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REVIEW ARTICLE

Nature of cervical cancer and other HPV - associated cancers

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Summary

Papillomaviruses are small DNA viruses that infect and multiply in cutaneous or mucosal epithelial tissue. Human papillomavirus (HPV) 16 and 18 cause more than 99% of cervical carcinomas. Simultaneous presence of HPV is found in cervical intraepithelial neoplasia, vaginal intraepithelial neoplasia, vaginal and anal cancer. Invasive vulvar squamous cell carcinoma in younger women under the age of 50 are also associated with HPV. Most of the penile lesions are subclinical and the high prevalence of high-risk HPV suggests that they constitute a reservoir for high-risk HPV. Bowens disease and Buschke-Lowenstein tumors are associated with particular low- and high-risk HPV types. The potential role of HPV infection in the carcinogenic steps of breast, prostate, colorectal and lung cancers should be further tested. HPV-DNA might be transported from the original site of infection to the breast tissue by the bloodstream, and therefore is possibly involved in the carcinogenesis of breast neoplasia in some patients. HPV-DNA is detected in 40-70% of head and neck squamous cell carcinomas and in only 1% in normal epithelial cells.

In this paper we propose the hypothesis that many epithelial normal cells are susceptible to HPV infection, which are the most sexually transmitted viruses. Experimental and epidemiological data imply a causative role for HPVs and they appear to be the second most important risk factor for cancer development in humans, exceeded only by tobacco usage.

Key words: cervical cancer, HPV- associated cancers, HPV types

Introduction

Papillomaviruses are small DNA viruses that infect and multiply in cutaneous or mucosal epithelial tissues. More than 100 types of HPV exist and all of them have one thing in common - circular DNA genome composed of about 8000 base pairs. These small genomes are organized into an early, a late, and a long control region. The products of 2 genes from the early control region, genes E6 and E7, are essential in the HPV-induced processes of cellular transformation and immortalization [1], and 2 genes from the late control region, genes L1 and L2, encode for the viral capsid proteins. HPVs are implicated as a risk factor for many benign and malignant diseases - cervical cancer, anal cancer, penile, vulvar and vaginal cancer, cancer of the conjunctiva, head and neck tumors, laryngeal papilloma, genital and cutaneous warts etc.

There are 15 high risk types, according to their oncogenic potential: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82; 3 probably oncogenic types: 26, 53, 66; and 12 low risk types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP108 [2]. While the relationship between cervical cancer and HPV infection is certain and proven in more than 99% of all cases, this relationship varies greatly from 0 to 100% when other organs are infected. This broad range of variation explains our interest in that problem.

The aim of this paper was to review the scientific literature for evidence of a universal concept that some HPV types are associated with many types of human cancer.

Mechanism of neoplastic transformation in cervical cells

Cervical cancer is the 11th most common cancer among women in the United States. Among women in

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developing countries cervical cancer is the second most common cancer and is the leading cause in cancer-related deaths [3]. This association between certain subsets of HPVs and cervical cancer was first postulated in the late 1970s [4], when it was observed that some types of HPV were more frequent in malignant than in benign lesions. Now it is proven that infection with high-risk HPV types is a major risk factor for the development of cervical cancer [5] and these risk categories reflect the viral ability to promote the proliferation of infected cells by disrupting DNA stability of host cells [6,7]. For example, a subset of mucosotropic HPV types, which includes high-risk HPV16 and HPV18, 31, 33, 45, 39, 45, 51, 52 (Table 1), cause more than 99% of cervical carcinomas [8,9], where the viral genome is integrated into the host cell chromosomes [10]. HPV16 integration leads to expression of the viral genes E6 and E7 [1] and their products - oncoproteins E6 and E7, respectively. These oncoproteins bind and inactivate cell tumor suppressor proteins p53 and pRB.

In addition, the continuous expression of these early proteins can cause accumulation of DNA mutations, which in turn promotes malignant transformation. Although these events of HPV-mediated genome transformation occur early, they are better characterized in the stage of invasive cancer [11]. Abnormalities include aberrant chromosomes - monosomies and trisomies, chromatid gaps and breaks etc. Contemporary knowledge of the relationship between HPV DNA integration and the resultant genome instability is still insufficient, especially *in vivo*. Progress in this area has been hampered by lack of experimental models and methods suitable for population samples.

