

The epidemiology of genital human papillomavirus infection

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Abstract

Clinical and subclinical human papillomavirus (HPV) infections are the most common sexually transmitted infections in the world, and most sexually-active individuals are likely to be exposed to HPV infection during their lifetimes. More than 40 genotypes of HPV infect the epithelial lining of the anogenital tract and other mucosal areas of the body; of these, 13–18 types are considered to be high-oncogenic risk HPV types (HR-HPV). Persistent infection with HR-HPVs is now unequivocally established as a necessary cause of cervical cancer and is likely to be responsible for a substantial proportion of other anogenital neoplasms and upper aero-digestive tract cancers. Low oncogenic risk HPV types (LR-HPV) are also responsible for considerable morbidity as the cause of genital warts. Youth and certain sexual characteristics are key risk factors for HPV acquisition and persistence of HPV infection, but other mediating factors include smoking, oral contraceptive (OC) use, other STIs (e.g. chlamydia, herpes simplex virus), chronic inflammation, immunosuppressive conditions including HIV infection, parity, dietary factors, and polymorphisms in the human leukocyte antigen system. Not surprisingly, these factors are also established or candidate cofactors identified in epidemiologic studies of cervical cancer. HPV transmissibility and molecular events in HPV-induced carcinogenesis have been the focus of recent multidisciplinary epidemiologic studies. This shift in research focus coincides with a shift in cancer prevention techniques towards immunization with HPV vaccines and HPV testing of precancerous lesions.

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1. Introduction

More than 120 different human papillomavirus (HPV) types have been catalogued so far [1,2], of which more than 40 infect the epithelial lining of the anogenital tract and other mucosal areas of the body. Some 13–18 types have been identified as probable or definite high-oncogenic risk HPV types (HR-HPV) (Table 1). It is now widely accepted that HR-HPV infections are a necessary, but not sufficient, cause of virtually all cases of cervical cancer worldwide and are a likely cause of a substantial proportion of other anogenital neoplasms and oral squamous cell carcinomas. Infection with low oncogenic risk HPV types (LR-HPV), such as HPV 6 and 11, can cause benign lesions of the anogenital areas known as condylomata acuminata (genital warts), as well as a large proportion of low-

grade squamous intraepithelial lesions of the cervix. LR-HPV clinical infections are responsible for substantial morbidity and invoke high costs associated with the treatment of clinically relevant lesions. In this report, we review the essential aspects of the epidemiology of genital HPV infections and outline the risk factors for becoming infected with an emphasis on the role of HPVs as cancer causing agents, particularly cervical carcinomas.

2. Descriptive epidemiology of genital HPV infection

2.1. How common is genital HPV infection?

HPV infections are the most common diagnosed sexually transmitted diseases today. Studies utilizing HPV DNA testing of asymptomatic women in the general population estimate the prevalence of HPV infection to be in the range of

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Table 1
HPV types designated as of high oncogenic risk in representative studies and reviews

HPV type	Original taxonomic designation	Lorincz et al., 1992 [90]	Bauer et al., 1993 [91]	Nindl et al., 1998 ^a [92]	Walboomers et al., 1999 ^b [62]	Bosch et al., 1995 ^c [93]	Munoz et al., 2003 [35]	IARC, 2005 ^d [66]
16		X	X	X	X	X	X	X
18		X	X	X	X	X	X	X
26						X	Probable	
31		X	X	X	X	X	X	X
33		X	X	X	X	X	X	X
35		X	X	X	X	X	X	X
39			X	X	X	X	X	X
45		X	X	X	X	X	X	X
51		X	X	X	X	X	X	X
52		X	X	X	X	X	X	X
53							Probable	
55						X		
56		X	X	X	X	X	X	X
58			X	X	X	X	X	X
59				X	X	X	X	X
66					X		Probable	X
68				X	X		X	
73	Pap238A, MM9					X	X	
82	W13B, MM4, IS39 (subtype)					X	X	
83	Pap291, MM7					X		
No. types		9	11	13	14	18	15–18	13

^a The HR-HPVs listed have become widely used as probes in diagnostic assays used in epidemiologic and clinical studies. For instance, the HR-HPVs under Nindl et al., 1998, are part of the probe B set in the commercially available Hybrid Capture 2 assay (Digene Co.).

^b As above, for the GP5/6+ general primer polymerase chain reaction (PCR) widely used in many international studies of cervical cancer etiology and screening.

^c As above, for the PGMV line blot PCR protocol produced by Roche Diagnostics that is currently under evaluation as a diagnostic tool.

^d Based on a consensus review panel of all published studies by the International Agency for Research on Cancer as part of its Carcinogenicity Evaluation Monograph, vol. 90.

2–44% [3–9]. This wide variation in prevalence estimates is largely explained by age differences among population samples studied, and by differences in the molecular sensitivity of the various HPV DNA assays used to detect viral DNA [7]. It is well appreciated that sexually active young adults are most at risk for acquiring HPV, as epidemiologic studies have shown that the prevalence of HPV infection is highest among young sexually active women [10,11].

Many epidemiological studies have found an age-related decline in HPV prevalence (Fig. 1). Even in a study of prostitutes, a group which is highly exposed to HPV, Kjaer et al. observed a substantial decrease in HPV prevalence with age despite continuously high levels of sexual activity [12]. One possible explanation for this finding is that infected individuals develop adaptive immune responses against HPV that prevent future infection. Also common in many studies, however, is a second pattern with a peak in HPV prevalence among women younger than 25 years of age, followed by the expected decline in prevalence until around age 45–50 and then a second peak in the peri- or post-menopausal years [13–16]. Although the reason for this second, menopausal peak is not clear, it could be plausibly attributed to one or more non-mutually exclusive mechanisms, such as reactivation of latent infections acquired earlier in life due to a gradual

loss of type-specific immunity, or to acquisition of new infections due to sexual contacts with new partners later in life. Also, plausible is a cohort effect: age-related variations in prevalence may reflect the diverse HPV exposure of successive birth cohorts. Sexual mores have changed during the last several decades, which may have influenced the HPV exposure of different age cohorts. Unfortunately, the lack of data

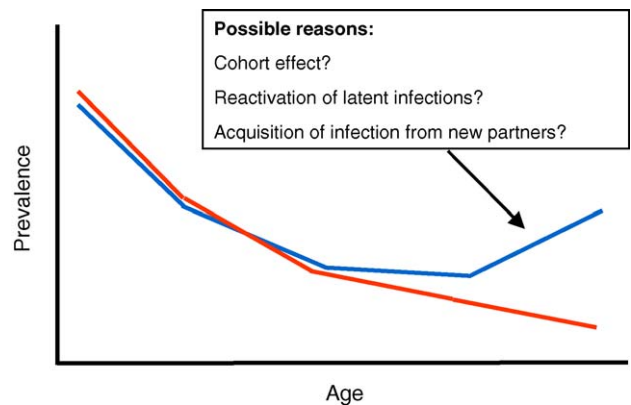


Fig. 1. Two patterns of age-specific prevalence of cervical HPV infection that are found in most epidemiological studies.

about historical HPV prevalence or cohort studies with long-term follow-up (>15 years) makes it impossible to empirically refute or confirm this hypothesis. Nonetheless, it is clear that the two patterns of age-specific risk are observed for incident HR-HPV infections [17,18].

