The risk of cervical cancer in female partners of HPV –infected males

Marek Sikorski
Faculty of Medical Sciences, The Jan Kochanowski University of Humanities and Science, Kielce, Poland

KEY WORDS

cervix of uterus ◗ HPV ◗ cervical cancer ◗ circumcision ◗ condoms

ABSTRACT

Persistent cervical infections with highly oncogenic strains of HPV risk are considered to be a necessary though not sufficient cause of cervical cancer development, the second most common malignant neoplasm in terms of incidence in young women (after breast cancer). Sexually active men, independently of age, in whom genital HPV infections are the most commonly sexually transmitted conditions, are most important reservoir and vector of HPV transmission to their sexual partners. Infectivity of HPV is extremely high, therefore the risk of acquiring the infection by women is considerably high even after a single sexual encounter (even if non-penetrative) with infected male, and significantly increases along with the lifetime and the recent number of sexual partners, decreasing age of sexual debut and intensity of sexual contacts. Due to the characteristics of HPV infection, condom use reduces the risk of acquiring the infection moderately but its efficacy under optimal conditions does not exceed 70%. Polygamic male sexual contacts significantly increases the risk of infection of permanent partner. Circumcision seems to reduce the risk of cervical cancer in female partners by reducing the prevalence of HPV infections in circumcised males, particularly in promiscuous ones and those lacking in genital hygiene.

INTRODUCTION

Cervical cancer is the second most common malignant neoplasm in terms of prevalence and incidence in females globally (after breast cancer). Age-adjusted incidence reaches 10 cases per 100 000 females in many developed countries and peaks around 40 cases per 100 000 in some developing regions. For several years the statistics have shown that every four out of five cases of invasive cervical cancer were diagnosed in developing countries [1]. Decrease in the incidence of cervical cancer observed in the United States and several European countries is mainly ascribed to the introduction and strict execution of prophylactic programs, based on exfoliative cervical cytology (Papanicolau tests).

The etiology of cervical cancer is complex, however for several years it has been widely accepted that apart from numerous factors increasing probability of the development of this cancer (cofactors) there is one in particular, which is necessary though not sufficient. Epidemiological and laboratory data strongly show that the persistent cervical infections with highly oncogenic strains of Human Papillomavirus (HPV) are reguired for cervical cancer development.

CERVICAL HPV INFECTION AS THE NECESSARY FACTOR IN CERVICAL CANCER DEVELOPMENT

The concept of necessary factor assumes that it is present in all the cases of cervical cancer and in the absence of this factor cervical cancer can not develop. Simultaneously, it is not sufficient for carcinogenesis [2]. Muluiple epidemiological observations, reveal that extremely frequent genital HPV infections do not result in any significant morphological lesions being in vast majority only transient and quickly and spontaneously resolving (usually during 1 year), supporting the idea that HPV alone is not enough to effectively transform the cervical epithelium.

The influence of additional factors (smoking, prolonged hormonal contraception, high parity, coinfections of other pathogens – HIV, EBV, HSV, *Chlamydia trachomatis*, genetic predispositions, immune deficits), can be linked in many ways to the, natural history of cervical cancer, though the precise point(s) of their interaction is hardly known so far [3]. They can increase the susceptibility of cervical epithelium to HPV infection, cause prolonged retention of replicating HPV virions, induce integration of HPV DNA into the host genom, stimulate the growth receptors, or/and cause mutations. Accumulation of uncorrected mutational defects in the pool of hyperproliferating keratinocytes, driven by the influence of HPV oncoproteins which deregulate epithelial cell cycle, may lead to acquisition of neoplastic geno- and phenotype of these cells. The relation between HPV infection and cervical cancer meets all criteria defined by IARC, which must be met to be consided as a causative agent [2]. Below the summary of most important pieces of data confirming the causality of HPV and cervical cancer relation is presented bellow.

1. Strenght of the association. The parameters reflecting the strength of the association are odds ratio – in retrospective studies, and relative risk – in prospective studies. The broad and multicenter epidemiologic studies carried out by Muńoz and al. under auspices of IARC revealed the presence of HPV DNA (detected by PCR method with consensus primers GP5+/6+) in 96.6% of women with cervical cancer and in 15.6% of women from the control group [4]. For all HPV types assessed in this study the odds ratio for its relation to cervical cancer was calculated to be higher than 158. Most frequently detected HPV types were HPV 16 (in over 50% of cervical cancer cases), HPV18 (20% cases), 31 and 45 (odds ratio for particular HPV type respectively: 434, 248, 198, 129). It is a unique relation of factor to cancer in oncology with such a high odds ratio value; in contrast, the odds ratio in the relation between HBV infection and primary liver cancer is between 50 and 100, and between smoking and lung cancer – 10.

