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Permalink

<https://escholarship.org/uc/item/2bt7h0hd>

Journal

Vaccine, 30(0 5)

ISSN

0264-410X

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Publication Date

2012-11-01

DOI

10.1016/j.vaccine.2012.05.089

Peer reviewed



Published in final edited form as:

Vaccine. 2012 November 20; 30(0 5): F24–F33. doi:10.1016/j.vaccine.2012.05.089.

Updating the Natural History of Human Papillomavirus and Anogenital Cancers

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Abstract

This chapter addresses the natural history of anogenital human papillomavirus (HPV) infection. Cervical infections are the best understood HPV infection. Cervical HPV persistence is the known necessary event for the development of cervical cancer. New infections appearing at any age are benign unless they persist. Several long-term natural history studies have now shed light on the very low risk of cervical intraepithelial neoplasia (CIN) 3+ in women past the peak of HPV acquisition (e.g., 30 or older) who are HPV-negative or clear their HPV. Although data on transmission of HPV are finally emerging, rates of transmission between heterosexual couples vary widely among studies. Factors that affect the calculations of these rates include a) intervals between testing points, b) rates of concordance or discordance at baseline, and c) difficulty in defining established infections versus contamination. Both cervix to anus and anus to cervix autoinoculation in the same woman appears to be quite common. Whether either site serves as a

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Disclosed potential conflicts of interest

Authors have disclosed no potential conflicts of interest.

long-term reservoir is unknown. Studies show that anal infections in women and in men who have sex with men are quite common with cumulative rates up to 70–90%. Similarly, clearance of anal HPV is also common, with few individuals showing persistence unless they are human immunodeficiency virus (HIV)-infected. HIV strongly influences the development of anal intraepithelial neoplasia (AIN). The few studies on the natural history of AIN in HIV-infected men suggest that high-grade AIN is a precursor to invasive anal cancer. Although no natural history studies of AIN are available in women, women with other HPV-associated lesions, including CIN3+ and vulvar cancer, have higher rates of anal cancer. Data on the natural history of HPV of the male genitalia are also emerging, although penile intraepithelial neoplasia is poorly understood. Cumulative rates of HPV are extremely high in men and risks are associated with sexual behavior. Unlike women, prevalence rates are steady across all ages, suggesting that men do not develop protection against reinfection.

Keywords

HPV; Natural history; Transmission; Male infections; Anal disease

1. Summary of previous chapter

As detailed in the previous update, the cervix provides the best model of the natural history of human papillomavirus (HPV) and anogenital neoplasia [1]. Piecing together data from multiple prospective studies, we have arrived at a reasonably complete view of the natural history of HPV leading to cervical intraepithelial neoplasia (CIN) 3 with less insight into the final steps of carcinogenesis. Prospective studies of cervical HPV infection published in the past few years have generally confirmed the previous chapter, while adding precision to risk estimates. The early natural history of HPV infection, once acquired, and first steps of cervical carcinogenesis have been directly observed in prospective studies of the kind illustrated in Fig. 1 [2]. Of note, the moment of acquisition is not known exactly in prospective studies of infections found during cross-sectional screening, which comprise the great majority of natural history studies. The data are “left-censored” and the infections followed are a mixture of shorter and longer duration infections. Nonetheless, follow-up studies of incident infections (following a previous negative HPV test) and prevalently-detected infections among young women yield similar pictures, and have demonstrated that up to half of infections clear within 6 months and the great majority (~90%) clear within a few years after acquisition [3,4]. There is no single definition of persistence; different studies use different, arbitrary cut-points. There is conflicting evidence regarding whether any type of oncogenic HPV (especially HPV16) persists longer than others [5,6] in the absence of development of CIN3+. However, it is clear that viral type (and even viral variant lineage within some types) is a major predictor of risk of CIN3+ [7].

Based on limited data, it appears that long-term (e.g., 7-year) persistence of carcinogenic types of HPV without development of CIN3+ is less common than might have been anticipated [8]. Of note, due to the relative insensitivity of colposcopic or even microscopic diagnosis of CIN3+ compared with molecular detection of HPV DNA, it is not possible to know exactly when an infection “becomes” a CIN3+ lesion. We do not even know for sure that viral persistence precedes development of a clone of transformed cells (i.e., in some cases, CIN3+ could lead to persistence).

The main points of the previous chapter that remain important and relevant are reiterated here for background.

- The major steps in cervical carcinogenesis include 1) infection of the metaplastic epithelium of the cervical transformation zone with one or more carcinogenic types

of HPV, 2) viral persistence rather than clearance, 3) clonal progression of the persistently infected epithelium to cervical precancer, and 4) invasion.

