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1. Introduction

Human papillomavirus (HPV) infection has been identified as a major risk factor for cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (zur Hausen, 2002; Bosch et al., 2002; Munoz et al., 2003). HPV infection is one of the most common sexually transmitted infections, generally asymptomatic, with the worldwide prevalence in women with normal cytology of 11.4% (11.3-11.5%; 95%CI) (WHO/ICO Information Centre on HPV and Cervical Cancer. Summary report 2010). Epidemiological studies in the USA have reported that 75% of the 15-50 year-old population is infected with genital HPV during their lifetime. Among those, 60% are with transient infection, 10% with persistent infection (confirmed by detection of HPV-DNA in genital samples), 4% with mild cytological signs, and 1% with clinical lesions (WHO/ICO Information Centre on HPV and Cervical Cancer. Papillomavirus and Related Cancers in United States of America. Summary Report 2010). To date, more than 100 genotypes of HPV have been identified, with more than 40 anogenital types, at least 15 of which are oncogenic (Munoz et al. 2003; Clifford et al., 2005). Anogenital HPV types have been further classified into low-risk types (lrHPV, e.g., 6 and 11), which are associated with anogenital warts and mild dysplasia, and high-risk types (hrHPV, e.g., 16, 18, 31, and 33), which are associated with high-grade dysplasia and anogenital cancers, such as cervical and anal carcinoma. (Bosch et al., 2002; Smith et al., 2007). In Croatia, HPV testing is widely used as a secondary test to triage borderline cytology and as a follow-up after treatment of severe cervical lesions, in addition to conventional cytological screening (Grce et al., 2007). Grahovac et al. (2007) investigated the HPV prevalence and type distribution among 361 women regularly attending gynecological examinations, and showed 67.9% overall prevalence of hrHPV in women with abnormal PAP smears compared to 35.6% in women with normal cytology. Study done by Hadžisejdić et al., (2006) on prevalence of HPV genotypes in cervical cancer also revealed high prevalence of HPV-DNA in cervical lesions; 93% in CIN III, 92.6% in squamous cell carcinoma (SCC) and 92.5% in adenocarcinoma (ADC).

While much is known about the epidemiology and pathogenesis of genital HPV infections in women, relatively little is known about the natural history of anogenital HPV infection and diseases in men. Available data suggest that, as with women, most genital HPV infections in men are asymptomatic and unapparent (Baldwin et al., 2003; Partridge & Koutsky, 2006; Dunne et al., 2006; Bleeker et al., 2008; Colon-Lopez et al., 2010). Each year in the U.S. there are about 400 men who get HPV-related penile cancer and 1,500 men who get HPV-related anal cancer (US Center for Disease Control and Prevention, STD Facts-HPV and Men, 2009).

According to the Croatian National Cancer Registry (Croatian National Cancer Registry, 2010), the average incidence of cervical cancer in 2008 was 15.6 new cases per 100,000 women, and incidence of penile and anal cancer were 1.3 and 0.4 new cases per 100,000 men, respectively.

Compared with cervical cancer, penile and anal cancers are rare diseases in the general population. However, its incidence is increasing in the general population with age. Majority of cervical, penile and anal cancers are caused by HPV-16 and HPV-18, together accounting for about 70% cases globally. The importance of different hrHPV varies between countries and regions, but type 16 has the greatest contribution to the genital cancer in all regions (WHO/ICO, Summary Report, 2010.).

Anal HPV infection and disease also remain poorly understood. Although HPV is transmitted sexually and infects the genitals of both sexes, the cervix remains biologically more vulnerable to malignant transformation than does the penis or anus in men. An understanding of male HPV infection is therefore important in terms of reducing transmission of HPV to women and improving women's health (Palefsky, 2007, 2010; Monsonego, 2011; Giuliano et al., 2011.). Improved sampling techniques of the male genitalia and cohort studies in progress should provide important information on the natural history of anogenital HPV infection and disease in men, including risk factors for HPV acquisition and transmission (Bleeker et al. 2002, 2005; Weaver et al. 2004.; Lajous et al., 2005; Nielson et al., 2007; Dunne et al., 2006; Giuliano et al., 2007.). The understanding of HPV infection and associated diseases in men has increasing importance due to advent of highly efficacious HPV prophylactic vaccines and possibility that the same vaccines may be also useful in preventing HPV infection in men. (Palefsky, 2010., Elbasha & Dasbach, 2010). Also, the impact of HPV vaccination in women, on male anogenital HPV infection needs to be assessed as well.