2.2. Burden to the health care system

HPV infections and their clinically relevant sequelae pose a substantial burden to the health care system. There are an estimated 6.2 million new cases of HR-HPV infection occurring in the US each year, and approximately 20 million Americans are infected with HPV at any one time [19]. HR-HPV infections can cause precancerous cervical lesions that are detected by routine cytological screening with the Papanicolaou (Pap) test. If these lesions are left undiagnosed, they may progress to invasive cervical cancer within a few months to several years (depending on the precancerous lesion grade). Invasive cervical cancer is the second most common cancer in women worldwide [20]. In the US, even though rates have declined during the past 50 years from levels that were comparable with those found in developing countries today, there are still more than 12,000 cases of cervical cancer and more than 4000 deaths from the disease annually [21].

For each new case of invasive cancer found by Pap cytology, estimates suggest that there are approximately 50–100 squamous intraepithelial lesions (SILs). Women with these precancerous lesions need close monitoring by cytology and, if results persist, also by colposcopy and biopsy. Additionally, many women are diagnosed with atypical squamous cells of undetermined significance (ASC-US). Current screening guidelines suggest that these women may undergo repeat cytology or HPV testing, or be sent for colposcopic examination. Altogether, ASC-US and SIL findings account for more than 10% of all Pap smears that are processed in cytopathology laboratories. The diagnosis, management, and follow-up of patients with HPV-induced cervical abnormalities place an important burden on the health care system of nations with opportunistic or organized cervical cancer screening programs. Moreover, in the US, false-negative Pap smears from women with precancerous lesions caused by HPV infection are among the most frequent reasons for medical malpractice litigation [22]. HR-HPV infections are also thought to cause many other anogenital and upper aero-digestive tract cancers. An estimated 85% of anal cancers; 50% of the cancers of the vulva, vagina, and penis; 20% of oropharyngeal cancers; and 10% of laryngeal and esophageal cancers are attributable to HPV [23–25].

LR-HPV infections cause anogenital warts (condylomata acuminata) and low-grade cervical lesions. Unlike malignant neoplasms whose incidence can be measured based on statistics compiled by population-based tumor registries, or syphilis and gonorrhea, sexually-transmitted diseases (STD) of compulsory notification, the occurrence of anogenital condylomata can only be measured indirectly, via hospital series or physician consultation statistics. Although we can-

not measure the incidence of genital warts directly, there is strong indication that it has increased substantially in most Western countries during the last few decades. It is estimated that such lesions affect about 1% of all sexually active adults in the United States [26].

The true incidence of genital warts was measured in a study conducted by Mayo Clinic investigators in Rochester, Minnesota, during the period 1950–1978 [27]. This study found that rates had increased substantially during the 29-year period, peaking in 1975 with an average annual incidence of 107 new cases per 100,000. Although a population-based study in a small community in a midwestern state may not truly reflect national trends, the rates seen in the Rochester study probably represent a lower bound for present-day rates in most urban centers in North America. At an approximate annual rate of 100 per 100,000, genital warts are as common a disease as two common malignant neoplasms of grave concern for Americans, namely, breast and prostate cancers. Such a level of incidence can be translated into a lifetime cumulative risk approaching 10% [28].

In addition to the above population-based statistics, the National Disease and Therapeutic Index (NDTI) (IMS America Ltd.) counted the number of initial consultations for diagnosis and treatment of genital warts in a stratified random sample of private practitioners in the US. Although they do not represent true incidence rates, and fail to account for subclinical warts, the NDTI data have been widely used as a nationwide surveillance indicator for genital warts for inclusion in the STD surveillance reports by the Centers for Disease Control and Prevention [29]. Such clinical visits increased from 56,000 in 1966 to more than 350,000 in 1987. A downward trend occurred until 1997 (145,000 visits), but the numbers have since then increased to 264,000 visits in 2003.

2.3. Incidence of HPV infection measured by molecular detection techniques

A number of cohort studies that began in the early 1990s have provided useful data concerning the natural history of HPV infections. These studies take repeated measurements over time and use DNA hybridization techniques based on target amplification or signal amplification to test for HPV infection. Despite the heterogeneity of study designs and HPV testing systems, some clear similarities in results have emerged. The clearest and most consistent finding is the relatively high incidence of HPV infections among women who were initially HPV negative. Table 2 summarizes the findings from the cohort studies that used polymerase chain reaction (PCR) for HPV detection. The incidence rates in these studies indicate that up to 3% per month of the women who are initially free of HPV DNA may be found on subsequent testing to have acquired an HPV infection.

This translates into high cumulative risks. For instance, among women aged 15–19 years in England, and among two cohorts of college women in the US, the cumulative incidence

Table 2
Incidence rates of genital HPV infection in different cohort studies that used PCR for viral detection

Study	Age range of study sample	HPV types detected	Rate (per 100 women-years)
Ho et al., 1998 [30]	17–25	All	20.4
Franco et al., 1999 [17]	18–60	All	15.6
		HR types	8.4
Woodman et al., 2001 [32]	15–19	All	14.0
Richardson et al., 2003 [8]	17–42	All	18.0
		HR types	16.8
Winer et al., 2003 [31]	18–20	All	19.0
Munoz et al., 2004 [18]	18–80	HR types	5.0
		LR types	2.0
Syrjanen et al., 2005 [94]	15–20	All	36.0
	21–25	All	32.4

of HPV infection exceeded 40% after 3 years [30–32]. In the Brazilian Ludwig–McGill cohort (women with mean age of 33.3), the cumulative incidence was 24% over 18 months [17]. In addition, the incidence of HR types seems to be higher than the incidence of LR types, but this observation is partially dependent on how many HPV types the different studies classified as high risk. In a cohort study of American women aged 18–35 years, Giuliano et al. found the cumulative risk of new HR types at 12 months to be 32% compared with 18% for LR types [33]. Acquisition of infections was highest for HPV 16, HPV 39, HPV 84 and HPV 51: 5.9, 4.6, 4.2 and 3.4 new infections per 1000 women-months, respectively [34]. Incidence rates in a Canadian cohort of female university students were 14.0 cases/1000 women-months for HR-HPVs and 12.4 cases/1000 women-months for LR-HPVs [8]. HPV 16 is usually the most common type, irrespective of study design and geographical area. HPV 18 is also a common type [35], but the prevalence/incidence of HPV 18 varies according to the population studied. For example, Richardson et al. found the 24-month cumulative incidence rates to be highest for HPV 16 (12%), followed by HPV 51 and HPV 84 (8%) [8]. Munoz et al. found that the highest incidences in Colombia were for HPV types 16, 58, 31 and 18, representing 16, 11.2, 10.9 and 10.6% of all infections, respectively [18].

