

RESEARCH ARTICLE

Frequency and Type Distribution of Human Papilloma Virus in Patients with Prostate Cancer, Kerman, Southeast of Iran

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Abstract

Prostatic cancer is the second cause of cancer-related death among men worldwide. The human papilloma viruses (HPVs) are a family of sexually transmitted viruses which may have roles in the etiology of inflammation in prostate leading to benign prostatic hyperplasia (BPH) and prostate cancer (PCa). In this study, we evaluated the frequency of different HPV types in prostatic cancer and benign prostatic hyperplasia (BPH) in Kerman province, southeast of Iran, using real-time PCR techniques. The aim of the present research was to clarify any association with prostatic carcinogenesis. Real Time PCR showed that HPV DNA was found in 20% of 200 PCa samples, 80 percent of these with high-risk HPV types, 40% with type-16,18, 30 % type-31,33 and 10% type 54. High risk HPV DNA was detected in only 2% of BPH samples. Values for low risk types were much higher. Our study provided a support for the role of high risk HPV infection in prostatic disease in Iranian patients, and association between presence of HPV DNA and prostate carcinoma. In particular, HPV 16 and 18 might have an important role in prostate cancer.

Keywords: Benign prostatic hyperplasia - prostate cancer - human papillomavirus real time PCR - Kerman

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Introduction

Human papillomavirus (HPVs) are classified in Papillomaviridae family and consist of 8 kb double stranded circular DNA with a nonenveloped capsid. More than 120 types of HPVs have been classified into low-risk or Non-oncogenic HPV-types (e.g., HPV-6 and 11), and high-risk or oncogenic (e.g., HPV-16 and HPV-18) types (Pierce Campbell et al., 2013). There are about 40 types are associated with lesions of the anogenital tract and with high-risk HPV infection like HPV-16, 18, 31, 33, 35, 39, 45, 52, 56, 58, and 68 is a well established risk factor for the development of carcinoma (Printz, 2015).

Prostatic cancer is an abnormal proliferation of epithelial cell of the prostate gland and it is the most prevalent cancer among men and the secondly prevalent cause of cancer mortality (Reza et al., 2012; Stolten et al., 2015). HPV types 16 and 18 are present in normal and cancer tissues of human prostate. HPV infection is a common sexually transmitted infection and its prevalence is 20-70% among men (Lupi et al., 2014; Orlando et al., 2014). Infected prostate gland by HPV can act as reservoir to spread virus by sexual activity. So this virus is sexually transmitted in adults and persistently infects prostate epithelium and sexually transmitted HPV infection can cause intra prostatic inflammation and prostate cancer (Rotola et al., 1992; Pierce et al., 2013). Recent epidemiological studies have shown that men with

a history HPV associated tumor have an increased risk of developing prostate cancer and the fifth most common cancer in the world and the second most common cancer in men is Prostate cancer (Sadjadi et al., 2007). The rate of prostate gland malignancy in the U.S.A is 154.8 per 100,000 men and in Iran, reported that the rate of prostate cancer was 5.1 per 100,000 in 1996-2000 and also In Iran, HPV prevalence was 29-37% in zabol among men (Safarinejad, 2006). The incidence of prostate cancer in Asian countries is lower than North American and North and Western European countries, and Southern European and South American countries show an intermediate prevalence (Carroll et al., 2015).

Different risk factors such as age, race, and Human Papillomavirus (HPV) infection for prostatic cancer and benign prostatic hyperplasia (BPH) have been proposed (Brody, 2015). It has been shown that prostate inflammation can be a factor in the development and progression of prostate cancer. It has been reported that environmental factors such as diet, alcohol consumption, smoking, occupation, sexual behavior, vasectomy, and physical activity influence the development of prostate cancer (Barzi et al., 2015). Due to extensive changes in epidemiological studies of various cancers and new information about the prevalence and HPV types in different countries and also non-uniform prevalence, it is concluded that Iran is one of the countries where the incidence of cancer and the HPV prevalence is high in

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Iran, which is creating a fair system for death registration, it is predicted that nearly 30 thousand people annually die from their cancer (Sadjadi et al., 2007). According to the study which is done by International Agency for Research on Cancer (IARC), the cancer incidence in Iran is located in the East Mediterranean, about 140 thousand cases, but according to other studies, this figure is estimated to be 250-200 thousand patients (Safarinejad, 2006; Sadjadi et al., 2007; Reza et al., 2012).

