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Review

Human papillomavirus (HPV)-induced neoplasia in the urinary bladder: a missing link?

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Summary. The discovery that the role human papillomavirus (HPV) plays in the induction of human cancer represents an important achievement in oncologic research. It has taken on even greater importance since the development of vaccines, which promise the hope of preventing these cancers from ever occurring. Because of these important implications, many have attempted to determine a possible role for the virus in cancers of the urinary bladder-an organ in close anatomic proximity to the primary sites of HPV-induced neoplasia and one which already has an established oncogenic infectious agent in *Schistosoma haematobium*. Here we review the current literature exploring this possible role in the most common subtype of cancer of the urinary bladder, urothelial carcinoma, and two much more rare histologic subtypes that have well established roles for HPV-induced neoplasia in other anatomic sites-squamous cell carcinoma and adenocarcinoma.

Key words: Urinary bladder, Viral carcinogenesis, Human papillomavirus (HPV), Transitional cell (urothelial) carcinoma, Squamous cell carcinoma, Biomarker

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Introduction

Viral induction of neoplasia has long been known to be a major contributor to the overall burden of cancer on the general population. It is estimated that up to 10-15% of all human cancers are attributable to a viral agent (Moore and Chang, 2010). These cancers are of particular interest for a number of reasons. They allow for a defined approach in determining the cellular and genetic mechanisms involved in oncogenesis. Perhaps more importantly, a known viral agent related to cancer allows for selected screening, monitoring and, ideally, vaccination against the causative agent.

Despite this heavy burden placed on public health due to viral-induced neoplasia, only seven human viruses have been identified as definitive agents involved in this process (Moore and Chang, 2010). The first was the Epstein-Barr virus. Its discovery as an etiologic agent of Burkitt lymphoma in 1964 began the search for more cancers caused by viruses (Epstein et al., 1964). Despite this vigorous search for more, only six others have since been conclusively identified as human cancer viruses: HTLV-1, HHV-8, MCV, HPV, HBV, and HCV (Moore and Chang, 2010). Of these human cancer viruses, there is perhaps none as important from a public health perspective as HPV, the human papillomavirus. The virus is said to contribute up to 10% of human cancers worldwide (zur Hausen, 1996). The identification of this virus as the etiologic agent of cervical cancer (amongst others) has led to successful public health screening and vaccination programs (zur Hausen, 1989; Hendrix, 2008; Assmann and Sotlar,

2011; Cobos et al., 2014).

Because of the significant role HPV is known to play in cervical, anogenital, and oropharyngeal cancers, many have questioned whether the virus might play a role in the development of urinary bladder cancers (Bryant et al., 1991; Anwar et al., 1992; Lopez-Beltran et al., 1996; Lopez-Beltran and Escudero, 1997; Tekin et al., 1999; Weiss, 2008; Cobos et al., 2014). The supposition is indeed logical-the urinary bladder has a direct connection to the genital area through the urethra, providing a natural passageway for viral migration.

We investigated the evidence in the literature relating to this question. In addition, this review was not only limited to the most common form of bladder malignancy, urothelial/transitional cell carcinoma, but explored less common malignancies like squamous cell carcinoma (SCC) and adenocarcinoma of the urinary bladder, as those histological patterns are known to be associated with HPV in other body sites.

The Role of HPV in neoplasia

The mechanism of action for HPV-induced neoplasia has been well studied. This action is primarily controlled by two oncogenes, *E6* and *E7*, which control the production of oncoproteins of the same name (Cobos et al., 2014). HPV E7 inactivates the cell cycle protein Rb1 (the product of the *RB* gene), a tumor suppressor protein (zur Hausen, 1994; Munoz et al., 2003; Subhawong et al., 2009). This disruption of the cell cycle is furthered by the actions of HPV E6. This other oncoprotein serves to degrade the important tumor suppressor protein, p53 (Scheffner et al., 1990). In this manner, HPV works to disable two important tumor suppressor proteins within the cell cycle which leads to the initiation of tumorigenesis in patients where the virus is incorporated into the DNA of the host cell.

