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Incidence and prevalence of multiple types of genital human papillomavirus (HPV) infection in men: A study in Poland

Częstość występowania zakażeń różnorodnymi typami wirusa brodawczaka ludzkiego (HPV) mężczyzn w Polsce

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Abstract

Objectives: *Infections with human papillomavirus (HPV) are sexually transmitted. Their prevalence in males is comparable to females, but infection in men is largely unknown. Since such information is needed to establish prevention strategies, the goal of our study was to estimate the incidence of type-specific genital HPV infection among men in Poland.*

Material and Methods: *Within a multi-center clinical preventive trial, penile sampling of 826 (100%) uncircumcised and sexually active males (aged 25–69 yrs.) was studied. Peniscopy was performed in addition to routine clinical examination. DNA HPV in smears was detected by hybrid capture (HC2) and in the biopsy material by means of polymerase chain reaction (PCR).*

Results: *Twenty-three HPV types were detected, including 11 high-risk oncogenic (53–6.4% men) and in 65 (7.87%) individuals both oncogenic and nononcogenic simultaneously – altogether 118 (14.3%) and also 12 low-risk multiple nononcogenic types (248-30% men). Penile HPV prevalence was approximately 26.8%. In 53 (6.4%) cases we detected multiple oncogenic types (single HPV16 in only 17 cases – 2.1%). Penile HPV DNA was detection did not appear to be associated with age.*

Our analyses also suggested a lower prevalence of HPV infection among male participants who reported consistent condom use and fewer sexual partners. In men with history of having more than 10 sexual partners over their lifetime increased the likelihood of detecting HPV DNA.

Conclusions: *Data from our study showing a high prevalence of HPV infection in the Polish population of men will be helpful for future studies on HPV transmission dynamics.*

Key words: **human papillomavirus** / **HPV** / **genital infection** / **cervical cancer** / /**sexually transmitted disease** /

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Streszczenie

Wprowadzenie: *Oceniono, że zakażenia wirusem brodawczaka ludzkiego są przenoszo-ne drogą płciową. Występowanie ich jest porównywalne u obojga płci, ale u mężczyzn pozostaje w znacznej mierze niepoznane.*

Cel pracy: *Istnieje potrzeba opracowania strategii prewencji i celem naszych badań było ustalenie występowania zakażeń HPV i ich typów u mężczyzn w Polsce.*

Materiał i metody: *W wieloośrodkowych badaniach prewencyjnych przebadano 826 (100%) nieobrzezanych i aktywnych seksualnie mężczyzn w wieku od 25 do 69 lat. Poza rutynowymi badaniami klinicznymi wykonywano penisoskopię. DNA HPV wykrywano w wymazach metodą Hybrid Capture (HC2) oraz w materiale biopsyjnym metodą reakcji łańcuchowej polimerazy (PCR).*

Wyniki: *Wykryto 23 typy HPV łącznie z onkogennymi jedenastoma wysokiego ryzyka u 53 (6,4%) oraz u 65 (7,87%) mężczyzn onkogennymi i nieonkogennymi – łącznie u 118 (14,3%) a także 12 różnorodnych niskiego ryzyka nieonkogennych typów HPV u 248 (30%) mężczyzn. W obrębie prącia HPV DNA wykryto u 26,8% badanych. Pośród 53 (6,4%) mężczyzn, poza różnymi typami onkogennymi, samych HPV 16 wykryto u 17 (2,1%). Wykryte w obrębie prącia HPV DNA nie zależało od wieku badanego. Nasze badania również sugerują mniejszą częstotliwość zakażeń HPV u stosujących kondomy i mających mniej partnerek seksualnych. U mężczyzn mających w przeszłości powyżej 10 partnerek rosła częstotliwość wykrywania HPV DNA.*

Wnioski: *Uzyskane wyniki przedstawiają wysoką liczbę zakażeń HPV mężczyzn w badanej populacji w Polsce, a to może posłużyć do przyszłych badań dynamiki przenoszenia zakażeń HPV.*

Słowa kluczowe: **wirus brodawczaka ludzkiego** / **HPV** / **zakażenia genitalne** / /**rak szyjki macicy** /**choroby przenoszone drogą płciową** /

Background

Genital human papillomavirus (HPV) infections may be connected with the development of carcinomas and other dermoepithelial changes (intraepithelial neoplasia). Multidirectional studies showed that chronic HPV infection is a necessary, but not sufficient factor for the development of cervical cancer [1]. The presence of HPV infection in men is largely unknown. Although men are regarded as a dominant factor in infection transmission to their female sexual partners they do not develop clinically significant HPV-related lesions very often and are usually asymptomatic during relatively short lasting infections [2]. Little is known about multiple-type HPV prevalence and associated factors such as anal intraepithelial neoplasia and anal cancer in men, but probably the most common type is HPV16 [3]. The frequency of HPV infections is lower in males than in females, a finding which may be due to the lower incidence and shorter duration of infection as well as technical difficulties in selecting appropriate sites for cellular material sampling for molecular studies in males [4].