2.4. Persistence of HPV infection

HPV infections are common, but most infections seem to clear spontaneously; cohort studies have consistently found that only a small proportion of women positive for a given HPV type are found to have the same type in subsequent specimens [8,17,30,36–38]. Whether infections clear completely or the virus remains latent in basal cells at undetectable levels is a matter of debate and cannot be verified empirically. What is clear, however, is the fact that risk of subsequent cervical intraepithelial neoplasia (CIN) is proportional to the number of specimens testing positive for HPV [39,40]. This suggests that carcinogenic devel-

opment results from HPV infections that persist productively (i.e. with sustained viral replication within the squamous epithelium) for prolonged periods of time. Persistence of HR-HPV types (see Table 1 for HR-HPVs) is strongly linked to precancerous cervical lesions and invasive cancer [41–47].

Although the above observations concerning the importance of HPV persistence as a key intermediate in cervical carcinogenesis are not challenged, there is no consensus regarding the definition of what constitutes a persistent or a transient HPV infection. At a minimum, determination of HPV infection status at a baseline visit and at a subsequent follow-up opportunity 6 months or 1 year later allows good discrimination of infections that have higher propensity to develop into cervical lesions. However, a better understanding of the natural history of individual HPV infection episodes can only be obtained from cohort studies that resort to multiple, repeated measurements of viral endpoints over short intervals during several years. Such studies are ongoing in many populations.

There is considerable heterogeneity in study design and methods among the various published cohort investigations that have measured the natural history of persistent HPV infections. It is ascertained from all of these studies that there is no clear duration threshold that can be used to distinguish an HPV infection episode that is transient from one that is persistent. Furthermore, for common HPV types, such as HPV 16, it is virtually impossible to distinguish an instance of persistent infection from one that simply represents loss of, and subsequent reacquisition of, the same HPV type from the same or from a different sexual partner. Some experts have proposed testing for molecular variants of HPV, which may provide a finer scrutiny of same-type infections to distinguish true cases of persistent infection from those that represent clearance of one HPV variant and acquisition of another [48]; however, subsequent studies have shown that, at least for HPV types 16 and 18, the vast majority of persistent infections tend to involve the same variant over multiple testing opportunities [49].

2.5. Mean duration and clearance of HPV

Several studies have reported the duration and clearance rates of individual episodes of HPV infections (Table 3). Proper estimation of the mean and median duration and clearance rates requires using actuarial methods such as the Kaplan–Meier estimating technique, which takes into account the censoring of events at the time of data analysis. The importance of this analytical precaution cannot be overemphasized. For instance, if one wanted to measure the mean duration of all individual HPV 16 infections that occur in a cohort of women it would be wrong to average only those episodes in which clearance has already occurred. In any prospective cohort study with ongoing data and specimen collection, there will always be cases where infection has not yet cleared at the time of data analysis. These cases represent censored events in which the duration is likely to be longer than the time elapsed since the infection was first detected. Conditions caused by subject dropout, missing specimens, or pending (or missing) HPV test results are also consistent with the same interpretation. All such cases of incomplete events represent the reality of the HPV natural history and must be taken into account in the calculations. Excluding such cases (in order to opt for the simple arithmetic that includes complete episodes only) will substantially underestimate the true average duration of HPV 16 infection episodes in that cohort. Table 3 only includes studies that used actuarial methods to account for censored observations.

In general, across all studies averages of individual episodes last from 4 to 20 months, clearance rates vary substantially, but between 10 and 60% of all women who develop an infection will still be infected with the same type of HPV 1 year later. Most studies indicate, however, that less than half will continue to be positive at 12 months. HR-HPV infections tend to last longer than those of LR-HPV types. Among the former, HPV 16 infections tended to be among those of longer duration [8,32], but the difference does not seem to be substantial, particularly in view of the overlap among statistical confidence bands around the estimates. Other findings from some of the studies reviewed in Table 3 provide evidence for a longer duration of HPV 16 infections. For instance, in the cohort study of Brisson et al., HPV 16, 18, 21/33/35 appeared more persistent (odds ratio [OR], 2.5; 95% CI: 1.0–6.2) than other types [50]. Molano et al. found that HPV 16 had a significantly lower clearance rate than infections with LR types (rate ratio (RR) = 0.47; 95% CI: 0.32–0.72), HPV types related phylogenetically to HPV 16 (types 31, 33, 35, 52, 58) had intermediate clearance rates (RR = 0.62; 95% CI: 0.47–0.94), and other HR types did not show evidence of slower clearance compared with LR types [38].

2.6. Co-infection with multiple HPV types

Co-infection with multiple HPV types is a common finding of many epidemiologic studies. In the Brazilian Ludwig–McGill cohort, multiple types were detected at the

same visit in one-fifth of all women who tested positive for HPV at any time during follow-up [51]. Moreover, it seems that infection with a given type does not decrease the probability of being infected by phylogenetically related types. Thomas et al. found that acquisition of multiple infections occurred more often than expected by chance and that the risk of acquiring a specific HPV type was not substantially decreased among those with prior infection with a phylogenetically related type (HPV: 16 and 31; 18 and 45; 6 and 11) [52]. Rousseau et al. found that HPV 16 and 18 co-infections occurred less frequently than expected by chance as were other pairwise instances of HR-HPV types, such as HPV: 16 and 52; 16 and 68; and 18 and 6/11 [53].

The role of co-infections with additional HPV types on the duration of an episode with a given HPV type is not clear. In general, infections with single and multiple HPV types have comparable clearance rates. However, it is difficult to make cross-study comparisons because the definition of persistence varies appreciably across investigations. Ho et al. and Perrons et al. found that infection with multiple types of HPV was associated with persistent HPV infection [30,54]. Woodman et al. found that simultaneous infection with HPV 16 and another type resulted in longer duration of an HPV 16 episode as compared with single infection with HPV 16 [32]. However, not all data supports this. Rousseau et al. observed that persistence of HPV infection was independent of co-infection with other HPV types [55]. Liaw et al. found that the presence of HPV 16 was associated with an excess risk for acquisition of other types without affecting the persistence of the episodes with the additional types [56].

It is important to keep in mind that the PCR assays used in most epidemiologic studies have not been optimized for amplifying multiple types in the same reaction mixture and that the target DNA sequences of some HPV types are amplified less efficiently than others. These methodological issues may result in underestimates of the number of types in a specimen and handicap research into the interplay between multiple types of HPV infection.

3. HPV infection as the causal intermediate in cervical carcinogenesis

Fig. 2 shows the various components of the etiological model for the natural history of HPV infection and cervical carcinogenesis. The distal risk factor is sexual activity, which has been known for at least five decades to be the most important correlate of cervical cancer risk. As discussed above, the role of persistent HPV infection is central to this etiologic model.

