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Human Papilloma Virus (HPV) Infection and Non-Cervical Oncogenic Disease States

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Abstract

Human papillomavirus (HPV) infection is causative for cervical cancer and has been implicated in cancers at other sites. We review the English language literature in regard to the epidemiology of HPV infection as a risk for non-cervical cancer with a focus on the molecular evidence to support HPV having an etiologic role at each anatomic site. HPV DNA is detected in and/or serology provides evidence that HPV is associated with 35-50% of penile cancers, 80-95% of anal cancers, and ~35% of oropharyngeal cancers. HPV has also been implicated for cancer of the larynx, esophagus, lung, and urinary bladder with varying levels of linkage. Molecular studies at the respective anatomic sites provide evidence of HPV integration, E6 and E7 oncogene expression coupled with tumor suppressor down-regulation consistent with a role in the pathogenesis of tumor formation. HPV-associated cancer may represent a distinct disease entity relative to non HPV-associated cancers based upon natural history and outcome studies. Thus, the disease burden of HPV associated non-cervical cancers may be significant and justifies a comprehensive investigation of the utility of global prophylactic vaccination strategies.

Keywords Human papilloma virus; Vaccination; Penile cancer; Laryngeal papillomatosis; Anal cancer; Esophageal cancer; Lung cancer; Bladder cancer; P53; P16; E6 Oncogene; E7 Oncogene; Prostate cancer

Introduction

Human papillomavirus (HPV) is the most prevalent sexually-transmitted infection in the United States. Of the over 100 HPV genotypes, approximately 60 are considered pathogenic for the genital tract and are classified by oncogenic potential. High-risk genotypes, including HPV16, 18, and 33, are more commonly associated with cancers, whereas low-risk types such as HPV6 and 11 typically cause genital warts [1,2].

HPV is causative for cervical and vulvar cancer. In contrast, although HPV has been documented in cancers at other anatomic sites [3], there is not universal agreement as to the role of HPV in the pathophysiology of carcinomatous transformation. While evidence is strongly supported for a role of HPV in anal squamous cell cancer and for cancers of the head and neck, HPV as an independent risk factor for cancers at other anatomic sites is less clear. Moreover, some data has suggested that HPV-associated non-cervical tumors may represent distinct clinical entities than non-viral associated tumors [4]. This paper reviews the epidemiology, molecular basis, and clinical outcome for HPV-associated cancer, focusing on sites other than the female genital tract.

Methods

The English language literature was reviewed using Entrez-PubMed with search terms combining HPV, E6, and E7 and each respective cancer. All papers related to each tumor type were reviewed and articles were selected based on a sufficient sample set and methodological controls. When there was content duplication, representative articles were selected that addressed key issues of epidemiology of disease, molecular associations, and genotype specificity

Anal Cancer

Anal cancer presents primarily between the ages of 60 and 70, with an earlier peak among men who have sex with men [5]. While some studies have found a gender bias towards women with a 2-fold increase in incidence than men [6], or predominate in women [7], others studies have found that the rates of anal cancer are relatively equivalent between genders [8]. The incidence of anal cancer ranges from 1.2-1.3 [9] to 2.04-2.06 cases per 100,000 individuals [8]. Squamous cell cancer (SCC) accounts for 80% of cases, with adenocarcinomas, basal cell carcinomas, and melanomas accounting for the remainder [8,10]. Anal SCC develops from precancerous anal intraepithelial neoplasia (AIN), with AIN classification mirroring that for cervical intraepithelial neoplasia (CIN) and based on the extent of epithelial dysplasia and penetration [6].

HPV is detected in greater than 80% of anal SCC [6, 10-12], with two studies utilizing high-sensitivity assays demonstrating 90-100% detection [7,13] (Tables 1 and 2). Whereas HPV was absent in control samples of normal epithelial tissue and hemorrhoidal biopsy specimens [12]. Non-SCC tumor types had significantly lower HPV prevalence [10]. Multivariate risk factors for HPV-associated anal cancer include a history of persistent HPV infection, especially persistence of high-risk oncogenic genotypes, infection with multiple HPV genotypes, receptive anal intercourse, presence of anal condylomata, HIV co-infection (with a greater risk for those with a low CD4 count), immunosuppression in general and solid organ

transplantation in particular, cigarette smoking, and younger age [5,7,10] (Table 2).

