

Chapter 2: Natural History of Anogenital Human Papillomavirus Infection and Neoplasia

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This chapter suggests promising areas of future epidemiologic research on human papillomavirus (HPV) and anogenital cancer, organized around our understanding of cervical carcinogenesis. The major steps in cervical carcinogenesis include HPV infection, HPV persistence over a certain period of time, progression to precancer, and invasion. Backward steps include clearance of HPV infection and regression of precancer. Additional studies of incident HPV infections among virgins initiating sexual activity could clarify the earliest aspects of transmission and immune response. Research on older women and their male partners should focus on understanding the determinants of varying age-specific HPV prevalence curves and underlying dynamics of viral persistence, clearance, and latency. It will be particularly important for epidemiologists to define HPV persistence rigorously in order to guide clinical management and vaccine trials. Intensive longitudinal studies that collect visual, microscopic (cytologic and histologic), and molecular data will be needed to understand the fate of individual HPV infections and to clarify whether multiple, concurrent infections act independently on the cervix. Case-control designs will be useful mainly in searching for new biomarkers of risk of progression among HPV-infected women that could then be validated prospectively. Prospective confirmation is also needed for the etiologic cofactors established by case-control studies of invasive cervical cancer. Much of the knowledge about cervical cancer might apply to anal neoplasia. Epidemiologic studies of other genital tumors such as penile neoplasia are still needed, but multicentric groups must place great emphasis on measurement technology, given the difficulty in obtaining reliable comprehensive measurements. [J Natl Cancer Inst Monogr 2003;31:14-9]

Human papillomavirus (HPV) infection causes virtually all cases of cervical cancer and a less-defined, smaller fraction of vaginal, vulvar, penile, and anal cancers. Epidemiologists will likely continue to concentrate on cervical cancer because of its global prevalence and because it provides an excellent molecular epidemiologic model of carcinogenesis. Specifically, the cervical transformation zone is a ring of tissue with susceptibility to HPV carcinogenicity. Cervical HPV can be assessed visually, microscopically (via cytology or histology), and molecularly, and we know the basic steps that lead from the normal cervix to cancer. Accordingly, this chapter will summarize potentially promising areas of future research on HPV and anogenital cancer, organized along the lines of the natural history model of cervical carcinogenesis shown in Fig. 1.

As shown in Fig. 1, the major steps known to be necessary in cervical carcinogenesis include HPV infection, HPV persistence over a certain period of time, progression to precancer, and invasion. Backward steps are possible, including clearance of HPV infection and regression of precancer. As discussed below,

HPV infection might be usefully separated into low viral load infections without microscopically evident abnormalities as compared with higher viral load infections with microscopically evident abnormalities.

Because there are more than 100 types of HPV, with more than 40 anogenital types of which approximately 15 are oncogenic, it would be impossible in a short chapter to discuss each separately, although it is often important to distinguish type-specific infection (e.g., when discussing viral persistence). HPV type 16 (HPV16) is uniquely oncogenic and merits some separate discussion below. Otherwise, we will discuss general themes.

TRANSMISSION AND ACQUISITION

Studies among initially virginal women strongly confirm the sexually transmitted nature of the HPV infection (1,2). Sexual contact with an infected partner is necessary for transmission, presumably through microscopic tears in the mucosa or skin. HPV infections are easily transmitted, however, and it seems that intromissive intercourse in which an infected penis enters the vagina is not strictly necessary, based particularly on data from lesbians (3). In fact, transmission might take place in one anogenital site, such as the introitus, with spread by self-inoculation to another site (4). Considered as a group, anogenital HPVs are the most common sexually transmitted infections.