HPV genital infections in men can manifest in various clinical forms – from asymptomatic infection to squamous carcinomas. Most frequently the lesions present as genital warts, which are predominantly located at the distal parts of penis and are caused by low oncogenic risk HPV types – 6 and 11 [5]. Persistent infections with high-risk HPV types 16 and 18 are associated with development of nearly 50% of squamous penile cancer cases [6].

In Poland and worldwide, HPV infection poses a major problem for the healthcare industry since the lack of evident signs of infection in men cause the unknowing transmission of the virus to females in whom cervical cancer is prone to develop. The goal of our study was to estimate the incidence and number of type-specific genital HPV infection in men and identify the associated factors among patients in Poland.

Method

This multi-center clinical preventive trial studied 820 (100%) sexually active, HIV-seronegative, and uncircumcised patients (aged 19-80 yrs.) residing in Poland. Despite routine clinical examination, visual examination of the external genitalia, including the shaft of penis, prepuce, glans, corona, urethral meatus, navicular fossa and skin of the scrotum, as well as peniscopy to visualize the perineum were also performed. A cytologic smear was obtained from the urethra using cytobrash, and 5% acetic acid was applied to the aceto-white areas. HPV DNA was detected in the biopsy material by means of polymerase chain reaction (PCR) as described previously in other publications [8]. Five patient groups were created based on their reason for consultation and two groups based on percentile values of age. The age groups were: I – 19-33 years old (436 pts. – 54.2%), II – 34-70 (368 pts. – 45.8%). Reasons for consultation included prophylaxis (513 pts. – 62.6%), changes (ie. warts) (78 pts. – 9.5%), suspicion of HPV in their partner (46 pts. – 5.6%), changes in their partner (cancer) or HPV infection (160 pts. – 19.5%), and follow-up after HPV infection (23 pts. – 2.8%). Logistic regression analysis and Chi-square test were calculated using pack SPSS ver.17.

We searched for the relationship between the reason of consultation and the discovery of HPV, its types, and number of genotypes. We considered $p<0.05$ as statistically significant.

Results

Primarily asymptomatic men were examined for multiple-type HPV. Polymerase chain reaction (PCR) was used to estimate the amount of HPV in the materials sampled from the urethral meatus, navicular fossa, and pathological foci. Types 16, 18, 31, 33, 35, 39, 45, 51, 58, 59, and 66 were considered high-risk oncogenic, while types 6, 10, 11, 13, 30, 34, 40, 42, 53, 61, 62, and 68 were considered low-risk or nononcogenic.

Cases of mixed oncogenic/nonocogenic multi type HPV infection occurred in the following combinations: 6+16, 6+31, 6+33, 6+51, 6+53+59, 10+16, 13+51, 16+30, 16+53, 16+61, 31+30, 31+42, 31+61, 39+62, 51+61, 53+59, and 58+62; while multi type strictly oncogenic cases occurred in the following combinations: 16+31, 16+58, 31+35, and 31+59.

Overall 366 (44.3%) men had multiple HPV: high-risk was detected 118 (14.3%), and low-risk type HPV was found in 248(30%). Multi-type oncogenic HPV infection was detected in 53 (6.4%) of men and only 17 (2.1%) had infection with single oncogenic HPV16. Both oncological and non-oncological types were detected in 65 cases (7.87%).

The results of regression analysis include a 95% confidence interval (95% CI) for the odds ratio (OR), which estimated the association of the variables with the occurrence of HPV. The occurrence of HPV infection in men was significantly associated with the number of female sexual partners over the last 12 months. While men who had more that three female sexual partners (OR: 1.44, 95% CI: 1.17-1.77) in that same period suffered from greater occurrence of HPV infection than those with less than three partners (OR: 0.79, 95% CI: 0.67-0.92). Also, the occurrence of HPV infection was greater in men younger than 34 years of age than those who were 34 or older (OR: 1·08, 95% CI:0.92-1.26 and OR: 0.90, 95% CI: 0.73-1.11 respectively) as well as in those who did not use condoms when compared to those that used condoms (OR: 1.40, 95% CI: 1.14-1.72 and OR: 0.8, 95% CI: 0.68-0.93 respectively); however, the differences were not statistically significant. (Figure 1).