For women a systematic review of the literature of anal carcinoma notes a prevalence of high-risk HPV types ranging from 4-85% among HIV negative women and 16-85% among those HIV-positive, although the study did not differentiate histologic type in relation to HPV presence [14]. Veo et al. in a study of 117 women with cervical cancer, cervical sampling detected HPV16 in 66.7% of cases and HPV18 in 7.7% of cases with anal canal samples yielding HPV16 in 59.8% of women, with simultaneous presence of HPV in the cervix and anal canal detected for 53.8% of whom 19.2% had E6 oncogene expression in anal and cervical biopsy samples [15]. Similarly, Slama et al in a study among HIV-negative women detected anal HPV in 42.4% of women with high-grade cervical lesions [16]. While penetrative anal intercourse had the greatest association for HPV detection in anal samples (OR 3.87) on multivariate analysis, any any anal sexual contact including non-penetrating anal contact remained a significant risk (OR 2.62); other independent risk factors included >5 lifetime sexual partners (OR 2.43) and smoking>60 cigarettes per week (OR 2.33) [16]. Among HIV positive women with high CD4 counts and well controlled infection, Hasegawa et al. found that the presence of cervical squamous intraepithelial neoplasia predicted anal intraepithelial neoplasia with an OR of 4.2 [17]. Thus, cervical HPV infection represents a marker for the anal HPV infection in women with a significant proportion of anal samples demonstrating active oncogene expression. Risk factors associated with anal carcinoma are summarized in Table 1 for both men and women.

Risk factor	Odds Ratio
Penetrative anal intercourse: women	3.87
Penetrative anal intercourse: men	6.8
Any anal sexual contact	2.62
≥ 5 lifetime sexual partners	2.43
Smoking	2.33
Presence of cervical intraepithelial neoplasia	4.2
Immunosuppression: corticosteroids	3.2
Corticosteriod use in men not exclusively heterosexual	5.6
Genital warts	7.4
HIV infection	6.8

Table 1: Independent risk factors for squamous cell cancer of the anus in women and men. Risk factors are modified from Slama et al. [16], Hasegawa et al. [17], and Uronis and Bendell [5]. Additional independent risks have been reported to include anal presence of HPV, especially high-risk HPV types; immunosuppression, especially organ transplantation; and younger age [5]. Receptive anal intercourse was reported as an independent risk for both heterosexual women l [16] and homosexual men [5], data for men who are not exclusively homosexual are similar to that reported for women, whereas data for men who exclusively have sex with men are significantly greater.

With respect to genotype, HPV16 is found in 92-100% of HPV-associated anal cancers regardless of histologic type [6,7,10-12], with multiple high risk types commonly detected [6-11], although others have reported that while HPV16 is predominate it is found in a lower percentage of cases [18,19] (Table 2). In contrast, low risk types HPV6 and 11 are associated with AIN I and II [6,10]. A longitudinal study of HPV anal infection among HIV infected men who had sex with men found that while spontaneous lesion regression and HPV clearance was in general uncommon, those with E6-specific CD4+ T-cell responses had a high rate of clearance [20].

HPV prevalence		Histology	Primary HPV type	Secondary HPV types
Anal	80-100%	Squamous cell	16	
Bladder	0-80%	Transitional cell	16	6, 11, 18
Esophageal	0-100%	Squamous cell	16	
Laryngeal	8-59%	Squamous cell	16	
Lung	20-25%	Adenocarcinoma	16	6
	21-55%	Squamous cell	16	18, OHR
Oropharyngeal	20-58%	Squamous cell	16	18, OHR
Penile	15-92%	Basaloid	16	6, 11, 18, OHR
Prostate	12-75%	Adenocarcinoma	16	

Table 2: HPV prevalence, histologic type, and genotype associated with cancer by anatomic site. HPV prevalence is based on composite of epidemiologic studies. Histology type is that primarily associated with HPV positive cancers. For anatomic sites for which HPV 16 represents <90% of HPV genoptypes, secondary HPV genotypes are given; OHR: Other High Risk Genotypes.