To date, there are no relevant studies investigating genital HPV prevalence and type distribution among men in Croatia. The aim of our investigation is to assess the prevalence and type distribution of HPV among patients visiting outpatient sexually transmitted diseases (STD) clinic, urologic and dermatovenerologic clinics in Zagreb and Rijeka, Croatia, in period between 2006 and 2008 and to compare obtained results with available epidemiologic literature data. To date there is no consensus regarding methods and recommendations for sampling or optimal male anatomic sites for HPV DNA detection. We have adapted the analytical approach by using scraped materials from external genitals and brushed exfoliated cells from distal urethral canal for HPV DNA detection and genotyping. We used consensus and type-specific primers directed polymerase chain reaction (PCR) focusing on the most prevalent lrHPV (6,11) and hrHPV (16, 18, 31, 33) accounting together for more than 80% of HPV related genital lesions globally (WHO/ICO Information Centre on HPV and Cervical Cancer. Summary Report 2010.).

2. Materials and methods

The retrospective cross-sectional study was performed among men attending STD, urology and dermatovenerology outpatient clinics in Zagreb and Rijeka between 2006 and 2008. During this period 581 men participated in the study. All men who were included in the study signed informed consent previously approved by The Ethical Committee. Saline-wetted cotton swabs were taken from urethral canal (up to 1 cm into urethral meatus) with scrapes from the penile surface including glans, coronal sulcus and penile shaft and placed into a specimen transportation medium (Digene Corp., Gaithersburg, MD). The samples containing exfoliated epithelial cells were kept at 4°C until analyses were performed. DNA was isolated by Nucleospin Tissue isolation kit (Macherey-Nagel GmbH, Duren, Germany) according to manufacturer's instruction. HPV DNA detection and genotyping was performed by consensus and type-specific primers directed PCR (Gravitt et al., 2000, Walboomers et al., 1999, Shimada et al. 1990, Fujinaga et al., 1991). The samples for HPV DNA analyses were collected by experienced physicians.

2.1 PCR analysis

To assess the quality of extracted DNA, β-globin PCRs were performed using primer combinations spanning 250 and 408 bp (Takara Biomedicals, Japan). Poor or no β-globin amplification indicated a lack of sufficient cellular material for PCR or the presence of PCR inhibitors. Primers targeting highly conserved regions within the L1 and E6/E7 open reading frame (ORF) were used to detect HPV DNA. These included the MY9/MY11 (Gravitt et al. 2000) primers of the L1 ORF and primers from Human Papillomavirus Typing Set (Takara Biomedicals, Japan), which amplify sequences within E6 and E7 ORF (Fujinaga et al. 1991). The HPV types in positive samples were further characterized by restriction enzyme digestion and type specific PCR amplifying sequences of HPV-16, 18, 31 and 33 within E6 and E7 ORF (Human Papillomavirus Detection Set, Takara Biomedicals, Japan – Shimada et al., 1990) and primers recommended by Walboomers et al., 1999.

2.2 Statistical analysis

HPV prevalence was expressed as percentage of HPV positive samples against all HPV tested cases. When determining the prevalence of hrHPV and lrHPV types, men were counted more than once if they harboured multiple infections. The prevalence of individual HPV types was determined as they appeared as either single or multiple infections. Multiple HPV infection was defined as two or more HPV types. The two times two contingency tables and Fisher's exact test were used to assess statistical significance of differences in the prevalence and distribution of hrHPV and lrHPV, and to examine the relationship between HPV types within different anatomical sampling sites. Statistical significance was established at the $p<0.05$ level.