2. Consistency of the observations. Independen of molecular methods for HPV DNA detection (with signal amplification or amplification of DNA with different sets of primers) the consistency of results is striking in case-control studies. For the apparent reason the application of molecular methods with lower analytical sensitivity (studies from early 90s) yield lower prevalence of HPV DNA in cervical cancer tissue. Apart from differences in regional distribution of HPV types, the studies are consistent independen on the population under observation or cervical cancer incidence rates in the given area [5]. Currently there is no study available that contradicts the primary relation between HPV and cervical cancer. The question whether there is a very tiny subpopulation of squamous or glandular cervical cancers that do not constitutively host HPV DNA (apart from extremely rare cases of neuroendocrine HPV-

negative cervical caners) remains open. Several percent of HPV-negative cervical cancers may reflect their different etiology (which is unlikely) or this may be due to suboptimal sensitivity of applied methods for DNA detection (which seems to be plausible).

3. Specificity of the reaction. The specificity of the reaction is confirmed by observations that HPV is present in nearly all cases of cervical cancers, but only in about 50% of vulvar and vaginal cancers, and in about half of penile cancer cases in males. Based on cervical location it is now apparent that squamous cancers are mainly associated with HPV 16, whereas glandular cancers – mainly with HPV 18 [6].

4. Time-dependence. It is a *sine qua non* condition of causative relation, that the action of causative factor precedes the formation of cancer. Frequently cited data on incidence of cervical cancer emphasizes a long gap reaching 10 years between the peak incidence of HPV infections and the peak incidence of dysplastic lesions followed by another few years for the peak incidence of cervical cancer [7]. There are well-known results of multiple prospective studies which revealed that persistent HPV infection occurs many years prior to the formation/detection of cervical intraepithelial lesions [8, 9].

5. Dose dependency. Molecular quantitative analysis strongly suggest that the risk of cervical intraepithelial lesions is increased when a great number of HPV DNA copies (viral load), particularly HPV 16, are detected [10]. Simultaneously, the increase of HPV load in low grade cervical intraepithelial lesions (CIN-1 – cervical intraepithelial neoplasia) is associated with eight times higher risk of progression of these lesions to higher grades (CIN -2-3) [11].

6. Mechanisms of the neoplastic transformation, in which HPV is involved, are probably the best-known in oncology. The basis of oncogenic properties of HPV are formed by the interaction of viral protein E7 with cellular protein pRb which allows a potent transcription factor – E2F to disassociate, leading to a cell cycle block in G1 phase. Moreover, due to viral protein E6 activity there is a disruption of the p53 protein structure observed, which leads to inhibition of apoptotic elimination of genetically altered cells. The activation of telomerase and the amplification of the response to growth factors are the additional features of viral oncoproteins [12].

7. Experimental induction of the neoplastic lesions was successfully accomplished in the early 80s. both in keratinocytes cell cultures and in animal models. Epithelial cells gained neoplastic features after transfection with HPV oncogenes (E6/E7). Blocking expression of these transfected genes reduces significantly the neoplastic phenotype of the transformed cells [13].

8. Prevention of cervical cancer is possible through active immunization with HPV molecules, as it was demonstrated by the latest large studies on prophylactic vaccines against HPV: quadrivalent (HPV types 16, 18, 6, 11) and bivalent (HPV types 16 and 18). The immunization of HPV-naive young women with quadrivalent anti-HPV vaccine resulted in nearly 100% protection against necessary precursors of cervical cancer i.e. HPV 16 and/or 18 [14, 15]. It provided also the protection against precursors of vaginal and vulvar cancers (i.e. HPV 16 and/or 18), as well as against genital warts (benign condition) caused by HPV 6 and/or 11 [16]. The results from trials on bivalent vaccine confirmed its efficacy in preventing cervical intraepithelial neoplasia grade 2 or/and 3 of the HPV 16/18 origin [17].

HPV INFECTIONS IN MALES

The diagnosis of HPV infection in males, similarly to tests used in female diagnostics, is currently based on the detection of certain sequences of viral DNA with the use of signal amplification methods [as Hybride Capture (HC)] or with amplification of target fragment of DNA in PCR-based (polymerase chain reaction) techniques. In epidemiological studies clinical examination as well as cyto- or histological assessment methods are not applied due to their low sensitivity and suboptimal specificity [18]. Serological assays, due to their low specificity, are of limited value [19]. The proportion of positive results of HPV DNA examination increases along with the number of anatomical location which have been sampled in a given subject (penile shaft skin, foreskin, scrotum skin, glans penis, external urethral orifice, perianal region, urine).