- HPV infection is most likely to cause cancer at the transformation zone (TZ). The original TZ is where there is an abrupt transition from squamous cells to columnar cells. At the time of puberty, a process referred to as squamous metaplasia is accelerated. Squamous metaplasia results in the transformation of columnar epithelium into squamous, eventually creating a “new” TZ. In adolescents and young women, the cervix is a mixture of columnar, squamous, and metaplastic epithelium, whereas in adult women, the ectocervix is predominantly squamous. Squamous metaplasia can be found in anal and tonsillar tissue as well as cervical.
- The majority of high risk HPV-positive infections clear and the majority of women with infection do not develop cancer. The peak rate of HPV infection is seen in women under 25 years of age with a decline that plateaus around 30–35 years. In some countries, there is a slight increase in women aged 50+ years.
- If a woman is high-risk HPV-negative at any age, risk of cancer at least in the subsequent several years is near zero, so the focus of natural history studies is on the absolute risk and modifiers of clinical outcomes in HPV-positive women (i.e., the estimation of positive predictive value).
- Among HPV-infected women, the most important determinants of carcinogenic risk are persistence of infection and viral genotype. HPV16 is uniquely carcinogenic.
- Incident cervical HPV infections, at any age, (either with minor cytologic abnormalities (such as atypical squamous cells of undetermined significance [ASCUS], low-grade squamous intraepithelial lesion [LSIL] or not) tend to clear within months to a few years. On the other hand, prevalent infections, especially HPV16, are linked to higher risk.
- Minor cytologic and histologic abnormalities are correlated with, but less primarily important than, viral determinants of risk. They are diagnosed only in a minority of women with HPV detectable by DNA assays. The fraction is dependent on the thresholds of the molecular and microscopic tests (see Poljak M *et al.* Vaccine, this issue [9]).
- The disease endpoint for prospective studies of cervical HPV is ideally CIN3 or worse (CIN3+). CIN2 is treated for safety, and sometimes CIN2+ is studied as a prospective endpoint. However, some non-carcinogenic types (not found alone in cervical cancer) are capable of producing lesions diagnosed as CIN2, showing the etiologic heterogeneity of these lesions. There is no perfect surrogate endpoint of cancer risk; CIN3 is the best we have, and even some CIN3 lesions (especially very early, small lesions) never go on to invade.
- The time between infection with a carcinogenic type of HPV and clonal development of CIN3 cannot be determined with precision, because it depends on the intensity of surveillance and diagnostic limits of colposcopic biopsy. The time from infection to CIN3 is shorter, on average, than the typical decades-long sojourn time from first development of a small CIN3 lesion to invasion, if it occurs. However, there is substantial individual variability, leading to some early cases of invasive disease.
- The known behavioral co-factors, such as smoking, and parity that determine whether a woman develops CIN3 and eventual cervical cancer are less etiologically important than HPV genotype. Host immunity is an obviously important, but

difficult-to-study etiologic factor. Condom use is partially protective from initial infection; however, its role in clearance of persistent infections is less clear.

The remainder of the chapter summarizes new findings as it relates to the natural history of cervical HPV. In the previous chapter, little information was available regarding HPV transmission, anal HPV in men and women and male genital HPV infections—these sections have all been expanded.

2. Update on recent prospective studies of cervical HPV and CIN

Although numerous prospective studies have added to our knowledge of the natural history of HPV, the kinds of studies have varied by type of measurement (e.g., serology, DNA), outcome (e.g., viral persistence, CIN 3+), and study design. For brevity, this discussion will be restricted to prospective studies of HPV DNA and CIN, with the outcomes of type-specific viral persistence (versus clearance) and/or histologic CIN3+.

2.1. Risk of CIN3+ following a positive HPV test

A negative HPV test implies low risk of CIN3+, and a positive HPV test implies a higher risk [10], although many infections do clear. Prospective evidence linking HPV16 and HPV18 DNA positivity to subsequent elevated relative risk of cancer has now been extended to risk of adenocarcinoma [11]. Cohort studies have permitted estimation of absolute risks following one or two positive tests; data from a few large cohorts are listed in Table 1. As expected, repeated HPV positivity is a sign of HPV persistence and conveys substantially increased risk compared to a single positive test. In one cohort, women who tested positive for an oncogenic HPV test at baseline and 2 years later had an absolute risk of CIN3+ at 12 years of 19.3%. For HPV16, the risks of CIN3+ at 3, 5, and 12 years of follow-up among women with two positive tests were 8.9% (2.5–14.9%), 23.8% (14.1–32.4%), and 47.4% (34.9–57.5%), respectively. Interestingly, prevalent infections, at any age, are more likely to persist than incident and the risk of CIN3+ is highest in those with prevalent infections [3]. Although HPV16 has the highest risk for CIN3+, rates of HPV16 persistence after an incident infection are similar to other high risk HPV types [6]. Previous cross-sectional data showed that the peak of CIN3 was in the age group 25–29 years; however, this was based on data in countries where cervical cancer screening was initiated at age 25 years, hence, the CIN3+ may have represented cumulative risk. If we presume that detection of prevalent HPV in women aged 25 years or older was acquired shortly after the onset of vaginal intercourse, the time frame to detectable CIN3+ is likely 7–10 years. Data suggest that if the diagnosis of CIN3 is sought aggressively, the time from initial infection to CIN3 in those that persist is shorter than initially thought [12].