A role for HPV infection in the sexually transmitted disease model of cervical cancer was proposed in the mid-1970s [57]. Strong evidence for an etiologic role of HPV was slow in coming, largely due to inconsistency in epidemiologic findings (reviewed in [58]). The issue was further complicated because prevalence of HPV DNA in cervical tumor spec-

Table 3

Mean and median duration and clearance rates for genital (cervical) HPV infections in different cohort studies of women

Study (subjects' mean age)	Mean duration of HPV infection in months	Median duration of HPV infection in months (95% CI) ^a	Proportion of women who cleared HPV	Mean time between visits
Hildesheim et al., 1994 (26 years) [36]			~1 year 37%	14.6 month (2 visits only)
Hinchliffe et al., 1995 [95]			~4 months 93%	4 month (2 visits only)
Evander et al., 1995 [96]			2 years 80%	NA (2 visits only)
Brisson et al., 1996 (~29 years) [50]			~6 months 50%	3.5 month (2 visits only)
Ho et al., 1998 (20 years) [30]		Any HPV: 8 (7–10) HPV-16: 11 (7–12) HPV-18: 12 (6–17)	1 year, 70%	6 month (multiple visits)
Moscicki et al., 1998 (~20 years) (after 3 HPV-visits) [37]		Any HPV: ~15.0 HR: ~12.0 LR: ~10.0	2 years, 70%	4 month (multiple visits)
Franco et al., 1999 (33 years) [17]	HR: 8.9 (7.6–10.2) LR: 7.0 (6.2–7.8)	HR: 8.1 (7.8–8.3) LR: 4.8 (3.9–5.6)	1 year, 65%	4 month (multiple visits)
Elfgren et al., 2000 (35 years) [97]			5 years, 92%	5 years (2 visits only)
Woodman et al., 2001 (18 years) [32]		Any HPV: 13.7 (8.0–25.4) HPV-16: 10.3 (6.8–17.3) HPV-18: 7.8 (6.0–12.6)		NA (multiple visits)
Ahdieh et al., 2001 (~30 years) [83]			3 years, 85%	6 month (multiple visits)
Giuliano et al., 2002 (~28 years) [34]		Any HPV: ~9.0 HR: 9.8 LR: 4.3 HPV-16: 8.5		~5 month (3 visits)
Elfgren et al., 2002 (35 years) [98]			1 year, 91%	3 month (multiple visits)
Xi et al., 2002 (18.7 years) [99]		HPV-16 European variants: 17.2 non-European: 14.3		4 month (multiple visits)
Richardson et al., 2003 (23 years) [8]	Any HR: 17.0 (15.1–18.8) HR: 17.4 (14.7–20.1) LR: 15.8 (13.3–18.3) HPV-16: 18.3 (12.9–23.7) HPV-18: 11.6 (8.8–14.4) HPV-31: 14.6 (11.0–18.1) HPV-39: 11.0 (7.0–14.9) HPV-51: 10.5 (8.4–12.7) HPV-56: 10.6 (7.9–13.2)	Any HPV: 17.3 (12.8–21.7) HR: 16.6 (14.5–18.7) LR: 14.7 (10.9–18.4) HPV-16: 19.4 (11.4–27.5) HPV-18: 9.4 (4.8–14.0) HPV-31: 20.0 (13.4–26.6) HPV-39: 8.0 (5.8–10.1) HPV-51: 9.0 (7.7–10.4) HPV-56: 8.4 (3.2–13.6) HR: 7.5	~1 year HR: 38% LR: 41% HPV-16: 38% HPV-18: 60% HPV-31: 38% HPV-39: 68% HPV-51: 65% HPV-56: 60%	2 years (5 visits)
Dalstein et al., 2003 (~35.7 years) [100]			~1 year HR: 40.1%	6 month (multiple repeat visits)
Sellers et al., 2003 (32.7 years) [69]			~1 year 52%	1 year (2 visits)
Molano et al., 2003 (~29 years) [38]			~1 year, 77%	6–9 month (6 visits)
			~5 years, 93%	
de Sanjose et al., 2003 (~51 years) [101]			~9 years 100%	9 years (2 visits)
Munoz et al., 2004 (32.3 years) [18]		HR: 14.8 (13.1–17.0) LR: 11.1 (8.2–16.5) HPV-16: 13.7 (8.4–18.8) HPV-18: 11.9 (9.1–16.6)		6 month (multiple visits)

Table 3 (Continued)

Study (subjects' mean age)	Mean duration of HPV infection in months	Median duration of HPV infection in months (95% CI) ^a	Proportion of women who cleared HPV	Mean time between visits
Moscicki et al., 2004 (16.5 years) [102]	Any HPV: 13.4 HPV type 16-like: 15.6 HPV type 18-like: 15.2 HPV type 56-like: 14.1	HPV-31: 16.5 (11.2–20.5) HPV-33: 13.4 (7.0–17.0) HPV-45: 12.2 (7.7–19.3) HPV-52: 9.7 (6.9–14.6) HPV-56: 14.6 (9.0–18.1) HPV-58: 14.8 (8.4–23.0)	4 years, 75.9%	6 month (multiple visits)
Perrons et al., 2005 [54]			6 month (HIR) >30 year: 47% 30–40 years: 57% <40 years: 61%	6 month (2 visits only)
Brown et al., 2005 (15.3 years) [103]		HR: 8.5 LR: 5.7		3 month (multiple visits)

^a Except for the Woodman et al. [32] study which used inter-quartile ranges, all other intervals represent 95% CIs.

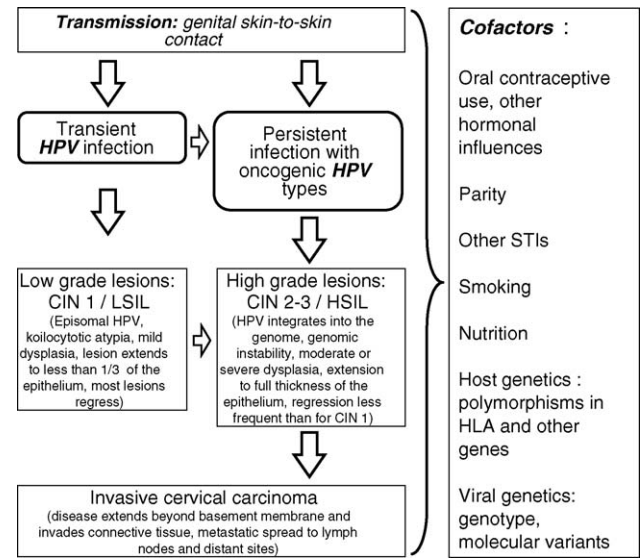


Fig. 2. Etiologic model of human papillomavirus (HPV) infection as a necessary cause of cervical cancer incorporating the role of host, reproductive, lifestyle, and viral co-factors. *Abbreviations:* CIN: cervical intraepithelial neoplasia (a histological classification); LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions (the SIL classification is the cytological analogue of the CIN scheme); HLA: human leukocyte antigen. *Source:* Franco and Harper, 2005, with permission.

imens, detected using DNA hybridization techniques, was low and variable, ranging from 15 to 92% [59]. However, with the advent of PCR techniques, which have much greater sensitivity than non-amplified DNA hybridization methods, strong molecular epidemiologic evidence for the central role of HPV in cervical carcinogenesis emerged [39,60,61].

