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Evidence and Impact of Human Papillomavirus Latency

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Abstract: At present, there is no consensus in the scientific community regarding the ability for human papillomavirus (HPV) infections to establish latency. Based on animal studies, a model of papillomavirus latency has been proposed in which papillomaviruses can be retained in the basal epithelial stem cell pool as latent infections and periodically induced to reactivate when the stem cell divides and one daughter cell is committed to terminal differentiation and induction of the viral life cycle. Tissue resident memory T-cells are hypothesized to control these periodic reactivation episodes and thus limit their duration. In this paper, evidence from human studies consistent with this model of papillomavirus latency is reviewed. Given the strong circumstantial evidence supporting a natural history of HPV infection which includes a immunologically controlled latent state, the longer term implications of HPV latency on a highly infected and aging population may warrant a more serious evaluation.

Keywords: Papillomavirus, HPV, latency, reactivation, cervical cancer.

INTRODUCTION

Viral latency, as defined by Siliciano and Greene, "is a state of reversibly nonproductive infection of individual cells" [1]. Despite the rapid progress made in characterizing the large family of papillomaviruses and their etiology in several human cancers, there is still uncertainty regarding the existence of a latent state in human papillomavirus infections. According to Fields Virology, "It is known that HPV can establish latency" [2]. However, a review of clinical and epidemiological literature uncovers a less certain perspective.

Recently, a new model of human papillomavirus (HPV) latency was proposed based on the evidence derived from models of rabbit oral papillomavirus infection (ROPV) [3]. This model proposes that, under a model of asymmetric epithelial cell replacement, each HPV infected basal stem cell will divide with a 1: 1 replication and division of viral episome. One infected daughter cell will enter the supra basal layers committed to terminal differentiation and induction of HPV viral replication, while the other infected daughter cell will remain quiescent in the basal epithelial stem cell pool. Under this model, the first component of the definition of viral latency - a state of non-productive infection of individual cells - appears to be met, since productive PV infection cannot occur in the absence of terminal differentiation. Thus, it is likely that the HPV-infected daughter cell that remains in the epithelial stem cell pool is the site of HPV latency. The second condition to meet the definition of viral latency is reversibility. The current model of PV latency predicts that this can readily occur anytime a latently infected, quiescent basal stem cell is induced to divide. At this time, it is anticipated that one infected daughter cell will be committed to terminal differentiation and renewed viral replication. However, the other daughter cell would be expected to again be retained in the epithelial stem cell pool, a life cycle which, in the absence of major external factors, would ensure lifelong HPV carriage.

EPIDEMIOLOGICAL EVIDENCE OF HPV REACTIVATION

Despite the expressed skepticism for a latent state in the natural history of HPV infection, recent epidemiological literature is quite consistent with a model of latency. Because there is constant turnover of the cervical epithelium, the model of epithelial stem cell latency would predict periodic recurrence of HPV detection. Epidemiological evidence supports this prediction [4-7] (Table **1**). In these studies, women observed to have cleared a specific HPV genotype during the study period were evaluated for the probability of recurrent detection of the same genotype. Recurrent detection was observed in all studies, ranging from 3.3% for HR-HPV recurrence in the Ludwig-McGill cohort study (Brazil) [4] to 19.4% in a study of college-aged women in Washington State (USA) [6]. In all studies, the authors acknowledge that there could be several alternative explanations for these observations besides latent virus reactivation. First, these could represent new infections (or re-infection) with the same genotype. However in 2 of the 3 studies which evaluated this [5, 7], no association was observed between recurrent type-specific detection and report of a new sexual partner, and one study reported that recurrent detections of HPV16 were confirmed to have identical sequence compared with the original HPV16 detection [6]. In addition, several studies have reported rates of 'incident' infection among sexually abstinent women that are similar to the recurrence rates reported in the studies in