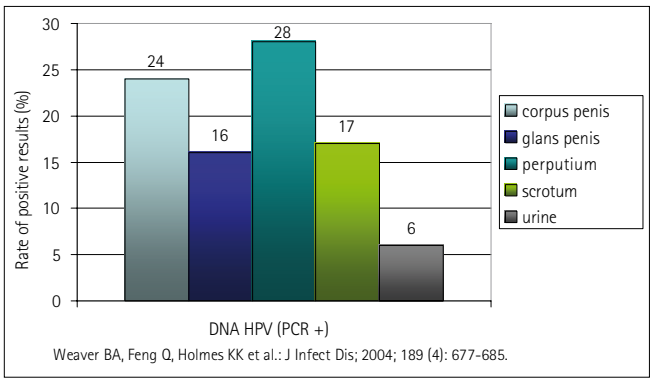

Fig. 1. Incidence of asymptomatic HPV infections in men in association with anatomic localization.

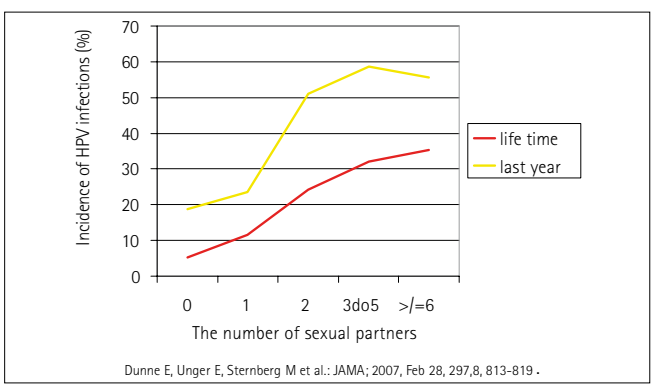

Fig. 2. Incidence of HPV infections in association with the number of all sexual partners and the number of sexual partners met during the last year.

Partridge and Koutsky analyzed several published epidemiological studies and reported broad range of asymptomatic HPV infections prevalence: from 3.5% to 45% [20]. Despite this diversity of prevalence, the association with male age, genital sampling site or type of PCR primers used were disclosed. Infections with highly oncogenic HPV types were diagnosed more frequently than with low risk types, with ranges respectively: from 2.3% to 34.8% and from 2.3% to 23.9%. Among all high risk HPV types, HPV 16 was the most frequent in all studies, apart from the work of Lajous et al, in which most frequently HPV 59 was found [21].

On the contrary, in females the dependency of age of HPV infection is very clear, with its peak prevalence in 20-25-year old females, reaching 20% then, or according to the newest data even exceeding 40% [22], and then slowly decreasing to the level of 5-8% at the age of 45 or more. Perimenopausal second peak of HPV prevalence is currently under discussion.

HPV TYPES CONCORDANCE BETWEEN SEXUAL PARTNERS

It should be emphasized that this concordance in not perfect, though far from random ($p = 0.01$) [23]. In the early, relatively large study of

Hippeleinen et al., in which 270 couples were enrolled, all women showed pathological cytological reports and simultaneous presence of HPV infection in both partners was documented in 24.4% of cases, from which only 22.7% showed concordance with the infecting HPV type, which gives a small proportion of partners being at the same time infected with the same type of HPV (6%) [24]. The study carried out in the fertility clinic yielded 17% concordance rate with simultaneous presence of HPV 16 in both partners [25]. Authors of this study claimed, that the concordant HPV types in both partners from the studied couples occurred in 35% of cases. The presence of HPV infection in female and no infection in male in the studied time point is far more frequent than the opposite situation. Similar results (32% HPV type concordance) have been obtained in the study from sexually transmitted diseases clinic. It was also noted that concordance is decreasing along with time elapsing from the last reported sexual intercourse [23]. In general population the concordance of HPV types in partners was significantly lower. Among couples enrolled by Castellsague et al. the presence of HPV infection was documented in 66%. However, the study showed only 2% concordance rate with HPV types [26]. At the same time the prevalence of HPV in males who were partners of females with CIN was significantly higher than in males being partners of HPV positive females, but with negative cytology results. The other study revealed the correlation between proportion of HPV 16 present simultaneously in both partners with the morphological lesions of the cervix: if negative cytology results were obtained, HPV 16 was detected in both partners only in 0.02% of couples, whereas in 3% in cases with preinvasive cancer or CIN 3, and in 4% in invasive cervical cancer [27].