2.2. Risk of CIN3+ following a negative HPV test

Several recently reported, large cohort studies have confirmed that there is a very low risk of CIN3+ in the years following one or two HPV negative tests at any age (Table 2). Follow-up for the longest of the cohorts has lasted up to 15+ years. The risk predicted by a negative HPV test has been vanishingly low for invasive cancer. This makes sense, given that the moment of HPV infection is the start of the carcinogenic process, which typically takes decades to transition from infection to cancer [3].

2.3. Once cleared, HPV infections do not pose a large risk of subsequent CIN3 +

The group of HPV-negative women includes many who were once positive but cleared their infection(s), as well as those who were never positive for a given type or types; due to the lack of accurate serology, we cannot distinguish the two sub-groups. Population studies showing low risk following an HPV negative test imply that infections, once cleared, do not

re-appear and do not cause large numbers of CIN3+ cases. This largely remains a deduction, because there have been few studies directly addressing the natural history of re-appearing HPV infection (see below). Young women are likely to become reinfected with different and same HPV types after documented clearance [4,13]. Because the rate of incident infections declines steadily with age, the bulk of cancers in a population can be attributed to infections acquired at a young age (see below-risk factors) that do not clear [14].

2.4. Non-viral co-factors for HPV persistence and diagnosis of CIN3 +

The best established etiologic co-factors for invasive cancer among HPV-infected women are smoking, long-term hormonal contraceptive use, multiparity and human immunodeficiency virus (HIV) infection. The same co-factors might operate at least in part by increasing the risk of progression to CIN3, not necessarily the risk of invasion given CIN3 [15,16]. However, data are very conflicting on whether these etiologic cofactors increase the risk of viral persistence measured by repeated HPV testing [17]. As an exception, several studies have indicated that HIV infection increases the risk of HPV persistence at all ages (see Denny LA *et al.*, Vaccine, this issue [18]). An interesting study by Hwang LY *et al.* [19] found both smoking and oral contraceptives enhance squamous metaplasia. As squamous metaplasia is a process of cell replication and differentiation, it likely supports viral persistence. Squamous metaplasia is most active in adolescents, the age where HPV peaks. Several studies have found age of first intercourse as a risk factor for cancer [20]. In addition, the study by Rodriguez AC *et al.* [3] showed that CIN3+ risk was increased for prevalent infections but not incident, suggesting that infections that occurred long ago (and likely shortly after the onset of sexual intercourse) are at highest risk of developing into cancer if they persist. The strongest factor resulting in these persistent infections is likely a lack of an adequate immune response. The role of *C. trachomatis* infection as a co-factor for persistence and CIN3+ is especially controversial. A recent study [21] did not find an association between *C. trachomatis* and CIN2+ lesions and suggested that previously observed positive associations could partly be due to an increased susceptibility to HPV infection as chlamydia infection has been linked to an increased risk of prevalent and incident HPV detection.

2.5. Re-infection vs. reactivation

Although several recent studies have given us insight into the issue of re-infection vs. reactivation of latent infection, the picture remains complex. The frequency of redetection after a documented clearance ranges from 5% to almost 20% depending on age, length of follow-up and definition of clearance. In a group of recent sexually active women, redetection was quite common (20%) but the study used only one intervening negative test, which may have resulted in false negative tests [4]. Moscicki AB *et al.* [22] found that over a 2-year period, only 3–5% had redetection of HPV16 after clearance defined by at least two consecutive negative tests. After 5 years, 10–17% had another visit with HPV16 detected. In this study, sexual behaviors were found to be highly associated with re-detection of these infections, suggesting that these were infections due to re-exposure. There is good evidence that transient infections are cleared by innate immune responses [23]; hence, are less likely to result in a memory immune response, leaving women vulnerable to reinfection [24]. Trottier H *et al.* [25] also summarized that redetection of HPV in adult women was likely due to new exposures. Using serology as a marker of previous infection, rates of reinfection range significantly between studies [22,25,26]. Moscicki AB *et al.* [22] showed that in women who had serologic evidence of a past infection (i.e., the initial infections were likely not transient), the redetected infection was not associated with a new sexual partner, suggesting some of these were in fact reactivation of latent infections. However, most if not all of these redetections rapidly cleared. Examining rates of reinfection after serologic evidence is limited, since serology may not be specific to the HPV type being measured.

This is likely one of the reasons why the literature varies in whether antibodies are protective from second infections [21,22,25,26]. Wentzensen N *et al.* [27] using two serologic methods found from 8.5–9.6% of women with serologic evidence of HPV16 had a recurrent detection—a rate much lower than those without seroevidence. Among women who were positive by both methods, only 6.8% had recurrence, compared to 15% in women who were negative by both methods. Notably, no HPV16-associated CIN2 occurred within the 7 years follow-up, suggesting that whether these were latent or reinfections, they were well controlled with some type of immune memory. Certainly the largest studies were in the HPV vaccine trials—less than 1% of the women in the placebo arm who were HPV16/18 seropositive at entry and DNA negative at entry developed HPV16/18 CIN2/3, whereas twice the number developed disease in the seronegative group [28,29]. Another reason the data are mixed is that antibodies are not the likely mechanism of protection involving natural infections. Rather other immune mechanisms come into play, such as the cell-mediated immune response, which is more difficult to measure. Redetection may also be due to autoinoculation from other mucosal sites (discussed below). Studies that examined intratypic variants suggest that the appearance of ‘new’ types is the exception. In a prospective study, Xi LF *et al.* [30] examined sequenced HPV variants in longitudinal pairs from women with HPV persistence and showed that 9 of 11 women who had an intervening negative test had the same variant. The conclusions are limited since most of the negative intervals were defined by a single negative test which likely reflects sampling error or a false negative test. In addition, re-appearance of the same HPV type does not rule out reinfection since repeated transmissions between partners is common [31].

