Clinical lesions in the anal and genital area related to HPV infection in males

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KEY WORDS

HPV ◗ genital warts ◗ penile cancer ◗ anal cancer ◗ prostate cancer

ABSTRACT

Infections with mucosotrophic types of Human Papillomaviruses (HPV) are the sexually transmitted infections that occur most frequently. Their prevalence in males is comparable to females. The majority of HPV infections in males produce no clinical symptoms and are transient in their nature. The most frequently present clinical manifestation of HPV infection is genital warts formation, which are predominantly located in the distal parts of the penis. In more than 90% of cases warts are caused by low oncogenic risk HPV types – 6 and 11. Despite being benign in their character, genital warts considerably decrease the patients' quality of life. Persistent infections with high-risk HPV types (type 16 and 18) are associated with the development of nearly 50% of cases of squamous penile cancer. These cancers usually arise from penile intraepithelial neoplasias, which are HPV positive in the majority of cases (above 80%). Histologically HPV-related penile cancers are papillary or basaloid. On the other hand, the mechanism of penile carcinogenesis of low relation to HPV infection is implicated in the development of keratinizing cancers. Squamous cancer of the anal canal are, in the majority of cases related with the high-risk HPV infections of the anal mucosa, which are acquired by receptive anal intercourse. In the men who heve sex with men (MSM) population, HPV DNA is detected virtually in all cases of anal canal cancers, whereas in heterosexual males – in nearly 60% of cases. Epidemiological trends show clearly the increasing incidence of HPV-related anal canal cancers. HPV is thought to play a role in the etiology of prostate cancers; however, the currently available evidence is not sufficient enough to confirm HPV association with the development of these cancers.

INTRODUCTION

Anogenital infections with about 40 types of Human Papillomaviruses (HPV) are sexually transmitted infections that occur most frequently worldwide. Chronic infection of epithelium in this area may be connected with the development of carcinomas, genital warts, and other dermoepithelial changes (intraepithelial neoplasia). Coherent and detailed pictures of the correlation between highly oncogenic HPV infections in the uterine cervix and cervical cancer is nowadays well known – multidirectional studies showed that chronic HPV infection is a necessary, although not sufficient, factor for the development of cervical cancer [1].

Our knowledge of the pathology of HPV infection in males is not complete. Although men are regarded as a dominant factor in infection transmission to their sexual partners, they do not develop clinically significant HPV-related lesions very often. The available data reveals that as in females, the majority of cases of HPV anogenital infections in males are asymptomatic and relatively short lasting. Similarly as in women, probably the most common type is HPV 16. In age-matched populations the frequency of HPV infections is lower in males than in females. This may be due to the lower incidence and shorter duration of infection, but also because of technical difficulties in the selection of proper sites for cellular material sampling for molecular studies in males [2].

HPV anogenital infections in males can manifest in various clinical forms – from totally asymptomatic infections to squamous carcinomas. Common criteria used to determine whether HPV is an etiological factor in a given group of cancers have been developed by Gillison and Shah [3]. Characteristic features of such an etiological correlation are [1] squamous epithelium as the primary site of cancer, [2] presence of HPV DNA in neoplastic cells nuclei, with the expression of viral oncogenes, (3) localization in anatomical sites exposed to direct infection, (4) presence of antibodies against E6 and/or E7 HPV proteins, (5) correlation with sexual activity and (6) an increased incidence in immunocompromised persons.

Although the correlation between HPV and the majority of anal canal cancers, as well as high percentage of penile cancers, is causal, the suggested effect of HPV infection in the development of prostate cancer has not been sufficiently documented. One of characteristic features of HPV-related cancers is the precedance of intraepithelial neoplasia: PIN – *penile intraepithelial neoplasia* and AIN – *anal intraepithelial neoplasia*. Apart from dysplastic changes associated with highly oncogenic HPV infections, genital warts are a frequent clinical manifestation of infections caused by HPV of low oncogenic risk.