The situation, in which the male partner of women with significant HPV- related cervical lesion is negative as for respective HPV type, is rather frequent. It can be explained by differences in dynamics of HPV infection between males and females – quick remission of infection in male is accompanied by prolonged retention (in favorable circumstances) in female, which may lead to CIN or invasive cancer formation. In some cases the examined partner of woman with positive HPV DNA results may be „inadequate" to be tested – the infection might have been acquired from the other partner. It was widely described that in many cases of advanced intraepithelial lesions or cervical cancers HPV replication is extremely slow and virions release remains minimal – the possibilities of detection of infection are then limited. It was also suggested that the concordance in HPV types is increasing with the higher viral load (increased HPV DNA copy number) [28]. The cited study revealed that in 57.8% of infected males the HPV type detected in their female partner was of the same type. This relation, again, is statistically significant ($p < 0.001$).

The presence of HPV infection in females not having penetrative sexual encounters is infrequent, though possible. The examination of material sampled from vagina and vulva of virgins defined in Winer's et al. study as women having never been engaged in penetrative intercourse, revealed some small proportion of HPV positive cases (1.7%) [29]. In more than 20% of those infections HPV 16 was detected. Cumulated 24-months HPV infection incidence in virgins reached in this study 7.9%. It should be emphasized, however, that this incidence was mainly dependent on non-penetrative sexual activity of the questioned women. In the subgroup of virgins not engaged in any form of sexual contacts the incidence was only 2.4%, whereas in the subgroup of those who were engaged – 15.3%.

For women with penetrative sexual intercourse other forms of sexual contacts (finger-vulva, penis-vulva, oral) the risk of HPV acquisition was not increased, but any of these non-penetrative forms of contacts were associated with increased risk for virgins. Prevalence of genital HPV infections in virgins with such described activity reached 9.7%, while in virgins with no contacts – only 1.3% [29].

HPV INFECTIVITY

There is no empirical data available so far to demonstrate the proportion of HPV infection acquired after single exposition during sexual contact with infected partner. High infectivity is suggested indirectly by data coming from early observations on genital warts [30]. According to this data genital warts were developed in 60% of female partners of males with genital warts (9 months observation period), which strongly indicates high infectivity of low-risk HPV strains.

Observations concerning transmission of high-risk HPV types are mainly based on static studies on HPV types concordance in sexual couples, previously described in details. The main conclusions of these observations are that the HPV type concordance is higher than random and it increases with viral load and with shortening the time between the sexual intercourse and sampling. The published studies often enrolled women with preexisting morphological HPV-related cervical lesions and therefore the results may not reflect the HPV infectivity between partners with asymptomatic infections. The sexual intercourse, which resulted in HPV infection of a prolonged nature and eventually CIN, must have been encountered many months (or years) before the current partner was tested and in whom the infection might have already been cured.

In all cases of sexually transmitted infections the dynamics of pathogen transmission depend on three factors: (i) the infectivity of pathogen as a probability of transmission after exposition; (ii) the probability of exposition, sexual contact between infected and uninfected people (iii) the duration of infection. It is relatively easy to assess the last two factors. However, the major problem is the assessment of HPV infectivity.

Relying on data from HPV infection incidence among students from USA the stochastic simulation model was constructed. The 40% median of probability of HPV transmission from male to female during single sexual contact meant that 100% certainty of that transmission would be obtained after 11 unprotected penetrative intercourses [31]. The similar results only with higher probability of single intercourse transmission probability (60%) were obtained when calibrating the model according to the epidemiological data from Finland [32]. Such high infectivity of HPV allows to predict that the women would get infected after very few first contacts with infected partner.

The infectivity calculated in the presented model is relatively high in comparison to other viral infections but comparable to infectivity of some other sexually transmitted diseases of bacterial etiology. Probability of transmission of HIV or HSV-2 during single intercourse is 1/1000, however for HIV it may be even ten folds higher with high viral load in semen [33, 34]. According to Burchell, the infectivity of *Chlamydia trachomatis* reaches 20%, for gonococcal infection – 50%, for lues – 60% and even 80% for *Hemophilus ducreyi* [33].