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Table **1**, suggesting that at least a fraction of these infections cannot be explained by acquisition from a male partner [7-9]. Alternatively, these results could have occurred by simple misclassification (i.e., false positive or false negative results). The study reported by Insinga *et al.* [5], was able to evaluate the likelihood of these explanations quite carefully. In this study, endo/ectocervical swabs provided the primary outcome measure, but a second labial/vulvar/perineal/ perianal (LVPP) swab was taken concomitantly and was analyzed for type specific concordance with the cervical swab. At least some type-specific concordance was observed in a majority of cervical and LVPP pairs taken from women with initial and reappearing infections (71.4%). Taken together, these results suggest that it is unlikely that false positive detection or missed detection explained a majority of the recurrent detection episodes detected. It should be noted that in the immune competent host, reactivation is likely brought quickly under control by immune surveillance such that replicative infection and lesion development would be unlikely.

THE INFLUENCE OF STUDY DESIGN ON NATURAL HISTORY INFERENCE

The results across these few studies which have directly measured recurrent detection of the same genotype show a wide range of cumulative probability of recurrence, and unfortunately offer little insight into the frequency or duration of recurrence. However, the study designs which rely on HPV DNA assessment at long intervals may be limiting our ability to accurately characterize the frequency and duration of recurrent detection. Fig. (**1**) illustrates the limitations of the standard HPV natural history study designs on the characterization of HPV recurrent detection. Using these long interval sampling designs forces some important restrictions on the interpretation of natural history data.

The first is a problem of what epidemiologists refer to as 'left truncation' of data. This occurs when the natural history of an infection prior to study entry is unknown, as is the case for HPV. The result of this left truncation is that we cannot know, among all women entering the study negative for a specific HPV type, which ones had infection with that type in the past, and which ones did not. This has two implications in our study inferences. First, any newly detected HPV type among women entering the study negative for that type will be recorded and analyzed as an 'incident' infection. However, given the fact that we have demonstrated a non-negligible rate of new type-specific detection following a period of non-detection, we are likely misclassifying some unknown fraction of recurrent detection as 'incident'. These natural history designs thus not only are likely to underestimate the rate of recurrent detection, but overestimate the rate of 'incident' infection (i.e., acquisition).

The second problem is that of 'right truncation' of data, which occurs when we are unable to know the longer term natural history of an infection observed during our study after the observational period has ended. In the context of estimating recurrence rate in studies with anywhere from 2-10 years of follow-up, infections first observed to become undetectable late in the study have less opportunity to be observed to recur compared with infections first observed to become undetectable early in follow-up. These issues can be addressed using appropriate statistical methods, but the power of the study to estimate recurrence will be highly dependent on the total study duration.

A third problem particular to the issue of characterization of recurrence patterns in the long interval designs is essentially a combination of left and right truncation - that of the detection patterns of HPV in the unobserved time between study visits. The scarcity of data available to provide insight on HPV natural history over shorter time frames is a major limitation to an accurate understanding of

Table 1. Epidemiologic Studies Evaluating Recurrent Detection of Type-Specific HPV Following a Period of Non-Detection

Column1	Study Population	Sample Size at Risk of Recurrence	HPV Detection	Age	Mean Follow-Up	Sampling Interval	Incidence or Proportion of Recurrent Detection	Cumulative Proportion with New Partner	Recurrence Associated with New Partner?
Trottier, *et al*. Cancer Res 2010; 70 [21]	Ludwig-McGill Cohort Study, Brazil	566	MY09/11 PCR; 38 types	mean 32.7 (18.59)	59.0 months	Y1: every 4 months Y2+: every 6 months	all types 1.5 (0.9-2.3) per 1000 woman-mo	19.3%	3.7 (1.1-13.8)[a]
Insinga, *et al*. CEBP 2010; 19 [6]	Placebo arm of Merck Protocol V501-012 Gardasil trial	827	Merck PCR; 9 types	16-23	up to 48 months	every 6 months	8.2% (est from Table 4)	16.3%	Not significant, no estimate reported
Rodriguez, *et al*. Int J Cancer 2011 Epub ahead of print doi: 10.1002/ijc.27418	Guancaste Cohort Study, Costa Rica	1052	MY09/11 PCR; 50 types	range 18-84	7.01 years (IQR 6.95-7.05)	yearly or semi-annually	7.7%	not reported	7/81 (8.6%) of reappearing infections occurred in women reporting a new sex partner
Winer, *et al*. CEBP 2011; 20 [4]	University of Washington students	173	PGMY09/11 PCR; 37 HPV types	19.2 (SD 1.5)	24.3 months (SD 15.7)	every 4 months	19.4%	not reported	not reported

