Journal of
Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

Spring 2022. Vol 26. Num 1

Research Paper

Frequency of Human Papilloma Virus 16/18 Patients With Prostate Cancer by Polymerase Chain Reaction Method in Hospitals of Tabriz City, Iran

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Citation Faghany Baladehi R, Bazmani A, Ahangar Oskouee M, Jafari Sales A, Pirzadeh T, Shokouhi B, et al. Frequency of Human Papilloma Virus 16/18 Patients With Prostate Cancer by Polymerase Chain Reaction Method in Hospitals of Tabriz City, Iran. Journal of Inflammatory Diseases. 2022; 26(1):19-26. http://dx.doi.org/10.32598/JID.26.1.2

http://dx.doi.org/10.32598/JID.26.1.2

Article info:
Received: 23 Nov 2021
Accepted: 02 Jan 2022
Publish: 01 Mar 2022

Keywords:
Prostate cancer (PCa), Human papillomavirus (HPV), HPV16, HPV18, Carcinoma, Benign prostatic hyperplasia (BPH)

ABSTRACT

Background: Prostate cancer (PCa), as the fifth leading cause of death, is the second most common cancer diagnosis in men worldwide. Human papillomavirus (HPV) can potentially contribute to PCa development and chronic inflammation. HPV infection leads to malignant and benign lesions in the genital areas of men and women. The data on the role of HPV in PCa development is contradictory.

Objective: This study aims to investigate the frequency of HPV in PCa samples in hospitals in Tabriz City, Iran.

Methods: This study was conducted in a cross-sectional descriptive manner. Paraffin tissue blocks including 50 patients with primary prostate adenocarcinoma and 50 patients with benign prostatic hyperplasia (BPH) were selected from Tabriz hospitals. All samples were examined for the presence of HPV16/18 by the polymerase chain reaction (PCR) method.

Findings: 3 out of 50 PCa patients are infected with HPV18. None of the benign and malignant prostate samples are infected with HPV 16. Therefore, in our study, no connection exists between HPV and PCa. The Mean±SD age of HPV positive samples was 61.33±11.50 years.

Conclusion: The result of this research does not support the role of HPV in the development of PCa. Therefore, additional studies are necessary to clarify the possible role of HPV in prostate carcinogenesis.

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1. Introduction

Prostate cancer (PCa), as the fifth leading cause of death, is the second most common cancer in men worldwide [1]. Iran's Ministry of Health reported that cancer is the third cause of death in Iran and PCa is one of the ten most common cancers [2]. Several aspects may affect the risk of PCa in men, including ethnicity, age over 50 years, acquired and inherited genetic mutations, as well as sexually transmitted infections [3]. Few data exist about the mechanisms that cause this disease. By the way, both hereditary and environmental factors play critical roles in prostate carcinogenesis [4]. Recently, some studies have shown that some viruses, particularly human papillomavirus (HPV), may be involved in PCa development [5]. Sutcliffe et al. suggested in a study that sexually transmitted diseases (STDs) that are the main cause of HPV may play an important role in the initiation of PCa. Also, viral infections may lead to chronic prostatitis, and it is hypothesized that STD-induced prostatitis may increase the risk of PCa [6]. According to several studies, high-risk HPV interferes with apoptosis and inflammation. Also, HPV16 and HPV18 cause PCa by blocking this pathway [7].

The prevalence of HPV infection as a common sexually transmitted infection among men is 20%-70% [8]. HPV potentially contributes to PCa development and chronic inflammation [5, 9]. 5% of human cancers are related to HPV, and in meantime, HPV16, which is one of the most dangerous types of HPV with the highest prevalence in the world, plays a prominent role in all HPV-related cancers [10]. HPV infection is associated with some cancers, including cervix carcinomas, vulva, vagina, anal, head and neck, and penile cancers [11].

These viruses are categorized in the papillomaviridae family and contain 8 kb of double-stranded DNA with a non-enveloped capsid. HPV is a sexually transmitted virus and includes more than 200 genotypes. HPVs can be classified into low-risk (6, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70) and high-risk (6, 11, 42, 43, and 44) HPV types based on their association with cervical cancer [12]. HPV gene sequences are in most prostate tissues, including normal, benign, and malignant specimens [3, 5, 13, 15]. In high-risk HPV types, E5, E6, and E7 proteins overlap with tumor-suppressor proteins in cells. In addition, HPV E6 and E7 oncoproteins can alter the tumor environment by regulating some chemokines and proinflammatory cytokines and affect the host immune response [7, 16-18].

Nevertheless, the possible role of HR-HPV infection in PCa progression has not been identified. Besides, a few types of HPV (6, 11, 15, 16, 18, and 33) are associated with PCa (3, 5). It can be concluded that the incidence of PCa and HPV prevalence in Iran is high. It is predicted that approximately 30 thousand people die from this cancer every year [19]. Because high-risk papillomaviruses play a role in causing various cancers and in Tabriz, the relationship between DNA HPV detection in prostate tissue and the frequency of viral genotypes has not been well investigated. The present study examines the frequency of HPV 16 and 18 in patients with PCa.

