women and the percentage of single and multiple infections were 9.5%. The most common HPV types were HPV51 and HPV52 while the two more worldwide common HPV16 or HPV18 were not found.

The prevalence of HPV in healthy women in Hungary was assessed in 2002 by Kornya et al (Kornya et al., 2002). The HPV DNA was detected using the Digene Hybrid Capture HPV-DNA assay and the virus could be shown in 60 out of 1018 cytology normal samples, (prevalence of 5.9%) (Table 1).

In 2010, Anton et al. analyzed the distribution of HPV genotypes in Romanian healthy women. HPV was detected and genotyped using the commercially available INNO-LiPA. From the 285 women, 43.5% had an HPV infection and the most common type was HPV16 (15.4%), followed by HPV18, 31 and 51 (Table 1).

3.4.4 Western Europe

In France, Vaucel et al (2010) assessed the HPV overall and type-specific prevalence in 980 women with normal cytological diagnosis (mean age 38.5). PCR was performed with MY09/MY11 primers and genotyping by sequence PCR products. About 13% of women were HPV positive, and 3% showed multiple HPV infection (Table 1). The proportion of HPV positive women varied significantly according to age with the highest prevalence (44%) observed bellow 20 years of age. Thereafter, the prevalence decreased with increasing age reaching about 10% above 35 years. The most prevalent HPV genotypes were, by descending order of frequency HPV16 (3.6%), HPV53 (1.4%), HPV6 (1.0%), HPV31 (0.9%) and HPV33 (0.7%).

In a study on the occurrence and distribution of HPV infection in the Flemish region (Belgium), 581 cytological normal women, ranging from 17 to 85 years old, were studied (Sahebali et al., 2003). All samples were tested with MY09/MY11 consensus primers and the HPV positive group was retested with type-specific primers for 14 HR types. HPV prevalence was 26.7% (Table 1). HR HPV and LR HPV prevalence were 17.9 and 8.8%, respectively.

The prevalence of HPV types in women screened by cytology in Germany was evaluated by Klug et al in 2007 (Klug et al., 2007). HPV detection was performed by HC2 test and all positive samples for this assay were genotyped using PGMY09/PGMY11 PCR followed by reverse line blot assay. The study included 7833 women with no cervical abnormalities aging between 30 and 60 years. 4.4% of tested women had an HPV infection, 3.1% resulted single infections and 1.2% multiple infections. (Table 1). The most HR common types were HPV16 (1.1%), HPV31 (0.5%) and HPV52 (0.4%). In the LR HPV infections, HPV73 was the commonest type (0.4%).

In the Netherlands, a study compared two molecular detection tests using 1437 women with normal cytology findings aging from 40 to 60 (Hesselink et al., 2010). The authors compared

the clinical performance of Papillocheck HPV assay with that of the GP5+/6+ PCR method. The Papillocheck assay found a HPV prevalence of 5.2%. About 3.7% of the infections were HR HPV positive and 1.5% were LR HPV positive (Table 1).

In Switzerland, Dobec et al. (2009a) analyzed HPV genotype distribution in women without cervical abnormalities. It comprised 680 cervical specimens of females with ages from16 to 88 years (mean age, 40 years) tested for HPV with Linear Array HPV genotyping. Any HPV was detected in 17.2% of women and HR HPV was found in 8.1% of the study group (Table 1). The highest HPV prevalence was observed in age group 21-30 and showed a continuous decrease in older age groups. The seven most common HR HPV types were HPV16 (12%), HPV31 (9.4%), HPV52 (6%) and HPV45, 58 and 59 (4.3%, each). HPV6 was detected in 4.3% of the 117 HPV positive specimens and infection with single and multiple HPVs was found in 10.9% and 6.3%, respectively.

4. Discussion and conclusions

Our analysis included 47 countries with studies testing HPV infection in women with normal cytological findings. Figure 2 shows HPV prevalence by age and continent. In all regions, a peak in HPV infection was found at teen-agers (≤25 years), declining until middle age. In America and Asia, a modest second peak is observed at age ≥45 years, while in Europe, Africa and U.S.A. There is not an increase of infection but a continuous decline.

In HPV prevalence worldwide (Figure 1), there were significant differences not only between continents but from region to region. In America, the prevalence starts increasing from the South to the North, ranging from 11.20% to 25.60% respectively. Despite the high rates of HPV infection in North America (Canada and U.S.A.), the widespread availability of Pap tests and effective cervical screening programs, there are low rates of cervical cancer. In the South and Central American countries, the incidence of cervical cancer varies between poor and rich countries as well as the HPV prevalence rates.

In Asia the distribution is heterogeneous presumably because of the ample geographical and cultural diversities but nevertheless is lower than in other world regions. In Western and South-eastern Asia the prevalence is approximately 5% and arises to 12 and 14% in Southern and Eastern Asia with a maximum prevalence in Japan (21.7%).

In Europe, the low rates of HPV infection are located Western countries, such as Germany (4.4%) and Netherlands (5.2%) probably due to a correct vaccine implementation and high population knowledge about the virus. The prevalence starts increasing in Southern and Northern Europe countries (12.6%) and reaches the maximum European prevalence in Eastern countries (43.5%).

The highest prevalence percentages are found in the African continent (Guinea,47.9% and Mozambique, 75.9%). The Southern and Northern countries have the lowest continent prevalence, 20.4 and 23.5% respectively. The poorest countries have the highest infection rates with 24.6% in Western and 25.3% in Eastern African countries.

There is an increasing effort in generating epidemiological data on the carriage of cervical HPV in normal cytological samples. In most cases, the regions with high HPV prevalence are the ones with the highest cervical cancer incidences and the regions with lower

prevalence had the lowest incidences. These findings suggest that a correct vaccination program will affect dramatically the cervical cancer incidence.

5. References

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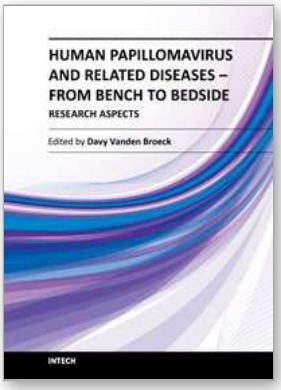

Human Papillomavirus and Related Diseases - From Bench to Bedside - Research aspects

Edited by Dr. Davy Vanden Broeck

ISBN 978-953-307-855-7
Hard cover, 406 pages
Publisher InTech
Published online 25, January, 2012
Published in print edition January, 2012

Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on epidemiological and fundamental research aspects in the area of HPV, and it will update those working in this fast-progressing field with the latest information.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

I. Dutra, I. Foroni, A.R. Couto, M. Lima and J. Bruges-Armas (2012). Human Papillomavirus Worldwide Distribution in Women Without Cervical Cancer, Human Papillomavirus and Related Diseases - From Bench to Bedside - Research aspects, Dr. Davy Vanden Broeck (Ed.), ISBN: 978-953-307-855-7, InTech, Available from: http://www.intechopen.com/books/human-papillomavirus-and-related-diseases-from-bench-to-bedside-research-aspects/human-papillomavirus-worldwide-distribution-in-women-without-cervical-cancer

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