Molecular studies have found sequence variation of the HPV E7 oncogene, which controls binding to the retinoblastoma (Rb) tumor suppressor, in anal SCC [12]. Also HPV E6 variants have been shown to correlate with high-grade disease through down-regulation of the p53 tumor suppressor [21]. Immunofluorescence studies have shown strong nuclear expression of the cyclin-dependent kinase inhibitor 2A (CDKN2A or p16) with concomitant loss of Rb and p53 tumor suppressor activity among HPV-positive anal tumors [11]. In HPV-positive tumors, expression of CDKN2A directly correlated with E7 mRNA expression [22].

Numerous groups have investigated the correlation between molecular markers of HPV infection and disease outcome for anal SCC (Table 3).

Tumor type	Molecular correlates of disease	Outcome in relation to HPV status		
		Improved outcome	Worse outcome	No outcome difference
Anal	p16INK4a expression	[23]	[24]	[22]
	p16INK4a levels			
	MCM7 expression			
Bladder	Clinical association		[52]	
	p53 mutations		[59]	[60]

Esophageal	Tumor grade	[130,134,136]	[135,140]	[141]
	Telomere length		[147]	
Lung	p53 expression	[107,108]	[96,99]	
Oropharyngeal	E7 expression	[84,85]		
Penile	Survival for HPV presence	[32]	[27]	
	p53 expression		[49]	[50,51]
	p16INK4a expression		[50,51]	
Prostate	E7 expression		[68]	[71]

Table 3: HPV infection and the risk for cancer progression in relation to molecular markers. For each tumor type, studies showing the respective outcome, either life expectancy or disease progression, for HPV positive tumors versus HPV-negative tumors are provided. Molecular correlates of when studied are cited; otherwise differences are based on clinical observations. For esophageal cancer, each of the molecular markers that have been studied with respect to outcome in relation to HPV infection are considered independently.

Expression of p16 was a marker of increased survival and disease-free progression in one study [23], versus a risk for poor prognosis and occurrence of distant metastases in a second study [24], but was indifferent to outcome in a third study [22]. The association between p16 and disease outcome is further clouded as one group found that high levels of expression correlated with a poor outcome relative to those with absent or low levels of expression [25] whereas a second study found the opposite result that a high level of p16 expression was protective on univariate analysis but had no prognostic significance on multivariate analysis [26]. Expression of minichromosome maintenance complex component 7 (MCM7), whose expression is regulated by the transcriptional regulator E2F, correlated with relapse-free survival following standard treatments [22].

Penile Cancer

Squamous cell cancer (SCC) of the penis is rare, with an incidence in the United States of 0.7-0.8 cases per 100,000 [9], and highest among men in their sixties [27]. Penile cancer has a five-year survival probability of 75-93% in the absence of metastases and provided that surgical resection has been performed [28].Formal epidemiologic studies of HPV infection as a risk for penile cancer are lacking. The prevalence of HPV DNA in penile cancers varies widely between 15 and 55% [27, 29-34], but has been detected in 92% of cases of carcinoma-in-situ [30]. HPV prevalence differs by histologic type with basaloid, warty and mixed tumor types having higher rates of HPV detection (45-100% of cases) versus keratinizing and verrucous tumor types (35% or less) [27, 29, 31, 33-35] (Table 3). In fact, a recent comprehensive review of HPV and its role in penile cancer confirmed this histologic differentiation and noted two distinct etiologic pathways of disease: one related to HPV infection and the other with phimosis as the major risk factor for penile cancer [36] (Table 4). Technical factors may affect the detection of HPV, as stored tissue blocks appeared to have lower yields inversely correlating with storage time [27,31].

Anatomic site	Risks
Lung	Female non-smokers: greater risk for HPV infection Male smokers: greater risk for non-HPV related cancer
Oropharyngeal	Anatomic difference versus HPV status Oropharynx, especially base of tongue & tonsils are typically HPV associated Oral cavity, lips, salivary glands are typically non-HPV associated Epidemiologic risks versus HPV status HPV related: sexual factors (number lifetime partner, oral sexual practice) Non-HPV related: alcohol use, smoking
Penis	Basaloid histology type: primary risk is HPV infection Keratinizing and verrucous histology type: primary risk is phimosis

Table 4: Tumors with distinct risks based on HPV status. For the tumors listed above, HPV-positive tumors appear to represent distinct clinical entities with separate primary risk factors as delineated. Additionally, for esophageal and lung cancer there is a marked geographic variation in cancer rates with Asians having greater association with HPV infection.