Genital warts (*condylomata acuminata*)

Genital warts are the most common clinical manifestation of infections with HPV of low oncogenic risk in males. Annual incidence in the USA is 1% of the population of sexually active males aged 15-49 years and is increasing [4]. In Poland it is estimated that genital warts causes over 30% of visits to dermatological and venereal out-patients offices. Retrospective studies conducted in Great Britain between 1971-1994 revealed that there was a 39% increase in the frequency of visits due to genital warts, while at the same time the ratio of males to females seeking help decreased from 1.85/1 to 1.34/1 [5]. According to British statistics from the last decade, the incidence of genital warts in males has increased by 34%, while in females only by 18%.

In 2005 – 6% of all genital warts cases were noted among MSM, as compared to 4.6% in 1996. The overall increase in the incidence of genital warts among MSM over 10 years was twice as high as in the general male population (76%). The highest incidence has been noted among males aged 20-24 years of age (in Great Britain 774/100 000). Epidemiological trends are presented in Figure 1. It has been stressed that the real incidence of genital warts is

not known, as the majority of men with condylomata (in particular with small lesions) never seek medical advice. Taking this fact into account, it may be estimated that the real incidence may be twice as high as that recorded by the official epidemiological statistics.

Global data clearly show the increased incidence of genital warts. It has been estimated that the life time risk of genital warts in every sexually active man is 10%. Transmission of HPV infection occurs via (in up to 95% cases) the sexual route; however, in case of genital warts it has been shown (although in a small group of males) that the genito-manual route is also possible. In men with condylomata studied by Sonnex et al., the presence of HPV DNA was found in smears from genital organs in 93% of cases and, at the same time, in 64% of the same men in smears from the finger tips and subungual plate [6]. Moreover, the consistency of HPV types in both areas was seen in 31%.

Genital warts almost always develop (90-100%) as a result of productive HPV infection with two low risk types: HPV 6 and 11 [7]. Condylomata acuminata are highly infectious; the transmission risk is 75%. However, genital warts have no oncogenic potential; they do not infiltrate and do not produce metastases. The exception is Buschke-Loevenstein giant condyloma, which is rare and develop only in immunocompromised persons; they show limited malignancy. Histologically, in condyloma acuminatum, the productive replication of HPV takes place in stratum spinosum and granulosum of the epithelium, resulting in the development of layers of abnormal keratinocytes (the so called koilocytes) due to the effect of E4 HPV protein. This protein deranges the whole cytoskeleton, causing the development of a typical koilocytotic cytoplasmatic translucence around the nucleus (the so called „halo" which looks like an oyster shell). Blood vessels penetrate the condylomatous icicle, which results in the formation of large exophytic lesions; intense cellular divisions create a molecular background for these lesions.

The most common localization in males is the penile corpus, although in non circumcised men they may develop in the distal part, especially in the sulcus of the glans penis, frenulum and internal surface of the prepuce [8]. Warts may also be present on the scrotum, groin and/or anal area. In over 20% of males with genital warts they are localized in the external urethral meatus. In receptive males, during anal contacts, there is a high risk of development of genital warts in the anal canal. Condylomata are usually pale pink, with a rough matte surface. They do not produce clinical symptoms, neither pain nor itching. Large genital warts in their typical location are presented in Figure 2. There are 3 types of condylomata acuminata, which may all be present in the same person: spiked, papillary and flat [9]. Spiked warts have good blood supply with punctuated or loop patterns. In men they are present mainly in mucous membranes in the subpreputial area and in the external urethral meatus. Papillary warts occur mainly on surfaces covered by keratinizing epithelium – corpus penis, scrotum, groin, or external surface of the prepuce. Their surface is smooth in comparison with the irregularities typical for spiked condylomata. In flat warts, lesions on mucosal surfaces are grayish, pale pink, or red-brown [9].

Sometimes clinically confounding may be *pearly penile papules* (PPP), a benign physiological phenomenon (Fig. 2). They are present as single or several rows of small smooth pearly nodules localized peripherally at the base of the glans penis or in the sulcus. They are not transmitted sexually and their occurrence is not connected with sexual activity or insufficient hygiene. They do not require treatment [10].

