

## Review

# HPV Implications in Benign Prostatic Impairments – A Literature Review

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### REZUMAT

#### *Implicațiile HPV în afecțiunile benigne ale prostatei – recenzie a literaturii de specialitate*

**Obiectivele studiului:** Hiperplazia benignă de prostată (HBP) este asociată cu prezența unui infiltrat inflamator local. Pe lângă numeroșii factori microbieni implicați în patologia benignă prostatică există multe date în literatura de specialitate care certifică prezența genoamelor virale la nivel prostatic, printre care și Papilloma virusuri (HPV). Oncogenitatea HPV a fost demonstrată cu ajutorul hibridizării in situ în cancerul de col uterin, ulterior fiind demonstrată și în cadrul altor neoplazii. Un număr ridicat de studii au enunțat ipoteza implicării HPV în patologia benignă prostatică. Obiectivul acestui articol este revizuirea principalelor publicații din literatura de specialitate, în care este abordat acest subiect.

**Metodologie:** Perfecționarea tehnicilor de detectare a HPV a permis apariția unor lucrări de specialitate care au studiat implicarea acestui virus în patologia prostatică. Până la momentul actual, majoritatea lucrărilor s-au adresat aspectului neoplazic, implicarea HPV în HBP rămânând subinvestigată.

**Concluzii:** Până la momentul actual rezultatele studiilor sunt contradictorii, datorită modului de recoltare, de prelucrare și de interpretare a datelor în context clinic. Astfel, un diagnostic standardizat al HPV în patologia benigna prostatică, este actualmente dificil de realizat. Deși rolul HPV în patogenia neoplasmului de col uterin a fost mult timp desconsiderat, implicarea sa în patologia prostatică, devine din ce în ce mai evidentă.

**Cuvinte cheie:** hiperplazie benignă de prostată, Human Papilloma Virus, infiltrat inflamator

### ABSTRACT

**Objectives:** Benign prostatic hyperplasia (BPH) is associated with the presence of local inflammatory infiltrate. In addition to many microbial factors involved in benign prostatic pathology, there are a lot of studies, which certifies the presence of prostate viral genomes, including the Human Papilloma Virus (HPV). HPV's oncogenicity has been demonstrated in cervical cancer using in situ hybridization, and also was subsequently demonstrated in other malignancies. A large number of studies have stated the hypothesis of HPV involvement in benign prostatic pathology. The objective of this article is to review key publications in

the literature that are addressed to this topic.

**Methods:** Improving HPV detection techniques has allowed the emergence of several papers that have studied the involvement of this virus in prostate pathology. But to date, most works have addressed the appearance of neoplastic involvement of HPV in BPH remains underinvestigated.

**Conclusions:** Until now the results of studies are contradictory, because of the harvesting method, processing and interpretation of data in the clinical context. Thus, a standardized diagnosis of HPV in the benign pathology of the prostate is currently difficult to achieve. Although the role of HPV in cervical cancer pathogenesis has been long time disregarded, it's involvement in the prostate pathology is becoming increasingly evident.

**Key words:** benign prostate hyperplasia, Human Papilloma Virus, inflammatory infiltrate

## INTRODUCTION

Benign prostatic impairments are a heterogeneous group of diseases that can coexist or be separate entities. Some of these conditions (prostatitis) are included in the pelvic pain syndrome, while the other is represented by the prostatic adenoma and its implications.

Benign prostatic hyperplasia (BPH) is histologically associated, in most cases, with the presence of inflammatory infiltrate at this level. Histopathological examination of the resected pieces and fragments of prostatic biopsy in many cases reveals stromal inflammatory infiltrate adjacent to the prostatic acini. (1, 2) In addition to the many factors involved in the prostate benign microbial pathology (*E. coli*, *Pseudomonas aeruginosa*, *Serratia* spp., *Klebsiella* spp., *Enterobacter aerogenes* and the great family of enterococci), there are numerous data in specialized literature, certifying the presence of viral genomes in both benign and malignant pathology of the prostate. (3, 4) Among them the following stand out: Papilloma virus (HPV), Polyoma viruses, cytomegaloviruses (CMV), Epstein-Barr virus (EBV), Herpes Virus 8 (HHV 8) and xenotropic murine leukemia virus recently (XMRV). (5)