Incident infection and clearance of HPV of the penis has been examined relative to circumcision status in two longitudinal studies with follow-up for 15-17 months [37,38]. Overall, incident infections of HPV did not vary although non-significant differences were noted in specific genotypes in one study [37]. And, while the rate of clearance did not differ between circumcised and uncircumcised men, the time to clearance was significantly shorter among circumcised men: 154 versus 91 days [38]. HIV status was examined with respect to HPV infection types and persistence in one study that examined 144 HPV positive men of whom half were HIV positive with samples taken at baseline and 6 months [39]. Overall, rates of HPV persistence were similar and high for both HIV positive (69.5%) and HPV negative men (66.9%). Notably, HIV infected men were more likely to have persistence with high-risk genotypes and to have multiple HPV genotypes detected.

HPV16 is the most common genotype found in penile cancer, detected in 52-80% of tumors [27,30-34]. In contrast to cervical cancer, HPV18 was no more prevalent than other high-risk genotypes, and there was a higher frequency of low risk genotype HPV6 [27,31,32,34,40] (Table 4). There was no apparent correlation between genotype and histologic subtype [29,33]. However one study from Brazil found that HPV11 was more common in pre-cancerous lesions (80%) with HPV16 and HPV31 and next most common (25% of lesions each) although in cancers, HPV16 still predominated (63% of tumors) followed by HPV11 (34% of tumors) [41].

Genomic profiling of penile carcinomas documented HPV integration at 9 of the 19 chromosomal sites associated with cervical cancer oncogenesis, with predilection for sites associated with chromosomal fragility [42]. Studies have additionally noted HPV E6 oncogene expression associated with p53 ubiquitination and breakdown in tumor tissue [43]. The presence of HPV DNA inversely correlated with p53 staining but directly correlated with mTOR expression, a gene within the AKT pathway of tumorigenesis, which was found to be upregulated in HPV-negative tumors [44]. However,

the finding of p53 regulatory differences in HPV related tumors is not universal as others found only that the retinoblastoma protein p16INK4A was associated with HPV positive tumors [45]. Evidence that tumor pathways such as p16INK4a, c-ras and myc are involved in HPV-related penile cancer is lacking [43] and MYC alterations were found at equal prevalence among HPV-positive and negative tumors [42]. Finally, upregulation of cyclooxygenase (COX-2) expression, implicated in the pathogenesis of cancers at other sites [46,47], has been demonstrated in some specimens [48]. Molecular correlates of disease outcome have been found with p53 expression inversely correlating with regional lymph node metastasis and survival [49] while others have found that p16INK4a allelic loss or promotor hypermethylation and not p53 was associated with negative clinical outcomes [50,51]. (Table 3) Observed survival differences has led to the postulate that HPV-positive and negative tumors represent different clinical entities [34,43]. However, studies have disagreed as to whether HPV affects the prognosis of penile cancer. While some have reported a significant survival advantage [32], others found that HPV presence correlated with local and nodal metastases [27], suggesting a poorer outcome.

Bladder Cancer

A 1997 review found that transitional cell cancer of the bladder was infrequently associated with HPV infection, with HPV DNA detected by PCR in approximately 10% of cases overall, although prevalence ranged as high as 80% in some studies [52].More recently, three separate subsequent meta-analyses examined the relationship between HPV infection and bladder cancer. The paper by Wiwanitkit et al. included 5 studies between 1993 and 1996, Jimenez-Pacheco et al. included 21 studies between 1991 and 2010, and Yang examined 52 studies and restricted their analysis to 19 studies over the time range of 1991 to 2010 [53-55]. Each of the three studies found a significant risk for bladder cancer associated with HPV infection with pooled OR ranging between 2.13and 2.84. HPV16, and to a lesser extent HPV18, were the most common HPV types in cancer tissue [52] . Geographic variation was striking as evidenced by two studies from North Africa with HPV DNA was detected in 22 (52.4%) of 43 of fresh bladder cancers from Moroccan patients whereas HPV DNA was not detected in any of 125 formalin fixed bladder cancers among Tunisian patients [56,57]. One study found that HPV risk for bladder cancer was greater than for non-smokers [58]. HPV6 was frequently associated with condylomata of the bladder, with HPV6 and 11 occasionally detected in bladder cancer.

HPV-associated tumors were more aggressive with poorer outcomes [52]. High-grade cancers were associated with p53 mutations that correlated with the presence of high-risk HPV types 16 and 18 [59], although the correlation between p53 status and outcome for HPV-associated bladder cancer was not universal [60] (Table 3).