3. Results

During study period 581 men were enrolled in the cross-sectional study, mean age was 34.6±8.3 years (range 18-54 years). They were mostly asymptomatic, self-referring to the clinics either for primary screening for STDs or having symptoms suggestive of an STD, unspecific urogenital problems, having partners with diagnosed STD or high-risk sexual

behaviour in the last several months (weeks). The patient's specimens were collected from the external genitals (scrapes from penile surface including glans, coronal sulcus and penile shaft) and exfoliated cells from the urethral canal. From the total of 581 men enrolled in the study we were able to collect 392 samples from the external genitals. In this group of 392 patients, 295 men also gave permission for urethral sampling in addition to the external genital swab (59 patients refused to give permission for urethral sampling). From 38 urethral samples β-globin PCRs were negative and subsequently considered as inadequate for HPV DNA testing. Additionally, in another group of 189 samples, swabs were taken from both anatomical sites, external genitals and urethra, and combined into one specimen. They were used in calculation of total HPV DNA prevalence as external swab specimens. By using several combinations of consensus and type specific primers, we were able to successfully amplify all specimens from external genitals and 86.8% urethral samples. The overall prevalence of HPV DNA in men was 27.4% (159/581) as shown on Table 1. and Fig. 1.

	HPV positive (%)	Low-risk HPV (%)	High-risk HPV (%)	HPV indeterm. types (%)	Multiple HPV infection (%)
Whole tested group N=581	159 (27.4%)	80 (13.8%)	82 (14.1%)	24 (4.1%)	25 (4.3%)

Table 1. Prevalence of HPV DNA in men and distribution of lrHPV, hrHPV, HPV of indeterminate type and multiple HPV infection in study group; values are number of HPV DNA positive samples and their percentage are indicated in parentheses. HPV positive = all samples with positive HPV DNA test result.

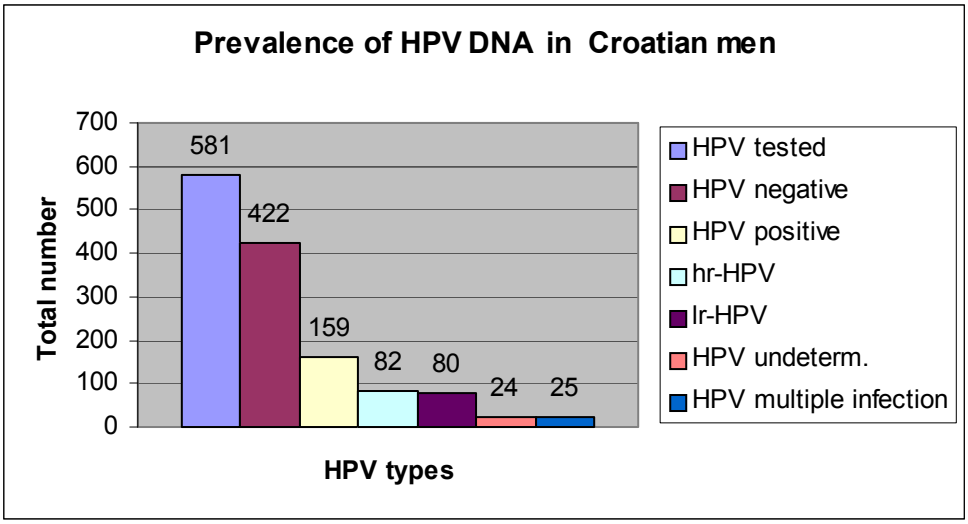


Fig. 1. Overall prevalence of HPV-DNA in study group of 581 Croatian men, presented as number of cases.

HrHPV DNA was detected in 82/581 (14.1%) and lrHPV DNA in 80/581 (13.8%) cases. Unclassified HPV type was detected in 24/581 (4.1%) and infection with multiple HPV types was detected in 25/581 (4.3%) cases (Table1.). LrHPVs and hrHPV types were detected as part of mixed HPV infections or as single infection as shown on Fig. 2.

