

REVIEWS

HPV and Bladder Cancer – Is There a Connection?

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Abstract

There are several studies which link the ubiquitously Human Papilloma Virus (HPV) to several malignancies. Some of them like cervix cancer had already been proven but others are still opened to discussions. One of them which we refer in this topic is the bladder cancer. We shall try to discuss it in a general and particularized manner given the fact that bladder cancer includes several types of neoplasia. The general term bladder cancer include urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, inverted urothelial neoplasia and last but not the least a mix between urothelial neoplasia with squamous cell carcinoma differentiation. Another concern seems to be related to a possible marker that can be used for this type of neoplasia and if it can be linked to HPV or not. There are studies which try to link p16 or p53 to HPV with conflictual results. There are also many papers which try to find out if there is or not any role for HPV in bladder cancer.

Keywords: bladder cancer, HPV, p16, p53

Rezumat

Sunt o multitudine de studii care leagă ubicuitarul virus papiloma uman de anumite neoplazii. În unele dintre ele, cum este cancerul de col uterin, rolul lui a fost demonstrat, în timp ce în altele există încă loc de discuții. Cea la care ne referim în această lucrare este cancerul de vezică urinară. Vom încerca să abordăm problema atât în maniera generală cât și într-una particularizată ținând cont de faptul că neoplasmul de vezică urinară cuprinde mai multe entități: cancerul urotelial, carcinomul scuamos, adenocarcinomul, neoplazia de câmp urotelial inversat și, nu în ultimul rând, un mix între carcinomul urotelial și cel scuamos. O altă preocupare a multor lucrări este legată de încercarea de a descoperi un marker pentru acest tip de neoplazie și dacă poate avea o conexiune cu infecția cu HPV sau nu. Aici ne referim la p16 sau p53 care au oferit rezultate contradictorii în mai multe studii. Sunt, de asemenea, studii care încearcă să afle dacă există o conexiune între HPV și neoplazia de vezică urinară sau nu.

Cuvinte cheie: cancer de vezică urinară, HPV, p16, p53

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INTRODUCTION

HPV represents without any doubt one of the biggest health problems nowadays. Since the early days of its discovery by zur Hausen¹ the importance of this pathogen has risen. Its role in cervix neoplasia has been already demonstrated and steps have been made to counter this threat (vaccine). There are proofs that link this virus to other ano-genital neoplasia (here we include the penis, vulva, ano-rectal region and later the laryngeal neoplasia).

We cannot forget that almost 10% of neoplasia worldwide is linked to this small epitheliotropic DNA virus².

Given its tropism for epithelial cells basically this virus can and actually does infect almost any type of organ. As such as we reviewed in another paper every part of the anogenital area can harbor this virus. HPV infection in men is often detected in the glans, corona, prepuce, shaft of the penis, and distal urethra. Most of the studies present lower detection rates in the urine³. A systematic review also reported that the HPV detection rate from urine samples was less than 7%⁴.

The highest prevalence of HPV depending on the place of sampling varies in each study; numerous papers indicate scrotum and penis as the areas with the highest prevalence followed by the anus, urethra (both the proximal and the distal), secretion of the prostate and urine. Aiming to adjust the information some studies prefer to elude some of those sites because they are not statistically significant.

Papilloma virus cannot be cultured *in vitro* so the molecular detection techniques are now used. *In Situ* Hybridization and Southern blot are used with satisfactory results but PCR is the gold standard.

A question mark has risen lately related to the implication of this virus in bladder neoplasia, unfortunately information is still intriguing. Bladder cancer is the fourth cause of neoplasia in men. In this paper we tried to approach this matter. Using Pubmed and Scopus we searched for "bladder cancer, HPV".

BLADDER CANCER AND HPV – A REVIEW OF THE LITERATURE

The results from literature are very various; starting from case presentation to meta-analysis. For instance Khambati et al presented a rare case of condyloma of the bladder which progressed to invasive squamous cell carcinoma of the bladder. In their work p16 was negative, still there was no information regarding the HPV strains they encountered⁵.

It is very important to understand that SCC of the bladder is divided in two major groups: those caused by *Schistosoma* and those who are not. This case did not have a history of bilharziasis.

On the same trend, Altan et al presented a rare case of SCC of exstrophic bladder associated with adenocarcinoma of the same organ. Using PCR as the standard method they detected four strains of HPV involved in this particular case namely: 16, 18, 35, 56⁶. Note that all the strains are High Risk HPV.

The risk of developing SCC of the bladder besides *Schistosoma* seems to rise in cases with neurogenic bladder, lithiasis, infection, auto-catheterization, and spinal cord injury. It seems to vary between 19%⁷ to 46.9%^{8,9}.

Bloch et al presented two cases of urothelial carcinoma with squamous differentiation; both of them were eventually surgically sanctioned (cystectomy). P16 was positive but in a diffuse way. The interesting part is that the in-situ hybridization detected high risk HPV strains in the SCC part of the neoplasia. Unfortunately we cannot link HPV of this malignancy¹⁰.