It is now well established that infection with HR-HPV types is a necessary but not sufficient cause of almost all cervical cancers [62]. Relative risks for the association between HPV and cervical cancer are in the 50–150 range, which are among the strongest statistical relations ever identified in cancer epidemiology. Both retrospective and prospective epidemiologic studies have demonstrated the unequivocally strong association between viral infection and risk of malignancy [63]. Furthermore, results from successive PCR analyses of a large, international collection of cervical tumour specimens showed that HPV DNA is present in 99.7% of cases [62]. Given sufficient sensitivity and adequate tumour sampling, it is likely that virtually all cervical tumors would be found to contain HPV DNA [62,64]. No other human cancer has been shown to have such a clear necessary cause [22].

In 1995, the International Agency for Research on Cancer (IARC) classified HPV types 16 and 18 as carcinogenic to humans and HPV types 31 and 33 as probably carcinogenic [3]. This classification was made based on the evidence published up until 1994. In 2005, the list of carcinogenic HPV types was expanded by the IARC to include 13 mucosotropic anogenital HPV types and two other HPV types that infect the dry skin (HPVs 5 and 8). Furthermore, HPV 6 and 11 have been classified as possibly carcinogenic [65,66].

The causative link between HPV infection and cervical cancer opens up new paths of prevention, including screening for infection with high-risk types of HPV and immunization to prevent infection with high-risk types of HPV. Indeed, prophylactic HPV vaccines directed against the most common LR- and HR-HPV types are expected to prevent a substantial number of HPV infections. Further methods of prevention may become available when more is known about the mechanism whereby HPV infection initiates cervical carcinogenesis and the transmissibility of HPV infection; however, prevention through vaccination is predicted to substantially reduce HPV-associated morbidity and mortality.

4. Risk factors for HPV infection

Risk determinants for HPV infection that have been identified in various cross-sectional and prospective cohort studies include number of sexual partners (lifetime and recent), age at first intercourse, smoking, oral contraceptive (OC) use, other STIs (e.g. chlamydia and herpes simplex virus), chronic inflammation, immunosuppressive conditions including HIV infection, and parity [8,31,47,67–70]. Results have been inconsistent partly owing to the fact that different populations have been studied. Furthermore, risk factor profiles have been found to differ depending on whether HR- or LR-HPV types were considered [33,71–73]. Nevertheless, in addition to sexual activity correlates, the most consistent determinant of HPV infection is age, with most studies indicating a sharp decrease in risk after the age of 30 [33,55,69]. The decrease in risk of HPV infection with increasing age seems to be independent of changes in sexual behavior, suggesting a role for immune response. As described above, however, a second peak at older ages (Fig. 1) is also a common feature of epidemiologic findings.

Ho et al. surveyed college-aged women and found that an increased risk of HPV infection was significantly associated with younger age, Hispanic ethnicity, black race, an increased number of vaginal-sex partners, high frequencies of vaginal sex and alcohol consumption, anal sex, and certain characteristics of partners (regular partners having an increased number of lifetime partners and not being in school) [30]. Richardson et al. found lifetime frequency of sexual intercourse and lifetime number of oral sex partners was associated with HR-HPV infections, whereas HPV infection with LR types was invariant with respect to markers of sexual activity [74]. Rousseau et al. found a strong negative association between age and HR-HPVs, but not with LR types, and OC use was strongly and exclusively associated with HR-HPV and HPV 16 infections [55]. Overall, markers of sexual activity were strongly associated with all types of infections.

Age at sexual debut may increase risk of HPV infection either as a marker for other sexual behaviors (e.g. young age at sexual debut may be associated with a greater lifetime number of sexual partners or with propensity to engage new sexual partners more frequently), or as a true causal

risk factor due to greater cervical ectopy during adolescence [75,76]. Research on the effect of condom use has found equivocal results [77,78]. A paradoxical effect is occasionally reported, such that condom use appears to increase risk of HPV infection [72,74,77]. This is likely a result of an increased probability of infection among partners with whom condoms are used. For example, people tend to use condoms with partners whom they consider to be more at risk (e.g. new partners, casual partners, sex trade workers), but not with partners whom they consider to be safe (e.g. long-term, regular partners or spouses) [79–81]. HPV transmission may also occur through non-penetrative sexual activity. Indeed, low-risk HPV has been detected on fingers of individuals with genital warts [82]. Furthermore, among virgin female college students, “any type of non-penetrative sexual contact” was associated with a 2.4% 24-month cumulative incidence of HPV infection, although this type of activity did not result in increased risk among women engaging in intercourse [31].

The thrust of epidemiological research in recent years has focused on understanding the role of risk factors that influence acquisition of persistent HPV infection or of factors that mediate progression in the continuum of lesion grades (Fig. 2). Some authors have shown that persistence is associated with older age [13,30,36,83]. A few studies have also found a protective effect on the risk of persistent infection associated with consumption of fruits and vegetables and dietary or circulating levels of vitamin C and E, beta- and alpha-carotene, lycopene, lutein/zeaxanthin, and cryptoxanthin [84–86]. Some studies have also suggested a role for viral factors (molecular variants and viral load) in persistence of HPV and progression [49,87]. The fact that HPV infection does not always progress to neoplastic disease also suggests that interpersonal variations in the immune system may play a role in the clearance of HPV infections and/or in their acquisition. Such a mechanism may be linked to genetic polymorphisms in the Human Leukocyte Antigen (HLA) system. The HLA genes, whose protein products are involved in antigen presentation to T cells, play a role in the regulation of immune response. Certain HLA alleles or haplotypes seem to be involved with susceptibility to HPV infection and cervical cancer probably by regulating the immune response against HPV infection and ultimately interfering in the establishment of productive persistent infections and lesion development [88]. Maciag et al. found that among the class II HLA genes, the DRB1*0301–DQB1*0201 haplotype was associated with a two-fold reduction in risk of any HPV infections, regardless of duration [89]. The DRB1*1102–DQB1*0301 haplotype was associated with reduced risk of persistent infections, whereas the DRB1*1601–DQB1*0502 and DRB1*0807–DQB1*0402 ones were associated with a seven-fold and a three-fold increase, respectively, in risk of persistent HPV infections. Although these associations seemed moderate to strong, the rarity of these alleles and haplotypes and the costs related to HLA typing have precluded replication of findings in multiple cohort studies.

Table 4

Summary of determinants that have been found to be predictive of cervical HPV infection risk in cross-sectional or cohort studies

Determinant or risk factor	Direction of association	Strength of the association ^a	Consistency ^b	Specificity for HPV types ^c
Age	Negative, U- or J-shaped ^d	++	++	Yes, country-dependent
Sexual activity markers	Negative for age at sexual debut	+	+	Yes (HR types)
	Positive for lifetime partners	++	++	Yes (HR types)
	Positive for recent partners	++	++	Yes (HR types)
Oral contraceptive use	Positive (duration)	+	+/-	Possibly
Condom use	Negative or inconsistent	+	+/-	Yes (HR types)
Smoking	Positive	+	+/-	No
HLA polymorphisms	Variable, allele and haplotype dependent	++	+/-	Yes, allele and haplotype dependent
Nutrition	Negative for specific carotenoids and other dietary or circulating micronutrients	+	+	No

^a Related to the average RR or OR across all studies: +: weak to moderate association, ++: moderate to strong association.