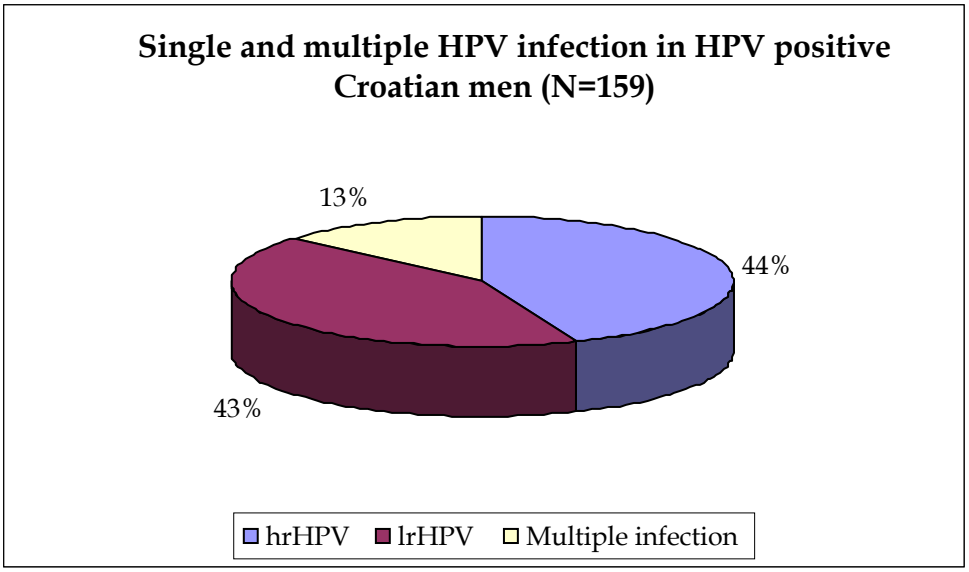


Fig. 2. Single hrHPV , lrHPV and multiple HPV infection in HPV positive Croatian men.

As single infection the most prevalent hrHPV type was HPV 16 detected in 32/82 (39%) cases followed by HPV 18 (10/82; 12.2%), HPV 31 (8/82; 9.8%) and HPV 33 (8/82; 9.8%). (Fig. 3.)

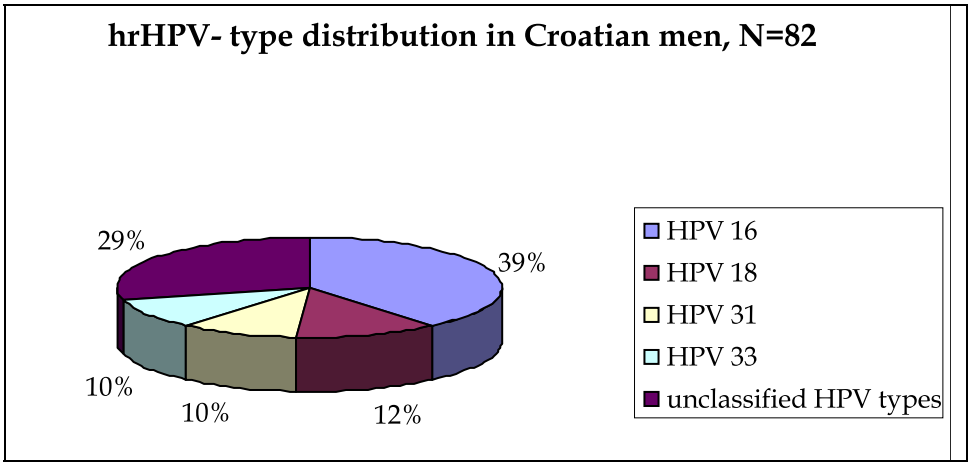
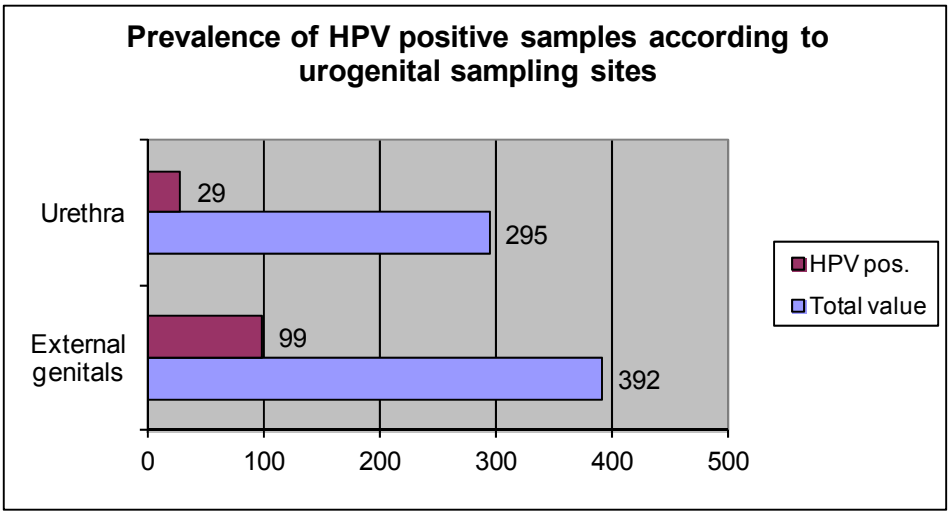