Apart from number of sex partners, other risk factors for HPV transmission might include both susceptibility factors and proxies for the likelihood that a sexual partner is infected, i.e., the age of the woman and her partner, the age at first sexual intercourse, barrier contraceptive use, co-infections, male sexual behavior, and male circumcision. Recent studies have clearly demonstrated the potential role of males as vectors by associating risk of cervical cancer with HPV DNA carriage in male partners. These observations are more readily reported from low-risk countries where male sexual behavior (i.e., the lifetime number of partners) spans an extended range than in high-risk countries where HPV exposure in males is virtually universal (5). Condom use might be somewhat but not completely protective (6). Circumcision apparently reduces the risk of transmission and acquisition of HPV as well as the risk of cervical cancer (5). Studies of the natural history of HPV in males are scarce. Major difficulties include the lack of validated methods to sample from the male genitalia and a moderate enthusiasm to investigate an exposure with few health outcomes among males. However, as with any other sexually transmitted infection, HPV prevention

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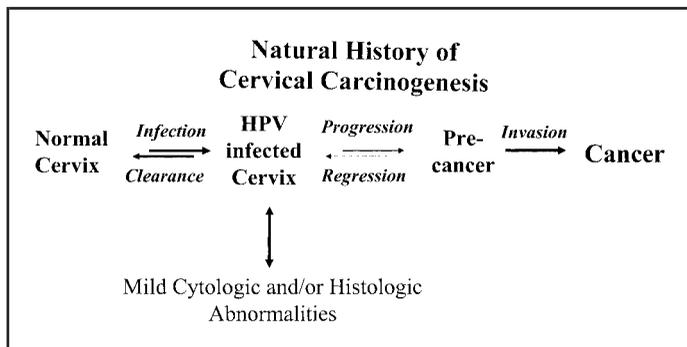


Fig. 1. An epidemiologic model of cervical carcinogenesis. The major steps in cervical carcinogenesis are human papillomavirus (HPV) infection (balanced by viral clearance), progression to precancer (partly offset by regression of precancer), and invasion. The persistence of oncogenic HPV types is necessary for progression and invasion. HPV infection is frequently but not necessarily associated with cytologic and histologic abnormalities.

could greatly benefit from a better understanding of the transmission and infection determinants among males.

There have been no recent important epidemiologic studies on HPV transmission by nonsexual routes, such as environmental fomite or vertical transmission. It would be particularly valuable to confirm the prevalence of established HPV infections in babies after vaginal birth, given the absence of convincing seroconversions (using assays that provide specific although insensitive biomarkers of infection) (7). Even if high viral load anogenital infections are rare in babies, exposure at birth could influence later immune response at the time of sexual exposure (8), but rigorous assessment of such a theoretical effect will require very difficult study designs.

Assessing HPV transmission in the studies of sexual partners is difficult to the point of daunting, because comprehensive measurements of HPV infection of the male and female are error prone, especially given multiple types and even variants, making the distinction between persistence, recurrence, and acquisition very difficult. Therefore, we know very little about the patterns of infection and reinfection among partners. Several other questions related to the transmission and acquisition of HPV are also outstanding. Any studies that can capture incident HPV infections among virgins initiating sexual intercourse would be useful, because the earliest aspects of transmission and immune response have not been clarified adequately. It is not known whether sexual intercourse near menarche is uniquely prone to establishing infection (or persistence and progression). The apparently limited protective role of a condom should be better estimated, to guide the debate on this issue. A possible role of susceptibility in the acquisition of multiple HPV types has not been assessed adequately. The currently available, limited data suggest that HPV types, although likely to be sexually co-transmitted, influence each other's transmission minimally if at all (9,10). The type specificity of serologic responses supports this conclusion (11). However, more studies of multiple infections would be important to guide vaccine strategies (e.g., we wish to confirm that preventing HPV16 infection will not influence the acquisition of other HPV infections).

PREVALENCE OF HPV INFECTION

The age-specific prevalence curve of cervical (and vaginal) HPV infection as measured by HPV DNA confirms sexual trans-

mission, with a large peak following typical population norms of sexual initiation (12). In some populations, age-specific prevalences decline sharply and reach very low levels at old ages, consistent with viral transience as well as low incidence at older ages [Fig. 2; and see (13)]. However, in other populations, there is not as steady a decline in HPV prevalence with advancing age; rather, the curve rises again in middle age or never substantially falls (14).