About 40% of clinically manifesting warts heal spontaneously, although time to regression varies and usually lasts at least 11-12 months. In other cases local treatment is necessary, which may be surgical (excision, cryotherapy, or laser vaporization) or pharmacological (podophilotoxine, 5-fluorouracyl, or imiquimod). Even spectacular early therapeutic success does not guarantee complete healing: recurrence of genital warts reaches about 40% and in the case of pharmacological treatment even 60% [11].

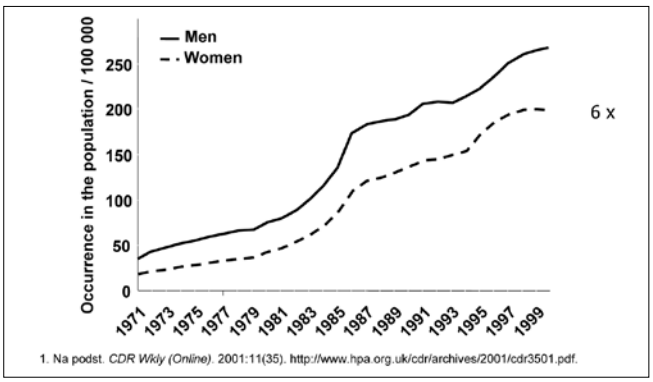

Fig. 1. Occurrence of genital warts in England and Wales between 1971-2000. Males, females. Occurrence in population.

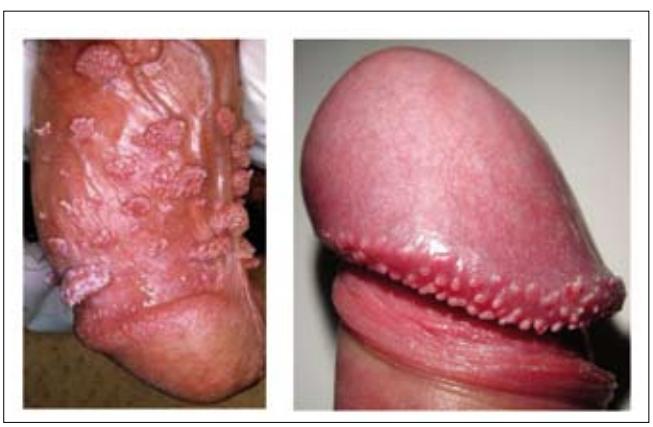

Fig. 2. Genital warts (condylomata acuminata – HPV 6/11) and non-infectious pearly penile papules (PPP).

Despite the benign character of genital warts, their presence significantly decreases the patient's quality of life and may completely destroy their sexual lifestyle. Patients with condylomata are most often afraid of recurrence and transmission of the infection to their partners, psycho-sexual disorders and pain, especially associated with surgical intervention [12].

Due to the high occurrence of genital warts, difficulties with obtaining permanent clinical effect and the significant influence of the disease on the patients' social life the key element is prevention, not only by modification of sexual behavior (monogamy, use of condoms), but also by prophylactic vaccination against HPV 6 and 11 with the quadrivalent vaccine.

Penile cancer

Penile cancer is a relatively rare disease in Europe and the United States, with annual incidence among whites below 0.29/100 000 [13]. Incidence is higher by at least one order of magnitude in some African (Uganda) and South American countries (Paraguay), where it reaches 4.4/100 000 and 4.2/100 000, respectively.

The etiology of penile cancer has not been fully elucidated. A classical factor reducing the risk of penile cancer is circumcision in the neonatal period, although a cause-effect correlation has not been univocally confirmed. The most relevant, confirmed factors that increase the risk of developing penile cancer are Bowen's disease and condylomatous lesions on the penis in the past [14]. Other risk factors (increasing the probability of cancer two-three fold) are

Table 1. HPV etiology in penile cancer of various histology [15].

