The role of human papillomavirus infection in prostate cancer

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ABSTRACT

Human papillomavirus (HPV) is the cause of the most common sexually transmitted diseases (STDs) of viral etiology worldwide. High-risk HPVs are the etiological agents of cervical and other anogenital malignancies and low-risk HPVs induce only benign genital warts. Since high-risk HPVs have been shown to possess oncogenic potential, an association between HPV infection and prostatic carcinoma (Pca) has been suggested. Some authors demonstrated that HPV infection play an important role in the pathogenesis of Pca. Active research is ongoing to highlight the mechanisms by which HPV involved in the development of cancer. The aim of this article is to review the studies that investigated the association between HPV and Pca and to explore the mechanism of HPV oncogenesis.

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Human papillomavirus (HPV) are a group of genetically related organisms that infect epithelium and induce proliferative changes in these cells that result in both benign and malignant tumors.[1] Papillomaviruses are small nonenveloped viruses with 55-nm-diameter icosahedral capsids that contain double-stranded DNA genomes of approximately 8,000 bp. They are widely distributed throughout the animal kingdom.[2] Approximately 30-50% of the general population is positive for HPV DNA.[3-5] Harald zur Hausen's laboratory was the first to demonstrate that genital warts contain human papillomavirus (HPV) genomes.[2,6] Approximately 200 different HPVs have now been characterized, and new types are regularly added to this list.[2] It is estimated that 15% of all cancers are etiologically linked to viral infection.[7] There are approximately 40 types are associated with lesions of the anogenital tract. Infection with high-risk (oncogenic) types of HPV (HPV16 [HPV type 16], -18, -31, -33, -35, -39, -45, -52, -56, -58, and -68) is a well-established risk factor for the development of cervical carcinoma.[8] Human papillomavirus are the etiological agents of cervical and other anogenital malignancies and low-risk HPVs induce only benign genital warts.[9-13] The best evidence supporting the role of HPV in the development of urological malignancy is for squamous cell carcinoma of the penis.[14] Evidence supporting the oncogenic role of HPV in other urological malignancies is conflicting, but HPV is unlikely to be a major factor.[14] It has been speculated that HPV might be a causative agent of transitional cell carcinoma.[15] Recent molecular studies reveal a likely role for HPV infection in skin carcinogenesis,[12,16] nonkeratinizing squamous cell carcinoma of oropharyngeal region and[12,17] cervical adenocarcinoma.[12,18]

Human papillomavirus and prostate cancer (Pca). Family history, age, testosterone, ethnic origin, environment and genetic factors are the only firmly established risk factors for prostate cancer.[19-22] In addition to these, a history of sexually transmitted disease has emerged as one of the stronger and more consistently reported risk factors; epidemiologic evidence of sexual history has emerged as a consistently found risk factor for prostate carcinoma.[23] Recently, based on observations using the polymerase chain reaction (PCR) amplification assay, HPV types 16 and 18 specific DNA sequences have been detected in prostate cancer specimens obtained by transurethral resection. Since HPV types 16 and 18 have been shown to possess oncogenic potential, an association between HPV infection and prostatic carcinoma has been suggested.[24] The literature show that investigations evaluating the presence of HPV in prostatic tissue by PCR technology have yielded detection rates of 0-100%.[25-43] In those studies (**Table 1**), HPV DNA was detected by PCR analysis,[30,32-34,44,45] in situ hybridization[31,34,44] or southern blot hybridization analysis.[36,42] High risk HPV infection

Table 1 - Summary of the studies evaluated the presence of HPV in prostate carcinoma.