Understanding the determinants of regional variation in age-specific HPV prevalence is an important remaining task, tied to our need for a better understanding of viral persistence, clearance, and possible latency. Some studies of highly exposed women such as prostitutes (15) have shown a significant decrease in the HPV prevalence with age, despite continuously high sexual activity, indicating that loss of viral detection and type-specific immunity to reinfection occurs. We need more longitudinal studies of prostitutes. We also need studies focused on older women and their male partners, particularly cohort studies with repeated measurements assessing male and female sexual practices and immunity.

PERSISTENCE VERSUS CLEARANCE

It is widely accepted that persistence of HPV is crucial for the development of cervical precancer and cancer. Fortunately, most HPV infections are transient instead, becoming undetectable within 1–2 years even by sensitive polymerase chain reaction (PCR) assays (16). In other words, anogenital HPV infections tend to resolve spontaneously, as do warts anywhere on the body. Presumably, they are cleared completely by the cell-mediated immune system, are self-limited, or are suppressed into long-term latency. It would be very interesting to know how

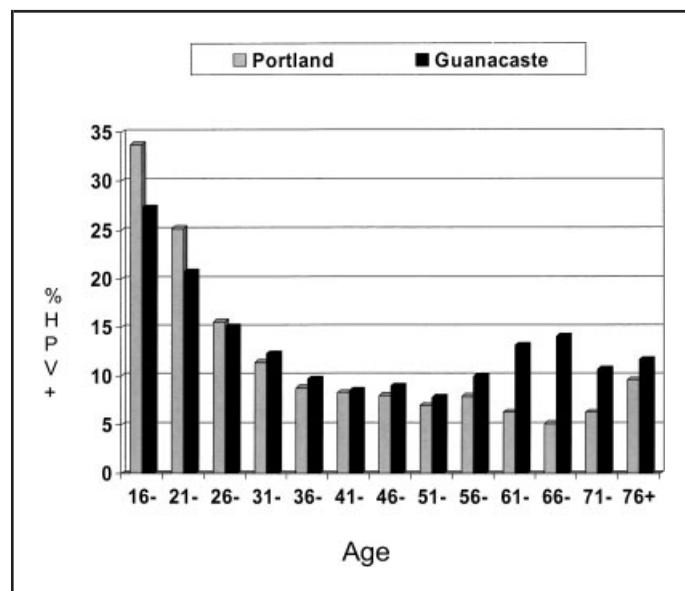


Fig. 2. Age-specific prevalence of oncogenic types of human papillomavirus (HPV) infection varies by region, for reasons that are not yet understood. For example, among 20 810 women in the Portland Kaiser cohort [see (13)], HPV prevalence measured by Hybrid Capture 2 decreased steadily with age until the oldest age groups. In contrast, among 9165, women in the Guanacaste Project (unpublished data), the prevalence of the same 13 types (measured at similar analytic sensitivity to Hybrid Capture 2 using consensus primer polymerase chain reaction) turned back up in middle age.

often HPV transience in the short term represents successful immune clearance versus a self-limited infection (perhaps a daughter cell destined to differentiate was infected rather than an immortal germinal cell). It is difficult to see how epidemiologists can help resolve these two alternatives using existent measurement technology.

A major unresolved question regarding HPV natural history is how often short-term viral clearance leads to long-term viral latency. Latency implies that no HPV DNA is detectable by conventional molecular tests but that very small foci of cells maintain infection at low DNA copy numbers. The existence of a latent state is supported by studies of immunosuppressed individuals (as discussed in chapter 6 by Palefsky and Holly), but we do not know how frequently latency occurs among immunocompetent individuals, how long it can last, what causes re-emergence into a detectable state, and what fraction of cancers arises after a period of latency. Answers to these questions will greatly affect prevention strategies reliant on HPV DNA detection. But finding epidemiologic clues will be very difficult until HPV DNA screening becomes common enough to generate huge HPV-tested cohorts as a byproduct. To fund the studies as research efforts would probably be prohibitively expensive. However, epidemiologists in collaboration with pathologists and laboratory scientists might consider intensive studies in search of latently infected cells, using the most sensitive research PCR methods to study microdissected germinal epithelial specimens in women who recently cleared HPV as measured by standard molecular techniques. As an alternative, benign hysterectomy specimens from women who have previously cleared HPV infections could be identified and studied intensively.