[a]Adjusted relative risk (95% confidence interval) of type-specific 're-infection' among women reporting new sexual partners.

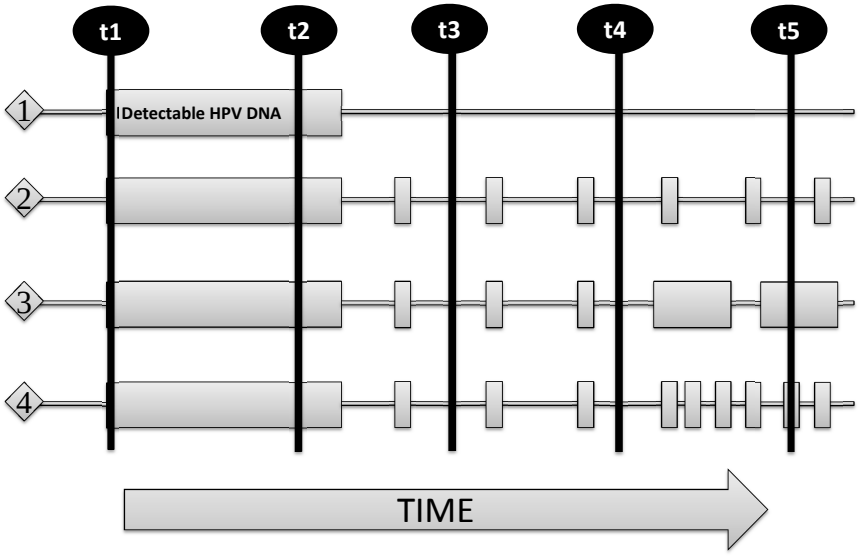

Fig. (1). Illustration of misclassification of HPV infection status in studies with long interval sampling. Four hypothetical women are represented from onset of sexual debut (diamond) through their lifetime of type-specific HPV infection. All women acquire HPV soon after sexual debut. Woman #1 then clears infection sometime between t2-t3, woman #2 has infrequent recurrent detection throughout her life, woman #3 has infrequent reactivation then reactivation with longer duration at later life, and woman #4 has an increase in reactivation frequency (but not duration) in later life. If all women were enrolled at t1, woman 1 & 2 would have no recurrent detection observed, despite periodic recurrence in woman 2. Woman 3 &4 would be found to have a single recurrence at time 5, and the multiple recurrent detection which occurs during the sampling interval would be missed. If all women entered the study at t3, the recurrent events in women 3 & 4 would be misclassified as 'incident' because the past HPV infection was never observed under study follow-up.

the dynamic natural history of HPV. One study of high-risk adolescent girls (n=60, age 14-17 years) has shown that if samples are collected frequently (weekly), the patterns of detection of type-specific HPV are highly variable [10]. A comparison of the point prevalence at study entry and exit with cumulative prevalence across all study visits provides a good illustration of the potential bias in our estimates of HPV infection when using long interval sampled designs; 28.3% and 40.0% any HPV prevalence at entry and exit samples compared with 81.7% ever positive over the 2.2 years median follow-up. We have also observed patterns of short term HPV detection variability in a similar study of 33 monogamously sexually active adult women self-sampling twice per week for 3 menstrual cycles, and found the average duration of detection before return to negative was around 7 days, and we estimated that infection status based on a single swab would underestimate the 16-week cumulative prevalence of high-risk (HR) HPV by 56% (IQR -60.2%--48.8%) [Su-Hsun Liu and Patti Gravitt, personal communication].