2.6. Natural history of CIN2

CIN2 has thought to be an intermediary step from CIN1 to CIN3. More recently, the existence of this intermediary step is questioned as is the actual diagnosis of CIN2. Many studies have shown that the reproducibility of CIN2 is quite poor. Although CIN3 appears to have more reproducibility, several studies have found quite poor reproducibility of CIN3 as well, specifically in young women [16,32]. Recent data have shown that regression rates of CIN2 among young women (defined as less than 25 years of age) are quite high. Moscicki AB *et al.* [32] showed in prospective study that the regression of CIN2 in women aged 13–24 years was overall 70% and HPV16 CIN2 regression was close to 50%. Other retrospective studies in young women found similar rates of regression [33–35]. In older women, regression rates are lower—around 30–50% over a 2-year period [35,36]. The discrepancy between young and older women might be due to misclassification. Rodriguez AC *et al.* [3] reported that the proportion of CIN2+ diagnosed later as CIN3+ increased by age. For all ages, the regression rate for CIN2 appears to be lower than that of CIN1, which is close to 90% and higher than that of CIN3, which is likely closer to 20–30%. These data can be interpreted as indicating that CIN2 is truly an intermediary step with its own regression/progression potential or that misclassification of lesions result in an average of the CIN1 and CIN3 regression rates. One cross-sectional study examined risks for CIN1, 2 and 3 in a single population and found that each had unique risks [16]. In an attempt to remove observer bias, Uleberg KE *et al.* [37] examined the protein expression from supernatants of fresh cervical biopsies and found that several proteins could differentiate CIN2 from CIN3 lesions. Specifically, Cytokeratin 2 was the strongest discriminator, with 90% correct classification. CIN1 was not examined in this study.

3. Heterosexual transmission

HPV transmission was largely an unstudied phenomenon until in recent years. Transmission can be calculated in many different ways, but commonly used approaches include the transmission probability per partnership (i.e., the probability that an infected partner transmits HPV to a susceptible partner, irrespective of the duration of that partnership) or the

quantity or nature of sexual encounters. One can also consider the transmission probability per coital act, defined as the probability that an infected partner transmits HPV to a susceptible partner in a single vaginal sexual encounter or act of coitus. This approach requires detailed sexual histories and greatly depends on the accuracy of reporting sexual acts. Transmission rates can also be estimated as an incidence density (i.e., number of transmissions per some quantity of person-time) and the cumulative incidence of transmission, which is analogous to transmission probability per partnership. The resulting estimates would depend on duration of time that subjects were followed up.

Four studies have reported transmission rates observed in initially HPV-discordant couples after longitudinal follow-up [38–41]. All but one observed a higher rate of female-to-male versus male-to-female transmission. Studies varied in their methods of genital sampling and calculation of transmission, which included both cumulative incidence and incidence density of transmission. Standardized to a cumulative incidence over a 6-month period to estimate the per-partnership transmission probability, rates ranged from 0.05–0.28 for male-to-female and 0.19–0.81 for female-to-male transmission. The highest rates of female-to-male transmission were observed in studies with short intervals (e.g., 2 months or less) between study visits [31, 41]. Transmission rate estimates may be heavily influenced by the type of specimens and also the frequency of follow-up, particularly if female-to-male transmission produces more transient infection in males [42].

Transmission rates observed in discordant couple studies were lower than estimates from calibration studies using mathematical modeling. Bogaards JA *et al.* [43] estimated a range of per-partnership transmission probabilities of 0.43–0.94, with that for HPV16 and HPV18 among the highest. Transmission rates observed empirically among initially discordant couples are likely lower than those calculated earlier in time due to (1) lower infectiousness due to clearance in the index partner; (2) lower susceptibility in the non-index partner due to depletion of susceptibles; or (3) increasing immunity to HPV and lowered susceptibility to re-infection because transmissions observed later in time may not be the first transmission event in the couple.

Couple-based studies have provided evidence that deposition may result in false HPV positivity, which in turn may produce over-estimates of infection rates. Two studies observed that the estimated transmission rate was considerably higher for those who had sex within 24 hours of their follow-up visit [38,41]. Analogously, there are high levels of detection of male human DNA on vaginal swabs collected within 2 days of vaginal intercourse followed by considerably reduced detection at 3 days and longer [44]. Taken together, this suggests that HPV-positive specimens collected soon after vaginal sex may not represent true, active infection but contamination or deposition from the sex partner.