Etiological factor		Precursor changes	Histology	Percentage of HPV(+) cases
Main primary	Additional secondary			
?	HPV	?	Squamous keratinizing carcinoma	30%
?	HPV	?	Verrucous carcinoma	30%
HPV	?	PIN	Basal cell and papillary carcinoma	80-100%

phimosis, smegma accumulation, high number (over 30) of sexual partners, and tobacco smoking. Many of the above mentioned factors may be treated as epidemiological indices of increased risk of HPV infection.

Contrary to uterine cervix cancer, where HPV DNA is detected using sensitive PCR methods in almost 100% of cases, the occurrence of HPV in penile cancer tissues is much lower and similar to that observed in vulvar cancer in women, namely between 42% and 80% [15,16]. The most common type of HPV is, similarly as in vulvar cancer, type 16. Higher occurrence of HPV DNA in non-invasive penile lesions (PIN 2-3 – *penile intraepithelial neoplasia*) in comparison to invasive cancers, is common. This may be due to the low fraction of invasive HPV-related penile cancers or to the technical difficulties connected with lower sensitivity of PCR in advanced neoplastic lesions (high content of inflammatory and necrotic elements in the sample). Infection with highly oncogenic HPV types may not be treated as a necessary point in the development of penile cancer – it may result from much lower susceptibility of epithelium of this organ to oncogenic activity of HPV. In contrast to cervical cancer, where a vast area of epithelial transformation (transformation from glandular epithelium in cervical canal to squamous epithelium in the portio exposes basal cells, which become targets of infection) in the penis it is practically absent. Small exposition of main permissive cells for HPV replication in men may explain the much lower occurrence of neoplastic HPV-related penile lesions. Epidemiological data indicate clearly that despite active screening towards cervical cancer, the incidence of this neoplasm is still several times higher than that of penile cancer (Fig. 3).

Among the three classical precancerous penis conditions (Bowen's disease, *bowenoid papulosis* and *Queyrat erythroplasia*), which are now classified as PIN, all show strong correlation with HPV infection, in particular with type 16 [17, 18]. Thus, the current hypothesis, according to which penile cancer – depending on histology – develops along different pathways, is justified. PIN lesions, which are usually HPV positive (in 80 to 100% of cases) lead to basal cell or papillary carcinoma, while keratinizing cancers are connected with HPV only in 33-35% of cases [19]. Table I presents a possible model of carcinogenesis in the penis including the effect of chronic HPV infection on the etiology of histologically varying cancers.

Ununified (at least double) and in many cases unclear etiology of penile cancer is explained by various molecular mechanisms, the activation of which leads to neoplastic transformation. Ferreux et al. suggested that induction of uncontrolled divisions of penile keratinocytes in the presence of chronic HPV infection with highly oncogenic types depends on the activity of oncogenes of E6 and E7, i.e. classic immortalization, so well described for cervical cancer [20]. This mechanism may be involved in cancers with detected HPV, where expression of transcripts of viral oncogene mRNA was seen significantly more often. In cancers without HPV, inhibition of the cellular cycle in G1 phase is broken by methylation of promoter p16 INK4a and may be found quite frequently (in up to 15%). Similar to vulvar cancer, penile cancers developing from dysplastic

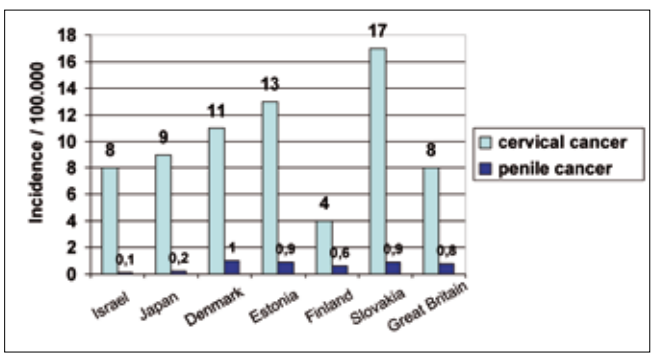

Fig. 3. Incidence of penile and cervical cancer (data from IARC). Incidence / 100 000. Cervical cancer. Penile cancer. Israel. Japan. Denmark. Estonia. Finland. Slovakia. Great Britain.

lesions (PIN), etiologically dependent on HPV, are more common in younger people in comparison to keratinizing cancers.