Human papilloma viruses are a group of DNA viruses form Papilloma Viridae family, whose main route of transmission is sexual. Currently it is estimated that about 75% of the men and women of childbearing age have been infected at some point with this virus. Of the 200 strains of HPV, about 40 infect the ano-genital area and about 20% have the potential for human infection. The neoplastic-promoter role of HPV was demonstrated in 1983 using in situ hybridization in cervical cancer, subsequently being demonstrated in other malignan-

cies: Buschke-Lowenstein disease, laryngeal cancer, tonsillar, vulvar cancer and skin cancer. Worldwide, cervical cancer remains the second most common cause of malignancy. (6, 7) A large number of specialized literature publications have high event in the pathology of HPV involvement esophageal, prostate, lung and breast. (8, 9)

HPV presents an epitheliotropic DNA structure and is divided in two groups: cutaneous and mucosal group, which in turn is subdivided into three subgroups according to oncological risk: low risk (strains 6, 11, 40, 42, 43, 44, 54, 61, 72 and 81), intermediate risk (strains 26, 53 and 66) and high-risk (strains 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 73 and 82). A particular interest is presented by the high-risk groups (HGSIL - high grade squamous intraepithelial lesion), which are involved in the majority of neoplastic phenomena. (10)

HPV's viral DNA is a double-stranded structure and presents two regions: a primary one, containing 7-8 gene (E1-E8) encoding non-structural proteins and a secondary one with two genes (L1, L2), encoding two structural proteins (major and minor capsid protein). Nonstructural proteins are responsible for DNA replication (E1, E8), cellular mutations (E5, E6 and E7) and cellular transcription (E2 and E8). (5)

The primary route of transmission for HPV infection is sexual, this being made by direct contact between the basal cells and virus. Secondary, HPV infection can also be transmitted iatrogenic through unsterilized surgical instruments, from mother to fetus and infant autoinfection. (8)

The existence and development of the virus is inexorably linked to the stratified epithelium, and in particular to keratinocytes, the cells in which the virus multiplies and encloses. The virus must come

to infect the basal layer, otherwise due the rapid cellular turn-over and surface layer peeling, the virus could not survive. In order to achieve that the virus is forced to overcome certain obstacles to survive and multiply. Then it integrates in the cellular genome, after previously being internalized and transported through the cytoplasm into an endosome. Such infected cells must maintain a delicate balance between synthesis and differentiation of genetic material, without which cell apoptosis is triggered. Having an elusive nature, the virus persists in the host organism by means of three contributing factors:

- The virus life cycle must not come in contact with the immune system of the host organism or must have very little contact;
- By not destroying the host cells, the virus cannot trigger an immune response of the body;
- Viral proteins have an active role in combating the host's immune response (5, 6, 8).

By being unable to be grown on specific media, virus detection techniques are based on immunology, serology, molecular biology and flux cytology. Hybridization techniques currently available are sufficiently sensitive, but may have numerous disadvantages: they are time consuming, difficult to perform, or too expensive. (6, 8)

## MATERIAL AND METHOD

As HPV virus cannot be cultivated in vitro, its detection method is based on molecular methods - Southern blot (electrophoresis of DNA particles), Northern blot (similar for RNA), in situ hybridization and PCR (Polymerase Chain Reaction). (10) Detection of the body's immune response to HPV has the advantage of revealing a recent infection and also an older one but has a lower degree of specificity than PCR. Although the presence of HPV DNA in the prostate has the disadvantage of highlighting a recent infection only, it still remains the gold standard in terms of specificity and sensitivity. (10, 11)

With the improvement of detection techniques, many papers have studied the involvement of this pleomorphic virus in the pathology of various organs. Most of these works addressed neoplastic appearance, their control population consisting mainly of patients with BPH. Some of these studies have provided indirect information on the prevalence of HPV in HBP.

## RESULTS

The coexistence of adenoma, inflammation and neoplasm in the prostate has been demonstrated by immortalizing virus proteins E6/E7 in prostate cells. But after more than 30 years of research, the results, unfortunately, are contradictory.

