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## Original Article

## Risk factors for human papillomavirus detection in urine samples of heterosexual men visiting urological clinics in Japan

Kazufumi Nakashima <sup>a, b</sup>, Kazuyoshi Shigehara <sup>a, b, \*</sup>, Tadaichi Kitamura <sup>b, c</sup>,  
 Hiroshi Yaegashi <sup>a, b</sup>, Masayoshi Shimamura <sup>b, d</sup>, Shohei Kawaguchi <sup>a</sup>, Kouji Izumi <sup>a</sup>,  
 Yoshifumi Kadono <sup>a</sup>, Atsushi Mizokami <sup>a</sup>

<sup>a</sup> Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Ishikawa, Japan

<sup>b</sup> Japanese Foundation for Sexual Health Medicine, Tokyo, Japan

<sup>c</sup> Department of Urology, Asoka Hospital, Tokyo, Japan

<sup>d</sup> Department of Urology, Nomi City Hospital, Ishikawa, Japan

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## ABSTRACT

**Objective:** The present study aimed to investigate human papillomavirus (HPV) prevalence and identify risk factors for HPV detection in urine samples among heterosexual men attending urological clinics.

**Materials and Methods:** Spot urine samples including initial stream were collected from 845 participants, and the cell pellets were preserved into liquid-based cytological solution. After DNA extraction from each sample, HPV-DNA amplification and genotyping were performed using Luminex multiplex polymerase chain reaction. Participants completed a questionnaire on their age, education, smoking status, sexuality, age of sexual debut, marital status, and present history of sexually transmitted infections.

**Results:** Data from 803 patients were included in the analysis. Overall HPV and high-risk (HR)-HPV prevalence in urine samples were 6.2% and 3.1%, respectively. HPV and HR-HPV prevalences were the highest in men with urethritis, and were significantly higher than those without urethritis. HPV detection was the most common in men aged 40–49 years, although significant detection differences were not age-related. Urethritis was an independent risk factor for HPV detection from urine samples, with an odds ratio (OR) of 4.548 (95%CI; 1.802–11.476) ( $p = 0.001$ ). On the other hand, a sub-analysis excluding men with urethritis demonstrated that prostate cancer was a significant risk factor for HPV detection, with OR of 2.844 (95%CI; 1.046–7.732) ( $p = 0.0410$ ), whereas was not a significant risk for HR-HPV detection in urine samples.

**Conclusion:** Prostate cancer may represent a risk factor for HPV detection in the urine of men without urethritis.

**Registration of clinical trials:** The authors did not register to Clinical Trial because this is observational and cross-sectional study.

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## 1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs) and is associated with various malignancies such as cervical, head and neck, anal, and penile cancers [1]. Recent studies have demonstrated that HPV infection

occurs in men as well as women, with the external genitalia, including the glans, penile shaft, and scrotum [2,3], being the most frequent HPV infection sites among men.

The urinary tract is reported to be an alternative site of HPV infection in men, although HPV prevalence in the urinary tract is far less common than that in the external genitalia [3–5]. Urine samples serve as a less invasive and convenient tool for HPV detection in the urinary tract. However, previous studies have suggested limited usefulness of urine for HPV screening in men because of its poor sensitivity and diagnostic capacity [2,3,5].

\* Corresponding author. Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, 13-1, Takaramachi, Kanazawa, Ishikawa, 920-8641, Japan.

E-mail address: [kshigehara0415@yahoo.co.jp](mailto:kshigehara0415@yahoo.co.jp) (K. Shigehara).

The etiological role of HPV infection in the development of urogenital cancer has been recently suggested [6–8], although the correlation between HPV infection and urogenital cancer remains controversial. Urine samples may be useful for investigating the possibility of pathogenesis of HPV infection in the urothelial epithelium. However, few studies have examined HPV prevalence in urine samples from the viewpoint of pathogenesis to the urinary tract. Hence, HPV prevalence in urine samples of heterosexual men who visited urological clinics in Japan was investigated and HPV detection rates were compared by background urogenital illness. In addition, risk factors mediating HPV detection in urine samples were identified.

## 2. Patients and methods

### 2.1. Subjects

The present study is a large-scale, cross-sectional study investigating the prevalence, genotype distribution, and risk factors of HPV infection in urine samples of Japanese male patients visiting urological clinics. Eight hundred and forty-five men who visited urological outpatient clinics in Nagareyama Central Hospital (Nagareyama, Japan), and Asoka Hospital (Tokyo, Japan) between September 2011 and October 2015 were enrolled in the study. The patients were aged 3–95 years, with the mean age of 53.4 years. Condyloma acuminata, homosexual, and bisexual patients were eliminated from the study.

Written informed consent was obtained from all patients or from their legal guardians if the patient was aged <19 years before participating in the study. The protocol and study procedures were approved by the Institutional Review Board of Kanazawa University Graduate School of Medical Science, Nagareyama Central Hospital, and Asoka Hospital.