Prostate Cancer

The role of HPV in the development prostate cancer is one of least well defined of urogenital sites. The epidemiology was explored in two meta-analyses of which one found no increase in risk for HPV infection and prostate cancer, although there was higher prevalence of HIV-16 in cases suggesting a possible relationship [61] whereas a second study found that HPV-16 in contrast to HPV-18 was significantly associated with a risk for prostate cancer [62] (Table 2). Case control studies from South Africa, Sweden, Saudi Arabia, and the US failed to show evidence of a relationship using a combination of serology and DNA detection in prostate cancer tissue [63-66]. In contrast, other studies have reported varying rates of HPV DNA in prostatic cancer tissue ranging from 12.5% in a study from Tehran Iran [67], an Argentinian study with HPV E6 expression detected in 41.5% of samples (17 of 45) of prostate adenocarcinoma, an Italian study that found that 112 (74.7%) of 150 paraffin embedded tumors demonstrated E7 expression [68], and a Greek study of prostate cancer tissue samples in paraffin blocks with HPV DNA in 16% of tumors versus 3.3% of normal tissue from patients without cancers [69], while cases of prostatic hyperplasia were negative [70]. In contrast to tumors at other sites there was no association with p53 codon polymorphism [69]. E7 expression was negatively correlated with survival [68] (Table 3). Finally, Tachezy et al also found no difference in the seroprevalence rates for the E6 and E7 oncoproteins between cases and controls; and the rate of HPV DNA detection in prostate cancer was the same (2%) as that for normal tissue that they concluded showed no pathophysiologic role in tumirogenesis but indicated that the prostate may serve as a reservoir for HPV infection [71]. Thus, the role of HPV infection in prostate cancer remains unproven.

Oropharyngeal Cancer

In the United States, cancer of the oral cavity and pharynx disproportionately affects males, with an incidence of 15.5-15.9 cases per 100,000 men versus 5.7-6.0 cases per 100,000 women [9]. Less than 50% of patients with advanced oral or oropharyngeal SCC survive past 5 years [72].

An etiologic role for HPV in cancer of the head and neck was posited in the early 1980's, when Syrjänen noted histologic and morphologic characteristics shared with HPV-associated genital tumors [73,74]. Subsequent serologic and PCR-based studies provided further evidence of association, although HPV was detected in only a fraction of tumor samples. More recent work has shown that while HPV is detected in a minority of cancers (~25%), there is a clear niche preference for the oropharyx [75] versus oral cavity [76] (Table 4). Additionally, HPV-related cancers of the oropharynx had a predilection for the base of the tongue (41.1% HPV positive) and tonsils (58.1% HPV positive), but was absent from cancers of the lip or major salivary glands [76] (Table 2).

Among HPV-positive tumors of the head and neck, HPV16 is detected in approximately 90% of oropharyngeal cancers and approximately 75% of oral cavity tumors [4,75,77]. High-risk genotypes HPV31, 33, and 35 were also frequently reported, with numerous cases infected with multiple HPV genotypes [4,75,77]. Gender differences in the incidence of oropharyngeal cancer have been found to parallel

HPV rates by some but not all investigators. Ryerson et al., reported an incidence for oropharyngeal and oral cavity cancers of 4.5 cases per 100,000 individuals for men and 1.7 for women [78]. In contrast, Smith et al. found no gender difference in the prevalence of HPV positive tumors [76]. Ryerson found that between 1998 and 2003, the rate for cancer of the base of the tongue and tonsils, two cancers with a higher likelihood of HPV-relatedness, increased 150-175% and inferred a causal role for HPV [78]. Ernster et al., using United States cancer registry data from the Denver metropolitan area, found a similar rise in oropharyngeal cancers in men from 1980 to 2004, but no change in cancer rates for women [79]. Moreover, while the rates of HPV-negative tumors were relatively static for both genders, HPV-positive

tumors increased 10-fold for men and 4.5 fold for women over the 25-year period [79].