2. Material and Methods

Study population and specimens and DNA extraction

This study was conducted in a cross-sectional descriptive manner. Among 50 patients with PCa and 50 patients with Benign Prostatic Hyperplasia (BPH) referred to Tabriz hospitals from 2016 to 2018, samples were randomly selected with formalin-fixed paraffin-embedded (FFPE). A review of patients' files and necessary demographic information was done using archive information. The number of samples is according to Cochran's sampling formula and a confidence factor of -/+5%. Patients with PCa and BPH, whose diagnosis has been proven pathologically, are the criteria for entering the study. All paraffin block samples containing tissue were cut using a scalpel blade. The samples were deparaffinized using xylene and 96% ethanol. DNA was extracted using the PAKGENE YAKHTEH DNA extraction kit (Cat. No.: 3050) and based on its protocol, it was stored at -20ºC until examination. A nanodrop device was used to measure the amount of DNA in the above solution. The OD280/OD460 ratio was used to determine the degree of DNA purity. The extracted DNA has good purity if this ratio is between 1.8 and 1.9. To control the quality of the extracted DNA, the beta-globin gene is subjected to PCR, and the optimal samples in terms of DNA extraction are suitable for conducting PCR to search for the HPV genome. DNA of HPV types 16 and 18 as positive controls from HeLa and CaSki cells.

Polymerase chain reaction (PCR) for detection of human papillomavirus (HPV) 16/18

The PCR test was conducted on all samples using HPV 18 forward and reverse primers at 0.2 pM of each (Cinnagen Co., Iran), 10×PCR buffer 2µL, MgCl2 2.5mM, dNTP 0.2mM, Taq DNA polymerase 2U (Cinnagen Co., Iran), and template DNA 1.6 µL. The final volume of each PCR reaction was 20 µL.

The PCR amplification program for the detection of HPV18 started with an initial denaturation at 94ºC for 6 minutes, followed by 35 cycles of denaturation at 94ºC 50 s, annealing at 57ºC for 50 s; extension at 72ºC for 55 s; and final extension at 72ºC for 6 minutes. The primer set for the detection of HPV18 was (F: 5-GCGCTTTGAGGATCCAACAC-3) (R:5- ACGAATGGCACTGGCCTC-3). The size of PCR product was 416 bp, which was detected using gel electrophoresis on a 1.5% agarose gel and 15 µL/dL safe stain (Cinnagen Co, Iran). The PCR amplification program to detect HPV16 was initial denaturation at 94ºC for 6 minutes, followed by 35 cycles of denaturation at 94ºC for 50 s, annealing at 57ºC for 50 s, extension at 72ºC for 55s, and final extension at 72ºC for 6 minutes.

The primer set used to detect HPV16 was (F: 5-ATGCACCAAAAGAGAACTGC-3) (R: 5-ACAAGACATACATCGACCGG-3). Gel electrophoresis was performed using 1.5% agarose gel containing 15 µL safe stain (Cinnagen Co, Iran) to detect PCR amplification of 438 bp representing HPV16. Genomic DNA of the HPV18-containing HeLa cell line and HPV18-containing CaSki cell line was used as a positive control for each PCR run.

Statistical analysis

The results were analyzed using SPSS software, version 20 (SPSS Inc. Chicago, USA) and using t test and chi-square statistical tests. $P<0.05$ was considered statistically significant.

3. Result

In the present study, 50 paraffin block samples from patients with PCa and 50 samples from patients with BPH were examined. Table 1 presents the clinical characteristics of the patients in this study. DNA of HPV types 16 and 18 are used as positive controls from HeLa and CaSki cells. The Mean±SD age of patients and BPH was 66.73±9.28 years (from minimum 47 years to maximum 90 years) and 9.80+64.38, respectively. As a result of a PCR test, only 3 of 50 prostate carcinoma samples were positive for HPV18.

Table 1. Clinical and pathological characteristics of the prostate cancer (PCa) group

Variables	Characteristics	No. (%)/Mean±SD
		PCa (n=50)
Age		66.73±9.28
Surgery	Radical prostatectomy	16(32)
	Cryosurgery	-
	No surgery	34(68)
Type of surgery	Surgery	27(54)
	Medicinal	14(28)
	No hormone therapy	9(18)
Radiotherapy	Yes	11(22)
	No	39(78)
Gleason score	Gleason <6	14(28)
	Gleason=7	4(8)
	Gleason >8	11(22)
	Indefinitely Gleason	21(42)
Place of birth	Urban	29(58)
	Rural	21(42)

PCa: prostate cancer.

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Table 2. Human papillomavirus (HPV) polymerase chain reaction (PCR) results and demographic and pathological results in prostate cancer (PCa) group

Variables		No. (%)/Mean±SD
		PCa (n=50)
Age		61.33±11.50
Surgery	Radical prostatectomy	-
	Cryosurgery	-
	No surgery	3(6)
Type of surgery	Surgery	-
	Medicinal	-
	No hormone therapy	3(6)
Radiotherapy	Yes	-
	No	3(6)
Gleason score	Gleason <6	-
	Gleason=7	1(2)
	Gleason > 8	2(4)
	Indefinitely Gleason	-
Place of birth	Urban	1(2)
	Rural	2(4)

PCa: Prostate cancer.