LIFETIME NUMBER OF SEXUAL PARTNERS

There is a large diversity in the lifetime number of sexual partners reported by questioned women: from 1 up to over 50. It is very likely that some women, particularly those who are more sexually active, consciously limited the declared number of partners they have had intercourse with. This may bring some important bias into the epidemiological studies, causing the occurrence of a *plateau* in relation between the lifetime number of sexual partners and the HPV infection prevalence. It was proved that the

odds ratio for acquiring HPV infection was nearly doubled (1.85) in women who had two lifetime sexual partners in comparison with females who reported only one partner. The risk of infection was statistically increased even more with three partners (OR – 2.26 in comparison to one partner), however, any additional increase in number of lifetime partners did not increase the risk significantly (OR 2.45 for four or more partners in comparison to one only) [35].

The risk of HPV infection associated with having more than one lifetime sexual partner is slightly elevated for younger females (<25 years – OR: 2.41) when compar with females over 25 year (OR: 1.70). Even in this report the data was not clear. Mościcki has proved continuous minimal increase of the infection risk with any additional lifetime sexual partner (1.06 relative risk of infection for any lifetime partner) [36], similarly to Dunne, who documented permanent, statistically significant elevation of HPV infection prevalence along with increasing lifetime number of sexual partners [37]. Women, diagnosed with multiple types HPV infection and women with high risk HPV types reported insignificantly higher number of lifetime partners than women with single type infection or infection with low risk HPV types. The differences are not significant, however [35].

NUMBER OF RECENT SEXUAL PARTNERS

It is suggested that the number of sexual partners the female had intercourse with in the time directly preceding the examination is far more important in acquiring incidental HPV infections than the lifetime number of partners. This phenomenon is clearly visible when one compares the prevalence of HPV infection with the number of last year sexual partners [37]. It is interesting that low prevalence of HPV infections can be observed even in women who have not declared having any sexual partner in their lifetime (5.2%) and the tendency of the curve to form a plateau displays relation between infection prevalence and both the lifetime and the last time number of sexual partners.

SEXUAL ACTIVITY OF A MALE PARTNER

Castellsague and Bosch emphasized that in women, who did not participate in adequate cervical cancer prophylactic programmes (cytological screening), the risk of cervical cancer preceded by HPV infections of highly oncogenic types probably depended more on sexual behavior of their male partners than on their own activity [38]. Obvious additional factor leading to increased risk of HPV infection in male is non-monogamous behavior of his female partner (wife). In conclusion, it can be said that the presence of HPV infection in male, even if of incidental nature, brings significant risk of transmission to female partner, even in non-penetrating intercourses.

CONDOM USE

The protective efficacy of condoms is well documented in HIV infections. However, their prophylactic value in HPV transmission in both directions (male to female and female to male) is not definitely elucidated. The key factors causing inconsistent results of the studies are as follows: (i) not always reliable reports of frequency of condom use; (ii) the use of condoms only in the final (penetrative) phase of intercourse and (iii) possibility of the HPV transmission through contact with skin areas not covered by condom. The metaanalysis of 20 published studies carried out by Manhart i Koutsky was disappointing [39]. It was concluded that the available data was too inconsistent to draw any firm conclusions. However, there is no unquestionable result of trials to prove that the condom use significantly reduces

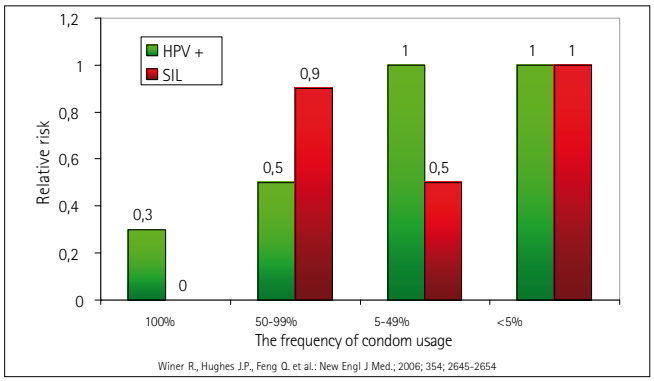

Fig. 3. The frequency of condom usage and the relative risk of incidental HPV infection and SIL formation.