There is a growing consensus that SCC of the head and neck represents distinct disease entities dependent upon risk group and HPV presence or absence (Table 4). Multivariate studies find that smoking, alcohol consumption, HPV seropositivity, sexual practices, and a greater number of lifetime oral and vaginal sex partners represent significant risks for cancer of the oral cavity and oropharynx [75,76,80-83]. While alcohol and tobacco exposure represent risks for HPV-negative cancers, sexual risk factors were linked to HPV-positive tumors [4,75,76,80] whereas HPV-positive cancers show no linkage to tobacco or alcohol use on multivariate analysis [75,81]. The 5-year survival for HPV-positive head and neck SCC is 71% versus 49% for HPV-negative tumors [84], with others reporting similar results [85], although, one group reported the survival benefit to be restricted to males [84]. Seroreactivity to the E6 and E7 oncogenes is associated with a 12-fold greater adjusted odds ratio for cancer risk relative to seronegative individuals, whereas seroreactivity to the L1capsid protein was not predictive [81]. Microarray genomic analysis demonstrated that HPV-negative tumors carried alterations in four distinct host cellular chromosomal regions not found in HPV-positive tumors [86]. In contrast, HPV-positive tumors express a variety of cell cycle genes expressed during meiosis, which correlate with E6 and E7 [87]. In cervical cancer, HPV16 E7 oncogene inactivates the pRB retinoblastoma tumor suppressor protein, allowing for an increase in the cyclin-dependent kinase inhibitor p16INK4a [88,89] (Table 3). This finding was replicated in HPV-positive oropharyngeal cancer specimens, and was associated with greater survival and lower recurrence rates versus HPV-negative tumors [85].

Laryngeal Papillomatosis, and Laryngeal Carcinoma

Laryngeal or respiratory papillomatosis (RP) is a benign tumor of the upper respiratory tract with juvenile and adult forms [90]. HPV has been detected in 76.2% of adult cases, typically associated with low-risk genotypes, particularly HPV6 and 11 [90]. While airway obstruction poses the greatest risk, a small number of cases may undergo malignant transformation into SCC [90].

Unlike adult laryngeal papillomatosis, the link between HPV infection and laryngeal carcinoma is less clear. The incidence of laryngeal cancer in the United States was 7.1-7.4 cases per 100,000 men, and 1.5-1.6 cases per 100,000 women [9]. HPV detection in laryngeal carcinomas ranges from 8.0-58.8% [90], with HPV16 as the most common genotype [90] .

Studies have demonstrated a potential genetic linkage to disease progression for RP, as HLA-DRB1*0102 was seen at higher frequency among those with cancer than HLA-DRB1*0301, DQB1*0201 and DQB1*0202 [91]. The differential expression of host genes supports a dominant Th2-like adaptive immune response [92]. Moreover, such patients typically manifest lower interferon-gamma (IFNγ) responses against the E6 oncoprotein of HPV11 [91]. Malignant transformation has been postulated to occur through upregulation of Rac1 by epidermal growth factor that mediates COX-2 expression [93] through phosphatidylinositol-3 kinase [94].

Lung Cancer

HPV had been postulated in the etiology of cancers of the respiratory tract since the mid-1960's [95]. Causality was inferred in earlier studies that showed a linkage between serology and lung cancer and the finding of HPV in tumors by immunofluorescence for 21.7% of cases [95]. There has been a notable geographic variation with Asian studies finding that 33.3-45% of non-small cell lung cancers were HPV DNA positive [96-98], and a similar prevalence was detected in a Chilean study [99] (Table 4). In contrast, among Western populations studies from Norway, Finland, Italy, and the United States found no correlation with HPV [100-103]. In high-risk regions, HPV DNA is detected in almost 55% of squamous cell lung cancers, versus 20-25% of adenocarcinomas [97,98] (Table 2) and more prevalent in males than females [97,98]. A comprehensive, systematic review of the literature examined the role of HPV in never smokers with lung cancer [104] (Table 4). Authors were contacted to provide information regarding smoking status if not provided in the primary references. As above there were significant geographic differences with the rate highest in Asia and lowest in Western countries, and even regional differences within the same country. None of the studies resolved the question of second-hand smoke as a confounder.HPV16 is the predominant HPV genotype detected, with other high-risk types comprising the bulk of the remainder of pulmonary SCC, whereas HPV6 is predominant in a small number of adenocarcinomas [99] (Table 2). Moreover, tumor cells actively shed virus, although with viral loads many logs lower than for cervical cancer cells [98,99,105].