Persistence (i.e., long-duration and detectable HPV infection) is uncommon compared with clearance. From a practical point of view, persistence can be defined as the detection of the same HPV type (or better yet, variant) two or more times over a certain period. There is no consensus yet as to how long a time period implies persistence, but several months to a year is the time frame that is usually chosen. Although commonly adopted, this definition of convenience does not correspond to our understanding of HPV natural history. We know that most prevalently detected cervical HPV infections remain detectable by PCR for a median of approximately 6–12 months (16). The average period of detectability starting at viral incidence is closer to 1–2 years (17). HPV16 tends to persist longer (10,18), but the other oncogenic types do not persist substantially longer than some nononcogenic types. It would be useful for epidemiologists to agree on a rigorous definition of HPV persistence, for example, taking into account whether viral variant analysis is required. More studies including HPV16, oncogenic types other than HPV16, and common nononcogenic types like HPV types 6, 53, 61, and 62 would also be useful to firmly establish whether average persistence parallels and predicts oncogenicity. We also are not sure whether viral load or the presence or the absence of associated, microscopically evident abnormalities alters the average times of persistence. More data are needed, particularly to clarify whether HPV infections act independently on the cervix, considering both immunology and direct interaction. The scant data conflict as to whether the presence or the absence of any one type alters the duration of any other type-specific infection (analogous to whether types influence each other's acquisition as mentioned above).

MICROSCOPIC ABNORMALITIES

Microscopic abnormalities are diagnosed in only a small minority of women with HPV detectable by DNA assays. The fraction depends on the thresholds of the molecular and microscopic tests and can range widely from 1 in 10 to 1 in 3. Microscopic diagnoses are prone to subjectivity and lack of interobserver reproducibility, particularly when mild or equivocal changes are involved. Therefore, misclassification is always a big concern when epidemiologists consider how best to conceive of HPV infection as a transition state in multistage models like the one shown in Fig. 1.

It is important to consider how HPV infections should be rationally divided for epidemiologic study. We personally favor considering all HPV infections as a single broad transition state between normal and precancer, with stratifications (not biologically separate states) according to various aspects of the infection (e.g., viral type and viral load, cytologic abnormality or not). As discussed below, it is the HPV persistence of at least one oncogenic type that is the necessary state for the emergence of precancer. However, aspects of infection influence risk. HPV type is the most important. Even among the oncogenic types, HPV16 is uniquely risky and, even for HPV16 (and other oncogenic types), variants are relevant to natural history. Viral loads detectable only by PCR (not the commercially available Hybrid Capture 2) are associated with microscopic normalcy and with low risk of subsequent precancer and/or cancer, but the prospective importance of increasingly high viral loads is not at all established (19).

It is still not known whether microscopically evident abnormalities represent a separate natural history stage from HPV detected by DNA testing alone (20,21). In a recent 24-month prospective follow-up of women with oncogenic HPV DNA, the presence or absence of mild histologic abnormalities did not materially affect the risk of subsequent precancer (22). Observations suggest that a fraction of precancers arise from HPV infections in the absence of mild or even equivocal microscopically evident abnormalities (23,24). This might also represent the misclassification of cytology or histology or rapid transit through the mildly abnormal phase. Some have posited that precancers develop in HPV-infected mucosa independent and adjacent (internal) to cervical intraepithelial neoplasia (CIN) 1 rather than as an internal subclonal event (25). These hypotheses can be addressed only through very intensive longitudinal studies combining visual, microscopic, and molecular measurements. Intensive studies of women infected with oncogenic HPV, with repeated measurements aimed at discovering the determinants of viral outcome, are now more important than the establishment of new large population-based cohorts.