An important role in the promotion of carcinogenesis in the penis is played by immunodeficiency, connected particularly with HIV infection. Higher frequency of HPV – positive lesions PIN 2-3 in men infected with HIV in comparison with HIV (-) men is significant, reaching 75% and 10%, respectively [21]. HIV (+) people are predisposed to develop basal cell and papillary cancers.

Anal cancer

In terms of epithelio-epidermic lining, the anus may be divided into two main parts: anal canal covered with epithelium and distal edges covered with epidermis. Anal cancers developing from epidermis are regarded as dermal cancers. Histological details of the proximal anal part (anal canal) closely reflect the situation within the uterine cervix, with a typical zone of epithelial transformation. The larger (distal) part of the anal canal is lined with stratified squamous epithelium, which turns into glandular epithelium of the anus or transitional epithelium (urothelial-like). This transition takes place within the *linea dentata*. Cancers which develop below this line usually are squamous keratinizing, while those developing above this line are squamous without keratinization [22]. Glandular cancers developing in the anal canal show features of rectal cancers and are treated similarly.

Morbidity in anal canal cancer within the last 50 years has gone through two stages. From 1960 to 1980, in many regions worldwide, the increased morbidity was more pronounced in women than in men (the increase in morbidity for women and men, Denmark, 2.64 and 1.5 times, USA –– 2.3 and 1.9 times, respectively) [23, 24]. Within the last 20 years the morbidity among women has not changed significantly, however morbidity in men still demonstrates a growing tendency (acc. to the National Cancer Institute data in the USA, from about 0.7/100 000 in 1980 to 1.5/100 000 in 2000) [25]. Anal cancer is also more common in men below 40 years of age, which in the 1970s was not seen. Epidemiological data for the MSM population before AIDS epidemics (1970s) showed a 4-5 fold higher morbidity for anal cancer in comparison with the general male population.

According to Partridge and Koutsky, morbidity of anal cancer among MSM, was in those days, 35 cases per 100 000 [25]. These values are often compared to the morbidity of invasive forms of cervical cancer before screening was introduced. Later decrease in the incidence of anal canal cancer may have been due to the widespread adoption of safe sex rules, including condom use, which was the result of an educational campaign on HIV infection prophylactics.

For many years physical trauma and /or chronic inflammation were regarded as the main risk factor in the pathogenesis of anal canal cancer; it was connected with the presence of fissures, fistulas or hemorrhoids. The study by Holly et al. conducted in a relatively small group showed that for MSM relative risk of anal canal cancer development increases 10 times if anal fissures or fistulas are present (in heterosexual men – 2.4 times) and over 12 times in the presence of genital warts in the anogenital area (for heterosexual men – 4.4 times) [26]. Later studies based on the Danish Cancer Register confirmed significant correlation between benign anal area lesions and anal canal cancer development (relative risk 4.4 within 6 years and as much as 12 within the first year after detection of benign lesions), although there were neither cases of anal canal cancers among 651 patients with Crohn disease, nor in any of 509 patients with colitis ulcerosa, despite numerous suggestions of such correlations from casuistic case reports [27].

Studies conducted before the HIV epidemics often emphasized the correlation between sexual behavior and the risk of anal cancer development. Relative risk of this cancer was according. to Daling et al. over 33 for men receptive during anal intercourse, although in women the correlation between anal cancer and anal contacts was weak (relative risk 1.8) [28]. In the same study, past or present, genital warts were seen in more than 47% of MSM, in 28.6% of heterosexual men and in 28.3% of women with squamous carcinoma of the anal canal. Multivariate analysis conducted by Frisch et al. in the 1990s, that were confirmed in many later publications, demonstrated that for heterosexual men, the risk of anal canal cancer increases significantly with having more than 10 sexual partners, with genital warts in the anal area in the past, syphilis and viral hepatitis [29]. In the studies quoted above, homosexual contacts were noted in 15% of persons with anal canal cancer (no cases in the control group).