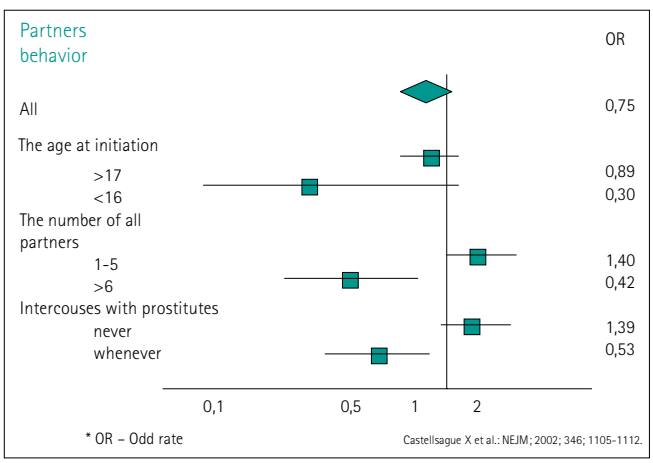

Fig. 4. Circumcision: Odds ratios for cervical cancer development in partners of circumcized vs not circumcized men in association with sexual behavior.

HPV infection. It was also suggested that the condom use may reduce the risk of genital warts development and in women CIN 2 and/or CIN 3 and invasive cervical cancer.

The randomized trial performed in Amsterdam among couples, in which women were either asymptomatically HPV positive or had CINs while males were either asymptomatically HPV positive or had different morphological forms of genital warts, revealed significantly shorter time to HPV remission or/and resolution of morphological lesions in couples consequently using condoms. Cumulated two-year regression rate of CIN and HPV remission rate was significantly higher in females from couples using condoms in comparison to group not using them (respectively: 53% against 35% and 23% against 4%) [40]. In males, who were partners of females with CIN, condom use was associated with significant shortening of time (nearly by a half) of penile genital warts presentation [41].

The low protective efficacy of condoms in HPV transmission may come from intensity and specificity of sexual behavior. It was widely recognized that condom use was preferred more frequently in incidental sexual contacts, in which probability of contact with infected partner is, by definition, increased in comparison to mutually monogamous couple. Interesting observations were drawn from IARC study executed in different geographic localizations with various HPV prevalence and sexual life intensity [35]. The protective feature of condoms was proven in Spain (OR: 0.54) but it was not observed in Argentina (OR: 1.04). Paradoxically, in Thailand condom use was associated with increased risk of HPV infection in females (OR: 3.18). The explanation of this astonishing result is that in many countries

condoms are used as a epidemiological surrogate of engaging in extremely sexually risky relations with a protective value of condoms being limited.

Recently published results of a cohort study carried out among female students initiating their sexual life (USA) emphasized two important aspects of potentially preventive application of condoms against HPV transmission [42]: (i) to achieve the real barrier benefit in the transmission of HPV condom must be used strictly in all the sexual intercourses. For the obvious reason, its application in every second contact hardly provides any protection. (ii) even very rigorous use of condoms in each of sexual engagement (in 100% of intercourses) does not eliminate the risk of incidental infection, even though it reduces it three times.

CIRCUMCISION

There is no clear explanation of mechanism how removal of penile foreskin would result in reducing the risk of HPV infection and the risk of transmission of the virus to the female partner [43]. Circumcision helps keeping genital hygiene, decreases the collection of smegma and contributes to gradually progressing thickening of glans penis epithelium, reducing its susceptibility to microtrauma. It is believed that external, epidermal surface of foreskin is relatively resistant to HPV infections, whereas its non-cornuated epithelial surface may be more predestined to infections [44]. Hence foreskin removal significantly limits epithelial surface, which might become a target for HPV at the same time reducing the risk of microtraumas unavoidable during sexual intercourse.

The suggestions, according to which in circumcised males the major and very limited place of HPV infection is the external urethral orifice [45], are coherent only with HPV-dependent morphological lesions. As it was previously stressed, HPV infections locate with high prevalence also in the areas of penile shaft skin, scrotum and perianal region. Therefore circumcision, for the apparent reason, would not influence on the infection in such locations. The protective value of circumcision in relation to persistent infections (lasting >/= 1 year) was documented, although no protection against new incidental infections was proved [46].

Apart from the unclear biological background, circumcision is associated with significant reduction of penile HPV infections, as was proved in the large multicenter epidemiological study by Castellsague et al. carried out under auspices of IARC on 1913 couples [47]. HPV infections were detected in 19.6% of uncircumcised males, which in comparison to the HPV prevalence of 5.5% in circumcised males and adjusted for age of sexual debut, lifetime number of sexual partners and other factors allowed to conclude that the probability of HPV infection of circumcised males was significantly lower (OR: 0.37). The main difference in HPV prevalence between circumcised and uncircumcised males was noted in the most sexually active male subgroup with at least 21 lifetime sexual partners. At the same time in this "promiscuous" male groups adjusting data to the use of condoms did not influence on the significance of the difference.