The occurrence of oncogenic HPV infection in men was significantly higher in men who did not use condoms (OR: 1.82, 95% CI: 1.41-2.35) when compared to those who used condoms (OR: 0.58, 95% CI: 0.39-0.84). While men who had more that three female sexual partners in the last 12 months (OR: 1.86, 95% CI: 1.44-2.04) in that same period suffered from greater occurrence of HPV infection than those with less than three partners (OR: 0.57, 95% CI: 0.39-0.83).

Although regression analysis did not reveal a relationship between condom use and the prevalence of oncogenic HPV, the Chi-square test showed a relationship regardless of age (p>0.0001). The failure of regression analysis to confirm the relationship of condom use may result from a common variance of this factor with the number of partners in the past 12 months.

The age of men was not associated with the occurrence of oncogenic HPV, despite the slightly greater occurrence of oncogenic HPV in men younger than 34 years of age (OR: 1.05, 95% CI: 0.80-1.37) when compared to those 34 or older (OR: 0·94, 95% CI: 0.66-1.33).

The occurrence of nononcogenic HPV infection in men was also significantly higher in men who had more than three partners in the last 12 months (OR: 1.14, 95% CI: 0.86-1.52) when compared to those with less than three partners (OR: 0.92, 95% CI: 0.77-1.10). Statistically insignificant results referred to the higher prevalence of nononcogenic HPV in men below 34 years of age (OR: 1.01, 95% CI: 0.82-1.24) when compared to men 34 or older (OR: 0.98, 95% CI: 0·77-1.26) and in those who did not use condoms (OR: 1.12, 95% CI: 0.84-1.49) when compared to those who did (OR: 0.93, 95% CI: 0.78-1.11).

The occurrence of mixed HPV infection was significantly higher among men with more than three sexual partners in the past 12 months (OR: 1.23, 95% CI: 0.72-2.10) when compared to men with fewer partners (OR: 0.88, 95% CI: 0.59-1.29).

A marginally higher occurrence of mixed HPV also occurred in men aged below 34 (OR: 1.37, 95% CI: 1.04-1.80) when compared to med aged 34 or older (OR: 0.56, 95% CI: 0.26-1.21). The use of condoms was not significantly associated with mixed HPV despite the greater incidence among men using condoms (OR: 1.20, 95% CI: 0.70-2.06) when compared to those who did not use condoms (OR: 0.88, 95% CI: 0.60-1.30).

It should also be noted that multi-type HPV was not significantly associated with age, condom use, or number of partners in the last 12 months. (Figure 2).

Penile HPV DNA detection did not appear to be associated with age. Our analyses also suggested a lower prevalence of HPV infection among male participants who reported consistent condom use, and fewer female sexual partners. In men having a history of more than 10 female sexual partners over their lifetime, an increased likelihood of detecting HPV DNA was observed (data not shown).

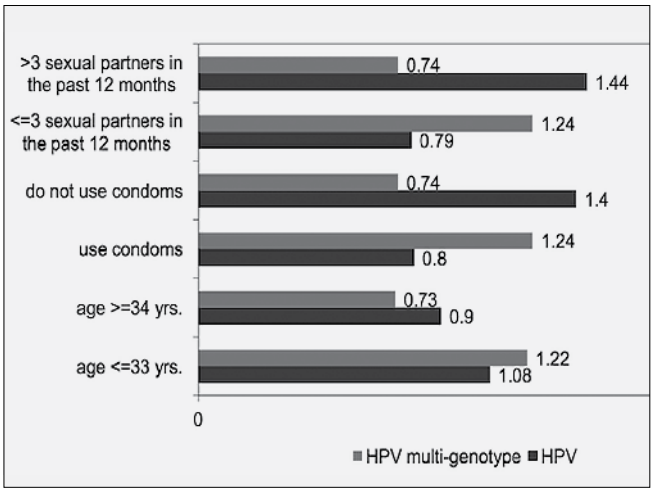

Figure 1. Odds ratio (OR) of single and multi-genotype HPV infections as related to age, condom use, and number of sexual partners in the last 12 months.