Human papillomaviruses detection was initially carried out using in situ hybridization, as well as direct probe hybridization, such as dot blot, and Northern or Southern blots. The molecular detection of HPV DNA using polymerase chain reaction (PCR), as well real-time PCR provide increased sensitivity and detecting a low-copy number of viral particles (Michopoulou et al., 2014). Our attempt was done to detect HPV DNA in benign prostate hyperplasia and prostate cancer specimens and we investigated the prevalence of HPV infection by different types in prostate cancer and prostate hyperplasia samples (Afshar et al., 2013). The most common infectious agents for cancer in Iran are HPV, Hepatitis B virus and Hepatitis C virus, and *Helicobacter pylori* infection which are including 85% of adult population. Therefore, with regard to incidence and high prevalence of HPV in Iran, the prevalence of HPV in patients with risk factors as well as common genotypes in patients can be documented in the report of the common genotypes of HPV in Iran, and also in the future to prevent this virus as well as comprehensive support program for cancer control and fighting with cancer in the country can be important. The present study examined the prevalence of various types of HPV viral infections in patients who are referred to the cancer center of Kerman .

Materials and Methods

Study population and samples

In a retrospective study , all samples were collected and received from different places of Kerman in Besat clinic during 2008-2015 and the Real Time PCR HPV typing test , was used to verify the positive result and their specific types . Paraffin embedded block Specimens were obtained from 100 Men with prostatic cancer and 100 Men with Benign Hyperplasia . Paraffin embedded blocks were processed using xylen for remove of paraffin that possibility of isolating DNA for HPV detection assays. This method has received approval for clinical use from the U.S. Food and Drug Administration .Cytological classification was performed by an experienced pathologist.

Specimen preparation

For isolation of nucleic acid from specimens in first step using xylen to remove paraffin from blocks in three steps and get rid of it by centrifuge, then add 200 µl of tissue lysis buffer and proteinase K for 24 hours at room temperature then material was isolated using the Total Nucleic Acid isolation kit (Roche Applied Science) as described by the manufacturer. Nucleic acid was resuspended in a final volume of 100 µl; that 10 µl was used for PCR analysis.

Real Time PCR

After isolation of DNA, samples were tested for the presence of HPV by the Real Time PCR HPV detection/genotyping assay kit (InterLab Service, Russia).General detection assays, with a broad spectrum of specificity for HPV, are now widely used for the detection of HPV in clinical specimens .HPV DNA detection kit is a hybridization assay capable of detecting 13 HR HPV genotypes simultaneously, with simultaneous assessment of the presence of the human β-globin gene as a Internal control.

Statistical analyses

Chi square and Fisher's exact Tests were used to analyze the data obtained by SPSS 11.5 software (SPSS Inc, Chicago; USA). The differences or association with $p < 0.05$ were considered statistically significant.

Results

Referring to the archive cancer registry center in Kerman, 200 paraffin-embedded tissue blocks of patients diagnosed with prostate disease with prostatic hyperplasia and prostate cancer from 2011 to 2015 were collected. All cases were diagnosed by pathologists and before study all were double checked and confirmed. According to documents of the pathology, the results represent that 100 cases have prostatic hyperplasia and 100 cases have prostate carcinoma. The distribution of patients by type of lesion diagnostic pathology and place of residence is shown in Figure 1, including urban and rural area. Also according to the type of injury, 4 different age groups were defined according to Table 1.