These data suggest that the 'true' duration of HPV infection is shorter than commonly reported. This is likely the case for the duration of 'detectable' HPV DNA. However, as Weaver, *et al.* have reported, re-analysis of "HPV negative" samples flanked by positive samples using highly sensitive PCR techniques identifies the presence of very low copies of viral DNA [11]. In fact, total median duration of detectable HPV16 infection increased from 428 days (SD 852.5 days) using standard HPV Linear Array tests to 1,022.5 days (SD 943.7 days) using more sensitive type-specific nested PCR assays. Thus, it appears that standard epidemiologic study designs and HPV detection methods lead to both overestimation of the duration of detectable runs of HPV and to underestimation of the true duration of HPV carriage. Even after HPV DNA becomes undetectable using super sensitive nested PCR from exfoliated swab samples, the negative test result does not preclude the retention of a few quiescent HPV-infected cells in the basal stem cell pool. In this case, in the absence of microdissection and genotyping every basal epithelial stem cell, it would be impossible to prove eradication of infection.

THE ROLE OF HOST IMMUNITY IN HPV LATENCY AND REACTIVATION

Recently, Doorbar, *et al.* reported an increase in ROPV reactivation following immune suppression of latently infected rabbits [12], suggesting a role for host immunity in suppressing viral reactivation. There are several studies suggesting a similar role of immune control of papillomavirus latency in humans. First, HPV-associated cancers are increased in patients with HIV-associated immune suppression and iatrogenic immune suppression following organ transplant [13]. Few studies have evaluated the natural history of cervical HPV infection in transplant patients, but there is an abundance of data to show the effect of HIV-mediated immune suppression on the natural history of HPV infection. It has long been shown that HIV-infected women have both a higher incidence and a longer duration of HPV infection compared with HIV-uninfected women [8]. Generally, persistence of infection was attributed to the immunosuppressive effects of HIV, but the higher rates of incident infection were attributable both to a loss of protective immunity against re-infection and a higher sexual risk profile in HIV-infected compared with HIV-uninfected women. However, recent data from two large natural history studies of HPV in HIV-infected women are strongly suggestive that HIV infection leads to loss of immunologic control of infection with more frequent reactivation of longer

duration. Both the Womens Interagency HIV study (WIHS) and the HIV Epidemiology Research Study (HERS) are large prospective studies of HIV-infected and 'risk-matched' HIV-uninfected women which have evaluated cervical HPV outcomes over an extended follow-up interval. Table **2** summarizes evidence from each study supporting a critical role for T-cell mediated immunity in suppressing HPV reactivation. To determine the possible influence of HIV on HPV reactivation, Strickler, *et al.* compared the cumulative proportion of new HPV DNA detection among sexually active women and women with at least 18 consecutive months of sexual abstinence in the WIHS [8]. The rate of new HPV DNA detection in sexually abstinent women without HIV infection was 5%, strikingly similar to the rate of recurrent type-specific detection observed in the studies in Table **1**. The rates of new HPV DNA detection in the sexually abstinent HIV-infected women were higher, and increased as the CD4 T-cell count dropped, from 13% in the most immune competent to 22% in the most immune compromised HIV-infected women. Theiler, *et al*, went one step further by reporting recurrent detection of type-specific HPV DNA following a period of non-detection among women reporting no current sexual activity in the HERS [9]. Rates of recurrent detection of HPV16 were 2.7/100 woman-years and 3.3/100 woman-years in sexually abstinent and sexually active women, respectively. Because women in both of these studies had similar baseline risks of past HPV infection (similar distribution of numbers of lifetime sex partners in WIHS and similar HPV seroprevalence in HERS) and by design removed any influence of unmeasured behavior of male sexual partners, the strong associations between new or recurrent HPV DNA detection and markers of immunity suggest a critical role for a competent T-cell immune memory in controlling HPV reactivation. Two studies evaluated HPV detection in periods before and after HIV acquisition and found that new HPV DNA detection increased rapidly (i.e., within weeks) following HIV-acquisition [14, 15]. Because HIV is known to rapidly obliterate the tissue-resident memory T-cell pool in the mucosal epithelium within weeks of infection [17, 18] the data from Wang and Nowak suggest more specifically that resident HPV-specific memory T-cells may be important in the control of HPV latency. Since activated memory T-cells contain the CCR-5 HIV co-receptor, a mechanism of HPV control through tissue resident memory T-cells may help to explain the recent reports of an increase in HIV acquisition among HPV positive women and men [16, 19-22].