Other types of HPV-associated genital tumors

Vaginal intraepithelial neoplasia (VAIN) and vaginal cancer (VC)

VAIN is thought to be a precursor of malignant disease [12]. Its incidence is about 1% of the lower genital tract intraepithelial neoplasia [13]. Risk factors for VAIN seem to be similar to those of the cervical and vulvar neoplasia. Previous hysterectomy for cervical neoplasia suggests increased risk for VAIN and HPV seems to be the responsible agent in both locations [14-17], as well as simultaneous presence of cervical intraepithelial neoplasia (CIN) [18]. This confirms that HPV is implicated in the etiology of this neoplasia [15,16].

In 2007 Frega et al. [19] found that in 830 women with prior hysterectomy HPV types 16 and 18 were present in all patients affected by VAIN (Table 1).

Table 1. Human papillomavirus types and their clinical associated cancers

HPV - associated cancers	*HPV type*
Cervical cancer/pelvic lymph nodes	16, 18, 31, 33, 45, 39, 51, 52
Vulvar cancer/vaginal cancer	16/16, 18, 33
Anal cancer/colon cancer	16
Penile cancer	16
HNSCC*	16 up 90% of the cases
Recurrent respiratory papilloma	6, 11
Bowenoid papulosis	16
Breast cancer / axillary lymph nodes	16
Prostate cancer	16, 18, 31, 33
Condyloma and laryngeal papillomatosis	6, 11

*head & neck squamous cell carcinoma

Women in the VAIN group who had relapsed or progressed to VC had significantly higher titers of high-risk HPVs. In that study it was found that the HPV-DNA testing had predictive value for monitoring patients previously treated for VAIN [19]. Thus it might be concluded that high-risk HPV-DNA testing would improve the current guidelines for follow-up of patients with VAIN in addition to cytological diagnosis, since it could indicate VAIN persistence/progression to VC before cytology becomes abnormal.

Vulvar intraepithelial neoplasia (VIN) and vulvar carcinoma (VuC)

VIN is a precursor lesion of invasive vulvar carcinoma. Many studies have demonstrated an association between HPV and VIN [20-22]. A significant number of investigated lesions were found positive for high-risk HPV, especially HPV16 (Table 1). VIN related to high-risk HPV is frequently chronic, multifocal, high -grade dysplastic disease that tends to recur after local surgical excision or laser therapy and represents a relative risk for progression to invasive VuC if left untreated [23]. Jones et al. demonstrated that women aged less than 50 years more often present with VuC associated with VIN, while they have lower incidence if older [24]. This increase of VIN in younger women may be explained by the recently changed sexual behavioral habits leading to higher prevalence of HPV infections and smoking.

Invasive vulvar squamous cell carcinoma has two types [25]. Those found in younger women under the age of 50 are associated with HPV, aneuploidy or warty lesions which are multifocal as a result of numerous sexual partners, HPV16, smoking and immunosuppression. In up to 40% of cases these lesions coexist with

other types of premalignant conditions of the genital tract, such as CIN and VAIN [26]. In older women the lesions are basaloid, unifocal, are not associated with HPV and arise in a background of lichen sclerosus.

VIN is a premalignant lesion of the lower genital tract. The frequency of VIN and VIN-related cancer has been increasing during the past two decades, while the mean age of patients is declining [27]. One explanation for this rise in incidence of VIN is the increase in the papillomavirus infections involving the lower genital tract. The presence of high-risk HPV-DNA in the preinvasive and invasive lesions may be as high as 90% in undifferentiated VIN III [28]. The most frequently found high-risk type is HPV16, followed by types 33 and 18.

External genital warts, recurrent respiratory papillomatosis (RRP) and HPV

HPV types 6 and 11 infections are responsible for over 90% of external genital lesions and the majority of recurrent respiratory papillomatosis [29,30]. These are visible warts that occur on the perigenital and perianal region: the penis, scrotum, and vulva; pubic, perineal, and perianal areas; and crural folds. Low-risk types 6 and 11 (Table 1) are commonly associated with either viral condyloma or mild dysplastic changes in cervical epithelium (CIN I), which do not usually progress to invasive disease [31,32]. RRP can occur in adults but principally presents in children; among children, it is thought to be due to birth-associated exposure to HPV [29]. RRP is rare, not malignant, and recurs often. It can be life-threatening if papillomas reach a size that obstructs the airway.