It is important to note that one of the effects of HPV E7's inactivation of Rb1 is the accumulation of the tumor suppressor protein p16 (zur Hausen, 1994; Munoz et al., 2003). The loss of Rb1 leads to a positive feedback loop that causes p16 to accumulate; however, the tumor suppressor effect is diminished or negated due to the loss of Rb1. This increase in p16 has become important as a diagnostic tool as immunohistochemical staining for this protein serves as a "surrogate" marker for HPV infection (Alexander et al., 2012, 2013, 2014).

With the adoption of Pap testing for cervical cancer, use of the cytomorphological effects has led to one of the most successful public health initiatives of the last century (Massad et al., 2009). As understanding of the central role that certain strains of HPV play in the development of cancer of the uterine cervix has evolved, use of testing for the virus has served as an important clinical adjunct to cytology in screening. This understanding has led to the realization that only a few strains of the many HPV strains are responsible for an overwhelming majority of cancers. Because of this, development of vaccines focusing on these particular strains can have maximumclinical benefit without the effort required in developing vaccines for the numerous non-/less oncogenic strains of HPV. These vaccines are now in clinical use and serve as the ultimate clinical goal for all other oncogenic viruses (Cobos et al., 2014). With the growing rates of other anogenital SCCs and the increasing appreciation for HPV's role in oropharyngeal carcinoma, the reach of this accomplishment only continues to grow. It is for this reason that such an interest has been given to any possible role HPV may play in cancers of the urinary bladder.

While much of the work has been focused on urothelial carcinoma due to its commonality, exploration into the role HPV might play in other less common malignancies of the urinary bladder have been explored. For the purpose of this review, we analyzed research that has been conducted on urothelial carcinoma, SCC, and adenocarcinoma of the urinary bladder.

HPV in urothelial carcinoma of the urinary bladder

Cancers of the bladder are responsible for up to 6% of all cancers in men and as many as 2% of cancers in women, with urothelial carcinoma representing the overwhelming majority of these (Silverberg, 1987). With the knowledge that infection with *Schistosoma haematobium* (bilharziasis) significantly increases the risk of urinary bladder cancer, consideration of other infectious etiologies has been strong (Malone et al., 1987). Amongst the most intensely considered and researched candidates has been HPV. Despite the amount of work that has been done to fully elucidate this possibility, significant controversy still remains as to the etiologic nature of HPV with regards to urothelial carcinoma in the urinary bladder (Griffiths and Mellon, 2000; Gutierrez et al., 2006).

Ever since HPV was reported in one of 10 bladder tumors, researchers have been working to more definitively prove an association between the virus and cancer of the urinary bladder (Kitamura et al., 1988). A number of studies have since detected HPV in at least a subset of the cases analyzed (Bryant et al., 1991; Kerley et al., 1991; Anwar et al., 1992; Chetsanga et al., 1992; Furihata et al., 1993; Agliano et al., 1994; Maloney et al., 1994; Kamel et al., 1995; Kim and Kim, 1995; Lopez-Beltran et al., 1996; Chan et al., 1997). The types and prevalence of infection in these cases varied dramatically. Of those studies that showed a strong presence of HPV in urinary bladder tumors, work from Shigehara et al. provided some of the most convincing evidence that HPV may play an etiological role in urothelial carcinoma in the bladder. In a large study involving 117 patients, 15% of the samples were found to have HPV present (Shigehara et al., 2013). These consisted primarily of the known oncologic HPV types 16, 18 and 33. Interestingly, HPV infection was found to be far more common in low grade tumors (38% of grade

1 tumors) and in those occurring in younger (<60 years) patients. The authors posited that HPV might play an etiologic role primarily in low grade tumors occurring in younger patients.

Despite the number of studies that have shown the presence of HPV in urothelial carcinoma in the bladder, the results are far from conclusive. A number of studies have failed to show the presence of HPV in any of the cases evaluated (Knowles, 1992; Saltzstein et al., 1993; Sinclair et al., 1993; Chang et al., 1994; Sano et al., 1995; Boucher and Anderson, 1997; Lu et al., 1997; Aynaud et al., 1998). Many of these investigations have included a large patient subset as well. Ben Selma et al. investigated a total of 125 cases; 119 were urothelial carcinoma, and found no evidence of HPV in any case (Ben Selma et al., 2010). The work conducted by Chang et al. looked at 108 cases and failed to detect any HPV (Chang et al., 1994). An investigation by the group of Youshya et al. looked at 78 cases of urothelial carcinoma and also failed to detect any evidence of HPV infection (Youshya et al., 2005).

