Human Papillomavirus Infection and Skin Cancer Risk in Organ Transplant Recipients

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Warts and squamous cell carcinomas are important cutaneous complications in organ transplant recipients. The role of infection with human papillomaviruses (HPV) in the development of cutaneous squamous cell carcinoma is still unclear. An extremely diverse group of HPV types, mainly consisting of epidermodysplasia-verruciformis (EV)-associated HPV types, can be detected in benign, premalignant, and malignant skin lesions of organ transplant recipients. Frequently, there are multiple HPV types present in single skin biopsies. Typically, the prevalence of viral warts rises steadily after transplantation and a strong association exists between the number of HPV-induced warts and the development of skin cancer. The interval between the transplantation to the development of warts is clearly shorter than the interval from transplantation to the diagnosis of the first skin cancer. A comparison of transplant recipients with and without skin cancer, however, showed an equally high prevalence of EV-HPV DNA in keratotic skin lesions in both groups of patients and the detection rate and spectrum of HPV infection in hyperkeratotic papillomas, actinic keratoses, and squamous cell carcinomas was also similar. HPV DNA can frequently be detected in patients with hyperproliferative disorders like psoriasis and antibodies against HPV in patients with regenerating skin (e.g., after extensive second degree burns). Latent infection with EV-HPV seems to be widespread. The hair follicle region might be the reservoir of EV-HPV. The E6 protein from a range of cutaneous HPV types effectively inhibits apoptosis in response to UV-light induced damage. It is therefore conceivable that individuals who are infected by EV-HPV are at an increased risk of developing actinic keratoses and squamous cell carcinomas, possibly by chronically preventing UV-light induced apoptosis. Key words: basal cell carcinoma/epidermodysplasia verruciformis/squamous cell carcinoma/UV light. Journal of Investigative Dermatology Symposium Proceedings 6:207–211, 2001

Risk of skin cancer in the immunocompetent population Skin cancers are the most common malignant tumors among the Caucasian population. Cutaneous squamous cell carcinoma and basal cell carcinoma, together commonly called nonmelanoma skin cancers, account for almost 90% of cutaneous malignancies (Harvey et al, 1989; Goldberg, 1996; Marks, 1996). Although the annual mortality rate from nonmelanoma skin cancers is relatively low, due to the high prevalence and substantial degree of morbidity, these tumors present a significant and costly health problem (Preston and Stern, 1992). Exposure to sunlight is generally considered to be the most important risk factor for nonmelanoma skin cancers (Brash et al, 1991; Marks, 1996). Infection with human papillomaviruses (HPV), however, may also be important, especially for the development of squamous cell carcinomas (Pfister and ter Schegget, 1997).

Risk of warts and skin cancer in organ transplant recipients Warts and squamous cell carcinomas are by far the most important cutaneous clinical problem in organ transplant recipients (Boyle et al, 1984; Barr et al, 1989; Hartevelt et al, 1990; Bouwes Bavinck et al, 1991; Glover et al, 1994; Hardie, 1995). In organ transplant recipients the most important risk factor for skin cancer is the immunosuppressive therapy.

Like in the immunocompetent population, exposure to sunlight is believed to be a major risk factor for the development of nonmelanoma skin cancer in organ transplant recipients. In countries with low exposure to sunlight, the cumulative incidence of skin cancer is 10% 10 y after the transplantation and 40% 20 y after the transplantation (Birkeland et al, 1995; Hartevelt et al, 1990; London et al, 1995). In Australia, Spain, and the U.S.A., these numbers are even much higher, namely 40% and 70% after 10 and 20 y, respectively (Hardie et al, 1980; Ferrándiz et al, 1995; Bouwes Bavinck et al, 1996; Lampros et al, 1998). Many patients develop 10 to more than 100 skin cancers in short time periods.