Transmission from index partners with detectable HPV DNA is likely heterogeneous, and would depend on the infectious dose (i.e., viral load and/or duration of infection), which in turn may depend on whether or not a lesion is present [45–47]. Burchell AN *et al.* [38] observed the highest transmission rate when the index partner had persistent infection, suggesting that transmission is more likely with extended exposure, probably at higher viral load. HPV positivity has been shown by others to correlate with viral load in the partner [48].

Recent studies have shed light on sexual transmission to the oral tract via oral sex and open-mouthed kissing. A large, pooled analysis of eight cohort studies observed positive associations between oral sex behaviors and cancers of the oropharynx, tonsil, and base of tongue [49]. Among young men, oral HPV was independently associated with having had

6 lifetime oral sex partners or 6 lifetime partners for open-mouthed kissing, after adjustment for lifetime number of vaginal sex partners [50].

4. Autoinoculation

Although it is difficult to establish the occurrence of ‘transmission’ between anatomic sites because of problems with contamination and potential latency, evidence is emerging which suggests that the anus may serve as a source or reservoir for HPV infection of the cervix and vice versa. Women who practice anal intercourse have a higher risk for HPV infections of the anus [51,52]. In this regard, it is somewhat surprising that a history of anal intercourse has not consistently been shown to be a significant risk factor for incident high-risk anal HPV infection in women [41–53]. Several studies have found anal HPV in women with no history of anal intercourse. Goodman MT *et al.* [54] have shown that it is common for anal and cervical HPV infections to occur consecutively, suggesting that the cervix (vagina) may serve as a source for HPV infection of the anus and vice-versa. The relative risk (RR) of acquiring an anal HPV infection after a cervical infection with HPV of the same genotype was 20.5 (95% confidence interval [CI], 16.3–25.7), and the RR of acquiring a cervical HPV infection after an anal infection with HPV was 8.8 (95% CI, 6.4–12.2).

The plausibility that the cervix (vagina) acts as a source for anal HPV infection is enhanced by the observation that vaginal discharge is frequently found on the perineum. Furthermore, hygienic habits, such as in the use of toilet paper, may facilitate transmission of vaginal discharge to the anus. The likelihood that anal infection acts as a source for cervical infection is somewhat less plausible. Aside from potential underreporting of anal sex, other sexual and nonsexual routes of transmission are possible, including non-penetrative sex or inoculation through fingers. Several studies found the same HPV type in the hand or fingertips as that in the genital area in men and in women [55–57]. Although HPVs on the fingers likely represent DNA deposition from the genitals rather than true infection, the possibility of infection from a recent sex partner or autoinoculation between the genitals or anus and the fingers cannot be ruled out. Interestingly, oral infections have been less likely to have matching HPV infections in either the genitals or hands [57].

Transmission studies conducted among younger sexual partners in Honolulu [31] and San Francisco [57] provide preliminary evidence for HPV transmission among heterosexual couples through non-penetrative sexual contact between the female anus and the scrotum, as well as the female hand and male genitals. Male autoinoculation in these couples frequently involved the scrotum, likely facilitated by passive contact between proximate genital sites. The scrotum may be an important source or reservoir of infection for penile infections that can subsequently be transmitted to partners.

5. Natural history of penile and external genital HPV

5.1. HPV prevalence

Several studies have recently been published reporting HPV prevalence among men. It is difficult to directly compare due to differences in the age structure of the study populations, inclusion criteria for study participation, as well as anatomic genital site of sampling. In a study from Brazil, Mexico, and the United States, the *HIM Study*, where samples from the coronal sulcus/glans, penile shaft, and scrotum were combined, the prevalence of any HPV type was 65.2% (by polymerase chain reaction or genotyping), 20.7% with non-oncogenic types only, and 17.8% both oncogenic and non-oncogenic types. Prevalence of the four HPV vaccine types (6, 11, 16, and 18) was 14.7%. Unlike in women, HPV prevalence was not associated with age [58]. Among heterosexual men participating in the five-continent quadrivalent HPV vaccine trial, the prevalence of the four HPV types (6, 11, 16, and 18)

was 8.8% at enrollment in specimens obtained from the coronal sulcus/penis, scrotum, and perineal/perianal sites [59]. HPV prevalence at the external genital sites was higher among men who had sex with men (MSM) compared with men who had sex with women (MSW) (23% vs. 8% considering only MSM external genital sites) [60]. When MSM, MSW and men who had sex with both men and women (MSMW) were compared in the *HIM Study*, HPV prevalence of any tested HPV type (by genotyping only) was higher among MSMW than among either MSM or MSW, 60%, 50%, and 53%, respectively. The prevalence of the four vaccine types among MSMW, MSM, and MSW was 26%, 23%, and 16%, respectively [61]. Nyitray AG *et al.* [61] also reported the HPV prevalence for nononcogenic HPV types (51%, 36%, and 42%, respectively).