Author/year	Reference	Methods	Summary of the results
McNicol and Dodd, 1990	33	Southern blot	Viral sequences were identified in DNA from 7 of 16 prostate samples including both BPH and Pca
McNicol and Dodd, 1990	32	PCR	Amplified sequences specific for HPV 16 were found in 14 of 15 BPH and in all of four Pca tested. In contrast, HPV 18 was identified in only three BPH. Four of five normal prostates demonstrated no HPV infection
McNicol and Dodd, 1991	34	PCR, prostate tissue from 88 individuals	Amplified sequences specific for HPV 16 were found in 34 of 56 BPHand in 14 of 27 Pca. In contrast, HPV 18 was identified in only three BPH.
Effert et al, 1992	30	A modification of PCR (D-PCR) and Southern blot, microdissected Pca from 30 paraffin-embedded prostate tissue	No evidence of HPV-DNA of either type in any of the 30 primary prostate cancers
Ibrahim et al, 1992	44	PCR and in situ hybridization, 60 formalin-fixed, paraffin-embedded tissues (24 Pca, 16 BPH and 20 normal specimens)	HPV DNA was detected in 2 normal tissues and 6 Pca. None of the BPH was positive for HPV. HPV typing results indicated that virus type 16 was present in each of the 8 positive specimens
Serfling et al, 1992	106	PCR followed by specific hybridization for HPV types 6, 11, 16, 18 and 33, Thirty samples representing both benign and malignant prostatic disease	No HPV amplimers could be obtained with appropriate primers.
Dodd et al, 1993	29	PCR for HPV 16.	The E6/E7 viral gene transcripts were identified in 5 of 10 BPH specimens and 3 of 7 Pca specimens known to contain HPV 16 DNA
Sarkar et al, 1993	45	PCR was used to amplify PIN and Pca in 23 surgically resected prostates.	The presence of HPV 16 in three Pca (13%), No other HPV types (HPV 6b/11 or HPV 18) in any of the samples using specific primers.
Tu et al, 1994	42	PCR and Southern blot for HPV 16 and 18 in a total of 61 prostatic tissue specimens: 43 primary Pca formalin-fixed, paraffin-embedded.	Only 1 out of the 43 prostatic specimens analyzed was positive for HPV 16 and 1 metastatic lymph node was positive for HPV 18
Gherdovich et al, 1997	107	PCR for HPV in 60 BPH and in 5 Pca.	The analyzed specimens were negative for HPV DNA.
Terris and Peehl, 1997	52	PCR , 41 archival radical prostatectomy specimens,	Of the normal prostatic tissues, 13.5% 126-bp E6 viral DNA as did 33.3% of BPH samples, 25% of dysplasia, , 6.7% -25.9% of Pca according to Gleason grade.
Noda et al, 1998	108	Nested PCR method that could detect HPV16, 18, 33 and others, formalin-fixed paraffin-embedded tissue of the prostate.	HPV DNA was detected in three of 71 specimens of BPH and in none of 38 Pca
Serth et al, 1999	46	PCR for 47 Pca and 37 BPH (as control)	A subgroup of Pca (21%) was detected as having significantly higher copy numbers of HPV16-E6 sequences when compared to the control tissue (3%)
Saad et al, 1999	109	PCR and Southern blot hybridization for HPV DNA, fresh tissue from 40 radical prostatectomy specimen for Pca	None of the samples contained detectable HPV DNA sequences
Carozzi et al, 2004	110	PCR	High-risk HPV type positivity was observed in 14 of 26 (53.8%) cancer and in five of 25 (20.0%) benign biopsies
Leiros et al, 2005	47	PCR and Southern blot	HPV DNA was detected in 17 out of 41 (41.5%) Pca, whereas all 30 BPH samples were HPV-negative.

PCR - polymerase chain reaction, HPV - Human papillomavirus, PIN - prostate intraepithelial neoplasia, Pca - prostate cancer , BPH - benign prostatic hyperplasia

(HPV16) has been reported recently in more than 50% of Pca and also in benign prostate epithelium.[31,34,36] Terris and Peehl[41] suggested that these discrepancies in HPV detection might be solely due to the differences in primer sets utilized. Some authors suggest that HPV infection may play important role in the Pca pathogenesis.[32-35,40,41,46] While others are not supportive of any role of HPV infection in the pathogenesis of Pca.[25,27,29,36,38,39,42] Leiros et al[47] found that HPV DNA was detected in 41.5% carcinoma samples, whereas all 30 hyperplasia samples were HPV-negative. Moyret-Lalle et al[35] found that HPV16 E6 does not show preferential association with malignant or benign prostate tumors and was present in 32% of adenomas and 53% of carcinomas. However, they found that carcinomas appear to display HPV DNA at a higher frequency. Dodd et al[29] found also that expression of the HPV viral genes is not associated preferentially with either benign prostatic hyperplasia (BPH) or Pca, nor is transcription observed in all samples which contain the viral genome. These findings suggest that the prostate may act as a site for HPV replication, but that HPV is unlikely to be involved in the transformation of prostatic cells. In a review article, Taylor et al[48] reported that a meta-analysis provides evidence of a higher rate of prostate cancer in men with a history of an exposure to gonorrhea, HPV, or any STD. Urethral contamination of prostate samples and the histological heterogeneity of prostate cancer can result in sampling errors, which may partly account for such discrepancies.[49] Although most studies analysed specimens obtained at trans urethral resection prostatectomy (TURP), a few only included specimens obtained at open surgery, such as radical prostatectomy, in which the HPV detection rates in studies using PCR are 2-21%.[49-52] Additional factors such as the duration of specimen storage before fixation, the number of times tissue is immersed in formalin, and the age of the tissue blocks can all influence the integrity of stored DNA.[49] Adami et al[53] demonstrated that HPV types 16 and 18 were not associated with prostate cancer. However, there was a possible association between HPV-33 and prostate cancer. A recent serological study found epidemiological evidence of an association between oncogenic HPV-18 and patients with Pca.[54] In that study, sera which had been collected up to 24 years earlier from 20,243 healthy Finnish men were assessed for IgG antibodies against HPV-11, 16, 18, 33. Seropositivity against HPV-18 was associated with a 2.6 fold increased risk of developing prostate cancer ($p<0.005$) while positivity for antibodies against HPV- 16 was not quite statistically significant as a predictor of subsequent prostate cancer occurrence. However, Korodi et al analyzed serum samples by standard ELISAs for the presence of immunoglobulin G antibodies against HPV types 16, 18, and 33 and their data do not support an association between serologic markers of HPV-16, HPV-18, and HPV-33 infections and risk of prostate cancer.[23]