The minimum age of the patients with prostatic hyperplasia is 49 year and the maximum age is 90 years. The minimum age of the patients with prostate carcinoma is 50 year and the maximum age of a patient with a lesion in the study is 88 year. The mean age of patients is 67.9 years. According to Table 1 the different age groups and types of injury have significant correlation and with increasing the age, the incidence of malignant or benign types of hyperplasia increased (P value=0.004).In this study 100 prostate cancer patients were studied and 20 (20%) positive samples for papillomavirus infection was diagnosed and also from 100 samples of benign prostatic infection, 8 (8%) samples were positive. Analysis data using SPSS software showed that there is no a significant association between human papillomavirus infection and benign prostatic hyperplasia (p -value=0.464) and the result is the same in the case of prostate carcinoma (p - value = 0.413).As shown in Figure 1 from total 100 patients with prostate cancer, 75 people are in urban areas and 25 in rural areas. And also from 100 patients with prostatic hyperplasia, 96 people are in the city and 4 people are in rural areas. As can be seen there is a significant relationship between living in city and prostate cancer as an environmental factor (p value=0.005). As seen in Figure2, with increasing age, the risk of prostate diseases, including prostate cancer and prostate hyperplasia increases. So the age can be a factor involved in the development of the disease. In figure3, reveals that,

the number of lower score is more than progressive cases (high score) which is referred to the early detection of the disease by doctors. In Figure 4 shows that the HPV positive cases can be detected more in high scored cases (score 8-10) and after that lower scores (score 5-7 or 2-4) should be considered for HPV. Different types of HPV are revealed in Figure 5, possibly the HPV type 6, 11 are more common in patients with score (2-4) and in cases with score (5-7) the HPV type 31, 33 are more than other types. HPV type 16, 18 are the most common types in cases with score (8-10). Based on Figure 6, from 20 prostate cancer samples, 16 cases (80%) have high-risk type and 4 (20%)

have low-risk type of HPV. Also, from 8 positive samples with prostatic hyperplasia, 2 (25%) have high-risk type and 6 (75%) have low-risk type of HPV. Figure 7 shows that in patients with prostate cancer from 20 positive HPV samples, 16 patients (80 percent) have High-Risk HPV type and from them, 8 (40%) have type-16, 18 and 6 cases (30 %) have type-31, 33 and 2 cases (10%) of have type-54. As well as in these patients, 4 (20%) were diagnosed with Low-Risk HPV type, of which 3 cases (15%) have type-6, 11 and one case (5%) has type-6. In patients with prostatic hyperplasia, from 8 positive HPV samples, 2 cases (25%) have High-Risk HPV type, of which 1 (12.5%) has

Table 1. Frequency of Different Types of HPV in Different age Groups of Patients with Prostate Disease

Age group (years)	Prostatic Cancer		Hyperplasia	
	Low Risk	High Risk	Low Risk	High Risk
<55	0(0%)	2(2%)	0(0%)	0(0%)
55-64	1(5.8%)	8(47.05%)	2(8%)	0(0%)
65-75	2(4.16%)	4(8.3%)	3(7.14%)	2(4.7%)
>75	1(4%)	2(8%)	1(3.3%)	0(0%)

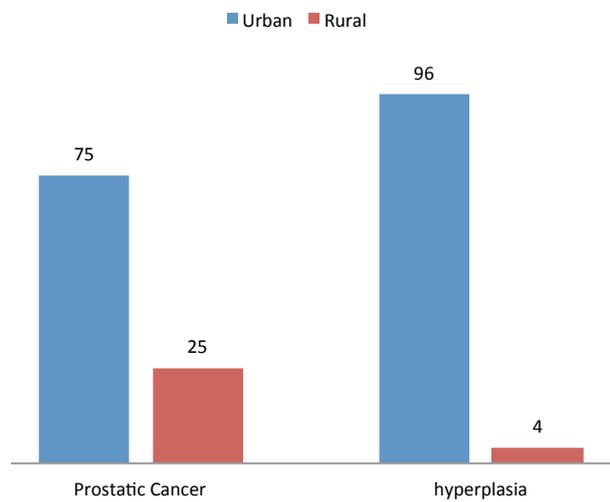


Figure 1. Distribution of Patients with Prostatic Diseases Based on the Lesion Type and Residential Area