^b Related to how consistent the association has been across studies.

^c Whether the association seemed to vary in magnitude for HR and LR HPVs or for individual HPV types, such as HPV 16.

^d See Fig. 1 and text for details on age-specific prevalence patterns in different populations.

Table 4 summarizes the above variables with respect to the strength of the association, their consistency, and specificity to different types of HPVs as obtained in multiple epidemiologic studies conducted during the last 15 years, since the advent of modern amplified DNA hybridization techniques (target or signal amplification). It is not surprising that most of these variables have been shown to be risk factors in case-control or cohort studies of pre-invasive and invasive cervical cancer because they are predictors of HPV infection as the distal causal intermediate in cervical carcinogenesis. It is possible also that some of the variables listed in Table 4 may also exert a role on cervical carcinogenesis that is “downstream” from HPV infection. For instance, smoking may contribute additional genetic damage to epithelial cells already harboring the initiating events triggered by HPV infection (e.g. interference with the cellular p53 and Rb gene pathways via over expression of the E6 and E7 viral oncogenes). Such additional damage may accelerate progression to malignancy. Likewise, the role of other STIs, such as chlamydia, is likely to occur via inflammatory activity that may result in oxidative damage to HPV infected cells. Chlamydia infection is also likely to lead to cervical inflammation, which may facilitate HPV infection to become persistent. In such a scenario, chlamydia infection would act as a risk factor for HPV infection and should thus be listed in Table 4. However, whether the latter biological mechanism occurs (and if it does, whether it can be distinguished from the inflammation-based mechanism) is very difficult to prove in an epidemiologic study because both microbial agents are strongly linked to sexual activity and adjustment for the latter variable would preclude assessment of an independent effect of chlamydia infection on the risk of HPV.

5. Conclusion

Molecular epidemiologic studies of the natural history of HPV infection and cervical neoplasia have provided much of the knowledge base that has led to the ongoing paradigm

changes in cervical cancer prevention via HPV screening and HPV vaccination. The contributions of epidemiology in this process during the last 15 years have been focused on the demonstration that HPV infection is the cause of cervical cancer, and as such, they have dealt with the virus mostly as an intermediate endpoint in cervical carcinogenesis. The majority of studies have included women only, and although we are beginning to learn more about the epidemiology of HPV infections in men, much still needs to be done.

A new generation of epidemiologic studies is now emerging with a focus on HPV as a sexually-transmitted infection. These studies are making judicious use of molecular tools and novel statistical approaches to understand HPV transmission and key steps in the natural history of HPV-related malignancies. Issues of transmissibility such as infectivity following a sexual encounter and the controversial effect of condom use can only be properly addressed in studies involving forming couples as the unit of observation. This new generation of studies will provide the answers needed by women and their health care providers as cervical cancer prevention shifts from an oncological to an STD perspective. Prevention of HPV infection through vaccination is preferable to treatment of precancerous and cancerous lesions, and is expected to dramatically reduce the morbidity and mortality associated with HPV infection.

References

- [1] De Villiers EM, Gunst K, Stein H, Scherubl H. Esophageal squamous cell cancer in patients with head and neck cancer: prevalence of human papillomavirus DNA sequences. *Int J Cancer* 2004;109(2):253–8.
- [2] zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. *J Natl Cancer Inst* 2000;92(9):690–8.
- [3] IARC. Epidemiology of infection: human papillomaviruses. *Carcinog Risk Chem Hum* 1995;64:60–5.
- [4] Gjoen K, Olsen AO, Magnus P, Grinde B, Sauer T, Orstavik I. Prevalence of human papillomavirus in cervical scrapes, as ana-

- lyzed by PCR, in a population-based sample of women with and without cervical dysplasia. *APMIS* 1996;104(1):68–74.
- [5] Franco EL, Villa LL, Richardson H, Rohan T, Ferenczy A. Epidemiology of cervical human papillomavirus infection. In: Franco E, Monsonego J, editors. *New developments in cervical cancer screening and prevention*. Oxford, UK: Blackwell Science; 1997. p. 14–22.
 - [6] Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol* 2005;32(Suppl. 1):S16–24.
 - [7] Bosch FX, de SS. Human papillomavirus and cervical cancer—burden and assessment of causality. *J Natl Cancer Inst Monogr* 2003;31:3–13 [chapter 1].
 - [8] Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, et al. The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiol Biomarkers Prev* 2003;12(6):485–90.
 - [9] Herrero R, Castle PE, Schiffman M, Bratti MC, Hildesheim A, Morales J, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. *J Infect Dis* 2005;191(11):1796–807.
 - [10] Schiffman MH. Recent progress in defining the epidemiology of human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst* 1992;84(6):394–8.
 - [11] Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiol Biomarkers Prev* 2001;10(2):101–6.
 - [12] Kjaer SK, Svare EI, Worm AM, Walbomers JM, Meijer CJ, van den Brule AJ. Human papillomavirus infection in Danish female sex workers. Decreasing prevalence with age despite continuously high sexual activity. *Sex Transm Dis* 2000;27(8):438–45.
 - [13] Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. *J Infect Dis* 2005;191(11):1808–16.
 - [14] Herrero R, Hildesheim A, Bratti C, Sherman ME, Hutchinson M, Morales J, et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst* 2000;92(6):464–74.
 - [15] Lazcano-Ponce E, Herrero R, Munoz N, Cruz A, Shah KV, Alonso P, et al. Epidemiology of HPV infection among Mexican women with normal cervical cytology. *Int J Cancer* 2001;91(3):412–20.
 - [16] Smith EM, Johnson SR, Ritchie JM, Feddersen D, Wang D, Turek LP, et al. Persistent HPV infection in postmenopausal age women. *Int J Gynaecol Obstet* 2004;87(2):131–7.
 - [17] Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, et al. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis* 1999;180(5):1415–23.
 - [18] Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *J Infect Dis* 2004;190(12):2077–87.
 - [19] Centers for Disease Control and Prevention. *Genital HPV Infection—CDC Fact Sheet*. Centers for Disease Control and Prevention; 2004. Available from: URL: <http://www.cdc.gov/std/HPV/STDFact-HPV.htm>.
 - [20] Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*. IARC Cancer Base No. 5, Version 2.0, IARC Press, Lyon, 2004–2005.
 - [21] Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. *Cancer statistics*. *CA Cancer J Clin* 2005;55(1):10–30.
 - [22] Franco EL, Duarte-Franco E, Ferenczy A. Prospects for controlling cervical cancer at the turn of the century. *Salud Publica Mex* 2003;45(Suppl. 3):S367–75.
 - [23] WHO Vaccine Report. The current status of development of prophylactic vaccines against human papillomavirus infection. Report of a technical meeting. World Health Organization; 1999. Available from: URL: http://www.who.int/vaccine_research/documents/en/hpv1.pdf.
 - [24] zur Hausen H. Papillomavirus infections—a major cause of human cancers. *Biochim Biophys Acta* 1996;1288(2):F55–78.
 - [25] Spence A, Franco E, Ferenczy A. The role of human papillomaviruses in cancer: evidence to date. *Am J Cancer* 2005;4:49–64.
 - [26] Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 1988;10:122–63.
 - [27] Chuang TY, Perry HO, Kurland LT, Ilstrup DM. *Condyloma acuminatum* in Rochester, Minn., 1950–1978. I. Epidemiology and clinical features. *Arch Dermatol* 1984;120(4):469–75.
 - [28] Franco E. Epidemiology of anogenital warts and cancer. In: Reid R, Lorincz A, editors. *Human papillomaviruses I*. Philadelphia, PA: WB Saunders; 1996. p. 597–623.
 - [29] Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2003*. US Department of Health and Human Services; 2004.
 - [30] Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338(7):423–8.
 - [31] Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003;157(3):218–26.
 - [32] Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001;357(9271):1831–6.
 - [33] Giuliano AR, Papenfuss M, Abrahamsen M, Inserra P. Differences in factors associated with oncogenic and nononcogenic human papillomavirus infection at the United States–Mexico border. *Cancer Epidemiol Biomarkers Prev* 2002;11(9):930–4.
 - [34] Giuliano AR, Harris R, Sedjo RL, Baldwin S, Roe D, Papenfuss MR, et al. Incidence, prevalence, and clearance of type-specific human papillomavirus infections: The Young Women’s Health Study. *J Infect Dis* 2002;186(4):462–9.
 - [35] Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348(6):518–27.
 - [36] Hildesheim A, Schiffman MH, Gravitt PE, Glass AG, Greer CE, Zhang T, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis* 1994;169(2):235–40.
 - [37] Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr* 1998;132(2):277–84.
 - [38] Molano M, Van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. *Am J Epidemiol* 2003;158(5):486–94.
 - [39] Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckmann AM, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992;327(18):1272–8.
 - [40] Ho GY, Burk RD, Klein S, Kadish AS, Chang CJ, Palan P, et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst* 1995;87(18):1365–71.
 - [41] Wallin KL, Wiklund F, Angstrom T, Bergman F, Stendahl U, Wadell G, et al. Type-specific persistence of human papillomavirus