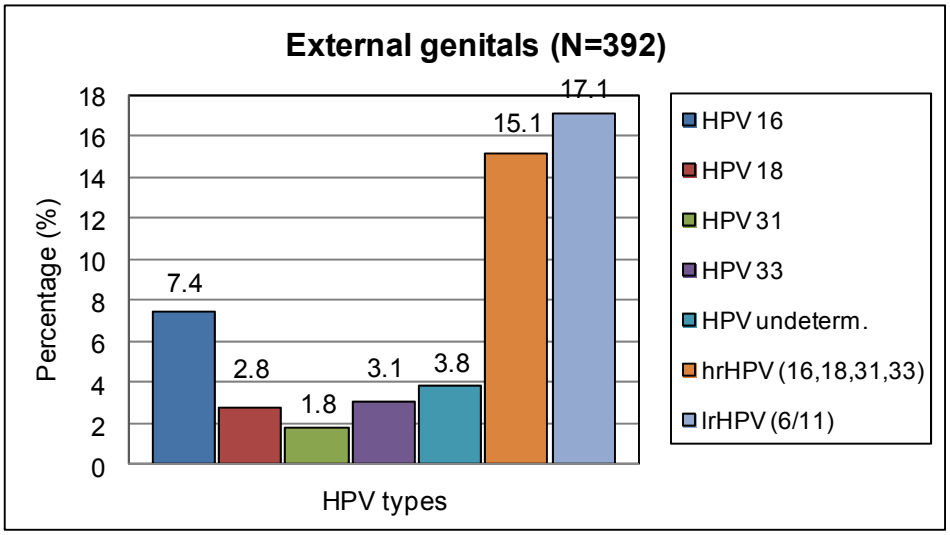
Fig. 3. Distribution of hrHPV types in HPV DNA positive cases.

Our findings indicate that in asymptomatic male the prevalence of major hrHPV, HPV 16 and HPV 18 exceeded 51.2% (42/82). Statistical evaluation revealed that the prevalence of HPV16/18 is significantly different ($p<0.0001$) compared to the prevalence of HPV31/33 (Table 3.). To determine the optimal genital anatomic site for the assessment of HPV DNA prevalence in men, we have analyzed the samples from two genital sites: penile surface and urethral canal (Fig. 4). The difference in overall HPV DNA prevalence between the penile surface including glans/coronal sulcus and penile shaft and the urethra was statistically significant ($p<0.0001$) with 25.3% (99/392), compared to 9.8% (29/295) respectively. The prevalence of lrHPV (17.1%) and hrHPV (15.1%) at external genitals was significantly different compared to the prevalence in urethral canal with 9.8% hrHPV and 7.1% lrHPV, ($p= 0.0051$ and 0.0016, respectively). Prevalence and distribution of HPV-DNA types in samples collected from external genitals (glans, coronal sulcus and penile shaft) and urethral meatus demonstrate that the external genitals are more likely to be HPV positive, harboring the risk of transmission of HPV infection between sexual partners (Fig.5).