In these cross-sectional studies, the factors associated with HPV detection in combined external genital specimens (coronal sulcus/penis/scrotal area) include not being circumcised [62], lack of condom use [63], a history of having ever smoked [64], and a high lifetime number of sexual partners [58,59]. In a randomized controlled trial of male circumcision in Kenya, laboratory diagnosis of *C. trachomatis* and *N. gonorrhoea* infections, as well as self-reported history of sexually transmitted infections and infrequent bathing, were also risk factors for HPV detection of the glans/coronal sulcus and shaft [65].

Among participants aged 14–59 years included in the 2003–2004 National Health and Nutrition Examination Survey in the United States, the seroprevalence for one or more of the HPV vaccine types (6, 11, 16, and 18) was significantly lower for men (12.2%) than that found for women (32.5%). However, in both men and women, the seroprevalence of any HPV vaccine type increased with age [66]. Among men aged 18–70 years from the *HIM Study*, seroprevalence to at least one vaccine HPV type (6, 11, 16, and 18) was 34% at enrolment and increased with age. Furthermore, seroprevalence of vaccine HPV types varied by sexual practice, 31.2% of MSW, 65.6% of MSM, and 59.4% of MSMW were seropositive to one or more vaccine HPV types [67].

5.2. Natural history of external genital HPV in men

Among men in the *HIM Study*, the incidence of a new genital HPV infection was 38.4 per 1000 person months during a median follow-up of 27.5 months. As with genital HPV prevalence, high numbers of sexual partners increases acquisition of oncogenic HPV infections. For any HPV type, circumcision was not significantly associated with HPV acquisition in this study [42]. Similarly, HPV acquisition did not differ by circumcision in several studies [62]. However, in a randomized controlled trial of male circumcision in Uganda, high-risk HPV incidence was statistically significantly lower in the male circumcision group than in the uncircumcised male group [68].

Overall, the median time to clearance of an HPV infection was 7.5 (6.8–8.7) months in the *HIM Study* population [42]. In several studies, slower clearance of HPV infection was observed in the uncircumcised males [39,68]. Interestingly, clearance of oncogenic HPV infection decreased in men with a higher number of lifetime female partners and was more rapid with increasing age, suggesting that eventually men developed some type of immune response that confers protection against subsequent infections [42]. However, in the only study to date to evaluate the association between HPV antibody status and subsequent infection with HPV, antibodies to HPV16 were not protective against new HPV16 infections in men [69].

5.3. Penile intraepithelial neoplasia

Penile intraepithelial neoplasia (PIN) is often referred to as a pre-cancerous condition since it shares histologic similarities to CIN. In contrast to CIN, PIN does not have standard

clinical protocols for diagnosis or management since the natural history of this lesion is completely unknown. As with CIN, the prevalence of PIN appears far greater than invasive cancer of the penis. Studies have been confusing, since misclassification of PIN is common without histological confirmation from a biopsy samples. In the literature, prevalence of HPV in PIN has ranged from 60–100% [70]. No other risk factors have been found for PIN.

6. Natural history of HPV infections in the anus in men and women

6.1. Anal cancer and HPV

Anal cancer is covered in more detail in Forman D *et al.*, *Vaccine*, this issue [71]. However, there are certain aspects that are worth underscoring in this discussion. While anal cancer is rare compared with cervical cancer, it is more common among women than men in the general population. However, the epidemiology of anal cancer in women is distinct from that of cervical cancer. The incidence of anal cancer has been rising by about 2% per year among both men and women in the general population since the 1970s [72]. The reason for the increasing incidence of anal cancer is not well understood but may at least in part reflect changes in sexual behaviors in the latter half of the twentieth century that increase the risk of exposure to HPV in the anal canal. Anal intercourse is likely an efficient mode of acquisition of anal HPV infection, but is clearly not the only mode of transmission of HPV to the anal canal (as described above).

The incidence of anal cancer is particularly high among men who have sex with men (MSM) and both men and women immunosuppressed due to transplantation or HIV (reviewed in Denny LA *et al.*, *Vaccine* this issue [18]). Risk factors for anal cancer largely reflect exposure to HPV, chronic irritation in the form of fissures or fistulas, smoking and immunosuppression, and are similar among men and women.

6.2. Anal HPV prevalence

Among men, the highest proportion with anal HPV infection are MSM, particularly HIV-infected MSM (see Denny LA *et al.*, *Vaccine*, this issue [18]). In several studies, over 90% of HIV-infected MSM have anal HPV infection, often with multiple HPV types. A substantially lower proportion of HIV-uninfected men who have sex with women have anal HPV infection, but even in this population, 12% in one study had anal HPV infection and 7% had at least one oncogenic HPV type [73]. Risk factors for anal HPV infection with any HPV type and with any oncogenic type in this population included duration of relationship with a primary sex partner and ever having oral or anal sex with a man. Lifetime number of female sex partners was associated with anal infection in the man with any HPV type. The natural history of anal HPV in men who have sex with women has not been studied.