- DNA before the development of invasive cervical cancer. *N Engl J Med* 1999;341(22):1633–8.
- [42] Ylitalo N, Josefsson A, Melbye M, Sorensen P, Frisch M, Andersen PK, et al. A prospective study showing long-term infection with human papillomavirus 16 before the development of cervical carcinoma in situ. *Cancer Res* 2000;60(21):6027–32.
- [43] Liaw KL, Glass AG, Manos MM, Greer CE, Scott DR, Sherman M, et al. Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst* 1999;91(11):954–60.
- [44] Nobbenhuis MA, Walboomers JM, Helmerhorst TJ, Rozendaal L, Remmink AJ, Risse EK, et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet* 1999;354(9172):20–5.
- [45] Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, et al. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. *JAMA* 2001;286(24):3106–14.
- [46] Kjaer SK, van den Brule AJ, Paull G, Svare EI, Sherman ME, Thomsen BL, et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. *BMJ* 2002;325(7364):572.
- [47] Schiffman M, Castle PE. Human papillomavirus: epidemiology and public health. *Arch Pathol Lab Med* 2003;127(8):930–4.
- [48] Franco EL, Villa LL, Rahal P, Ruiz A. Molecular variant analysis as an epidemiological tool to study persistence of cervical human papillomavirus infection. *J Natl Cancer Inst* 1994;86(20):1558–9.
- [49] Villa LL, Sichero L, Rahal P, Caballero O, Ferenczy A, Rohan T, et al. Molecular variants of human papillomavirus types 16 and 18 preferentially associated with cervical neoplasia. *J Gen Virol* 2000;81(Pt 12):2959–68.
- [50] Brisson J, Bairati I, Morin C, Fortier M, Bouchard C, Christen A, et al. Determinants of persistent detection of human papillomavirus DNA in the uterine cervix. *J Infect Dis* 1996;173(4):794–9.
- [51] Rousseau MC, Pereira JS, Prado JC, Villa LL, Rohan TE, Franco EL. Cervical coinfection with human papillomavirus (HPV) types as a predictor of acquisition and persistence of HPV infection. *J Infect Dis* 2001;184(12):1508–17.
- [52] Thomas KK, Hughes JP, Kuypers JM, Kiviat NB, Lee SK, Adam DE, et al. Concurrent and sequential acquisition of different genital human papillomavirus types. *J Infect Dis* 2000;182(4):1097–102.
- [53] Rousseau MC, Abrahamowicz M, Villa LL, Costa MC, Rohan TE, Franco EL. Predictors of cervical coinfection with multiple human papillomavirus types. *Cancer Epidemiol Biomarkers Prev* 2003;12(10):1029–37.
- [54] Perrons C, Jelley R, Kleter B, Quint W, Brink N. Detection of persistent high risk human papillomavirus infections with hybrid capture II and SPF10/LiPA. *J Clin Virol* 2005;32(4):278–85.
- [55] Rousseau MC, Franco EL, Villa LL, Sobrinho JP, Termini L, Prado JM, et al. A cumulative case-control study of risk factor profiles for oncogenic and nononcogenic cervical human papillomavirus infections. *Cancer Epidemiol Biomarkers Prev* 2000;9(5):469–76.
- [56] Liaw KL, Hildesheim A, Burk RD, Gravitt P, Wacholder S, Manos MM, et al. A prospective study of human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its association with acquisition and persistence of other HPV types. *J Infect Dis* 2001;183(1):8–15.
- [57] zur Hausen H. *Condylomata acuminata and human genital cancer*. *Cancer Res* 1976;36(2, Pt 2):794.
- [58] Franco EL. Viral etiology of cervical cancer: a critique of the evidence. *Rev Infect Dis* 1991;13(6):1195–206.
- [59] Munoz N, Bosch X, Kaldor JM. Does human papillomavirus cause cervical cancer? The state of the epidemiological evidence. *Br J Cancer* 1988;57(1):1–5.
- [60] Munoz N, Bosch FX, Desanjose S, Tafur L, Izarzugaza I, Gili M, et al. The causal link between human papillomavirus and invasive cervical cancer: a population-based case-control study in Colombia and Spain. *Int J Cancer* 1992;52(5):743–9.
- [61] Schiffman MH, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 1993;85(12):958–64.
- [62] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189(1):12–9.
- [63] Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55(4):244–65.
- [64] Walboomers JM, Meijer CJ. Do HPV-negative cervical carcinomas exist? *J Pathol* 1997;181(3):253–4.
- [65] Coglianò V, Baan R, Straif K, Grosse Y, Secretan B, El GF. Carcinogenicity of human papillomaviruses. *Lancet Oncol* 2005;6(4):204.
- [66] IARC. *Human Papillomaviruses*. IARC monographs on the evaluation of carcinogenic risks to humans; 2005.
- [67] Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997;102(5A):3–8.
- [68] Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *JAMA* 2001;285(23):2995–3002.
- [69] Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, et al. Incidence, clearance and predictors of human papillomavirus infection in women. *CMAJ* 2003;168(4):421–5.
- [70] Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol* 2005;32(Suppl. 1):S16–24.
- [71] Franco EL, Villa LL, Ruiz A, Costa MC. Transmission of cervical human papillomavirus infection by sexual activity: differences between low and high oncogenic risk types. *J Infect Dis* 1995;172(3):756–63.
- [72] Kjaer SK, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, et al. Determinants for genital human papillomavirus (HPV) infection in 1000 randomly chosen young Danish women with normal Pap smear: are there different risk profiles for oncogenic and nononcogenic HPV types? *Cancer Epidemiol Biomarkers Prev* 1997;6(10):799–805.
- [73] Richardson H, Franco E, Pintos J, Bergeron J, Arella M, Tellier P. Determinants of low-risk and high-risk cervical human papillomavirus infections in Montreal University students. *Sex Transm Dis* 2000;27(2):79–86.
- [74] Richardson H, Franco E, Pintos J, Bergeron J, Arella M, Tellier P. Determinants of low-risk and high-risk cervical human papillomavirus infections in Montreal University students. *Sex Transm Dis* 2000;27(2):79–86.
- [75] Aral SO, Holmes KK. Social and behavioural determinants of epidemiology of STDs: industrialized and developing countries. In: Holmes KK, Mardh P, Sparling PF, et al., editors. *Sexually transmitted diseases*. 3rd ed. New York: McGraw-Hill; 1999. p. 39–76.
- [76] Kahn JA, Rosenthal SL, Succop PA, Ho GY, Burk RD. Mediators of the association between age of first sexual intercourse and subsequent human papillomavirus infection. *Pediatrics* 2002;109(1):E5.
- [77] Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis* 2002;29(11):725–35.
- [78] Stone KM, Timyan J, Thomas EL. Barrier methods for the prevention of sexually transmitted diseases. In: Holmes KK, Mardh P, Sparling PF, et al., editors. *Sexually transmitted diseases*. 3rd ed. New York: McGraw-Hill; 1999. p. 1307–21.
- [79] Aral SO, Peterman TA. A stratified approach to untangling the behavioral/biomedical outcomes conundrum. *Sex Transm Dis* 2002;29(9):530–2.
- [80] Macaluso M, Demand MJ, Artz LM, Hook III EW. Partner type and condom use. *AIDS* 2000;14(5):537–46.