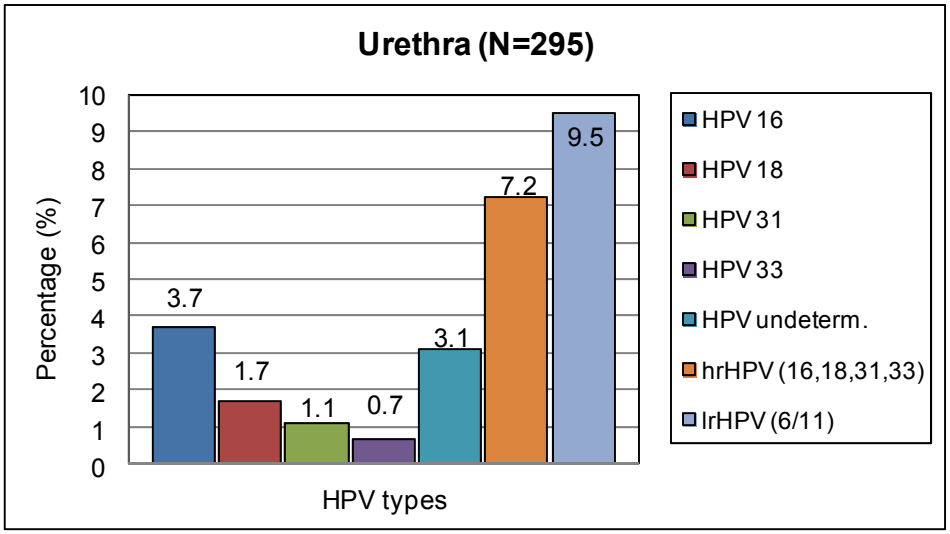
HPV pos - all samples with positive HPV DNA test result.

Fig. 4. Prevalence of HPV DNA positive samples related to different sampling site.



A

hrHPV-high risk HPV types; lrHPV-low risk HPV types; HPV undeterm.-unclassified HPV types.



B

hrHPV-high risk HPV types; lrHPV-low risk HPV types; HPV undeterm.-unclassified HPV types.

Fig. 5. Prevalence and distribution of HPV-DNA types in samples collected A) from external genitals (glans, coronal sulcus and penile shaft) and B) urethral meatus.

Anatomical sites	HPV positive	HPV 6/11	HPV 16	HPV 18	HPV 31	HPV 33	HPV indeterm.	Multiple HPV infection
External genitals (N=392)	99 (25.3%)	67 (17.1%)	29 (7.4%)	11 (2.8%)	7 (1.8%)	12 (3.1%)	15 (3.8%)	18 (4.6%)
Urethra (N=295)	29 (9.8%)	28 (9.5%)	11 (3.7%)	5 (1.7%)	3 (1.1%)	2 (0.7%)	9 (3.1%)	7 (2.4%)

Table 2. Prevalence and distribution of HPV types in HPV DNA positive samples taken from external genitals and urethra. Multiple HPV infections made impact on overall HPV prevalence while they were counted more than once; values are number of HPV DNA positive samples and their percentage is indicated in parentheses. HPV positive = all samples with positive HPV DNA test result.

Category	hrHPV positives cases	HPV 16/18	HPV 31/33	External genitals N=392	Urethra N=295	p Fisher's exact test
	82	42	16			<0.0001
HPV positive cases per sampling sites				99 (25.3%)	29 (9.8%)	<0.0001
lrHPV types *per* sampling sites				67 (17.1%)	28 (9.5%)	0.0051
hrHPV types *per* sampling sites				59 (15.1%)	21 (7.1%)	0.0016

hrHPV-high risk HPV; lrHPV-low risk HPV

Table 3. Statistical evaluation of differences in prevalence of hrHPV- HPV16/18 compared to HPV31/33 and prevalence of lrHPV and hrHPV in relation to genital sampling sites.

4. Discussion

Many questions exist regarding clinical utility of HPV testing in men. Screening for HPV infection is not recommended for men for many reasons: infection is very common, no FDA-approved test is available and finding HPV infection does not indicate an increased risk of disease or cancer in men or their sexual partners. In addition, there is no specific treatment for HPV per se (Palefsky, 2007; 2010). The evaluation and treatment of male sexual partners of women with clinical or subclinical infection (genital warts or abnormal Pap smear results) is also not known to have a clinical benefit (Bleeker et al., 2002; 2005.)