Human papillomavirus infection in Saudi population. We recently demonstrated that HPV infection is less common in Saudi women as assessed by cervical Pap smear.[55,56] We also demonstrated that cervical dysplasia and invasive cervical carcinoma which is strongly linked to HPV infection as well as the other sexual related infectious diseases are less frequently encountered in Saudi women and occur at older age compared to the western countries. Carcinoma of the prostate occurs at a low frequency rates in Kingdom of Saudi Arabia (KSA) and it is clear that the incidence of Pca in KSA is lower than the western countries.[57-60] Recently, we demonstrated that chromosomal instability as determined by interphase fluorescent in situ hybridization (IFISH) is present in the majority of Pca in Saudi patients similarly to those reported in other countries.[61-64] Human papillomavirus has been incriminated strongly in inducing chromosomal instability (CIN) ; however, no HPV testing in Pca in Saudi patients has been published so far. Al-Adal et al examined prostatic tissues of BPH from Saudi patients and found high risk HPV in 30% of the specimens.[65] They investigated the occurrence of both HPV-16 and HPV-18 DNAs by using the PCR followed by Southern blot hybridisation (SBH) with type-specific probes. Only 2 of the 13 BPH tissue specimens were positive for HPV-16. Both were a co-infection with HPV-18. For HPV-18, 4 specimens showed positive.[65]

Human papillomavirus and gleason grade and clinical stage of prostate cancer. Anwar et al[66] demonstrated that frequency of HPV infection increased in patients with advanced stages of the tumor and with the higher Gleason score. Other investigators demonstrated no relationship between HPV infection (HPV-16 and HPV-18) status and Gleason score, stage of disease, or a combined measure of disease aggressiveness.[49,51,52,67.]

Mechanism of human papillomavirus oncogenesis. The oncogenic potential of HPV can be related to products of 2 early viral genes, E6 and E7. Together, they interact with a variety of growth-regulating proteins encoded by oncogenes and tumor suppressor genes. The E7 protein binds to the retinoblastoma protein and displaces the E2F transcription factors that are normally sequestered by RB. E7 induce centrosome duplication errors (CDEs) may be linked to the re-programming of the host cell cycle machinery, including dysregulation of cyclin/cyclin-dependent kinase (cdk) 2 activity.[68] human papillomavirus-16 E7 oncoprotein

rapidly subverts mitotic fidelity by inducing abnormal centrosome numbers and multipolar mitotic spindles.[69] E7-induced centrosome abnormalities represent an early event during neoplastic progression potentially driving genomic destabilization.[70,71] The binding of Rb family members to E7 is not restricted to high-risk HPV types, since low-risk E7 proteins also associate with Rb, although this occurs at a much reduced affinity.[9] The E6 protein also has multiple effects. It binds to and inactivates the TP53 protein; it mediates degradation of BAX, a proapoptotic member of the BCL2 family; and it activates telomerase. E6 abrogates multiple cell cycle checkpoints and modulates apoptosis. Inactivation of the tumor suppressor p53 by E6 is an important mechanism by which E6 promotes cell growth. The molecular basis for apoptosis modulation by E6 is poorly understood.[2,72]