Correlation between sexual behavior and risk of anal canal cancer development has been supported by observations of women with cervical cancer – neoplasm of confirmed viral etiology, connected with sexually transmitted infections. For women with cervical cancer or CIN (*cervical intraepithelial neoplasia*), the risk of anal canal cancer was 5 times higher than that of colon cancer, 3.5 times higher than that of stomach cancer and 1.6 times higher than that of vulvar cancer [30]. A similar study demonstrated that for women with primary cervical cancer, relative risk of invasive anal canal cancer is 4.6 [31]. The same study showed significant increase in the risk of vaginal cancers (relative risk 5.6), laryngeal cancers (3.4), and oral cavity cancers (2.20 among women with cervical cancers), among others, i.e. HPV-related neoplasms in a high percentage of cases.

An additional anal canal cancer risk factor is smoking; according to classic publications smoking increases the risk of this neoplasm more than 10-times in men and 8-times in women [28]. This risk factor is also a relevant analogy to cervical cancer.

Epidemiological a characteristics of anal canal cancer are combined with significantly higher risk of this cancer in men (and women) with numerous sexual partners. A particularly high risk is noted among MSM who are receptive in anal intercourse. The risk is increased by the presence of genital warts in the anal area (HPV), other sexually transmitted diseases (syphilis, HBV, HSV, HIV), epithelium damage (enhancing infection), smoking and (in women) presence of HPV related cervical cancer or its precursor conditions. These observations, together with tissue structure of the uterine cervix and the anal canal, suggest that development of a significant part of anal canal cancers is due to HPV infection.

Classic Frisch et al. studies found the presence of HPV DNA in 88% of basal cell cancers in the anal canal, while at the same time it was not seen in any case of rectal adenocarcinoma [29]. The most common HPV type detected in the quoted studies was type 16, present in 73% of invasive anal canal cancers. Such a high frequency of HPV 16 occurrence is much higher than about 50% frequency of HPV 16 in basal cell cancer of the uterine cervix. Type 16 HPV is also significantly more frequently correlated with higher grade anal intraepithelial neoplasia (AIN) than other HPV types, which are isolated more commonly in low grade AIN, analogous to intraepithelial changes in the uterine cervix [32]. Viral status of anal canal tumors does not, however, change the prognosis [33].

Occurrence of anal canal cancers with the presence of highly oncogenic HPV DNA types (usually connected with the development of uterine cervical cancer) varies depending on the population: anal canal cancers in MSM are HPV (+) in almost 100% – in 90% of cases in women, and in 58% of cases in heterosexual males [34]. The observation that rectal adenocarcinoma does not harbor HPV DNA has been repeatedly confirmed. Anal squamous carcinomas developing from the epidermal layer may contain HPV DNA in a small percentage of cases, but the probability of HPV DNA presence in squamous cancers of the anal canal is almost eight times higher [34]. The percentage of HPV (+) skin cancers in the perianal area of men was only 28% in the study by Frisch et al [35].

Differences in the occurrence of highly oncogenic HPV DNA types in anal canal cancers and skin cancers of the perianal area points at the dominant role of viruses in the etiology of anal canal neoplasia, which is analogous to uterine cervix cancer. Etiology of skin cancers of the perianal area is not homogenous and HPV infections are present only in some cases (up to 50%), which is analogous to vulvar and penile cancers.

The increasing incidence of anal canal cancer observed over the last few years in men and the decreasing age of men in whom these neoplasms are diagnosed (especially in the MSM population) may be due to the increased frequency of anal canal exposure to HPV infection (and also HIV), in connection with higher frequency of anal intercourse between MSM and higher number of their sexual partners [36]. Receptive anal intercourse may be treated as a behavioral surrogate of exposure to HPV infection, increasing the risk of developing anal canal cancer. Anal canal HPV infection and intraepithelial changes connected with infection, as well as cancers of this area, are not necessarily connected with the anal activity. For example people with HIV infection are predisposed for infections without anal contacts – frequency of infection in heterosexual men in the study of Piketty et al was 46% (85% in MSM), intraepithelial low grade changes were found in 16% of patients (49% of MSM), and high grade changes in 18% of patients (same among MSM) [37]. According to the studies quoted above, factors that significantly increase the risk of abnormal anal cytology among people infected with HIV are decreased number of CD4+ cells (below $250x10^6$ /L) (risk ratio: 5.7). In immunocompromised individuals due to HIV infection, especially MSM, screening studies based on anal cytology have been postulated. Mathematical models have proven the cost effectiveness of screening by increasing the quality of life of these patients [38].