Significant controversy to any role the virus plays in the etiology of urothelial carcinoma persists-and for good reason. In addition to the number of studies that fail to show any evidence of HPV infection whatsoever, even in those that do, many show only a very small prevalence of the virus in cases examined. Questions remain as to why this significant variability exists. Many of these studies utilize different methods of detection: PCR, IHC, southern blot, etc. It does not appear, however, that any of the modalities can be specifically targeted for being the "culprit." Each of these modalities can be seen to find HPV and not detect it in other studies, so it appears that the testing method is not entirety to blame. It may be that there is significant variability within populations as to infection status with the virus and the ease with which it is detected in examined samples. What may be needed is a study that looks at HPV infection status in urinary bladder tissue samples in a population of people without cancer to determine if a there is a baseline infection rate within the population. The current evidence certainly fails to conclusively implicate HPV as an etiologic agent for urothelial carcinoma in the urinary bladder.

HPV in squamous cell carcinoma of the urinary bladder

SCC is the most common histologic type of cancer associated with HPV. This association in the uterine cervix has been mentioned many times already, but SCCs of the anogenital region in general (anal, penile and vulvar) also feature HPV as either a predominant or significant contributor to their etiology (Keating et al., 2001; Klaes et al., 2002; Agoff et al., 2003; Benevolo et al., 2006; Horn et al., 2006; Dehn et al., 2007; Doxtader and Katzenstein, 2012). Recently, a significant amount of interest has been given to the role HPV plays in SCC of the oropharynx. As smoking rates have declined in developed countries, the contribution that HPV plays in oropharyngeal SCC will continue to grow and, likely, become the predominant etiologic agent of oropharyngeal SCC. This discovery has further validated the potential benefits that vaccination for HPV may have on the population as a whole and increase the push to find other human cancers that may be attributable to HPV.

The role of HPV in SCC of the urinary bladder has been quite controversial. Much of this is due to to the rarity of this malignancy. While SCC of the urinary bladder may represent up to 75% of all bladder cancers in areas where bilharzial infections are endemic, SCC only represents 3-5% of all urinary bladder cancers worldwide (Kantor et al., 1988; Mostafa et al., 1999; Dahm and Gschwend, 2003; Shokeir, 2004; Kassouf et al., 2007; Lagwinski et al., 2007). In two small studies performed by Guo et al. and Westenend et al., no cases of HPV were detected in the 32 collective cases reviewed (Westenend et al., 2001; Guo et al., 2009). A larger, more recent, study from Alexander et al. was unable to find any evidence of HPV in 42 cases. Interestingly, Alexander et al. also performed the same analysis on 27 cases of urothelial carcinoma with squamous differentiation, a morphologically similar entity to pure SCC of the urinary bladder. Their results showed no evidence of HPV in this entity that presents as a diagnostic dilemma to SCC in the urinary bladder (Alexander et al., 2012). These results correspond to results reported on urothelial carcinoma with squamous differentiation from Blochin et al. (2012).

In all three of the studies on HPV in SCC of the urinary bladder cited, all used HPV in situ hybridization (ISH) as the primary method of detection. Research done on a wide spectrum of urinary bladder cancers by Ben Selma et al. used PCR to detect the presence of HPV. Though only five of the 125 cases reviewed were SCC of the urinary bladder, no evidence of HPV was found by this method (Ben Selma et al., 2010). In the large study from Shigehara et al. mentioned previously, no HPV DNA was found in any of their cases of SCC of the urinary bladder either. Despite having 11 cases, only 4 were eligible for their study and limited the yield of their results with regards to SCC as these lacked statistical significance (Shigehara et al., 2011). The analysis performed by Alexander et al. also used p16 immunostaining to determine if the marker correlated with HPV-ISH results, as it does in the uterine cervix and oropharynx (Alexander et al., 2012). This was not found to be the case as a number of cases showed intense staining with p16 and no HPV positivity by ISH-further concluding that p16 should not be interpreted as a surrogate marker for HPV status in the urinary bladder.