Another case of urothelial carcinoma with SCC differentiation was recently reported by Guma et al. Immunohistochemistry detected low risk HPV 6 and 16 infection. Low risk HPV are not oncogenic generally so the role of this infection remains unclear¹¹.

One of the most comprehensive works, in terms of number of patients, comes from Alexander Riley. Two papers one from 2012 and one from 2014 try to find out if there is any linkage between p16 and p53 and HPV in bladder carcinoma^{12,13}.

Both of them but p16 mostly tend to be used as surrogate marker for HPV infection and most important its oncogenic role. Both of his papers are supported by relative large number of patients, and both of them do not find any connection between P16 and HPV infection. Moreover it seems that p53 is a better marker, as Kapoor et al found, too¹⁴.

In his first paper, 69 cases of bladder carcinoma (47 SCC and 27 urothelial carcinoma with SCC differentiation) were tested using in situ hybridization and immunohistochemistry for HPV. The results were completely negative. Meanwhile 31% of the SCC and 33% of the others tested P16 positive.

In the second one, 36 cases of adenocarcinoma of the bladder were tested for HPV (by ISH and immunohistochemistry) and for P16 and P53 expression. The results were completely negative for HPV but P16 and P53 were present in 67% and 58% respectively. So as it goes for P16 the authors advise not to be used as a marker for HPV in bladder cancer.

In a 2013 paper, Steinestel on 60 patients with bladder cancer tries to identify the mechanism behind the activation of P16 pathway and if it is related to HPV infection¹⁵. They could not find any link between urothelial carcinoma in situ and HPV. Moreover in CIN lesions HPV was identified. As for p16 expression it cannot be associated with HPV. Furthermore, a 2010 study showed that even in HPV DNA positive bladder cancers, p16 expression did not correlate with the expression of HPV16 E7 oncoprotein¹⁶.

Pacheco et al in big meta-analysis on 21 studies find an association between HPV and bladder cancer¹⁷.

Li et al. presented the outcomes of a meta-analysis of articles published from January 1989 until August 2010 in which they showed an association between HPV and bladder cancer. The authors discussed important issues that were not analyzed in previous meta-analyses, such as the geographic variation in risk of bladder cancer with HPV infection and the most common HPV types identified¹⁸.

Berrada in a study on a cohort of 43 Moroccan subjects with urothelial carcinoma finds by PCR methods that 52.4% of patients were positive for HPV. Moreover the HPV 16 high risk strain appeared in 95.5% of patients¹⁹.

They could not find any correlation between viral infection and tumor stage or grade. The geographic region it is very important with different rates of infection^{20,21}.

Kim et al in a 2014 study on 35 patients with urothelial carcinoma find in six of them infection with HPV 18 strain. They used third generation PCR and IHC for P16. Even if there are patients with HPV and P16 positive that does not necessary means there is a causative effect between those two²².

Schmid et al on a lot of 109 bladder cancers try to find HPV infection using PCR and RT-PCR. They did not find any trace of the virus and consider the association between urothelial carcinoma and HPV unlikely²³.

A very interesting paper by McDaniel et al treats the cases of inverted urothelial neoplasia. Twenty cases of inverted papilloma were investigated by either ISH or by PCR. The results came back negative²⁴.

Shigehara et al find that prevalence of HPV greatly varies from 0 to 81.3%. In one of his older studies on a batch of 117 patients they found 18 with HPV infection using ISH method²⁵.

On the other hand, Cai et al found high-risk HPV-DNA in bladder carcinoma was detected in 27 of 78 (34.6%) samples, and was also detected in 36 of 78 (46.1%) urine samples obtained from the patients with bladder carcinoma²⁶.

DISCUSSIONS

Generally speaking the information linked to HPV and bladder cancer makes no exception. As it is for prostate and urethra so it is for the bladder; the information is intriguing and sometimes confuse.

Based on the histopathological type of bladder cancer we observed that the urothelial part is rarely involved in HPV related carcinogenesis.

Normally the virus tends to affect squamous cells, but there are cases in which they appear in the adenocarcinomas or inverted neoplasia.

There is commonly known that the geographic spreading greatly differs, the ascendant pathway of the infection (first urethra then bladder) and the tropism of the virus for SCC.

Most of the studies include small numbers of patients (<50), therefore the statistic power of them is small. On the other hand, there is no investigation consensus – we are talking about standardization so the information is very variate; some authors used different generation PCR, others used ISH or FISH, some IHC or a combination of methods which makes the information hard to even. Last but not the least the value of P16 or P53 as a surrogate marker for HPV infection is still debated.

CONCLUSIONS

The general trend is to accept that HPV has a role in bladder cancer but it still remains unclear. There is a lack in the literature of a sufficiently large number of cases and samples and that use a combination of microbiological techniques in the same subjects and samples to obtain a definitive answer to this question.

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