As a side note of some possible importance to screening, it is possible that some HPV infections produce lesions that exfoliate relatively poorly. These lesions might be better assessed by visual and histologic or molecular means (e.g., E-cadherin immunohistochemistry) than by cytologic methods (26). We do not understand how frequently this subclass occurs.

PROGRESSION TO CERVICAL PRECANCER

HPV infections, even with oncogenic types, are so common that getting infected might no longer be the usual limiting factor in cervical carcinogenesis. The critical step for most women might be whether precancer develops as an uncommon outcome of infection (Fig. 1).

The first difficult task is to define “precancer.” We are currently using this admittedly vague term to avoid using CIN 2, CIN 3, carcinoma *in situ*, or other pseudo-precise terms derived from histopathology. There is substantial heterogeneity in the microscopic diagnosis and biologic meaning of CIN 2 lesions in particular. Some certainly represent acute HPV infections of particularly bad microscopic appearance that, however, are destined to regress, whereas others are incipient precancers that are destined to persist with a high risk of invasion. Some nononcogenic HPV infections are capable of producing lesions diagnosed as CIN 2, showing that this level of abnormality is not a sufficient surrogate for cancer risk. We prefer to use cases of CIN 3 for analyses of precancer, leaving CIN 2 as a buffer zone of equivocal diagnosis, much like atypical squamous cells of undetermined significance for more minor cytologic abnormalities. It is generally a bad idea to do what we have done in the past, namely, to combine CIN 2 and CIN 3 because of small numbers. The possible exception is for studies aimed at clinicians who treat all lesions diagnosed as CIN 2 or worse. In that instance, CIN 2 is a valid part of the clinical case group.

In studying the transition from HPV infection to precancer, epidemiologists should restrict most studies to women with oncogenic types of HPV (unless we are making a particular controlled comparison). Within this group, we wish to determine viral characteristics, host factors, and behavioral cofactors that increase the risk of progression while decreasing the probability of viral clearance. We now believe that HPV persistence (defined at the type-specific level) in the absence of progression to precancer is less common (M. Schiffman and R. D. Burk: unpublished data) than had been previously thought based on studies relying on cytology or histology, which tended to misclassify sequential, distinct infections as persistent.

Ideally, we would like to study the uninterrupted natural history of each HPV infection separately, with frequent measurements and no censoring. The modal time between HPV infection occurring in the late teens or early 20s and precancer peaking around 30 years of age is about 7–10 years. More rapid progressions occur and should be studied, but we will likely not be able to study the other end of the curve, slow progressions, prospectively. Also, the absolute requirement in the United States for study-participant safety correctly forces treatment and censoring as soon as the first signs of possible precancer appear. Certain exceptions might apply in young women followed very closely for short periods. In certain countries, however, large CIN 3 lesions might serve as the end points (27).

Whatever the end point, the prospective study designs have progressed to complicated multiple measurement follow-up schemes. Very strong statistical collaborations are needed to maximize the yield of information from the data.

In searching for new biomarkers of risk for progression, case-control designs will be useful. Such designs in combination with new microdissection-microarray methods could be used to search for RNA-based biomarkers defining HPV infections at high risk of progression. Candidate markers should be validated prospectively. In these studies, the statistical challenges result from the problems of measurement error facing any new assays and from the multiple measurement issues resulting from microarrays.

We need to evaluate prospectively the strength of etiologic cofactors and implications for the prevention of risk factors established by case-control studies of cervical cancer. So far,

only smoking has been confirmed as a risk factor for precancer and cancer in cohort studies of HPV-infected women (21,28).