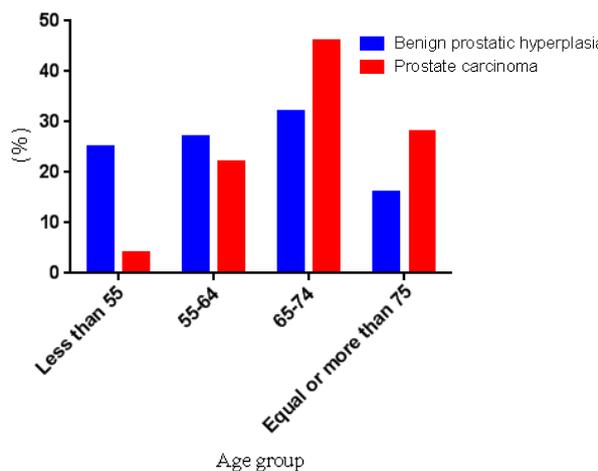


Figure 2. Distribution of Patients with Prostate Disease Based on the Type of Lesion and Age Group

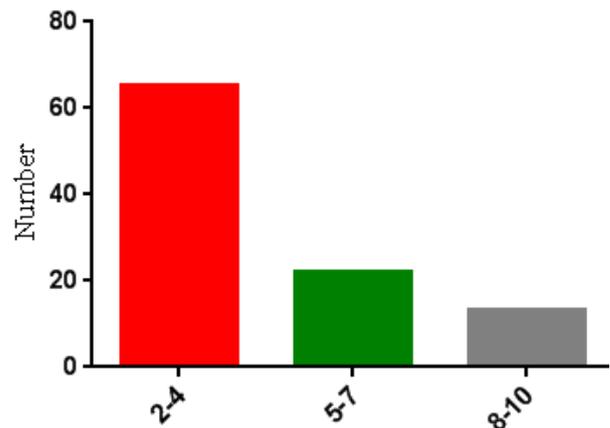


Figure 3. Distribution of Patients with Prostatic Carcinoma in Different Gleason Score (df=56, p=0.401)

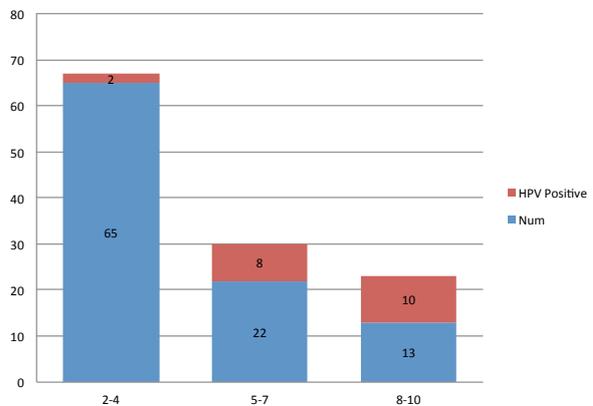


Figure 4. Frequency of Positive HPV Cases in Patients with Prostate Cancer in Different Gleason Scores

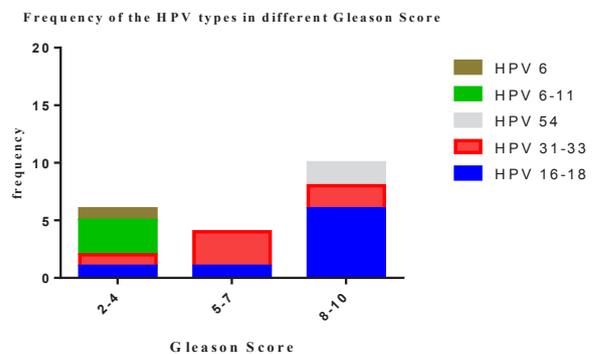


Figure 5. Frequency of Different Types of HPV in Patients with Prostate Cancer in Different Gleason Scores