Data on the natural history of anal HPV in women are also scant. The prevalence of anal HPV infection has been shown to be unexpectedly high in women of all ages [52,74,75]. The first studies of anal HPV infection were performed in HIV-infected and HIV-uninfected women at high risk of HIV infection. These studies showed that anal HPV infection was equal to or more common in these populations than cervical HPV infection [52,75]. Subsequent studies in healthy woman from the general population in Hawaii showed that the prevalence of anal HPV infection and cervical infection were similar, at approximately 29% and 27% positivity in the cervix and the anus, respectively. Among women followed prospectively, half had an incident anal HPV infection and of these, 58% cleared during a follow-up period of approximately one year [74]. Factors associated with anal HPV persistence included douching, long-term tobacco smoking and anal intercourse. As discussed above, anal intercourse does not appear to be required for acquisition of anal HPV infection [54]. Studies show a high degree of genotype-specific concordance among women with concurrent anal and cervical infections, consistent with a common source of infection

or spread from one site to the other [52,74]. The implications of anal HPV infection as a possible source of spread to other genital sites in a woman or her sexual partner are still unclear (see above), as is the role of anal HPV infection in generating a systemic immune response to HPV.

6.3. Anal intraepithelial neoplasia

As with PIN, anal intraepithelial neoplasia (AIN) shares similarities in its histologic appearance with CIN and data on its natural history are negligible in HIV uninfected persons. As CIN3, high-grade AIN (HGAIN) is thought to be a true precursor to invasive anal cancer. Most of the studies to date on AIN have been done in MSM. Not surprisingly, the prevalence of AIN and risk of HGAIN, specifically, mirrors that of anal HPV prevalence in various populations. The prevalence of AIN is highest among HIV-infected MSM (reviewed in Denny LA *et al.*, *Vaccine*, this issue [18]), followed by HIV-uninfected MSM [76]. In the only population-based data reported to date, a post-HAART study in San Francisco showed that the prevalence of any grade of AIN was 57% in HIV-infected MSM and the prevalence of HGAIN was 43% [76]. Of great concern as well was the observation that among HIV-uninfected MSM, the prevalence of any grade of AIN was 35% and the prevalence of HGAIN was 25%. Risk factors for HGAIN among HIV-uninfected MSM included having any anal HPV infection and infection with an increasing number of HPV types.

Even cross-sectional studies of AIN in women are very limited at this time. Most of the studies of women reported to date have been in HIV-infected women as reviewed in Denny LA *et al.*, *Vaccine*, this issue [18]. A recent analysis of immunocompetent women with CIN, vulvar or vaginal intraepithelial neoplasia showed that 12% had biopsy-proven AIN [77]. In that study, 8% of women had HGAIN. Another study of immunocompetent women found AIN in 17.4% of women with CIN—4% had HGAIN. Risks for AIN included concomitant VIN or VAIN, anal intercourse, unprotected anal intercourse and history of genital herpes [78]. Data are also limited in the transplant population. Among renal transplant recipients, using anal cytology to assess disease, AIN was found in only 6% of patients [79], but this may represent an underestimate of the true prevalence of disease given the limited sensitivity of cytology for detection of AIN.

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Highlights

- Development of CIN3 is rare in women aged 30 years who test HPV DNA-negative.
- Heterosexual transmission is extremely common.
- Transmission between the anus and cervix and vice versa are common in a woman.
- Prevalence of penile HPV is greater than cervical HPV but persistence is less likely.
- Persons with HIV, MSM, and women with cervical cancer are at risk for anal cancer.