INVASIVE CERVICAL CANCER

CIN 3 lesions tend not to regress over short-term follow-up; however, risk and timing of invasion versus eventual regression are probabilistic. Whereas the median age of women with precancer (CIN 3) in many countries with screening is approximately 30 years, the median age of women with invasive cancers is skewed to much older ages. The median age of cancer moves toward even older ages as the quality of screening decreases. Even women with screen-detected invasive cancer tend to be more than 10 years older, on average, than women with CIN 3, suggesting a long average sojourn time in the precancer state. Some groups are using the size of the precancer as a proxy for risk of invasion. This seems correct, but prospective proof will not be obtained for obvious ethical reasons. We rely on the historic literature to estimate that between one third and two-thirds of the women with precancer (CIN 3) will develop invasive cancer, in an unpredictable time-dependent fashion (29,30). Epidemiologic studies have not been able to suggest risk factors for invasion. The often-discussed phenomenon of HPV DNA integration is associated with invasion, but it is difficult to prove that integration is causal. Finally, rapidly invasive cancers among young women, although rare events, would be a useful topic for an intensive multidisciplinary study.

ACCURACY AND RELIABILITY OF MEASUREMENT METHODS

Advances in understanding HPV natural history have followed intensive methodologic efforts to standardize accurate and reliable measurements of HPV DNA. Improvements in cytology and serology (*see* the following) have been less complete but very important as well. In future cohort studies emphasizing multiple measurements over time, the importance of optimized methods will be even greater if we hope to observe and interpret the patterns of viral clearance, persistence, possible recurrence, and progression.

SEROLOGY

Virus-like particle serology is a very useful epidemiologic tool for defining past infection with HPV. The assays are type specific and are usually negative in never-infected individuals (2,7). This specificity is useful for the definition of HPV-infected cohorts, in which etiologic cofactors can be studied. For example, serology can be used to define HPV-exposed individuals for control subjects in case-control studies emphasizing analyses only among the exposed. However, only about one half of the women with currently detectable infections of the same type (with the use of DNA and microscopy) are seropositive, suggesting that our current techniques to measure the serologic response are still not sensitive. Therefore, HPV seronegativity does not exclude exposure, partly because no group currently assays seropositivity for more than a few types of HPV. As described in chapter 5, serologic assays have not proved to be useful yet in defining immunologic responses related to the natural history of HPV infection. It is worth discussing how to proceed in this research area.

OTHER ANOGENITAL CANCERS

HPV is found in virtually all cervical cancers (31) but is also associated with other anogenital cancers (cancers of the vagina, vulva, anus, and penis). These cancers are rare (approximately one per 100 000 per year), although HPV infection at these sites is common, suggesting a more benign course than cervical infection.

The prevalence of HPV in vaginal cancer is about 60%–65% in the studies using PCR methodology (32). Our current knowledge suggests that, in principle, the natural history of vaginal HPV and cancer is similar to that of cervical carcinogenesis, with the major difference residing in the risk of progression given infection (33). It is striking how common HPV infection of the vagina is because vaginal cancer is very rare. However, given its rarity, only a very few teams can study vaginal cancer.

Only a fraction of vulvar cancers (the basaloid and warty type that tends to be associated with vulvar intraepithelial neoplasia) is caused by HPV infection. HPV-related vulvar cancer occurs in younger women than the typical keratinizing squamous histology related to chronic inflammatory precursors. The prevalence of HPV in the basaloid and warty carcinomas is around 75%–100%, whereas only 2%–23% of the keratinizing carcinomas harbor HPV. The risk factors known from cervical cancer epidemiology, like the number of sex partners, early age at first intercourse, and a history of abnormal Pap smears, are associated with the basaloid and warty carcinomas but virtually not with the keratinizing carcinomas (34). The distinct epidemiology of the two histologic subtypes (35) argues that we should never combine the two in future etiologic studies. Thus, a rare disease must be divided into two even rarer diseases. Only a few multicentric groups can hope to study them. It would be interesting to know whether, among HPV-induced anogenital cancers, HPV16 has a higher etiologic fraction for vulvar than for cervical cancer as the small amount of data suggests.

