SHORT COMMUNICATION

Is prostatic adenocarcinoma in a relationship with Human Papilloma Virus in Isfahan -Iran

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Background: Prostatic adenocarcinoma is the most prevalent cancer and the second cause of cancer-related death among men. Human Papilloma Virus (HPV) considered as a preventable risk factor for prostatic adenocarcinoma. In this study, we detected the frequency of HPV infection in prostatic adenocarcinoma and benign prostatic hyperplasia (BPH) in Isfahan. **Materials and Methods:** In this study, 120 paraffin-embedded blocks (90 and 30 cases with definite diagnosis of BPH and adenocarcinoma, respectively) were selected. Immunohistochemical (IHC) staining was performed for all selected blocks to detect HPV infection. The rate of infection was compared in the two studied groups. **Results:** Totally, HPV was detected in four blocks. HPV infection was positive in 10% (3/30) of cases with adenocarcinoma and 1.1% (1/90) of cases with BPH (P = 0.04, OR = 9.88, CI 95%). Mean age of patients with positive and negative HPV infection was 61.75 ± 8.3 and 68.51 ± 11.7 years, respectively. **Conclusion:** Considering the higher prevalence of HPV infection in prostatic adenocarcinoma, it is suggested that HPV could be probable risk factor for prostatic adenocarcinoma. It is recommended to investigate the prevalence of HPV infection in Iranian men and the outcome of prevention and treatment of HPV infection on prostatic adenocarcinoma.

Key words: Adenocarcinoma, benign prostatic hyperplasia, Human Papilloma Virus, prostate

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INTRODUCTION

Prostatic adenocarcinoma is a neoplastic proliferation of epithelial cell of acini and ducts of prostate gland and it is the most prevalent cancer among men and the secondly prevalent cause of cancer mortality.[1] Studies indicated a significant increasing rate of prostate cancer worldwide. In the U.S.A, the rate of prostate gland malignancy (154.8 per 100,000 men) transcended the lung malignancy rate among men.[2-8] In Iran, Sadjadi *et al*., reported that the rate of prostate adenocarcinoma was 5.1 per 100,000 person-years in 1996-2000.[9]

Some researches proposed many different risk factors such as age, race, and Human Papilloma Virus (HPV) infection for prostatic adenocarcinoma and benign prostatic hyperplasia (BPH), whereas others did not confirm the motioned relation.

HPV, one of the mentioned risk factors, is a member of papovaviridae, containing double-stranded, circular deoxyribonucleic acid (DNA) about 8,000 kilobases in length and its human tissue oncogenesis is proven. Its oncogenicity is due to two proteins coded by *E6* and *E7* genes inhibiting tumor suppressor proteins in natural cell coded by *Rb* and *p53* genes.[9] HPV infection is a common sexually transmitted infection and its prevalence reported to be 20-70% among men depend on age.[10,11] According to some reports, about 80% of sexually active women are exposed to at least one genital HPV type in their lifetime.[12] In Iran, HPV prevalence was 5.5% in Bushehr among women[13] and 29-37% in zabol among men.[14] Prostate gland infected by HPV can act as reservoir of this virus, so that it could be easily spread by sexual activity.[15-17]

Evidences suggest that HPV infection is more frequent in prostatic adenocarcinoma samples than that of BPH.[18-21] Ramezani *et al*., reviewed the articles about association between HPV infection and risk of prostate cancer and showed conflicting results.[22]

Considering the different reports regarding the role of HPV infection in the etiology of prostatic adenocarcinoma and BPH in Iran.[20,23] and the higher sensitivity and specificity and utility of Immunohistochemistry (IHC) for detecting specific viral antigens,[24,25] the aim of this study was to investigate the prevalence of HPV infection in BPH and prostatic adenocarcinoma blocks in Isfahan.

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MATERIALS AND METHODS

In this cross sectional study, paraffin-embedded tissues of 90 patients with definitive pathologic diagnosis of BPH and 30 tissue sections from patients with definite diagnosis of prostatic adenocarcinoma retrieved from the pathology archives of Alzahra and Kashani hospitals in Isfahan-Iran, from 2001 to March 2006. All sections selected by convenience sampling method.

120 cases including 30 prostatic adenocarcinoma blocks as sample group and 90 BPH blocks as control group were selected by convenience sampling method.

Sample preparation

Blocks were sliced in 3-4 μm thick slices and slides were provided from them and sequentially placed in 60°C oven for 45 minutes, in xylol for 10 minutes, in absolute alcohol for 10 minutes, in 96% alcohol for 6 minutes, in buffer (pH = 6) into microwave for 15 minutes. After that, they were placed in buffer (pH = 7.2) in environmental temperature. For staining, the processed slides were sequentially placed in H_2O_2 for 5 minutes and washing by buffer (pH = 7.2) (BW), in primary antibody (Rabbit Anti Papilloma Virus, DAKO corporation, CA. U.S.A) for 10 minutes and BW, in secondary antibody (Link) for 10 minutes and BW, in Stereptavidin solution for 10 minutes and BW, in Diamino benzoic (DAB) for 5 minutes and washing by distilled water (WW) and BW, in hematoxylin for 30 minutes and washing, in ammonia solution for 10 seconds and WW and BW. Finally, stained slides were dried, mounted and then surveyed by pathologist to determine which of them were positive. Slides that any of their cells nuclei or their cells cytoplasm was stained were considered as HPV positive. We did not include the intensity or percentage of positive stained cells as distinct criteria.