Penile lesions and HPV in male sexual partners of women with CIN

The prevalence of HPV in males has been studied poorly. As determined by peniscopy, 50-65% of male sexual partners of women with HPV-associated genital disease were found to have genital lesions; half of the lesions were subclinical (ie, not visible without aceton white staining) [33,34]. Barrasso et al. [34] showed that penile lesions with histologic features of penile intraepithelial neoplasia (PIN) were found in about 30% of the sexual partners of women with cervical dysplasia. 68% of the male sexual partners had penile lesions. In another report a single lesion type was seen in 85% of the cases, and 15% had lesions of multiple categories [35]. In that study penile lesions were categorized in 2 types: flat type; and the more commonly observed in association with HPV infection condyloma acuminatum type (known as genital warts). In another study, one part of flat lesions showed histological features of PIN 2 and the other resembled mild dysplasia or PIN 1 (known as squamous hyperplasia in which atypia is absent) [35]. The low percentage of high grade PIN (PIN 2 and 3) in male partners of women with CIN was impressing. 59% of the penile scrapings were positive. 94% of these samples contained high-risk HPVs of which HPV16 was most common (Table 1), present in two thirds of the cases. The use of acetic acid is indispensable for the identification of these lesions, the majority of which were found around the coronal sulcus, the inner part of the foreskin, and the frenulum. Most of the lesions are subclinical and the high prevalence of high-risk HPVs among males suggests that they constitute a reservoir for high-risk HPVs. In a metaanalysis Van Howe concluded that the medical literature does not support the claim that circumcision reduces the risk for genital HPV infection [36]. To correctly assess the risk of HPV infection in circumcised males, the penile shaft needs to be sampled for HPV infection.

Other types of HPV-associated tumors

Skin lesions caused by HPV – Bowen's disease, Buschke -Lowenstein tumor

Bowens disease, an *in situ* squamous cell carcinoma, is confined to the epidermis and becomes invasive infrequently [37]. Associations between Bowens disease and both low and high-risk HPV types have been reported [38,39]. In Bowenoid papulosis skin condylomas normally consist of a number of small papules which histologically resemble SCC or Bowen's disease *in situ*. Due to its local stage it is analogous to the VIN in women [40]. Both low- and high-risk HPV types have been isolated from Bowenoid papulosis. Buschke-Lowenstein tumor is a rare highly differentiated genital carcinoma that is associated with some low-risk HPVs [41].

Breast cancer and HPV

Breast cancer is the most studied or investigated oncological disease in the world. In 1990, Band et al. reported that HPV-DNA could immortalize normal human mammary epithelial cells, and reduce their requirement on growth factors [42]. A number of studies have detected HPV-DNA in breast carcinoma tissues. This raises the question whether HPVs play a carcinogenic role in breast carcinomas. Liang and Tian [43] proposed the hypothesis that mammary epithelial cells that partly lose control in proliferation are more susceptible to per-

sistent HPV infection. There are controversial data on the meaning of viral induction of breast cancer. Lindel K et al. [44] found that all samples were negative for HPV-DNA in 81 patients with breast cancer analyzed by polymerase chain reaction (PCR). In contrast, Kroupis et al. [45] using 4 different PCR methods for detection and verification of genital HPVs in breast cancer found 16% positive tissues tested. 67% of all detected HPV types were HPV16 (Table 1). Breast cancer patients harboring high-risk HPV-DNA sequences in their tumor were younger than the rest of the patients. Furthermore, they were less estrogen receptor-positive and a possible association with acceleration of malignancy was examined [45]. Recently, patients having both a history of invasive cervical cancer and breast cancer as second primary cancer were selected for enrolment in a study of breast carcinomas for the presence of HPV [46]. Paraffin-embedded tissue from cervical cancer, pelvic lymph nodes, breast cancer and axillary lymph nodes of 11 patients were examined for the presence of HPV-DNA using PCR. Additionally, serum samples taken between diagnosis of cervical and breast cancer, were analyzed for the presence of HPV-DNA to examine a possible haematogenous spread of oncogenic HPV-DNA. All cervical carcinomas were HPV-positive. HPV-DNA was detected in 7 out of 11 cases in breast cancer and/or axillary lymph node tissue. These results suggest that HPV-DNA might be transported from the original site of infection to the breast tissue via the bloodstream, and that it is possibly involved in the carcinogenesis of breast neoplasia in some patients [46]. The potential role of HPV infection in the carcinogenic steps of breast cancer should be further tested.