It is likely that more subtle, and possibly transient, forms of immune suppression also contribute to HPV reactivation. For example, a study of women over age 45 years in Guanacaste, Costa Rica reported that 21% of new HPV detection could be attributed to a reduced lymphoproliferative response to *in vitro* antigenic or mitogenic stimulation of PBMCs, and this was the only factor associated with new HPV detection among women who were not currently sexually active [23]. We have shown that 85% of all newly detected HPV in women aged 35-60 years occurred in sexually abstinent or monogamous women, and that the population risk attributable to a higher number of lifetime sex partners was higher than that attributable to new sex partners in this population (PAR 71.7% and 13.0%, respectively) [24]. This data, in combination with studies showing an increase in HPV prevalence and incidence at older ages [25], suggest that the menopausal transition may represent a vulnerable window for immune suppression (possibly hormone-mediated) and HPV reactivation. In addition, the increased risk of HPV recurrence in patients with recurrent respiratory papillomatosis (RRP) [26] and the higher prevalence of HPV and cervical neoplasia reported in women with autoimmune conditions such as lupus [27], highlight additional populations who might contribute significantly to our understanding of the mechanisms of immune control of HPV infections.

IMPLICATIONS OF HPV LATENCY

Because the clinical and epidemiological communities have not systematically evaluated HPV latency, the clinical implications of a reactivated *vs* a recently acquired HPV infection are not clear. Certainly the increased risk of high grade neoplasia and cancer among HIV-infected and iatrogenically immune suppressed transplant recipients suggest that a reactivated infection carries a similar disease risk to a new infection. In addition, the high prevalence of high-risk (HR) HPV and low grade cytological abnormalities in these patients results in a high proportion of positive screening tests in the absence of detectable high-grade lesions [28]. The resulting management of these frequently recurrent low grade lesions creates a burden and inefficiency of standard screening practices in these patient populations [29].

Outside of the HIV and transplant populations, few other populations have been identified as being at high risk of reactivation. As reported earlier, there is mounting evidence that HPV reactivation, like other latent DNA infections, may increase at older ages. Many argue that the low prevalence of HR-HPV and cytological abnormalities in older women, as well as the plateau in incidence of invasive cervical cancer after age 55 [30], suggest that even if HPV reactivates at older ages, there is minimal disease risk in the post-menopausal woman. However, we must remind the reader that reactivation risk will be directly proportionate to the total burden of past HPV infection. The populations of women in the United States and United Kingdom which contributed data to the older age groups until now all had sexual debut well before the sexual revolution that occurred from 1965-1975. Rates of sexually transmitted infections, including HPV, doubled during this time period. As such, the women we have observed during menopause to date were likely to have at least half the risk of HPV reactivation as women who are now entering menopause (because they were half as likely to ever be infected). Because of this cohort effect, we cannot rely on past epidemiological data or clinical observation from older women to predict the HPV and associated disease risk that will occur in the large population of women who will enter the menopausal transition in the next ten years with twice the lifetime HPV prevalence as previous generations. The possible impact is particularly troublesome given the well-documented problems associated with screening and diagnosis of HPV and associated lesions in the post-menopausal woman [31-36]. Acknowledging that reactivation might account for a higher proportion of new HPV detection in older women, investigators evaluated the risk of CIN2/3 in the Guanacaste cohort following new HPV detection in younger and older