The role of infection with human papillomaviruses in the development of cutaneous squamous cell carcinoma is still unclear. This review focuses on the role of HPV infection in the development of skin cancer in organ transplant recipients and draws a parallel with the development of cervical cancer in HPV16-infected women.

Postulates for an oncogenic role of HPV infection Prerequisites for a role of HPV infection in the pathogenesis of
cervix carcinoma are (i) that the viral DNA can be detected in the majority of the carcinomas (preferably in high copy numbers), (ii) that the viral genes (most notably the oncogenes) are expressed in the tumor cells, and (iii) that the viral genome persists during metastatic spread of the tumor cells or passage of the cells in vivo (Pfister and ter Schegget, 1997; Walboomers et al. 1999; zur Hausen, 2000). This is in contrast to a large series of rather frustrating attempts to demonstrate HPV-DNA in nonmelanoma skin cancers by conventional nucleic acid hybridization techniques (Pfister and ter Schegget, 1997). When discussing a possible role of HPV in skin cancer, one should therefore be prepared to acknowledge a more indirect and maybe transient effect of HPV on the pathogenesis of skin cancer (Pfister and ter Schegget, 1997). Arguments in favor of and against a possible role of HPV infection in relation to skin cancer are discussed later in this review.

HPV16 INFECTION AND THE RISK OF CERVICAL CARCINOMA

Risk of cervical carcinoma in the immunocompetent population During the past 20 y, several types of HPV have been identified that cause specific types of cancers (zur Hausen, 2000). High-risk HPV types like HPV16 are a necessary cause of squamous cell carcinoma of the cervix (Walboomers et al. 1999). These tumors are characterized by the presence of mostly integrated HPV DNA in all tumor cells. Viral oncogene expression (E6 and E7) can be demonstrated in tumor material. Furthermore, extensive evidence has been presented for an important role of these high-risk HPV types in the pathogenesis of cervical cancer (zur Hausen, 2000). Transforming properties of the E6/E7 genes have been identified. E6 and E7 expression is required for maintaining the malignant phenotype of cervical carcinoma cell lines and both oncoproteins interact with growth-regulating host-cell proteins. Finally, epidemiologic studies identified these HPV infections as a risk factor for the development of cervical cancer (zur Hausen, 2000).

Risk of anogenital warts and cervical carcinoma in organ transplant recipients A number of studies have been conducted to estimate the prevalence of anogenital and cervical lesions among groups of women who are immunosuppressed following organ transplantation (Schneider et al., 1983; Alloub et al., 1989; Kelly et al., 1991; IARC, 1995; Euvrard et al., 1996). In an Australian cohort of transplant recipients a standardized incidence ratio for cervical cancer of 3.3 was calculated compared with the normal population (Fairley et al., 1994), and in a Nordic cohort a standardized incidence ratio of 8.6 was found (Birkeland et al., 1995).

EPIEDEMOLOGY OF CUTANEOUS HPV INFECTION IN ORGAN TRANSPLANT RECIPIENTS

High incidence of warts and skin cancer Many organ transplant recipients have a highly increased incidence of both viral warts and squamous cell carcinoma, and DNA of human papillomaviruses can frequently be detected in nonmelanoma skin cancers, raising the question of a possible causal contribution of these viruses to skin carcinogenesis (Boyle et al., 1984; Penn and Brunson, 1988; Bouwes Bavinck et al., 1991, 1998; Bouwes Bavinck et al., 1994; Bouwes Bavinck and Berkhout, 1997; Pfister and ter Schegget, 1997; Harwood et al., 1999a, 2000; Jensen et al., 1999; Wieland et al., 2000). Sooner or later after the transplantation, almost all patients will experience warts.