Head and neck squamous cell carcinomas (HNSCCs) and HPV

The development of HNSCCs has also been related to HPV infection [47]. HNSCCs have common predisposing factors - smoking, alcohol consumption, or both in combination, as well as chronic inflammation and gastroesophageal reflux disease (GERD) [47-49]. These factors induce hyperplastic inflammatory response, which is considered as a premalignant condition.

Thanks to the extremely fast development of diagnostic methods of molecular biology, our understanding of HNSCC tumorigenesis has increased tremendously. Using these methods, HPV is isolated from precancerous and dysplastic tissues, as well as from advanced tumors [50]. For example, using PCR, HPV-DNA is detected in 40-70% of HNSCCs [49]. In contrast, HPV-DNA is found in only 1% in normal epithelial cells [49,51,52]. Gillison et al. found that only 23% of recurrent HNSCCs were positive for HPV-DNA and that those patients had better prognosis [53]. HPV 6 and 11 subtypes and other rarer low-risk subtypes have been found in recurrent laryngeal papillomatosis. This condition is characterized by multiple relapsing papules on the vocal cords which spread to other parts of the respiratory tract.

Laryngeal papillomatosis has distinct age predilection, seen mostly in patients before the age of 5 and between 20 and 30 years. This is related to the type of transmission - at birth and later during sexual contact. Laryngeal papillomatosis rarely progresses to malignancy, which is seen after many years of persistence and is facilitated by radiotherapy or smoking. In those cases, such malignant transformations are usually positive for HPV 6 and 11. This means that only under certain conditions HPV could exert its carcinogenic potential. HPV is a prerequisite, but not the only factor for papilloma development. Its role as a cofactor remains to be further explored [51].

Using *in situ* hybridization, viral DNA is localized in the nucleus of the preinvasive tumor cells, invasive carcinoma and metastatic lymph nodes. The reported rate of HPV-DNA detection in laryngeal carcinomas varies significantly - from 0 to 100% [51]. The exact percent is not known, because of great differences in the specificity of the HPV-detection methods used. When HNSCCs are seropositive for HPV, they are subtype 16 in more than 90% of the cases (Table 1) [53].

Dahlstrom et al. found that seropositivity for HPV16 was present in 58.6% of patients with oropharyngeal tumors and in 35.7% of those with laryngeal tumors [52]. They suggested that exposure to HPV16 is a risk factor for HNSCCs, particularly in non-smokers [52,54]. We reported similar results in a recently published study [17].

Prostate cancer and HPV

Since 1990, approximately 13 published studies looked for the presence of HPVs in prostate carcinomas. These investigations revealed that the presence of these viruses vary from 4.2 to 53% [55,56]. Nevertheless, these studies were carried out in different countries, and the types of HPVs detected in prostate carcinomas were mostly limited to HPV types 16, 18, 31 and 33 (Table 1). In parallel, several investigations were able to demonstrate that E6/E7 genes of HPV types 16 and 18 can immortalize human normal and cancer prostate epithelial cells [55]. On the other hand, few studies have revealed that HPVs could not be detected in normal and cancer prostate tissues [57,58].

Colorectal, anal cancer and HPV

Associations between HPV and vaginal, vulvar, and anal cancers are well established, but the full extent in terms of age and time since diagnosis of these associations is not well known. In addition, several studies have assessed the pattern of anogenital cancer after diagnosis of CIN or invasive malignancies [59,60]. Anal cancer has also been related to HPV infection. Using PCR Frisch et al. found HPV in 88% of the patients with anal cancer [61]. They also found greater incidence of HPV in anal cancer in people who were promiscuous with early first sexual contact, especially anal, or people who were single and divorced, or women with a promiscuous partner. They concluded that HPV is a sexually transmitted disease and should be easily preventable.

HPV is present in the colon and rectum of most patients with colorectal adenocarcinoma, suggesting that this virus may be related to the pathogenesis of colorectal cancer. Kirgan et al. [62] studied tissue samples by *in situ* hybridization, detecting HPV-DNA in 27% of colorectal adenomas, 31% of invasive colorectal carcinomas, and 69% of colorectal carcinomas *in situ*. Cheng et al. [63] analyzed tissues by HPV type-specific PCRs, finding HPV-DNA in 29% of adenomas and in 53% of colorectal carcinomas. Perez et al. [64] investigated tissue samples by MY/GP nested PCR, detecting HPV in 74% of colorectal carcinomas. Bodaghi et al. [65] used MY/GP nested PCR and *in situ* PCR to detect HPV-DNA in 51% of samples from patients with cancer, but in none of the samples collected from controls without cancer. HPV16 was the most prevalent viral type, being detected in 82% of the positive samples (Table 1).