### 2.2. Sampling

A spot urine sample including initial stream urine was collected from each patient in an individual urine cup, and 15 mL of the urine was placed into a separate tube. Each sample (15 mL) was centrifuged at approximately 1500 × g for 10 min, and the sediment was placed into a separate tube containing 2.5 mL of preservative solution for liquid-based cytology (LiquiPrep; LGM International Inc., Melbourne, FL, USA) and stored at 4 °C until use [9]. All samples were transferred to Kanazawa University for HPV analysis.

### 2.3. HPV-DNA test and genotyping

Aliquots of 800 µL of preservative solution containing the urine sediment were centrifuged at approximately 1500 × g for 10 min, and the supernatants were discarded. Cell pellets were washed twice with 300 µL of 10 mmol/L Tris-HCl (pH 8.0). DNA was extracted from the cells using a DNA extraction kit (SMI Test; G&G Science Co., Fukushima, Japan) according to the manufacturer's instructions [9]. All samples were shipped to LSI Medience Corporation (Tokyo, Japan), and HPV-DNA test and genotyping were performed using the GENOSEARCH-HPV31 kit (Medical and Biological Laboratory, Nagoya, Japan). This kit contains a probe for detecting β-globin to determine the adequacy of the extracted DNA in all samples; samples without β-globin amplification were eliminated from the analysis. This assay can be used to determine 31 HPV genotypes, including high-risk (HR) types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) and others (types 6b, 11, 26, 42, 44, 53, 54, 55, 61, 62, 66, 70, 71, 84, 90, and CP6108), by a combination of multiplex polymerase chain reaction with Luminex technology [10,11].

### 2.4. Questionnaire

At the time of enrollment in the present study, all participants completed a questionnaire on their age, education, smoking status, sexuality, age of sexual debut, marital status, and present history of STIs. All questionnaires were collected through patients' interviews with attending physicians. In addition, urological background diseases of all patients visiting the outpatient clinic were recorded.

### 2.5. Statistics

Multivariate logistic regression analysis for all variables was performed to determine the risk factors mediating HPV detection in urine samples. Odds ratios and 95% confidence intervals (CIs) were calculated, and p value of <0.05 was considered to be statistically significant. The SPSS statistical software package (version 22.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

## 3. Results

Of the total 845 patients, 7 with condyloma acuminata and 10 homosexual or bisexual participants were excluded. An additional 25 patients (3.0%) with no β-globin gene amplification based on the GENOSEARCH-HPV31 kit were excluded as their samples were considered inadequate. This resulted in 803 patients being included in the study. The patients' urological backgrounds included 38 cases of prostate cancer, 26 of bladder cancer, 73 of urethritis, 262 of benign prostate hypertrophy, 98 of urolithiasis, 113 of urinary tract infection, 37 of neurogenic or overactive bladder, and 156 of other urological diseases. Thirty-two cases with current androgen deprivation therapy, 5 post-prostatectomy cases, and one with radiotherapy were included in prostate cancer patients. All bladder cancer cases had no current disease without any additional therapies after transurethral resection.

HPV and HR-HPV prevalence across all urine samples were 6.2% and 3.1%, respectively (Table 1). HPV and HR-HPV were most frequently detected in urine samples of men with a history of urethritis, with prevalence rates being 13.7% and 9.6%, respectively. These prevalence rates are significantly higher than the rates in men without urethritis (p < 0.05). HPV detection was the most common in men aged 40–49 years, although HPV urinary detection rates did not differ significantly by age (Fig. 1). Of the HPV type distribution, HPV16 was the most frequent type followed by HPV84 and 90 (Fig. 2).

**Table 1**  
HPV prevalence by the patients' background diseases.

Data	n	Any HPV (%)	HR HPV (%)
Prostate cancer <sup>a</sup>	38	5 (13.1)	2 (5.3)
Bladder cancer	26	2 (7.7)	2 (7.7)
Urethritis	73	10 (13.7)	7 (9.6)
Benign prostate hyperplasia	262	16 (6.1)	8 (3.1)
Urolithiasis	98	6 (6.1)	5 (5.1)
Urinary tract infections <sup>b</sup>	113	1 (0.9)	0 (0)
Neurogenic bladder, overactive bladder	37	1 (2.7)	0 (0)
Other <sup>c</sup>	156	9 (5.8)	1 (0.6)
Total	803	50 (6.2)	25 (3.1)

HPV; human papillomavirus.

<sup>a</sup> 32 cases with hormonal therapy, 5 cases after prostatectomy, and one with radiotherapy.

<sup>b</sup> Urinary tract infections excluding urethritis.

<sup>c</sup> Other included 5 cases with renal cell cancer and one case with renal pelvic cancer.

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