Results were analyzed by Statistical Package for Social Sciences (SPSS) software (SPSS, Inc., Chicago, IL) using Chi-square test. *P* values <0.05 was considered statistically significant.

RESULTS

Using IHC method, one hundred and twenty archive BPH and prostatic adenocarcinoma blocks were studied. The mean age for BPH group (90 cases (as control group)) and prostatic adenocarcinoma group (30 cases (as sample group)) was 68.48 ± 11.89 and 67.70 ± 11.1 years, respectively (*P* = 0.753).

The overall prevalence of HPV infection in all studied samples was 3.33% (4/120). Mean age of patients with positive and negative HPV infection was 61.75 ± 8.3 and 68.51 ± 11.7 years (*P* = 0.256). Frequency of HPV infection in patients with BPH and prostatic adenocarcinoma was reported in Table 1. Ten percent of prostatic adenocarcinoma cases and 1.1% of BPH cases were HPV positive in this study. Prevalence of positive HPV infection in patients with prostatic adenocarcinoma was significantly higher than those with BPH (*P* = 0.048, OR = 9.88, CI 95%).

Table 1: Frequency of HPV infection in patients with BPH and prostatic adenocarcinoma

	Prostatic Adenocarcinoma	BPH	Total
HPV positive	3	1	4
HPV negative	27	89	116
Total	30	90	120

DISCUSSION

In this study, the prevalence of HPV infection was investigated among patients with BPH and prostatic adenocarcinoma in Isfahan. Though the overall frequency of HPV positivity in our studied population was low but the rate of HPV infection was significantly higher in prostatic adenocarcinoma than BPH.

The most frequent malignancy among American men is prostatic cancer causing 10% of all death in mentioned population. It is the main cause of new cancer among men and the second frequent cause of death related to cancer.

The fifteen-year survival for well treated patient is more than 90%.[1,25]

The prevalence of prostate cancer in Iran has been reported to be 3.6% in male aged over 40 years. The prevalence rate of prostate cancer in Iran likewise other Eastern Mediterranean Regions is lower than other developed countries but it is expected to have a dramatically rise in future.[26] It seems that the lower rate of prostate cancer in our community might be due to lower rate of sexual behavior. Another explanation is circumcision which is a routine procedure because of religious belief. Studies indicated that the protective role of circumcision for prostatic cancer is due to its role in reducing the rate of sexually transmitted infections (STIs).[27-29]

HPV is one of several suspected causes of this cancer as reported by many studies worldwide.[16,20,21] Its oncogenicity in human tissue is proven specially in genital system.[21] Some studies have been reported the HPV prevalence of 28.2-45.5% in men in the U.S.A.[30-34] In Iran, HPV prevalence is lower and is about 5.5-29%.[13,14] Other sexual transmitted disease (such as *Trichomonas vaginalis*) has lower incidence in Iran in comparison to other countries.[35]

In our study, overall HPV positive cases were 3.3% that was lower in comparison to other study in other countries. Low HPV rate in Iran may be due to inadequate study or racial, geographical, cultural, technical differences or previously mentioned factors.

Several studies have investigated the relationship between BPH or prostatic adenocarcinoma and HPV. Wideroff and colleagues revealed that HPV was identified in 65.3% and 48% of prostatic cancer and BPH, respectively.[11]

In Italy, Carozzi F *et al*., detected HPV in 48% of BPH (12 from 25 cases) and 65.3% of prostatic adenocarcinoma cases (17 from 26 cases) in 2004.[18] Leiros GJ *et al*., in Argentina reported that HPV DNA was detected in 17 out of 41 (41.5%) carcinoma samples, whereas all 30 hyperplasia samples were HPV-negative in 2005.[19] Gherdovich *et al*., in Italy studied 60 BPH and five prostatic carcinomas samples and HPV was not found in any sample in 1997.[20] Noda *et al*., in Japan reported that they founded HPV DNA in three of 71 BPH (4.2%) and none of 38 prostatic carcinomas (0%) in 1997.[21] Mc Nicole PJ *et al*., in Canada identified HPV DNA in seven of 16 prostate samples including both hyperplastic and carcinoma tissues and including tissues obtained by transurethral resection or suprapubic prostatectomy in 1990.[16]

Kuczyk and colleagues in Germany found HPV in 10 samples from 47 prostate cancer samples (21%) versus one sample from 37 control group (BPH) samples (3%) in 2000.[36]

In our study, though the overall rate of positive HPV infection cases was low but obtained odds ratio showed that HPV infection could be a risk factor for prostatic adenocarcinoma.

The limitations of current study were lack of specific antibody for IHC to detect different subtypes of HPV and lack of accurate data regarding the exact prevalence of HPV in Isfahan.

In conclusion, the higher rate of HPV infection among cases with prostatic carcinoma than those with BPH indicates a probable role of HPV in the pathogenesis of prostatic carcinoma. For obtaining conclusive results further etiologic studies is necessary. Our findings, in line with many previous studies, confirm the role of HPV infection in the occurrence of prostatic adenocarcinoma. In addition, it is recommended to investigate the prevalence of HPV infection in Iranian men and the outcome of prevention and treatment of HPV infection on prostatic adenocarcinoma.

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