Until the last few years relatively little was known about the epidemiology of penile HPV infection, in part due to the lack of standardization of penile cell sampling techniques for HPV DNA detection. Several techniques have been published and have been used to better define the prevalence, incidence, and clearance of penile HPV infection (Giuliano, 2007; 2011; Nielson, 2007). However, the epidemiology of penile disease, its relationship to HPV infection, and the role of penile disease in transmission of HPV between partners remains poorly understood (Palefsky, 2010). Global data on prevalence of HPV infection in men are essential for future efforts to prevent HPV-related diseases.

Recent literature data demonstrate a wide range of HPV DNA prevalence among men, depending on the study population and the type and number of anatomic sites evaluated.

In populations of similar age, the prevalence of specific HPV types is usually lower in men than in women (Partridge & Koutsky, 2006). Whether this observation could be related to natural history of HPV infection in men with lower incidence or shorter duration of infection has to be determined. Differences in sexual behaviour may also be important predictors of genital HPV infection (Partridge & Koutsky, 2006).

We have obtained similar results in the pilot study conducted in Zagreb from 2003 to 2004. The prevalence of HPV DNA was investigated by consensus and type specific PCR methods in the group of 340 patients attending the outpatient STD clinic (205 female and 135 male patients). The results demonstrated that overall HPV and hrHPV prevalence (HPV 16, 18, 31 and 33) in women was 43.4% and 22.4%, respectively, and in men 25.2% and 11.9%, respectively. The lrHPV prevalence (HPV 6 and 11) in women and men was almost the same (11.2% and 11.1%, respectively) (Grahovac, 2004, unpublished data).

To our knowledge, this was the first study to examine HPV prevalence among men in Croatia. The current retrospective cross-sectional study performed among men attending STD, urology and dermatovenerology outpatient clinics in Zagreb and Rijeka between 2006 and 2008 is the first large study performed in Croatia. During this period 581 men participated in the study. The overall prevalence of HPV DNA among men in current Croatian study group was 27.4% (159/581), which is almost identical result to our previous study. For comparison, the overall HPV prevalence in men in HPV Study group from Brazil, Mexico and USA (HIM Study) was between 40% to 72.3% in Brazil, between 42% to 44.6% in Mexico and between 28.2% to 45.5% in USA. In our study hrHPV was detected in 14.1% (82/581) and lrHPV in 13.8% (80/581) cases. Unclassified HPV type was identified in 4.1% (24/581) cases and HPV infection with multiple HPV types occurred in 4.3% (25/581) cases. In HIM Study prevalence of oncogenic HPV types (type 16 and 18) was detected in 8.2% cases while non-oncogenic types (6 and 11) were identified in 8.1% of participants.

Approximately 15% of men (10-20%) in HIM Study were positive for unclassified HPV types while in our study group it accounted only for 4.1% cases. The differences should be interpreted with caution since method of genotyping in HIM Study was based on hybridization, using Linear Array HPV genotyping test (Roche Diagnostics), while we were using type specific PCR method directed to recognize the main lrHPV and hrHPV types, relevant for prophylactic vaccination. Out of hrHPV positive specimens, HPV 16 was the

predominant type found in 39 % cases, followed by HPV 18 (12.2%), HPV 31 (9.7%) and HPV 33 (9.7%). Our findings indicate that in asymptomatic male, prevalence of major hrHPV, HPV 16 and HPV 18 exceeded 51.2% (42/82). Statistical evaluation revealed that the prevalence of HPV16/18 is significantly different ($p<0.001$) compared to the prevalence of HPV31/33. HPV DNA detection was higher at the penile surface including glans/coronal sulcus and penile shaft with frequency of 25.3% (99/392), compared to 9.8% (29/295) in the urethra.