Human papillomavirus P53 and prostate cancer. Recently, we demonstrated that p53 mutation is an early change in at least a subset of Pca in specimens resected from Canadian patients. We also showed that p53 mutation is associated with the presence of CIN as determined by IFISH.[61-64] We demonstrated almost similar findings in prostate specimens resected from Saudi patients.[63] In agreement with other studies,[73-78] our result showed that p53 mutation occurs relatively infrequent in Pca (20%). The low incidence of p53 mutation in Pca, associated to a significant proportion of tumors showing HPV16 DNA, could suggest that in prostate cancer HPV16 infection could participate in p53 inactivation by E6 and lead to CIN. E6 bind to host p53 causing inactivation of its function through the mechanism of ubiquitin-dependent degradation.[48,79,80] In most of the previous studies, it is obvious that HPV genomes in prostate tumors are more frequent than p53 mutation; however, the number of HPV copies was generally low. It might be that HPV is important for tumor initiation and less so to maintain the cancer phenotype. This possible role of HPV in causing functional inactivation of p53 may result in CIN with wild type p53 in a subset of Pca.

Human papillomavirus and chromosomal instability in prostate cancer. Chromosomal instability is a common feature of malignant umors.[81] It is frequently characterized by an abnormal number of chromosomes, a condition known as aneuploidy.[82-85] In CIN, the defects in chromosome number are thought to occur through missegregation of chromosomes,[84,86,87] but the mechanism by which this occurs has not been elucidated. Defect in mitotic spindle organization and function could directly lead to chromosome missegregation.[86-89] Furthermore, because spindles are organized in part by centrosomes,[90,91] it is possible that abnormal centrosome function could contribute to CIN. Support of this ideas comes from the recent observation suggesting the centrosome number is amplified in genetically unstable cells mutant for tumor suppressor p53.[92] Centrosome are comprised of a pair of centrioles, the duplication of which occurs once and only during the normal cell cycle, and the surrounding pericentriolar material, the substance involved in microtubule nucleation.[93] To assay for CIN in tumor cells, different techniques could be used including fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH). Spindle assembly and spindle-mediated movements during chromosome segregation are controlled in part, by cell cycle regulators.[86-89] The overall frequency of numeric chromosomal anomalies in prostate intraepithelial neoplasia (PIN) and Pca is remarkably similar which suggest that PIN is a precursor of carcinoma.[94,95] Allelic loss is common in PIN and Pca.[96-100] Epithelial tumors develop through a multistep process driven by genomic instability frequently associated with etiologic agents such as HPV infection.[101] Genomic instability is a hallmark of most human cancers including high-risk HPV-associated anogenital neoplasia. The 2 HPV-encoded oncoproteins, E6 and E7, can independently induce chromosomal abnormalities.[102] The continued combined expression of high-risk HPV E6 and E7 proteins in cervical cancers causes inactivation of the pRB and p53 tumor suppressor pathways and induces genomic instability in normal human cells. They cooperate to generate mitotic defects and aneuploidy through the induction of centrosome abnormalities.[2]

Human papillomavirus and telomeres in prostate cancer. Telomeres are terminal, repeated deoxyribonucleic acid (DNA) sequences that stabilize and protect the ends of the chromosomes. By initiating chromosomal instability, short dysfunctional telomeres may be involved in prostate carcinogenesis.[103] Each round of DNA replication leads to erosion of the chromosomal telomeric termini. Telomere shortening represents a cell-autonomous mechanism that restricts the proliferative capacity of normal somatic cells. Certain cell types that must undergo a large number of cell divisions, such as stem cells, express telomerase that prevents telomere erosion.[2] Telomerase activity was detected in 96.5% of cervical tumor samples, in 68.7% of premalignant cervical scrapings but was not detected in control hysterectomy samples, or in cervical scrapings of normal healthy controls. There was 71% correlation between telomerase activity and HPV-16/18 infection.[104,105] Primary human keratinocytes transduced with the HPV-16 E6 gene express significant telomerase activity.[105] At late passages, E7-transduced cells partially restore telomere length.[105]

Recently, we demonstrated that a significant decrease in telomere length was shown in Pca in comparison with normal epithelium.[64] Such observations lend support to the hypothesis that telomere erosion may be a consistent feature of Pca oncogenesis and may also be associated with the generation of chromosomal instability that characterizes this malignancy.[64] The relationship between HPV and telomerase activity is not yet clear and need to be evaluated in further studies.

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