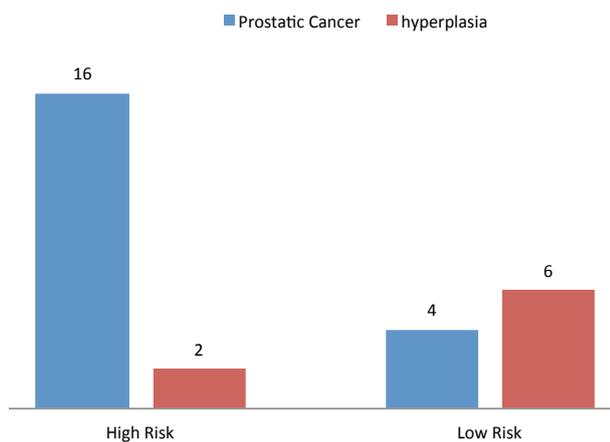


Figure 6. Frequency of High-Risk and Low-Risk HPV in Patients with Hyperplasia and Prostate Cancer

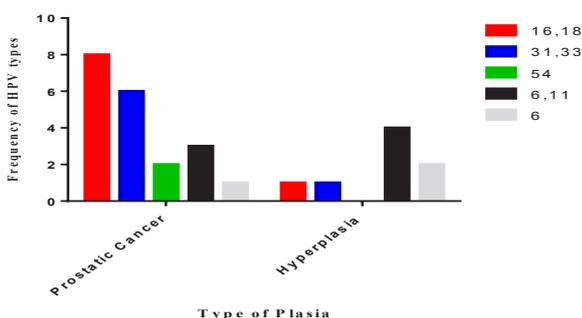


Figure 7. Frequency of High-Risk and Low-Risk HPV Types in Patients with Hyperplasia and prostate cancer

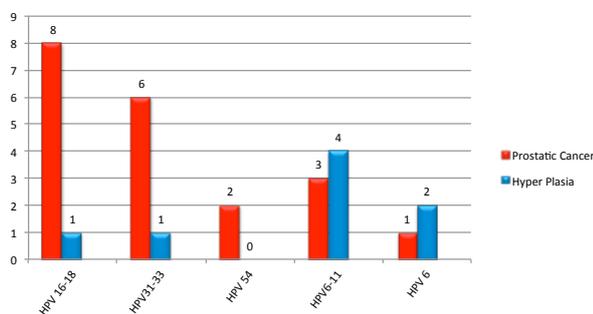


Figure 8. Distribution of Different High-Risk and Low-Risk HPV types in Patients with Prostate Disease

type- 16, 18 and one case (12.5 %) has type-31,33. Also in these patients, 6 Low-Risk HPV type detected, of which 4 (50%) have type-6, 11 and 2 cases (25%) have type-6. Distribution of HPV in Figure 8 reported that HPV type-16,18 are more common in prostatic cancer and after that type-31,33 and type 54 are placed in our data. On the other hand, type-6,11 are more detectable in hyperplasia cases. As seen in the Figure 9, the most age group with prostate diseases is between 65 and 74 year and in this group the percent of cases with prostate cancer is more than hyperplasia. The lowest age group is under 55 year and even in this group the rate of prostate cancer is more than hyperplasia. On the other hand, in age group of 55-64 or more than 75 years, the higher rate of hyperplasia has been reported. Based on Table 1, in the age group of less than 55 year only 2 percent High-Risk HPV type was detected in prostatic cancer samples. In group age of 55-64 year, 8 cases (47.05%) High-Risk and 1 case (5.8%) Low-Risk