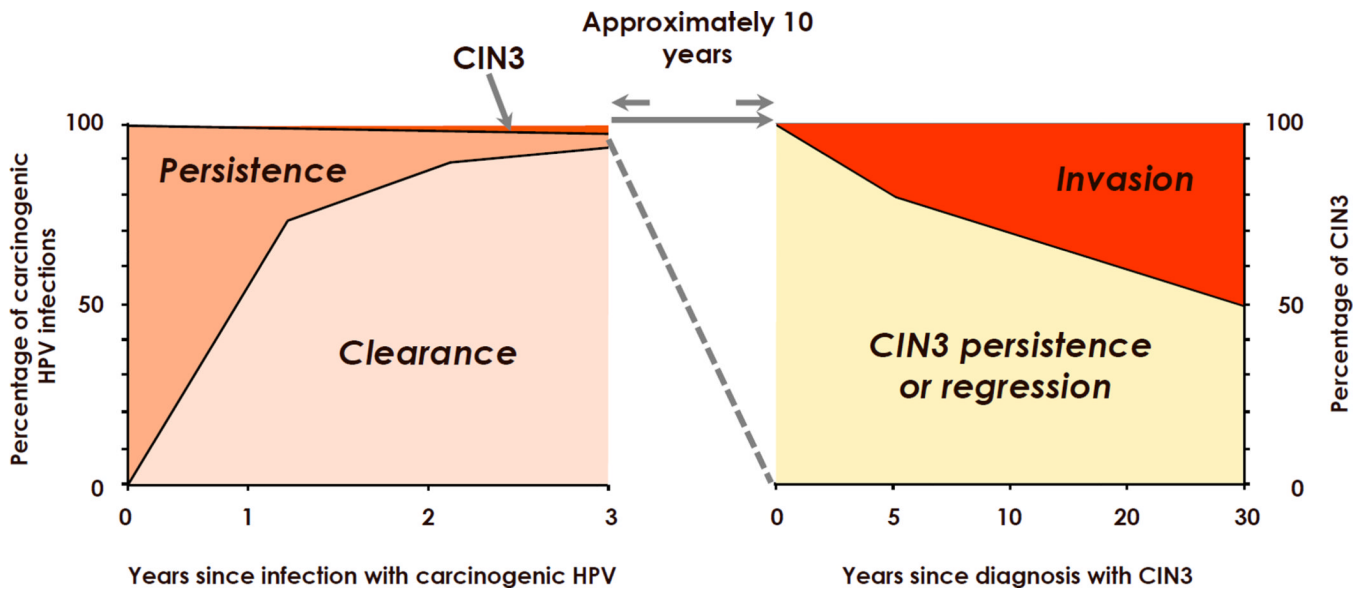


Figure 1. Natural history of HPV infection. CIN3: Cervical intraepithelial neoplasia grade 3. Adapted from reference [2].

Table 1

Risk of CIN3+ following a positive HPV test

Authors, date	Country	Cohort size	Age (Yrs)	Median follow-up (Yrs)	HPV methods	Risk of disease among HPV-positive
Dillner J <i>et al.</i> , 2008 [80]	6 European countries	2,799	Varied	6	Mainly GP5+/6+ PCR and HC2 ^c	CIN3+ 10% (6.2–15.1)
Sankaranarayanan R <i>et al.</i> , 2009 [81]	Rural India	2,812	30–59	8	HC2	ICC 0.03%
Kjaer SK <i>et al.</i> , 2010 [82]	Denmark	1,281	22–32	12.9	HC2	CIN3+ HPV16 26.7% HPV18 19.1% HPV31 14.3% HPV33 14.9% Other hrHPV 6.0%
Schiffman M <i>et al.</i> , 2011 [83]	United States of America (Portland)	1,291 (<30 yrs) 579 (30 yrs)	16	4.3 (<30 yrs) 10.5 (30 yrs)	MY09/MY11 PCR, HC2	CIN3+ (<30 yrs) HPV16 14.6% (10.0–20.9) Other hrHPV 7.0% (4.2–11.4) CIN3+ (30 yrs) HPV16 8.5% (4.1–17.2) Other hrHPV 3.1% (1.6–6.1)
Katki HA <i>et al.</i> , 2011 [84] ^a	United States of America (Northern California)	16,757	30	5	HC2	CIN3+ 7.6%
Chen HC <i>et al.</i> 2011 [85]	China	1,343	30–65	14.5	MY11/biotinylated GP6+ PCR, EasyChip [®] HPV Genotyping Array ^d	ICC/CIS HPV16 13.5% (6.5–28.0) HPV58 4.0% (2.6–6.2) Other hrHPV 2.1% (0.7–6.6)

^aKing Car, Taiwan.CIN3+: Cervical intraepithelial neoplasia grade 3 or worse; CIS: Carcinoma in situ; HC2: Hybrid Capture[®] 2 (HC2), Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.); hrHPV: High-risk human papillomavirus; ICC: Invasive cervical cancer; PCR: Polymerase chain reaction.

Table 2

Risk of CIN3+ following a negative HPV test

Authors, date	Country	Cohort size	Age (Yrs)	Median follow-up (Yrs)	HPV methods	Risk of disease among HPV-negative
Dillner J <i>et al.</i> , 2008 [80]	6 European countries	18,552	Varied	6	Mainly GP5+/6+ PCR and HC2	CIN3+ 0.27%, (0.12–0.47)
Sankaranarayanan R <i>et al.</i> , 2009 [81]	Rural India	24,380	30–59	8	HC2	ICC 0.0003%
Kjaer SK <i>et al.</i> , 2010 [82]	Denmark	6,201	22–32	12.9	HC2	CIN3+ 3.0% (2.5–3.5)
Schiffman M <i>et al.</i> , 2011 [83]	United States of America (Portland)	5,736 (<30 yrs) 11,855 (30 yrs)	16	4.3 (<30 yrs) 10.5 (30 yrs)	MY09/MY11 PCR, HC2	CIN3+ 0.7% (< 30 yrs) CIN3+ 1.8% (<30 yrs)
Katki HA <i>et al.</i> , 2011 [84]	United States of America (Northern California)	315,061	30	5	HC2	CIN3+ 0.17%
Chen HC <i>et al.</i> , 2011 [85]	China	8,780	30–65	14.5	MY11/biotinylated GP6+ PCR, EasyChip® HPV Genotyping Array ^a	ICC/CIS 0.26% (0.17–0.41) (baseline)

^aKing Car, Taiwan.

CIN3+; Cervical intraepithelial neoplasia grade 3 or worse; CIS: Carcinoma in situ; HC2: Hybrid Capture® 2 (HC2), Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.); ICC: Invasive cervical cancer; PCR: Polymerase chain reaction.