In the two studies of Siobhan Sutcliffe, control groups were composed of a large number of patients: 691 and 614 respectively. The results of both studies were disappointing both with adenocarcinoma patients and also in the control group patients: no statistically significant association between HPV and adenocarcinoma respectively BPH has been found. (3, 12)

An article published in 2003 by Hans Olov Adami took into account a number of 238 patients with ADK-P and 210 patients in the control group, which were seropositive for HPV-16 and HPV-18 between 11-15% and for HPV 33 was about 23%. (13) Conversely J. Bergh's study on a group of 402 patients found inflammatory infiltrate in the prostate, but no viral involvement. (14)

The publication of Alice C., H. Chen (2011), which is based on a study carried out on a smaller batch, state that there is a prevalence of HPV DNA of 14% (7/51) for patients diagnosed with prostate cancer and 27% (3/11) for patients diagnosed BPH. The only type of HPV detected in tissue samples was HPV-18. (15)

In the study conducted by Margarita L. Martinez-Fierro the presence of HPV sequences was detected in 15 subjects (11.5%), of which 11 (73.0%) were patients diagnosed with ADK-P, and 4 (27.0 %) were in the control group. The most common histopathological diagnosis of the control group was chronic prostatitis (84%), which was found in association with normal prostate tissue (41%), hyperplastic prostatic tissue (28%) and atrophic tissue. (15%). Only 10 subjects (13%) had a histological diagnosis of normal prostate tissue. (16)

Taghreed F. Al-Mahbobi used in situ hybridization technique for detection of viral DNA HPV-16 and HPV 18. Thus in a group of 20 patients diagnosed with BPH, 9 patients (45%) were positive for HPV 16, and 7 patients (35%) were positive for HPV-18. Infections for both HPV types 16 and 18 was confirmed in 5 patients (25%). (17)

Gustavo J. Leiros detects HPV DNA using PCR and Southern blot techniques for HPV: 6, 11, 16, and 18. The study demonstrates the inconsistency of

the results in this type of viral involvement in BPH. (11)

The inconsistency of results from different studies can be attributed to the contamination from adjacent tissues samples since HPV DNA was detected in the urethra and anus. On the other hand, if there is contamination from the anal HPV during the process of sample collection and handling, HPV DNA would be expected to be detected in both HBP and adenocarcinoma of the prostate. (18-21)

It is clearly demonstrated the existence of the virus in the urethra, penis and anus. Studies performed on patients whose spouses have developed cervical cancer strains reveals the presence of both high risk and low risk strains at penile or urethral level. Such assumptions are supporting samples contamination at harvest.

Following this hypothesis Hrbacek et al, in a study published in 2011, used strict surgical methods that avoid the possibility of contamination: simple prostatectomy (105 cases) and radical prostatectomy (329 cases), with positive results for HPV 18 strain among prostatic adenoma. By not including endoscopic harvesting methods, they avoid the risk of contamination and could analyze the samples entirely. There was a high seropositivity for HPV 18 strain prostate adenomas and not in adenocarcinoma. (22)

T. Cai and collaborators published a paper in 2011 that raises the hypothesis involving this virus at bladder level, precisely at 34.6% of patients who had surgery (TUR-TV - trans-urethral resection of bladder tumor) for non-invasive urothelial cancer and 13.5% of control cases (TUR-P). Note that in both groups of patients high-risk strains of HPV were detected. (23)

In an earlier publication dealing with HPV detection by PCR, Noda T. et al found only in 3 of 71 cases with BPH infection with HPV 16 using a kit that allowed the detection of a much richer set of HPV types: 16, 18, 31, 33, 35, 52, 58. (24)

The article published in 1997 by H. Strickler and R. Burk has become one of the most cited sources of information in the field both for its negative results but also for the methods used. The authors used three different PCR kits and two different serological tests for virus identification on a group that included patients with ADK-P and HBP. But the review authors reported numerous conflicting results. One of the reasons for this heterogeneity of results could be the existence of unequal variables and statistical power. Thus the type of samples, sampling conditions

(TUR-P, adenomectomy), processing conditions and methods of analysis are unstandardized variables to be taken into account. (25)

One of the most relevant studies to present conducted by K. Rosenblatt, analyzes a batch of 642 patients with adenocarcinoma of the prostate and a control group of 570 patients by immunological methods. None of the groups showed a statistically significant degree of positivity for HPV 16 and 18. (26)

## DISCUSSIONS

The papers on this topic published to date provide conflicting results. Many variables presented in each study make a standardization process to be very difficult, at least at this time.