The enthusiasm which accompanied the results of the presented study was somehow tempered: the prevalence of male HPV infections was significantly lower in circumcised males when one considered the aggregated population as a whole ($p < 0.001$), however, that significance disappeared when having looked at any single country as an individual population (lowest p value = 0.16 for Spain). What is more, taking into consideration such a simple maneuver as washing the genitalia after intercourse made the difference in HPV prevalence between the two groups insignificant. It seems to be plausible then that circumcision may play an important role in prevention of HPV infections, particularly in males more sexually active and with lacking personal (genital) hygiene, independently on whether they use condoms or not.

In the study presented above, so far the largest one, there was no assessment of HPV transmission to female partners in relation to circumcision. However, these authors proved that the circumcision of male partner was associated with moderate but significant reduction of cervical cancer risk in female partners (OR: 0.72; 95%CI: 0.49-1.04).

If circumcision contributes to limiting the HPV spread is yet unclear, no matter if it is accomplished by reducing the susceptibility of males or by reduction of viral retention time in male genitalia.

REFERENCES

1. Parkin DM, Muir CS: *Cancer Incidence in Five Continents. Comparability and quality of data.* IARC Sci Publ 1992; 45; 173.
2. Bosch FX, Lorincz A, Munoz N et al: *The causal relation between human papillomavirus and cervical cancer.* J Clin Pathol 2002; 55; 244-265.
3. Moscicki AB, Schiffman M, Kjaer S, Villa LL: *Chapter 5: Updating the natural history of HPV and anogenital cancer.* Vaccine 2006; 24 Suppl 3; S42-51.
4. Munoz N, Bosch FX, de Sanjose S et al: *Epidemiologic classification of human papillomavirus types associated with cervical cancer.* N Engl J Med 2003; 348; 518-527.
5. Bosch FX, Manos MM, Munoz N et al: *Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group.* J Natl Cancer Inst 1995; 87; 796-802.
6. Bulk S, Berkhof J, Bulkmans NW et al: *Preferential risk of HPV16 for squamous cell carcinoma and of HPV18 for adenocarcinoma of the cervix compared to women with normal cytology in The Netherlands.* Br J Cancer 2006; 94; 171-175.
7. Lowy DR, Schiller JT: *Prophylactic human papillomavirus vaccines.* J Clin Invest 2006; 116; 1167-1173.
8. Sherman ME, Lorincz AT, Scott DR et al: *Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis.* J Natl Cancer Inst 2003; 95; 46-52.
9. Wallin KL, Wiklund F, Angstrom T et al: *Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer.* N Engl J Med 1999; 341; 1633-1638.
10. Schlecht NF, Trevisan A, Duarte-Franco E et al: *Viral load as a predictor of the risk of cervical intraepithelial neoplasia.* Int J Cancer 2003; 103; 519-524.
11. Ho CM, Cheng WF, Chu TY et al: *Human papillomaviral load changes in low-grade squamous intraepithelial lesions of the uterine cervix.* Br J Cancer 2006; 95; 1384-1389.
12. zur Hausen H: *Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis.* J Natl Cancer Inst 2000; 92; 690-698.
13. Wu S, Meng L, Wang S et al: *Reversal of the malignant phenotype of cervical cancer CaSki cells through adeno-associated virus-mediated delivery of HPV16 E7 antisense RNA.* Clin Cancer Res 2006; 12; 2032-2037.
14. Villa LL, Costa RL, Petta CA et al: *Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial.* Lancet Oncol 2005; 6; 271-278.
15. *Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions.* N Engl J Med 2007; 356; 1915-1927. Notes: CORPORATE NAME: FUTURE II Study Group.
16. Garland SM, Hernandez-Avila M, Wheeler CM et al: *Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.* N Engl J Med 2007; 356; 1928-1943.
17. Paavonen J, Jenkins D, Bosch FX et al: *Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised*

controlled trial. Lancet 2007; 369; 2161-2170. Notes: CORPORATE NAME: HPV PATRICIA study group.