Damin et al. [66] found no significant differences in clinical and pathological variables between HPV-positive and HPV-negative colorectal carcinomas. In contrast, opposite results have been observed in head and neck and lung carcinomas where the presence of HPV was considered as a marker of better prognosis [53].

Lung cancer and HPV

The epidemiological and morphological observations, the detection of HPV-DNA in lung cancer and *in vitro* studies are in agreement with the concept that HPV might be involved in bronchial carcinogenesis [67]. The detection rates of HPV in lung carcinomas are subject to wide variations. In a review of 85 studies [67] and some others [68,69] recording about 2739 cases described a detection rate of 22.16%.

Discussion

Our clinical oncological practice directed our attention to the idea that HPVs may be a causal factor for development of other types of tumors excepting cervical cancer (Table 2). It has often happened a simultaneous presence of a second or third type of tumor in women with cervical cancer or concurrent development of genital warts and nasopharyngeal cancer in very young patients. In a study of ours the causal and effective connection between cervical cancer, vaginal cancer and laryngeal cancer *in situ* with common etiological agent - HPV-was proved in one of the studied patients [17].

The theory that cancer could be caused by a virus began to be developed in 1911 by Peyton Rous. Rous transmitted solid tumors of chicken by transplanting tissue between them. By the early 1950s it was known that viruses could remove and incorporate genes and genetic material in cells.

The main viruses associated with human cancers are HPV, hepatitis B and C viruses, Epstein-Barr virus, and human T-lymphotropic virus.

Between 5 and 10% of human cancers are a consequence of HPV infection. Although there are many carcinogenic mechanisms, it seems that there exist few key players among them in the development of cancer. HPV seems to be the paradigm in oncogenesis. 100% of cervical cancer is caused by HPV infection. In addition to cancer of the cervix, a major proportion of anal, perianal, vulvar, and penile cancers appears to be linked to the same HPV infections, some head and neck cancers, and some rare cancers at mucosal/squamous epithelial junctions. There are controversial data on the

Table 2. The degree of risk in certain tumor types when HPV infection is present

Degree of risk	*Localization*	*Percent of risk*
High level of probability-established	Cervical cancer	99
	Vaginal cancer (in young women)	99
	Vulvar cancer	up to 90
	Anal cancer	88
Middle level - probable predisposing factor	HNSCC*	40-70
	Laryngeal cancer	35.7
	Oropharyngeal cancer	58.6
Low level - just a potential risk factor	Breast cancer	0-16
	Prostate cancer	4.2-53
	Colorectal cancer	27-69
	Lung cancer	22.16

*head & neck squamous cell carcinoma

meaning of viral HPV induction of breast cancer, lung cancer and colon cancer, thus future basic research and clinical trials should be carried out.

Results of Widschwendter et al. [46] suggest that HPV-DNA might be transported from the original site of infection to breast tissue by the bloodstream, and therefore to all organs and may possibly be involved in the carcinogenesis of breast and other neoplasias in some patients. This indicates a possible common risk factor of oncogenic HPV-DNA in developing certain second primary cancers after HPV-related primary neoplasia.

How should we use this evidence? Strengthening of the evidence linking persistent HPV infection and human cancers suggests that prevention of HPV infection, possibly through vaccination, might be a way of eliminating cervical cancer and other HPV-assosiated tumors in the future. Vaccines to protect against HPV infection have recently become available, based on virus-like particle technology [70,71]. Virus-like particles are produced by expressing the capsid proteins of the virus using recombinant DNA technology. These highly immunogenic particles can protect not only against infection with the HPV types incorporated in the vaccine and some cross-reactive HPV types but also against the other malignant disease (anal, perianal, vulvar, and penile cancers) etiologically connected with HPV. Protection is durable over at least 5 years, and the vaccine appears to protect nearly 100% of the immunized subjects.

Conclusions

In this paper, we propose the hypothesis that many normal epithelial cells are susceptible to HPV infection, which are the most sexually transmitted viruses. Experimental and epidemiological data imply a causative role for HPVs and they appear to be the second most important risk factor for cancer development in humans, exceeded only by tobacco usage.