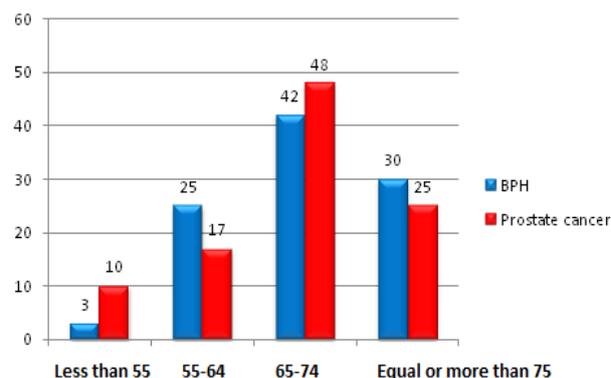


Figure 9. Prevalence of HPV in Patients According to A ge Group and type of Disease

for prostatic cancer and 2 cases (8%) Low-Risk HPV for hyperplasia samples reported. In group age of 65-75 year, 4 cases (8.3%) High-Risk and 2 cases (4.16%) Low-Risk for prostatic cancer and 2 cases (4.7%) High-Risk and 3 cases (7.14%) Low-Risk HPV for hyperplasia samples reported. In group age of >75 year, 2 cases (8%) High-Risk and 1 case (4%) Low-Risk for prostatic cancer and 1 case (3.3%) Low-Risk HPV for hyperplasia samples reported.

Discussion

In our research, the prevalence of HPV infection was investigated among patients with BPH and prostatic cancer in Kerman. The frequency of HPV in our samples was high and the rate of all HPV infection was significantly higher in prostatic cancer than BPH except typ-6, 11. The prevalence of prostate cancer in Iran is 3.6% in male aged over 40 years and likewise other Eastern Mediterranean Regions is lower than other developed countries but it is expected to have a dramatically rise in future. The rate of HPV in Iran may be due to inadequate study or racial, geographical, cultural, or other co-factors (Afshar et al., 2013).

It seems that the lower rate of prostate cancer in our samples might be due to lower rate of sexual behavior based on religious belief and culture which play an important role in reducing of sexually transmitted infections (STIs) (Boccalini et al., 2012; Chelimo et al., 2013). Some studies have been reported the HPV prevalence of 28.2-45.5% in men in the U.S.A and In Iran, HPV prevalence is lower and is about 5.5-29% (Vinodhini et al., 2012). In 2013, there were 580,350 cancer deaths in USA and among them, 306,920 were male deaths, including 29,720 from prostate cancer. The American Cancer Society proposed that about 233,000 new cases of prostate cancer will be diagnosed and approximately 29,480 men will die of prostate cancer for 2014 in the USA (Walczak et al., 2013).

Our attempt was also made to detect HPV DNA in benign prostate hyperplasia and prostate cancer specimens in Iran. To evaluate the frequency of HPV infection in prostatic samples, the INNO-LiPA test was used as a sensitive assay for the detection of all HPV types. In our study, 80% of prostate carcinoma samples showed High-Risk HPV infection and in BPH samples 25% showed High-Risk HPV infection (Afshar et al., 2013).

Several studies have focused on HPV detection and

its correlation with prostate cancer.

In a study HPV was identified in 65.3% and 48% of prostatic cancer and BPH, respectively. Carozzi F et al detected HPV in 48% of BPH and 65.3% of prostatic cancer cases in Italy (2002; Carozzi et al., 2014; Denny et al., 2014). In Argentina reported 41.5% for HPV positive in carcinoma samples, whereas all 30 hyperplasia samples were HPV-negative.

the presence of HPV DNA in 17/41 prostate specimens by PCR whereas benign hyperplasia remained negative (Niclis et al., 2011). Researcher demonstrated that there is no relation between serologic markers of HPV-16, HPV-18, and HPV-33 infections and the risk of prostate cancer (Adami et al., 2003; Rosenblatt et al., 2003). In many studies researchers demonstrated an association of prostate cancer with sexual history, particularly sexual transmitted diseases like HPV infection (Agorastos et al., 2009; Anastos et al., 2010; Antonsson et al., 2014; Alemany et al., 2015). In our survey, in patients with prostate cancer 80 percent have High-Risk HPV type and 40% have type-16,18 and 30 % have type-31,33 and 10% have type-54. As well 20% were diagnosed with Low-Risk HPV type, of which 15% have type-6,11 and 5% has type-6. In patients with prostate hyperplasia, 25% have High-Risk HPV type, 12.5% has type- 16,18 and 12.5 % has type-31,33. Also Low-Risk HPV type detected in 50% with type-6,11 and 2 25% with type-6.