Table 2. Epidemiologic Studies of HIV-Infected and HIV-Uninfected Sexually Inactive Women Supporting a Critical Role for T-Cell Immunity in Suppressing HPV Reactivation

		Strickler, *et al.* J Natl Cancer Inst 2005; 97 [8]		Theiler, *et al.* Obstet Gynecol 2010; 115 [6]	
		HIV-Positive	HIV-Negative	HIV-Positive	HIV-Negative
		n=1848	n=514	n=634	n=264
Age	<26	8%	17%	58.0%	58.7%
	26-29	10%	12%		
	30-35	28%	24%		
	36-45	44%	39%	37.5%	36.4%
	>45	10%	7%	4.4%	4.9%
Lifetime sex partners	0-4	22%	20%	not reported	
	5-9	18%	22%		
	10-49	32%	37%		
	50+	27%	21%		
HPV seropositive*	not reported			98.3%	93.2%
New HPV detection in absence of sexual activity				HPV16: 3.3/P-Y	
		CD4>500: 13%		HPV18: 3.8/P-Y	
		CD4 200-500: 18%	5%	HPV31: 1.1/P-Y	
		CD4<200: 22%		HPV35: 0.6/P-Y	
				HPV45: 3.7/P-Y	
Evidence for association with immune suppression		Increasing incidence with decreasing CD4+ T-cell count		HIV-infected women 1.8-8.2 times more likely to have recurrent shedding than HIV-uninfected	

*Seropositive for HPV16, 18, 31, 35, or 45.

women [7]. They conclude that reactivation carries no unique risk compared with new infection. However, given the limitations of screening and diagnosis of pre-invasive lesions using standard screening algorithms, the risk of a higher proportion of undiagnosed lesions in the older population cannot be ruled out. Longer term follow-up with invasive cancer endpoints in this extensively followed population will be important to clarify the risk of cervical disease following HPV reactivation in older women.

In addition to the clinical implications of HPV latency, there are potentially important policy implications to continued disregard of the possibility of lifelong HPV infection as a latent infection at risk of reactivation. The development of cervical cancer screening and HPV vaccine policy and guidelines are guided by evidence-based review of the literature and mathematical prediction modeling. The issues raised in the section "The Influences of study design on HPV natural history inference" are most important in this context. Multiple parameter sets can provide a good fit to observed data, but inappropriate attribution of a model can lead to ineffective or possibly even harmful interventions. To this end, an unbiased evaluation of multiple possible models and collection of data to fill influential data gaps is prudent given the billions spent on global cervical cancer prevention.

SUMMARY

HPV and cervical cancer has served as a model for rapid and effective translation of research to practice. The interdisciplinary efforts that contributed to the success are arguably unparalleled. It is thus incredible that a consensus on whether HPV is a lifelong latent or transient infection has proven so elusive. In part, this can be attributed to the lack of molecular tools to definitively distinguish a latent from a recently acquired infection. We have faced similar methodologic challenges in the past - HPV is not readily culturable, it cannot infect other animals, and few other mammalian papillomaviruses infect and cause disease in the genital tract of their hosts. Despite these limitations, the research community relied heavily on overwhelming circumstantial evidence to move the field forward in the face of uncertainty. Understanding more clearly the longer term implications of HPV latency on a highly infected and aging population is of paramount importance, and the influence of latency and reactivation must take a central role in interpretation of both epidemiological and clinical observations moving forward.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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