References

1. Munder K, Howley PM. Human papillomavirus immortalization and transformation function. Virus Res 2002; 89: 213-228.
2. Munoz N, Bosch XF, De Sanjoses et al. Epidemiologic classification of human papilloma virus types associated with cervical cancer. N Engl J Med 2003; 348: 518-527.
3. Stewart BW, Kleihues P (Eds): World Cancer Report. IARC Press. Lyon 2003, p 215.
4. Zur Hausen H. Human papillomaviruses and their possible role in squamous cell carcinomas. Curr Top Microbiol Immunol 1977; 78: 1-30.
5. Baseman JG Koutsky LA. The epidemiology of human papillomavirus infection. J Clin Virol 2005; 32 (Suppl 1): 516-524.
6. zur Hausen H. Human papillomaviruses in the pathogenesis of anogenital cancer. Virology 1991; 184: 9-13.
7. International Agency for Research on Cancer. Evaluation of Carcinogenic Risk in Humans: Human papillomavirus. Lyon, France: IARC; 2006. IARC Monograph, 2005.
8. Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189: 9-12.
9. Zlatkov V, Kostova P, Makaveeva V, Ganchev G, Danon S. A study on the cervical epithelium of women in early pregnancy - histological findings and human papillomavirus characterization. J BUON 2003; 8: 269-272.
10. von Knebel, Doeberitz M. New markers for cervical dysplasia to visualise the genomic chaos created by aberrant oncogenic papillomavirus infections. Eur J Cancer 2002; 38: 2229-2242.
11. Duensing S, Munger K. Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. Int J Cancer 2004; 109: 157-162.
12. Rutledge F. Cancer of the vagina. Am J Obstet Gynecol 1967; 97: 635-655.
13. Sillman FH, Sedlis A, Boyce JG. A review of lower genital intraepithelial neoplasia and the use of topical 5-fluorouracil. Obstet Gynecol Surv 1985; 40: 190-220.
14. Gallp DG, Morley GW. Carcinoma in situ of the vagina. A study and review. Obstet Gynecol 1975; 46: 334-340.
15. Minucci A, Cinel A, Insacco E et al. Epidemiological aspects of vaginal intraepithelial neoplasia (VAIN). Clin Exp Obstet Gynecol 1995; 22: 36-42.
16. Sugase M, Matsukura T. Distinct manifestations of human papillomaviruses in the vagina. Int J Cancer 1997; 72: 412-415.
17. Georgieva S, Iordanov V. A woman with synchronous cervical, vaginal and laryngeal squamous cell carcinomas and positive human papillomavirus type 16; case presentation with literature review. J BUON 2008; 13: 109-113.
18. Sillman FH, Fruchter RG, Chen YS et al. Vaginal intraepithelial neoplasia: risk factors per persistence, recurrence and invasion and its management. Am J Obstet Gynecol 1997; 176: 93-99.
19. Frega A, French D, Piazze J et al. Prediction of persistent vaginal intraepithelial neoplasia in previously hysterectomized women by high-risk HPV DNA detection. Cancer Lett 2007; 249: 235-241.
20. Gupta J, Pilotti S, Rilke F, Shah K. Association of human papillomavirus type 16 with neoplastic lesions of the vulva and other genital sites by in situ hybridization. Am J Pathol 1987; 127: 206-215.
21. Hording U, Daugard S, Iversen T et al. Human papillomavirus type 16 in vulvar carcinoma, vulvar intraepithelial neoplasia, and associated cervical neoplasia. Gynecol Oncol 1991; 42: 22-26.
22. Park JS, Jones RW, Mc Lean MR et al. Possible etiologic heterogeneity of vulvar intraepithelial neoplasia. A correlation of pathologic characteristics with human papillomavirus detection by in situ hybridization and polymerase chain reaction. Cancer 1991; 67: 1599-1507.
23. Jones RW, Rowan DM. Vulvar intraepithelial neoplasia III: a clinical study of the outcome in 113 cases with relation to