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The Mean age of the patients in the HPV 18 positive group was 61.33 years with a standard deviation of 11.50 years (50, 61, and 73 years) and the Gleason score in the HPV 18 positive samples had 1 sample Gleason score of =7 and 2 samples had a Gleason score ≥8. HPV 18 samples were positive without surgery, hormone therapy, and radiotherapy, one sample had an urban residence and two samples had a rural residence. It should be noted that the patients who underwent radiation therapy in this study were in the last stage of the disease, and radiation therapy was selected to reduce pain (Table 2). No significant relationship was observed between positive HPV18 and PCa (P=0.083). Other high-risk genotypes, such as HPV16 were not found in both group. No significant relationship was observed between PCa, BPH, age, residence, type of surgery, hormone therapy, and Gleason score with HPV infection (P>0.05).

4. Discussion

In this study, the presence of HPV in tissue samples of two groups of patients with PCa and patients with BPH was investigated. HPV18 was detected in 3 out of 50 PCa tissue samples by the PCR method. BPH tissues were selected as the control group, and DNA extracted from HeLa and CaSki cells was used as a positive control for HPV16 and HPV18.

The HR-HPV infection is the most common infection among young and sexually active individuals. Indeed, it is estimated that about 75%-80% of sexually active individuals will be infected in their lifetime. Even with the immune system clearing, HPV infection can persist in many people. Patients with persistent HPV infection are at high risk of developing abnormalities for various reasons, including chronic inflammation [12]. Several factors exist with a clear/less clear effect on PCa risks, such as age (>50), geographical region, mutations in some cellular genes, inflammation, and infectious agents [20, 21].

Viral infections are crucial risk factors involved in the initiation and development of approximately 18%-20% of cancers [22]. Usually, the prostate gland is caused by HPV sexual transmission through semen and infection of the mucous membrane of the genital tract, leading to the proliferation of mucous cells and the development of malignancy [23]. The incidence of PCa has increased in Iran and the death rate of this cancer is high among elderly Iranian men. There are contradictions in different studies regarding the existence of an association between HPV and PCa. In Aydin et al. 's study, only 1.7% of PCa samples had HPV DNA, and the virus genome was not seen in BPH samples [24]. In the Iranian research conducted by Abdolmaleki et al. in Sanandaj and Jafari et al. in Kerman, no relationship was observed between HPV and PCa [25, 26]. In a study conducted by Aghakhani et al. in Iran, 12.5% of the samples had HPV DNA [27]. In the studies conducted by Salehi and Hadavi in Iran, 4.41% of the samples were HPV-positive [28]. Mokhtari et al. in a study conducted in Iran showed that 10% of the samples were HPV-positive [29]. In a study conducted by Yow et al. in Australia among 115 samples, none of the samples were positive for HPV [30]. However, in another study conducted in Australia by Glenn et al., 28.57% of the samples were HPV-positive [31]. Serth et al. conducted a study in Germany, indicating that 21/27% of the samples were HPV positive [32]. Rosenblatt et al. in a study conducted in the USA showed that 12/61% of samples were HPV positive [33]. In Sweden, Bergh et al. in a study showed that none of the samples were positive for HPV [34]. In Russia, Smelov et al. in a study showed that 3/28% of the samples were HPV positive [35]. In Mexico, Medel-Flores et al. in a study indicated that 19/57% of samples were HPV positive [36].

5. Conclusion

The difference between the results of the present study and the previous studies reviewed in Iran and abroad can be due to the use of different methods to detect HPV in cancer samples, the difference in genome detection, the small number of samples examined, as well as the frequency and prevalence of HPV in infected patients. In our study, no connection was observed between HPV and PCa. In similar studies conducted in Iran and Australia, no connection was observed between HPV and PCa. Therefore, to obtain more precise results about whether HPV is related to PCa, studies with more samples and techniques are needed. If HPV infection is associated with the risk of PCa, the use of the HPV vaccine will be necessary to prevent PCa.

Ethical Considerations

Compliance with ethical guidelines

The present study was approved by the Tabriz University of Medical Sciences Ethics Committee (No.: IR.TBZMED.REC.1397.1046.

Funding

This study was supported by the Infectious And Tropical Diseases Research Center, at Tabriz University of Medical Sciences.

Authors' contributions

Interviews, sampling, sample processing, design of the study, and manuscript drafting: Robabeh Faghany Baladehi; Verification of the accuracy of the data analysis and study concept: Ahad Bazmani, Ahad Ahangar Oskouee, Abolfazl Jafari Sales, Tahereh Pirzadeh, and Behrouz Shokouhi; Co-supervision: Mohammad Yousef Memar, and Hossein Bannazadeh Baghi; All other authors honorably revised the final version of the paper, approved the manuscript, and accepted accountability for all aspects of the work.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors gratefully acknowledge the generous funding of the Infectious and Tropical Diseases Research Center, at Tabriz University of Medical Sciences, Tabriz, Iran. The authors thank the Clinical Research Development Unit, Shohada Hospital, and Tabriz University of Medical Sciences for their kind support.

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