HPV chromosomal integration has been demonstrated among HPV-positive lung cancers [98,99,105], along with cellular expression of HPV oncogenic proteins [96,97]. HPV infected lung cancer cells demonstrate inhibition of the tumor suppressor p53 and increased IL-6 production, the latter which appears to be induced via expression of the antiapoptotic protein Mcl-1, a finding documented for paraffin embedded tissue samples and then confirmed for the A549 adenocarcinoma cell line [106]. The presence of HPV DNA inversely correlated with p53 expression [96,99], although other studies demonstrated a direct correlation for SCCA of the lung [107,108] (Table 3). Pro-inflammatory cytokine production of IL-8 and IL-17 is induced in E6 transfected adenocarcinoma cell line H1299 inducing metalloproteinases MMP-2 and MMP-9 upregulating angiogenesis [109]. A549 cells and the human non-small cell lung cancer cell line NCI-H460 transfected with the HPV E6 and E7 oncogenes also induce angiogenesis in mouse xenograft models through upregulation of HIF-1 which in turn promotes vascular endothelial growth factor (VEGF) production [110]. In fact, HPV infected tissue samples were more likely to have endothelial growth factor receptor (EGFR) mutations versus uninfected tissue samples from China [111] a finding also noted in a study of Japanese patient samples [112]. The latter study found non-significant trends in EGFR mutation rates for female non-smokers which was postulated to promote lung cancer for that demographic [112].

Esophageal Cancer

In 1982, Syrjänen reported on a case series of invasive esophageal SCC (ESCC) manifesting morphologic changes similar to cervical cancer, suggesting a etiologic role for HPV [113] further supported by detection by immunofluorescence of HPV antigens within esophageal papilloma keratinocyte nuclei [114]. A large number of studies, including a group of recent meta-analyses have concluded an etiologic role although there are significant geographic differences.

A review of the literature in 2002 noted a wide variation in HPV prevalence ranging from 0% to 100% [115] (Table 2). Overall, 22.9% of samples assessed by *in-situ* hybridization were HPV-positive versus 15.2% tested by PCR [115]. Countries with the highest prevalence of

positive cases were from South Africa and Southeast Asia [115]. A case control study from China of 300 cases of ESCC reported that HPV represented a significant risk for disease with an OR of 6.4 and even higher (OR of 10.3) when the analysis is restricted to the presence of high-risk HPV genotypes [116]. Agreement between studies, even from the same regions was not universal as Chinese study found that 56% of cancers harbored HPV [117] whereas a contemporary Chinese study from the same region reported no association [118]. In Africa, South Africa has reported a high rate of HPV in esophageal cancer as a group from Cape Town detected HPV DNA in 46 of 114 tumor samples (46%) versus only 3 of 41 (7%) of normal tissue samples [119,120]. In Europe, a group from Uppsala, Sweden detected HPV DNA by PCR in 16 or 100 (16%) of esophageal tumors [119,120]. Other conditions such as tylosis, Barrett's esophagus, and basaloid SCC of the esophagus do not appear to harbor HPV [121-123].

A number of recent meta-analyses concluded that HPV does represent a risk for esophageal cancer [124-129] with pooled odds ratios (OR) between 3 and 3.7 although one study calculated a pooled OR of 6.36 for the association of HPV16 to esophageal cancer in China [129]. Differences are considered to relate to methodological differences between studies as well as study design [125].

In contrast, there have been a number of studies that reported a lack of correlation between HPV and esophageal cancer. Methodologic issues were raised as one study detected HPV in both tumor and surrounding normal tissue raising questions about the etiologic role of HPV [130] and a Chinese study that carefully avoided DNA contamination during sample preparation found HPV in only 0.4% tumor samples [118]. And Brazilian study found that while 13% of esophageal tumors were HPV positive, most with HPV16, correlation with molecular markers was negative and concluded that there was no association [131].

There is a growing consensus of a multifactorial pathogenesis for esophageal cancer with environmental, exposure, and infectious etiologies driving tumorigenesis [119,132]. A sero-prevalence Chinese study found that HPV infection increased the risk for ESCC among those with a history of ethanol intake and smoking but did not increase the risk for non-smokers and non-drinkers [133].