the later development of invasive vulvar carcinoma. Obstet Gynecol 1994; 84: 741-745.
24. Jones RW, Baranyai J, Stable S. Trends in squamous cell carcinoma of the vulva: influence of vulvar intraepithelial neoplasia. Obstet Gynecol 1997; 90: 448-452.
25. Beutner KR, Spruance SL, Houghham AJ et al. Treatment of genital warts with an immune-response modifier (imiquimod). J Am Acad Dermatol 1998; 38: 230-239.
26. Fehr MK, Hornung R, Schwarz VA et al. Photodynamic therapy of vulvar intraepithelial neoplasia III using topically applied 5-aminolevulenic acid. Gynecol Oncol 2001; 80: 62-66.
27. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. J Obstet Gynecol 2005; 106: 1319-1326.
28. Kirwan JM, Herod JJ. Premalignant vulval disorders. Curr Obst Gynecol 2002; 12: 90-96.
29. Wiley DJ, Douglas J, Beutner K et al. External genital warts: diagnosis, treatment, and prevention. Clin Infect Dis 2002; 35: S210-S224.
30. Derkay CS, Darrow DH. Recurrent respiratory papillomatosis of the larynx: current diagnosis and treatment. Otolaryngol Clin North Am 2000; 33: 1127-1141.
31. Crum CP, Mitao M, Levine RU, Silverstein S. Cervical papilloma viruses segregate within morphologically distinct precancerous lesions. J Virol 1985; 54: 675-681.
32. Willett GD, Kurman RJ, Reid R, Greenberg M, Jenson AB, Lorincz AT. Correlation of the histologic appearance of intraepithelial neoplasia of the cervix with human papillomavirus types: emphasis on low grade lesions including so-called flat condyloma. Int J Gynecol Pathol 1989; 8: 18-25.
33. Hippelainen M, Yliskoski M, Saarikoski S, Syrjanen S, Syrjanen K. Genital human papillomavirus lesions of the male sexual partners: the diagnostic accuracy of peniscopy. Genitourin Med 1991; 67: 291-296.
34. Barrasso R, de Brux J, Croissant O, Orth G. High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. N Engl J Med 1987; 317: 916-923.
35. Bleeker MC, Hogewoning CJ, van den Brule AJ et al. Penile lesions and human papillomavirus in male sexual partners of women with cervical intraepithelial neoplasia. J Am Acad Dermatol 2002; 47: 351-357.
36. Van Howe RS. Human papilloma virus and circumcision: A meta-analysis. J Infect 2007; 54: 490-496.
37. Ihin CW, Park SL, Sung SY, Lee IS. Bowenoid epidemiotopic metastatic squamous cell carcinoma. J Cutan Pathol 1996; 23: 479-484.
38. Collina G, Rossi E, Bettelli S et al. Detection of human papillomavirus in extragenital Bowens disease using in situ hybridization and polymerase chain reaction. Am J Dermatopathol 1995; 17: 236-241.
39. Ikenberg H, Gissmann L, Gross G, Grussendorf-Conen EI, zur Hausen H. Human papillomavirus type-16-related DNA in genital Bowens disease and in Bowenoid papulosis. Int J Cancer 1983; 32: 563-565.
40. Wade TR, Kopf AW, Ackerman AB. Bowenoid papulosis of the genitalia. Arch Dermatol 1979; 115: 306-308.
41. Lehn H, Ernst TM, Sauer G. Transcription of episomal papillomavirus DNA in human condylomata acuminate and Buschke-Lowenstein tumours. J Gen Virol 1984; 65: 2003-2010.
42. Band V, Zajchowski D, Kulesa V, Sager R. Human papilloma virus DNAs immortalize normal human mammary epithelial cells and reduce their growth factor requirements. Proc Natl Acad Sci USA 1990; 87: 463-467.
43. Liang W, Tian H. Hypothetic association between human papillomavirus infection and breast carcinoma. Med Hypotheses 2008; 70: 305-307.
44. Lindel K, Forster A, Altermatt HJ, Greiner R, Gruber G. Breast cancer and human papillomavirus (HPV) infection: No evidence of a viral etiology in a group of Swiss women. The Breast 2007; 16: 172-177.
45. Kroupis C, Markou A, Vourlidis N et al. Presence of high-risk human papillomavirus sequences in breast cancer tissues and association with histopathological characteristics. Clin Biochem 2006; 39: 727-731.
46. Widschwendter A, Brunhuber T, Wiedemair A, Holzner EM, Marth Chr. Detection of human papillomavirus DNA in breast cancer of patients with cervical cancer history. J Clin Virol 2004; 31: 292-297.
47. Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. J Clin Virol 2005; 32 (Suppl): S59-S66.
48. El Serag HB, Hepworth EJ, Lee P, Sonnenberg A. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. Am J Gastroenterol 2001; 96: 2013-2018.
49. Wen S, Tsuji T, Li X. Detection and analysis of human papillomavirus 16 and 18 homologous DNA sequences in oral lesions. Anticancer Res 1997; 17: 307-311.
50. Mitsuishi T, Kawana S, Kato T, Kawashima M. Human papillomavirus infection in actinic keratosis and Bowen's disease: comparative study with expression of cell-cycle regulatory proteins p21Waf1/Cip1, p53, PCNA, Ki-67, and Bcl-2 in positive and negative lesions. Human Pathol 2003; 34: 886-892.
51. Herrero R. Human papillomavirus and cancer of the upper aerodigestive tract. Natl Cancer Inst Monographs, Ch 7, 2003; 31: 47-51.
52. Dahlstrom RK, Adler - Storthz K, Etzel JC et al. Human papillomavirus type 11, 16 infection and squamous cell carcinoma of the head and neck in never smokers. Clin Cancer Res 2003; 9: 2620-2626.
53. Gillison ML, Koch WM, Capone RB et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000; 92; 709-720.
54. Sugiyama M, Bhawal UK, Kawamura M et al. Human papillomavirus 16 in oral squamous cell carcinoma: Clinical correlates and 5-year survival. Br J Oral Maxillofacial Surg 2007; 45: 116-122.
55. Sutcliffe S, Giovannucci E, Gaydos CA et al. Plasma antibodies against Chlamydia trachomatis, human papillomavirus, and human herpesvirus type 8 in relation to prostate cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2007; 16: 1573-1580.
56. Al Moustafa AE. Involvement of human papillomavirus infections in prostate cancer progression. Med Hypotheses 2008; 71: 209-211.
57. Strickler HD, Burk R, Shah K et al. A multifaceted study of human papillomavirus and prostate carcinoma. Cancer 1998; 82: 1118-1125.
58. Rosenblatt KA, Carter JJ, Iwasaki LM, Galloway DA, Stanford JL. Serologic evidence of human papillomavirus 16 and 18 infections and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2003; 12: 763-768.