- [81] Warner L, Newman DR, Austin HD, Kamb ML, Douglas Jr JM, Malotte CK, et al. Condom effectiveness for reducing transmission of gonorrhea and chlamydia: the importance of assessing partner infection status. *Am J Epidemiol* 2004;159(3):242–51.
- [82] Sonnex C, Strauss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. *Sex Transm Infect* 1999;75(5):317–9.
- [83] Ahdieh L, Klein RS, Burk R, Cu-Uvin S, Schuman P, Duerr A, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis* 2001;184(6):682–90.
- [84] Garcia-Closas R, Castellsague X, Bosch X, Gonzalez CA. The role of diet and nutrition in cervical carcinogenesis: A review of recent evidence. *Int J Cancer* 2005;117(4):629–37.
- [85] Giuliano AR, Siegel EM, Roe DJ, Ferreira S, Baggio ML, Galan L, et al. Dietary intake and risk of persistent human papillomavirus (HPV) infection: the Ludwig–McGill HPV Natural History Study. *J Infect Dis* 2003;188:1508–16.
- [86] Richardson H, Abrahamowicz M, Tellier PP, Kelsall G, du Berger R, Ferenczy A, et al. Modifiable risk factors associated with clearance of type-specific cervical human papillomavirus infections in a cohort of university students. *Cancer Epidemiol Biomarkers Prev* 2005;14(5):1149–56.
- [87] Schlecht NF, Trevisan A, Duarte-Franco E, Rohan TE, Ferenczy A, Villa LL, et al. Viral load as a predictor of the risk of cervical intraepithelial neoplasia. *Int J Cancer* 2003;103(4):519–24.
- [88] Wang SS, Hildesheim A. Viral and host factors in human papillomavirus persistence and progression. *J Natl Cancer Inst Monogr* 2003;31:35–40 [chapter 5].
- [89] Maciag PC, Schlecht NF, Souza PS, Rohan TE, Franco EL, Villa LL. Polymorphisms of the human leukocyte antigen DRB1 and DQB1 genes and the natural history of human papillomavirus infection. *J Infect Dis* 2002;186(2):164–72.
- [90] Lorincz AT, Reid R, Jenson AB, Greenberg MD, Lancaster W, Kurman RJ. Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. *Obstet Gynecol* 1992;79(3):328–37.
- [91] Bauer HM, Hildesheim A, Schiffman MH, Glass AG, Rush BB, Scott DR, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland. *Oregon Sex Transm Dis* 1993;20(5):274–8.
- [92] Nindl I, Lorincz A, Mielzynska I, Petry U, Baur S, Kirchmayr R, et al. Human papillomavirus detection in cervical intraepithelial neoplasia by the second-generation hybrid capture microplate test, comparing two different cervical specimen collection methods. *Clin Diagn Virol* 1998;10(1):49–56.
- [93] Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) Study Group. *J Natl Cancer Inst* 1995;87(11):796–802.
- [94] Syrjanen S, Shabalova I, Petrovichev N, Podistov J, Ivanchenko O, Zakharenko S, et al. Age-specific incidence and clearance of high-risk human papillomavirus infections in women in the former Soviet Union. *Int J STD AIDS* 2005;16(3):217–23.
- [95] Hinchliffe SA, van VD, Korporaal H, Kok PL, Boon ME. Transience of cervical HPV infection in sexually active, young women with normal cervicovaginal cytology. *Br J Cancer* 1995;72(4):943–5.
- [96] Evander M, Edlund K, Gustafsson A, Jonsson M, Karlsson R, Rylander E. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis* 1995;171(4):1026–30.
- [97] Elfgrén K, Kalantari M, Moberger B, Hagmar B, Dillner J. A population-based five-year follow-up study of cervical human papillomavirus infection. *Am J Obstet Gynecol* 2000;183(3):561–7.
- [98] Elfgrén K, Jacobs M, Walboomers JM, Meijer CJ, Dillner J. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 2002;100(5, Pt 1):965–71.
- [99] Xi LF, Carter JJ, Galloway DA, Kuypers J, Hughes JP, Lee SK, et al. Acquisition and natural history of human papillomavirus type 16 variant infection among a cohort of female university students. *Cancer Epidemiol Biomarkers Prev* 2002;11(4):343–51.
- [100] Dalstein V, Riethmuller D, Pretet JL, Le Bail Carval K, Sautiere JL, Carbillet JP, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. *Int J Cancer* 2003;106(3):396–403.
- [101] de Sanjose S, Bosch FX, Tafur LA, Nascimento CM, Izarzugaza I, Izquierdo A, et al. Clearance of HPV infection in middle aged men and women after 9 years' follow up. *Sex Transm Infect* 2003;79(4):348.
- [102] Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. *J Infect Dis* 2004;190(1):37–45.
- [103] Brown DR, Shew ML, Qadadri B, Neptune N, Vargas M, Tu W, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *J Infect Dis* 2005;191(2):182–92.