In HIM Study the prevalence of anogenital HPV infection, identified on the penis, scrotum, and perianal area, was remarkably constant as a function of age. The prevalence of anogenital HPV infection in these men was high, approximately 60%, a prevalence that is also remarkably similar to recent report of the age-related prevalence of HPV infection in men (Smith et al., 2011). In this global review, the data demonstrate that genital HPV infection in men varies widely, from 2 to 93%, both between and within high and low-risk men groups and by geographic region.

Giuliano et. al., 2011, presented recently in The Lancet a prospective study on the incidence and clearance of HPV infection in men. The results revealed important new information demonstrating considerable differences between the natural history of male and female HPV infection. Although the prevalence of HPV infection in men is higher or similar to that in women, the HPV-related disease rate in men is lower. Penile intraepithelial neoplasia (PIN) is 10-20 times less frequent than CIN and HPV-induced cancers of the penis, which are extremely rare (Monsonego, 2011).

HPV prevalence in men was between 1.3%–72.9% in studies in which multiple anatomic sites or specimens were evaluated; HPV prevalence varied on the basis of sampling and processing methods. The best anatomic sites for sampling in men—taking into consideration convenience of sampling, adequacy of the sample, and detection of HPV DNA—appear to be the glans, corona, prepuce, and shaft of the penis. It is possible that combined samples from these sites may be optimal. Scrotum samples are often adequate, but, in most studies, they were less likely to yield HPV DNA. The prepuce, when present, is possibly the best single site for HPV DNA detection. Specimens that are less useful include urine, semen, and urethral swabs. Semen and urethral specimens often have adequate β-globin and HPV DNA but are difficult and sometimes uncomfortable to collect. β-globin and HPV DNA detection is often poor from urine specimens, although these specimens could be the easiest to obtain (Bleeker et al. 2002, 2005; Weaver et al. 2004.; Lajous et al., 2005; Nielson et al., 2007; Dunne et al., 2006; Giuliano et al., 2007; D`Hauwers & Tjalma, 2009).

Persistent infection with hrHPV is the main risk factor for developing cervical, penile and anal cancer. Large and worldwide epidemiological studies will enable better understanding of natural history of HPV infection in men. They will also support the future decision making whether HPV infected men should be treated as HPV reservoir and transmitters of HPV disease and consequently screened for HPV.

5. Conclusion

Our study revealed that the overall prevalence of HPV DNA in Croatian men study group was 27.4% (159/581). HrHPV was detected in 14.1% (82/581) and lrHPV in 13.8% (80/581)

cases, respectively. Out of hrHPV positive specimens, HPV 16 was the predominant type found in 39 % cases, followed by HPV 18 (12.2%), HPV 31 (9.7%) and HPV 33 (9.7%). Our findings indicate that in asymptomatic male carriers prevalence of oncogenic types, HPV 16 and 18 exceeded 51.2% (42/82). HPV DNA was detected more frequently at the penile surface, including glans/coronal sulcus and penile shaft, with 25.3% (99/392) positive samples, in comparison to 9.8% (29/295) positive sample in the urethra. The external genitals are more likely to be HPV positive, harbouring the higher risk of oncogenic HPV type transmission between sexual partners. Our study demonstrated that the optimal anatomic sites for sampling in men considering convenience of sampling, adequacy of the sample, and detection of HPV DNA—appear to be combined sample of scrapes from glans/coronal sulcus and penile shaft.

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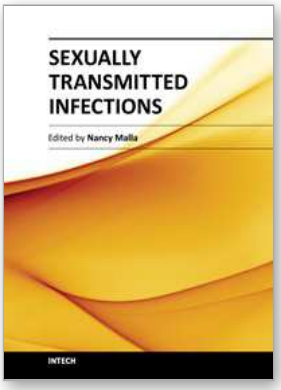

Sexually Transmitted Infections

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Sexually transmitted infections (STIs) are infections that are spread primarily through person to person sexual contact. There are more than 30 different sexually transmissible bacteria, viruses and parasites. STIs lead to high morbidity and complications. This book entitled as Sexually Transmitted Infections is not a text book but provides useful information for general reference work for physicians, researchers and students interested in the subject. Each chapter is abundant in tips useful to general readers as well. It also includes the Introductory chapter providing an overview with special emphasis on syndromic approach to the management of STIs in clinical setting.

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