59. Hemminki K, Dong C, Vaittinen P. Second primary cancer after in situ and invasive cervical cancer. Epidemiology 2000; 11: 457-461.
60. Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. BMJ 2005; 331: 1183-1185.
61. Frisch M, Glimelins B, Van den Brule AJC et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med 1997; 337: 1350-1358.
62. Kirgan D, Manalo P, Hall M, McGregor B. Association of human papilloma virus and colon neoplasm. Arch Surg 1990; 125: 862-865.
63. Cheng JY, Sheu LF, Meng CL, Lee WH, Lin JC. Detection of human papillomavirus DNA in colorectal carcinomas by polymerase chain reaction. Gut 1995; 37: 87-90.
64. Perez LO, Abba MC, Languens RM, Golijow CD. Analysis of adenocarcinomas of the colon and rectum: detection of human papillomavirus (HPV) DNA by polymerase chain reaction. Colorectal Dis 2005; 7: 492-495.
65. Bodaghi S, Yamanegi K, Xiao SY, da Costa M, Palefski JM, Zheng ZM. Colorectal papillomavirus infection in patients with colorectal cancer. Clin Cancer Res 2005; 11: 2862-2867.
66. Damin DC, Caetano MB, Rosito MA et al. Evidence for an association of human papillomavirus infection and colorectal cancer. EJSO 2007; 33: 569-574.
67. Syrjanen KJ. HPV infections and lung cancer. J Clin Pathol 2002; 55: 885-891.
68. Brochest L, Valmary S, Dahan M et al. Detection of oncogenic virus genomes and gene products in lung carcinoma. Br J Cancer 2005; 92: 743-746.
69. Chiou HL, Wu MF, Liaw YC et al. The presence of human papillomavirus type 16/18 DNA in blood circulation may act as a risk marker of lung cancer in Taiwan. Cancer 2003; 97: 1558-1563.
70. Leggatt GR, Frazer IH. HPV vaccines: the beginning of the end for cervical cancer. Curr Opin Immunol 2007; 19: 232-238.
71. Frazer IH. Prevention of cervical cancer through papillomavirus vaccination. Nat Rev Immunol 2004; 4: 46-55.