18. Strand A, Rylander E, Wilander E et al: *Histopathologic examination of penile epithelial lesions is of limited diagnostic value in human papillomavirus infection*. Sex Transm Dis 1996; 23; 293-298.
19. Carter JJ, Koutsky LA, Hughes JP et al: *Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection*. J Infect Dis 2000; 181; 1911-1919.
20. Partridge JM, Koutsky LA: *Genital human papillomavirus infection in men*. Lancet Infect Dis 2006; 6; 21-31.
21. Lajous M, Mueller N, Cruz-Valdez A et al: *Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men*. Cancer Epidemiol Biomarkers Prev 2005; 14; 1710-1716.
22. Dunne EF, Unger ER, Sternberg M et al: *Prevalence of HPV infection among females in the United States*. JAMA 2007; 297; 813-819.
23. Baken LA, Koutsky LA, Kuypers J et al: *Genital human papillomavirus infection among male and female sex partners: prevalence and type-specific concordance*. J Infect Dis 1995; 171; 429-432.
24. Hippelainen MI, Yliskoski M, Syrjanen S et al: *Low concordance of genital human papillomavirus (HPV) lesions and viral types in HPV-infected women and their male sexual partners*. Sex Transm Dis 1994; 21; 76-82.
25. Kyo S, Inoue M, Koyama M et al: *Detection of high-risk human papillomavirus in the cervix and semen of sex partners*. J Infect Dis 1994; 170; 682-685.
26. Castellsague X, Ghaffari A, Daniel RW et al: *Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia*. J Infect Dis 1997; 176; 353-361.
27. Franceschi S, Castellsague S, Dal Maso L et al: *Prevalence and determinants of human papillomavirus genital infections in men*. Brit J Cancer 2002; 86; 705-711.
28. Bleeker MC, Hogewoning CJ, Berkhof J et al: *Concordance of specific human papillomavirus types in sex partners is more prevalent than would be expected by chance and is associated with increased viral loads*. Clin Infect Dis 2005; 41; 612-620.
29. Winer RL, Lee SK, Hughes JP et al: *Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students*. Am J Epidemiol 2003; 157; 218-226.
30. Oriel JD: *Natural history of genital warts*. Br J Vener Dis 1971; 47; 1-13.
31. Burchell AN, Richardson H, Mahmud SM et al: *Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada*. Am J Epidemiol 2006; 163; 534-543.
32. Barnabas RV, Laukkanen P, Koskela P et al: *Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses*. PLoS Med 2006; 3:e138.
33. Burchell AN, Winer RL, de Sanjose S et al: *Epidemiology and transmission dynamics of genital HPV infection*. Vaccine 2006; 24 Suppl 3; S52-61.
34. Wald A, Langenberg AG, Link K et al: *Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women*. JAMA 2001; 285; 3100-3106.
35. Vaccarella S, Franceschi S, Herrero R et al: *Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys*. Cancer Epidemiol Biomarkers Prev 2006; 15; 326-333. Notes: CORPORATE NAME: IARC HPV Prevalence Surveys Study Group.
36. Moscicki AB, Hills N, Shiboski S et al: *Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females*. JAMA 2001; 285; 2995-3002.
37. Dunne EF, Unger ER, Sternberg M et al: *Prevalence of HPV infection among females in the United States*. JAMA 2007; 297; 813-819.
38. Castellsague X, Bosch FX, Munoz N: *The male role in cervical cancer*. Salud Publica Mex 2003; 45 Suppl 3; S345-53.
39. Manhart LE, Koutsky LA: *Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis*. Sex Transm Dis 2002; 29; 725-735.
40. Hogewoning CJ, Bleeker MC, van den Brule AJ et al: *Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial*. Int J Cancer 2003; 107; 811-816.
41. Bleeker MC, Hogewoning CJ, Voorhorst FJ et al: *Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia*. Int J Cancer 2003; 107; 804-810.
42. Winer RL, Hughes JP, Feng Q al: *Condom use and the risk of genital human papillomavirus infection in young women*. N Engl J Med 2006; 354; 2645-2654.
43. Partridge JM, Koutsky LA: *Genital human papillomavirus infection in men*. Lancet Infect Dis 2006; 6; 21-31.
44. Szabo R, Short RV: *How does male circumcision protect against HIV infection?* BMJ 2000; 320; 1592-1594.
45. Aynaud O, Piron D, Bijaoui G, Casanova JM: *Developmental factors of urethral human papillomavirus lesions: correlation with circumcision*. BJU Int 1999; 84; 57-60.
46. Lajous M, Mueller N, Cruz-Valdez A et al: *Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men*. Cancer Epidemiol Biomarkers Prev 2005; 14; 1710-1706.
47. Castellsague X, Bosch FX, Munoz N et al: *Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners*. N Engl J Med 2002; 346; 1105-1112. Notes: CORPORATE NAME: International Agency for Research on Cancer Multicenter Cervical Cancer Study Group.

Correspondence

Marek Sikorski
GENIX – Prywatne Centrum Medyczne
ul. Romera 25
20-470 Lublin, Poland
phone: +48 81 74 90 185
centrum@genix.com.pl