The anus resembles the cervix in that both have a transformation zone, which is especially susceptible to HPV infection with a high risk of neoplastic transformation. Studies have shown that 46%–94% of the anal cancers harbor HPV DNA. The nonkeratinizing squamous cell types of anal cancer are much more strongly associated with HPV than the keratinizing types (36). The risk of anal cancer has been associated with the number of sex partners of the opposite sex, homosexual contact (for men), other sexually transmitted infections (men and women), and receptive anal intercourse. Some findings also suggest that, in addition to HPV, constant irritation and chronic inflammatory changes may play a role. Patients with acquired immunodeficiency syndrome have a strongly increased risk of anal cancer, but it is still unknown whether this increased risk is caused primarily by the impaired immune system related to human immunodeficiency virus (HIV) infection as opposed to specific sexual practices (37). Before the onset of the HIV epidemic, the incidence of anal cancer among men who have sex with men (MSM) was estimated to be as high as 35 per 100 000, an incidence rate that is similar to that of cervical cancer in women before the introduction of routine Pap smear screening. With the start of the HIV epidemic, it became clear that HIV-positive MSM were at even higher risk than HIV-negative MSM, with recent data showing that the incidence of anal cancer in HIV-positive MSM is twice that in HIV-negative MSM. It has also been shown that anal cancer in many HIV-positive individuals develops at a younger age than was typically the case before the

HIV epidemic, when most of the individuals with anal cancer were older than 60 years. Epidemiologists need to compare the natural history of HPV in the cervix with that in the anus more thoroughly to fully understand the degree of etiologic similarity. Because cervical neoplasia is common, it would be fortuitous if lessons that were drawn from studies of the cervix could inform our understanding of anal carcinogenesis. Also, anal cancer can be difficult to treat, and it is especially important to understand the possible points of prevention before progression and invasion. The important research directions related to immunosuppression are covered in the chapter by Palefsky and Holly (*see* chapter 6).

Little is known about the early natural history (acquisition, clearance, or persistence) of penile HPV infection. As measured by serology and by DNA testing (despite difficulties in standardizing measurements), HPV is nearly as common in men as in women, with a similar type distribution and risk factor pattern. In addition, age-specific prevalences seem to be similar to those seen in women. On all parts of the penis, HPV-related lesions can be observed commonly based on whitening following application of acetic acid. Sometimes the lesions appear to be precancers microscopically but, given the low risk of cancer, they are not true surrogates for cancer. Penile cancer is similar to vulvar cancer in that HPV is related to certain histologic subtypes that tend to be found in the context of intraepithelial lesions that are HPV DNA positive (38). The HPV DNA-negative cancers of the penis, in contrast, seem to be more related to chronic inflammation as a precursor state (39). The overall prevalence of HPV in penile cancers has ranged from 15% to 71% in the largest published studies (40).

We believe that epidemiologic studies of penile HPV are still needed, but with great emphasis on measurement technology given the difficulty in obtaining reliable comprehensive measurements. More work is needed on the reliability of viral DNA assessment, given that HPV can infect the penile shaft, scrotum, and other anogenital skin. It is still unclear whether prospective studies are possible that can accrue sufficient meaningful outcomes or whether the studies in men will inform mainly our understanding of transmission. For example, it would be valuable to know whether penile HPV prevalences parallel female prevalences in the same communities and age groups.

CONCLUSION

Trials of preventive strategies like prophylactic vaccination are already proceeding with justifiable scientific optimism. However, epidemiologists working on etiology, molecular pathogenesis, and diagnostics are still very interested in understanding what lies between the causal exposure and the disease end point, namely, the natural history of HPV leading to anogenital neoplasia.

Parts of the natural history pathway are more studied than others. It appears that transformation zones in the cervix, anus, and oropharynx are especially susceptible to HPV oncogenesis. This clue should be pursued with high priority by multidisciplinary teams of pathologists, clinicians, molecular biologists, and epidemiologists.

Epidemiologic study of invasion is very difficult and has shown little worth. Studies of transmission are very difficult and might not be absolutely critical, given that we know transmission to be mainly sexual. Therefore, most future natural history projects might concentrate on defining the risk factors and bio-

markers for HPV clearance versus persistence and progression to precancer.

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