In some studies have investigated a high frequency of HPV infection in BPH and PCa samples and in a study, has found a possible association between HPV and prostate carcinogenesis (de Sanjose et al., 2007; Damay et al., 2010; Iftner et al., 2010; Bosnjak et al., 2013). Our data shows that there is a relationship between living in city and prostate cancer and also the age can be a factor involved in the development of the this disease. Based on our result the lower number of Gleason Score is more than (high scored cases in progressive samples which is referred to the early detection of the disease in Iran. And also HPV positive can be detected more in high scored cases (score 8-10) but in our data, HPV type 16,18 are the most common types in score (8-10) samples.

Martinez-Fierro et al in 2010 reported no association between HPV infections and tumor aggressiveness represented by Gleason score and development and progression of the disease (Martins et al., 2014). Kuczyk et al found HPV-16, 18 in 41% of PCa cases and none of the controls and Leiros et al also found HPV- 16 and 11 in 41.5% of PCa and none of the BPH samples (Kuczyk et al., 2000). Frequency of HPV DNA in a study in USA 4.8% of prostate cancers and HPV-16 and 18 in 2% of PCa cases and 6% of metastasis but in none of the controls (Rosenblatt et al., 2003; Samsonov et al., 2012). In other study in iran HPV-16 in 13% of PCa and in Japan HPV-16 in 16% of PCa samples (Pourmand et al., 2007).

In our study, HPV type-16,18 are more common in prostatic cancer and after that type-31,33 and type 54 are important and type-6,11 are more detectable in hyperplasia cases. We designed a cross sectional study of HPV infection in prostatic diseases in Iranian population in Kerman. This study revealed higher rate of HPV infection in PCa patients than BPH patients. Thus there is a link

between HPV infection and prostate carcinogenesis. Based on our data, the HPV infection in BPH samples have been detected so the relation between HPV infection and tumor genesis can be proved. Although human papillomavirus type 16,18 are known to play a role in neoplastic disorders of the urogenital organs, the presence of HPV-6,11 and HPV-31,33 in prostatic tissues or benign hyperplasia could be interesting and weird. The differences in the percentages of results are a reflection of prevalence of HPV in patients and countries that may forms a probable cause for the differences between studies in worldwide. Other factors and co-factors might play a role in initiation and promotion of prostate carcinogenesis in our country.

Our results show possible early role for HPV in prostatic carcinogenesis as initiating agent at an earlier stage (grade) of prostatic cancer disease rather than later enhancing or promoting roles.

Because of the rate of positive HPV infection in our study, this infection could be a risk factor for prostatic cancer (in Kerman) in Iran. The higher rate of HPV infection in prostatic carcinoma than BPH indicates the role of HPV in the pathogenesis of prostatic carcinoma. The frequency of HPV in prostate cancer may be due to population, environmental, geographical, and genetic heterogeneities, beyond methodological detection differences. Some factors such as age, marital status, habitant and type of surgery can be important in HPV infected and non- infected PCa and BPH samples. It is recommended to investigate the prevalence of HPV infection in other cities in Iran with different culture and the outcome of prevention and treatment of HPV infection on prostatic cancer or hyperplasia.

In conclusion, Our results support the role of HPV infection in prostatic cancer in Iranian population in Kerman, and also this study reveals that the HPV might have a critical role in development, transformation and / or progression of prostate cancers and benign prostatic hyperplasia. This study shows that there is a relationship between living in city and prostate cancer. Also the age can be a factor involved in the development of the this disease. In this research HPV type-16,18 are more common in prostatic cancer and type-6,11 are more detectable in hyperplasia cases.

The presence of high risk or low risk HPV associated with BPH or prostate cancer might reflect an important role for this important sexually –transmitted disease in the pathogenesis of prostate. It is recommended to investigate the prevalence of HPV infection in other Iranian cities and the outcome of prevention and treatment of HPV infection on prostatic cancer.

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