Overall, HPV16 has been the most prevalent genotype detected including some investigators who have found only HPV16 [119,120] (Table 2). Other high-risk types, particularly HPV18, have been frequently detected albeit at lower prevalence rates [115,117,134,135]. However, some studies found a substantial number of cases with HPV6, 11, and other low-risk types [117,119,120,130,136]. Although, one group reported that HPV16 and 18 predominated in tumors and precancerous lesions, whereas HPV6 and 11 were most common in normal tissue [137]. In contrast, for esophageal papillomas, HPV6 and 11 predominated while HPV16 was relatively infrequent [138].

Despite the epidemiologic controversies, molecular studies appear to support an etiologic role for HPV in the pathogenesis of esophageal cancer. Greater than 90% of HPV-positive esophageal SCC carry integrated rather than episomal viral forms [135,139], which are associated with excretion of low levels of intact virus [139]. Investigators have reported an inverse correlation between HPV presence and tumor grade [130,134,136] and a Chinese study across different ethnic groups reported a non-significant trend towards higher HPV copy number and tumor grade [140]. Although one case-control study in China found no association between HPV presence and disease progression [141].

Esophageal tumors have increased p16 staining and decreased p53 expression, whereas HPV-negative tumors maintain normal levels of both regulators [142]. Others have found that while p53 expression did not correlate with HPV infection [120,135,142], its homolog p73 was significantly associated [120]. Yang found that esophageal cancer typically harbored mutations at p53 codon 72 [143] and that patients with a single nucleotide polymorphism at rs1042522 conferring either an Arg/Arg or Arg/Pro mutation [144] demonstrated a significant increase in the risk for esophageal cancer but only for those with a history of tobacco and ethanol use. Moreover, However, some reported an association between p53 expression and HPV presence only for HPV16 and not HPV18-associated tumors [134] (Table 3). The role of p16INK4A was similarly at odds between studies. While one study reported that p16 represented a prognostic indicator for overall survival and disease progression, others found no association [135,145]. Other correlates of pathogenesis include the transcription factors AP-1 and Fra-1 that were typically present in HPV-negative tumors but absent in HPV-positive tumors [146]. Finally, telomere length which has been inversely associated with tumorigenesis, was found to be progressively shortened with increasing atypia and further in HPV-associated esophageal cancer tissue that correlated with increasing decline of DNA methylation [147] (Table 3). Moreover, short telomere length represented a further independent risk for HPV related esophageal cancer among those carrying p53 Arg/Arg polymorphisms [148].

Discussion

While HPV is considered causative for cervical cancer, its role at other anatomic sites is less well understood and more controversial. As reviewed here, there is evidence to support a role for HPV in cancers of the anus, oral cavity, tonsils, esophagus, lung, and possibly the bladder. The literature is limited by a relative lack of rigorous case-control or cohort epidemiologic studies at many of the anatomic sites, with the bulk of evidence relying on pathogenic studies that demonstrate the presence or absence of HPV DNA in archived specimens. Detection of DNA from preserved specimens is however subject to contamination during sample preparation unless rigorous procedures are employed.

Cervical cancer represents a single disease state with a clear progression from cellular atypia to invasive cancer. However for cancers of the anus, head and neck, and penis, HPV-associated tumors may be restricted to certain histologic subtypes and ecologic niches. Moreover, studies imply a multifactorial etiology for cancers at many sites, with HPV infection being one of many factors. Tumor grade, survival, and risk factors differ in relation to HPV-presence suggesting that HPV-positive and negative tumors may represent distinct clinical entities.Molecular support for an etiologic role for HPV is evident in the finding of viral integration and E6 and E7 expression in tumor tissue, coupled with differential expression of cell cycle regulators such as p53 and p16. Moreover, the latter has been linked to tumor grade and survival differences, and helps to explain the growing consensus that at many anatomic sites, HPV-caused cancer is a separate clinical condition from non-virally associated disease. The potential number of cancers attributable to HPV would infer a significant case burden. Moreover, HPV-associated cancers of the head and neck cancer, esophagus, and penis are male predominant.

Whether the commercially available bivalent, quadrivalent, and nonovalent HPV prophylactic vaccines can reduce the rates of non-cervical cancer is unknown. Cost-benefit studies that have modeled cervical cancer rates have predicted benefit [149,150]. Studies have also

modeled the effect of bivalent, quadrivalent, and nonovalent vaccines for anal and head and neck cancers – all demonstrating a beneficial role of vaccination [18,151-154], although the high effectiveness assumed by these studies for non-cervical cancers has yet to be borne out and still awaits study.

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