One of the greatest impediments in achieving such studies and the reason for which the studied groups generally do not include a large number of patients remains the difficulty of obtaining adequate biological material. Thus was created the hypothesis of sample contamination with fragments of adjacent tissues during the harvesting procedure, since HPV DNA was detected in urethra and anus. In this regard Hrbacek preferred to use parts of radical or simple prostatectomy, precisely to avoid this impediment. (22) On the other hand, if there is HPV contamination from the anus during the process of sample collection or handling, would be expected to detect viral DNA, both in prostatic adenocarcinoma and benign prostatic hyperplasia. But there are studies that invalidate this correlation, by the fact that the strains found in the samples were different from those in the control group. (16)

The processing and especially the quality of the biological material have a crucial importance. With improving techniques of sample processing, it was found that the best DNA sample is collected from a fresh piece, unprepared chemically. Analysis of paraffined pieces requires additional efforts to extract viral DNA, which involves supplementary methods of processing, from which the genetic material can be altered, thus compromising the final result. (13, 27)

The most accurate technique of HPV genome processing and detection is PCR, unlike in situ hybridization, to which false negative results were found. Thus, in some samples, the viral DNA could not be detected by in situ hybridization, but its presence was confirmed by PCR. (17) In some

studies in which VLP ELISA method has been used, in some patients "hit and run" HPV infection have been detected, which means that the infection had been discovered many years before the diagnosis of prostate adenocarcinoma, but then it was absent at diagnosis time. (19, 28) Mostly was found HPV high risk subgroup, but without clear predominance of one of the strains, which certifies that HPV 16 and 18 strains are not particularly involved in malignant or benign prostatic pathology. (16)

The vast majority of neoplasms produced due to HPV infection are squamous type, while in prostate cancer the main component is adenocarcinoma. Based on this assumption many studies have detected HPV 18, involved in 70% of cervical adenocarcinomas. (17) In cervical cancer pathology HPV involvement was undoubtedly demonstrated. Studies performed on patients whose wives have developed cervical cancer reveal the presence of both high risk and low risk strains at penile or urethral level. However it should be remembered that HPV seroprevalence among healthy male population ranges between 3% and 45%. These discrepancies can be explained only by the difference of screening methods and also by differences in sexual behavior according to country. (11, 16)

Most information related to HPV infection in prostate, is addressed to neoplastic aspects, very few are regarding the benign diseases. Serologic studies (anti-HPV) adjacent to classical methods of PCR and in situ hybridization (ISH) on small plots of patients could not find a direct connection between the virus and prostatic neoplasia or adenoma. (29) Although the viral material was detected in a number of cases, these were not statistically significant, their number being too small to draw certain conclusions.

Given the fact that these clear variations are present in the results of several studies that will demonstrate causality between detection of HPV DNA in prostate and BPH presence, more investigations should be carried out in order to support this hypothesis. But still most studies focus on the neoplastic aspect, neglecting BPH. This effect was recently issued the hypothesis that high risk subgroup of HPV may determine the existence of ADKP precursor lesions in prostate, lesions that would exist or may arise from the presence of BPH. This hypothesis was launched with the model precursor lesions of cervical cancer, but so far the connection between PIN and BPH could not be demonstrated. (17, 30, 31)

In recent years, many studies have focused on the association of other viruses and HPV positive results occurring on the association between papilloma virus and Epstein Barr virus in prostate cancer and prostatic adenoma. Presumption, from which the authors have started, appeared after detecting the association of the two viruses in cervical cancer, resulting in increased speed of tumor cell proliferation. It seems that in this case EBV acts as an oncogenic enhancer for human papilloma virus. (32, 33)

## CONCLUSIONS

In order to talk about a uniformity of views on this subject, a standardized investigation protocol is required to be widely accepted worldwide. If in terms of the female population the virus involvement is proven, in male population things are still unclear. To this matter the possible, if not certain, involvement of the virus in the prostate neoplastic process is being added, which is currently under investigation. As the most common route of transmission of the virus is sexual, the partner is necessary to be investigated, because even prevention of cervical cancer risk is decrease. It must not be forgotten that for a long time the role of HPV in the pathogenesis of cervical cancer has been disregarded. Therefore, the involvement of HPV in benign and malignant prostate pathology becomes increasingly evident, although up to date studies on this topic have not clearly proved its role.

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