Though the evidence is limited, the published literature examining a potential role for HPV in SCC of the urinary bladder indicates that the virus does not play a role in the tumorigenesis of this cancer.

HPV in primary adenocarcinoma of the urinary bladder

Much like SCC of the urinary bladder, primary adenocarcinoma of the urinary bladder is also quite rare. And also like SCC of the urinary bladder, the malignancy is more common in endemic areas of bilharziasis (el-Mekresh et al., 1998; Zaghloul et al., 2006). Despite this, primary adenocarcinoma of the urinary bladder only accounts for up to 2% of all bladder malignancies (Dahm and Gschwend, 2003; Ploeg et al., 2009). The rarity of the disease is further compounded by diagnostic challenges presented by morphology. In many cases, primary adenocarcinoma of the urinary bladder is indistinguishable by morphology from adenocarcinomas arising from other body sites, particularly the colon. Due to the much higher incidence of these other adenocarcinomas, all studies must also fully exclude the possibility that the tumor being examined is of true urinary bladder origin and does not represent invasive/metastatic disease.

Due to these challenges, only one significant publication was identified in the literature that rigorously evaluated the possible etiological nature of HPV on primary adenocarcinoma of the urinary bladder. A study performed by Alexander et al. on 36 cases of clinically confirmed cases of primary adenocarcinoma of the urinary bladder failed to identify the presence of HPV in any of the examined cases (Alexander et al., 2014). The authors of the study employed HPV-ISH as their means of detecting the virus, using both low-risk and high-risk kits. As HPV is known to affect p16 and p53, these cell cycle proteins were also evaluated to determine any possible connection with HPV infection. Both markers showed strong reactivity in a number of cases, but did not show any correlation between each other and obviously no correlation with the non-present HPV (Alexander et al., 2014). In the large study on bladder carcinoma by Shigehara et al., one of the six cases evaluated for primary adenocarcinoma of the urinary bladder was found to have HPV DNA present by PCR (Shigehara et al., 2011); however, the limited number of specimens sampled prevented any significant conclusions being drawn from the data.

Though significant difficulties exist to performing studies on this entity, the limited evidence available suggests it is unlikely that HPV plays a significant role in the tumorigenesis of adenocarcinoma in the urinary bladder, but additional studies are encouraged to further evaluate this possibility.

There is no question that HPV plays a significant role in the development of human cancers. The successful efforts at vaccination against the virus, thereby preventing the development of cancer, have only made identifying a potential role for HPV in other cancers that much more important from a public health perspective. The urinary bladder's proximity to the anogenital region and its known association with another oncogenic infectious agent, *Schistosoma haematobium*, present it as a natural target for exploring this possibility.

This review focused on three tumors in the urinary bladder that represent the overwhelming amount of cancers within the organ: urothelial carcinoma, SCC, and adenocarcinoma. Of these, urothelial carcinoma makes up the substantial majority of cases. While many have reported HPV present in the tumors evaluated, substantial evidence to indicate an etiologic role is not present, with a number of reports entirely lacking any presence of the virus. SCC and primary adenocarcinoma of the urinary bladder are much rarer tumors and studies are accordingly limited. These two tumors are of particular interest, however, because they represent the histologic subtypes most commonly associated with HPV-induced neoplasia-particularly SCC. Current evidence in the published literature fails to show any strong association between the virus and these tumors. This assertion is hindered by the size of the studies, but the rarity of the entities presents a serious logistical problem in conducting larger studies.

Conclusions

The published literature indicates that HPV is most likely not an etiologic agent in the three urinary bladder tumor types reviewed. Due to the significant nature HPV plays at a public health level, further determination of a possible role in the development of urinary bladder tumors is likely indicated. This is particularly true for urothelial carcinoma, where the most controversy for a possible role exists, due to its higher prevalence. Larger studies, controlling for geographical, demographic, and cultural differences, along with standardized or multiple testing modalities may be indicated to determine any true etiologic nature of HPV in this setting.

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