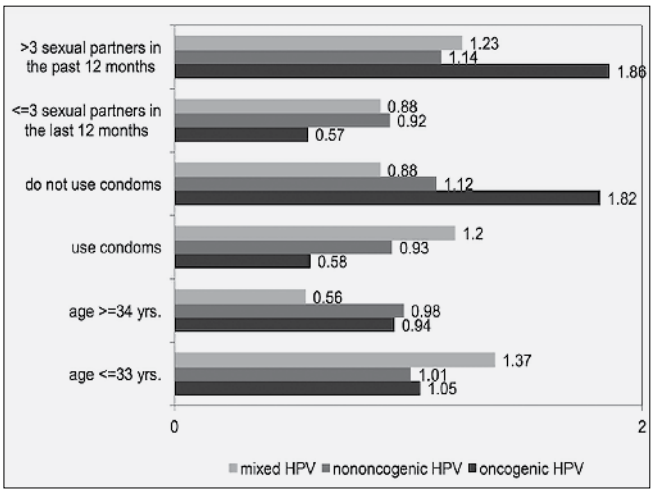

Figure 2. Odds ratio (OR) of oncogenic, nononcogenic, and mixed HPV infections as related to age, condom use, and number of sexual partners in the last 12 months.

Discussion

HPV prevalence and incidence is similar among men and women [8]. HPV causes infections in the stratified epithelium of the skin or mucous membranes. Many types of HPV are sexually transmitted and infect the anogenital region. Some HPV types cause genital warts, while persistent infections with other HPV types can lead to precancerous lesions and invasive cancer [9, 10]. The common sexually transmitted infection of HPV is the most important risk factor for cervical cancer. Little is known about multiple-type HPV prevalence and associated factors in men, although men contributed the main source of infection [11]. HPV infection of the uterine cervix is known to be a very important risk factor for the development of cervical intraepithelial neoplasia (CIN) and invasive cancer. Infection of HPV, even though it affects both sexual partners, is presently most often investigated in females; however, the male plays one of the most important roles in the causation of cervical cancer [12].

Many studies have confirmed the relationship between the presence of HPV infection in the male genitals and the risk of uterine cervix cancer in their partners. In many male studies only subclinical infections were detected [12]. Detection of multiple HPV types in our study of primarily asymptomatic men was common, particularly at the urethral meatus (navicular fossa) or any other external genital sites. Penile HPV prevalence was approximately 39-89% among men in Poland. This data will help inform studies on HPV transmission dynamics. In our opinion, urethral cytology should be routinely used in association with peniscopy as a screening test for the detection of HPV infection in men who are partners of women with HPV-induced lesions.

Studies performed in Mexico, Brazil, and the USA showed that half of adult men may be infected with the HPV and also that about 6% of men are newly infected with HPV 16 each year. The study was comprised of 1159 men who were HIV negative and reported no history of cancer, aged 18 to 70 years. Moreover, men who had 50 or more female partners were at 2.4 times increased risk for oncogenic HPV infections versus those with one or no partners. The risk for men who had at least one male sexual partner was 2.6 times higher than a man with no recent partners. To this point, HPV vaccination has been uncommon in males. It should be noted that as more diseases are prevented through the vaccination of males; however, routine vaccination for both sexes should prove to be more cost effective [2].

Recently it has been established that the HPV vaccines elicit robust antibody responses in men and are safe and efficacious against HPV infection and external genital lesions among young men [13, 14]. The vaccines against types 16 and 18 could prevent two-thirds of invasive anal cancers and one-third of penile squamous cell carcinomas [15, 16], and the quadrivalent HPV vaccine would prevent the majority of genital warts cases.

The clinical significance of multiple HPV infections (with both high-risk and low-risk types) is unknown, but it is possible that non-oncogenic HPV types contribute to enhanced keratinocyte proliferation resulting in facilitation of oncogenic HPV infection [17]. HPV infections with more than one HPV type were considered as high-risk if any HPV type detected was high-risk [18].

In summation, it is estimated that half of sexually active males and females will become infected with HPV during their lifetime [19]. Most individuals infected with HPV are asymptomatic, but 4% of sexually active males in the USA report having a history of genital warts, and persistent infection with HPV among males may lead to penile, anal, and head & neck cancers [20, 21, 22]. The HPV vaccine protects males and females against cancers caused by types 16 and 18 and genital warts caused by type 6 and 11 [23]. In addition, vaccinating males will indirectly assist in the prevention of HPV-related diseases (ie. cervical cancer) among females [22]. The clinical significance of multiple HPV infections (with both high-risk and low-risk types) is unknown, but it is possible that non-oncogenic HPV types contribute to enhanced keratinocyte proliferation resulting in facilitation of oncogenic HPV infection [22, 24].

Conclusion

Since men may transmit HPV infection to their female sexual partners, cervical cancer prevention strategies are needed and should include the use of prophylactic HPV vaccines.

The data obtained from our study showed that genital HPV infection is common in the Polish population of men and will be helpful for future studies on HPV transmission dynamics.

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