Prostate cancer

The incidence of prostate cancer in various areas of the world differs significantly, as much as 10-fold: the highest incidence is

among Afro-Americans in the United States (185/100 000) and the lowest is in China (2/100 000) [39]. These discrepancies may be due to genetic predispositions, but observations of men migrating from areas of low incidence to high incidence areas has revealed an increase in their occurrence, clearly pointing at an environmental influence, including sexual behavior, increasing the risk of prostate cancer.

Despite methodological difficulties, the correlation between the increased risk of prostate cancer and a young age of sexual initiation, large number of sexual partners (risk ratio 2.27 for >30 partners in comparison with one partner) and some sexually transmitted diseases - gonorrhoea (risk ratio 1.50) and syphilis, was demonstrated [40].

The connection between prostate cancer and sexual behaviors has led to the hypothesis of a correlation between this neoplasm and the most common sexually transmitted infection, HPV. It was suggested that the main HPV type involved in prostate carcinogenesis is type 18, due to its high tropism to glandular tissues and *in vitro* studies documenting immortalization of prostate cells [41].

Using different primers in PCR testing for HPV DNA in prostate cancer cells gave surprisingly different results: there were reports of viral DNA presence in 100% of cases [42, 43, 44] and reports that DNA HPV was not present in prostate cancer at all [45, 46]. Such discrepancy may result from difficulties in obtaining representative tumor samples with intact, uncontaminated DNA for PCR.

Previous exposure to HPV and transient infection may not be reflected in current viral status of neoplastic tissue. Therefore, comparative serological studies of antibodies against various types of HPV have been conducted. The results are mutually exclusive. Dillner et al. found 2.6 fold increase of the risk of prostate cancer development in men seropositive for HPV 18 [47]. At the same time the correlation between the presence of anti HPV 16 antibodies and prostate cancer did not reach statistical significance and merely indicated tendency to increased risk. In other population studies a correlation between the presence of anti HPV 33 antibodies and prostate cancer was suggested (odds ratio 1.6), while the correlation with anti HPV 16 and 18 antibodies was not significant [48].

The effect of past HPV infection (reflected in the presence of antibodies) on the development of prostate cancer, where no HPV DNA is detected, was explained by the hypothesis „hit & run" carcinogenesis. According to this hypothesis, the initiating factor is present only transiently and the cascade of reactions continues later without it. However, it is not consistent with the mechanism of HPV-related carcinogenesis, confirmed repeatedly in the past, where viral oncoproteins (E6 and E7) degrade or deregulate the cellular divisions control factors (mainly p53 and pRb).

Several latest population studies consistently excluded the existence of the correlation between previous HPV infection (presence of antibodies) and prostate cancer. In a nested population study based on the Scandinavian cancer register by Korowi et al. the occurrence of anti HPV antibodies (together type 16, 18 and 33) was almost identical in the group of patients with prostate cancer (13.4%) and in the control group (14%) [49]. The odds ratio for the correlation between the presence of anti HPV 16 and anti HPV 18 antibodies (respectively: 1.06 and 1.36) and prostate cancer did not show any statistical significance in the studies of Rosenblatt et al. [40]. Similar results were obtained by Sitas et al. [50].

In summary, the available data shows a clear correlation between the intensity and type of sexual activity and the development of prostate cancer, but it has not been clarified that an infectious, sexually transmitted factor is the main element initiating carcinogenesis. The role of HPV infections is not unequivocal; however, there is no sufficient data to totally exclude it.

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