A diverse group of HPV types can be detected An extremely diverse group of HPV types consisting of epidermodysplasia-verruciformis (EV)-associated HPV types (e.g., EV-HPV types of subgroup A: HPV5, 8, 12, 14, 19, 20, 21, 25, 33, and 47, EV-HPV types of subgroup B: HPV9, 15, 17, 22, 23, 37, 38, and 47, and EV-HPV types of subgroup C: HPV24) (Berkhout et al., 2000) and other cutaneous HPV types (e.g., HPV2, 3, 10, 27, 28, 29, and 58), as well as dozens of putatively new EV and cutaneous HPV types, can be detected in benign, premalignant, and malignant skin lesions of organ transplant recipients. The EV-HPV types prevail in all lesion types (Soler et al., 1993; Tieben et al., 1993, 1994; Berkhout et al., 1995, 2000; de Jong-Tieben et al., 1995, 2000; McGregor and Proby, 1996; Shammin et al., 1996; Arends and Benston, 1997; de Villiers et al., 1997; Höpfli et al., 1997; Bens et al., 1998; Harwood et al., 1998, 2000; Forslund et al., 1999).

Multiple HPV types can be found in single lesions Frequently, there are multiple HPV types present in single skin biopsy specimens of organ transplant recipients (Berkhout et al., 2000; Harwood et al., 2000). An approach with PCR techniques for the detection of distinct (sub)groups of genotypically related cutaneous HPV types, i.e., three subgroups of EV-associated HPV types and two groups of other cutaneous HPV types, generally allows a reliable identification of HPV genotypes by direct sequencing of the PCR products, despite the frequent occurrence of multiple infections (Berkhout et al., 2000).

The frequency of EV-associated HPV and other cutaneous HPV types is similar in biopsy specimens from hyperkeratotic papillomas (78%), actinic keratoses (68%), and squamous cell carcinomas (78%), but appears to be lower in specimens of basal cell carcinomas (36%), benign skin lesions (39%), and clinically normal skin (32%) (Berkhout et al., 2000) (Fig 1). Similar prevalence rates were found in another study in which HPV DNA was detected in 84% of squamous cell carcinomas and 88% of premalignant skin lesions (Harwood et al., 2000). The prevalence rate of 75% in basal cell carcinomas, however, was much higher in this study (Harwood et al., 2000).

Latent infection with EV-HPV seems to be widespread. The hair follicle region might be the reservoir of EV-HPV (Boxman et al., 1997, 1999a, b).

ARGUMENTS IN FAVOR OF A ROLE OF EV-HPV INFECTION IN SKIN CANCER ONCOGENESIS

The earliest evidence that HPV infection may play a role in skin cancer oncogenesis comes from studies in patients with the rare hereditary syndrome epidermodysplasia verruciformis (EV) (Orth, 1987). EV patients acquire characteristic skin warts during childhood and one-third of these patients develop squamous cell carcinomas on sun-exposed skin at young age (Orth, 1987). The HPV types found in the skin lesions of these patients by Southern blot hybridization are commonly referred to EV HPV types and include HPV5, 8, 9, 12, 14, 15, 19–25, 36, 38, and 47 (Pfister and ter Schegget, 1997).

There are several arguments supporting a causative role of HPV infection in the development of squamous cell carcinomas in organ transplant recipients. The prevalence of viral warts rises steadily after transplantation (Gassemiaert et al., 1986; Rüddinger et al., 1986; van der Leest et al., 1987; Barr et al., 1989; Dyall-Smith et al., 1991; de Jong-Tieben et al., 2000). The interval between the transplantation to the development of warts is clearly shorter than the interval from transplantation to the diagnosis of the first skin cancer (Bouwes Bavinck et al., 1993; de Jong-Tieben et al., 2000) and a strong association exists within organ transplant recipients between the number of HPV-induced warts and the development of skin cancer (Fig 2) (Bouwes Bavinck et al., 1991; Bouwes Bavinck et al., 1993; de Jong-Tieben et al., 2000).

In addition, DNA of the epidermodysplasia-verruciformis associated subgroup of HPV (EV-HPV) can frequently be detected in biopsies of premalignant lesions and nonmelanoma skin cancers of organ transplant recipients (de Jong-Tieben et al., 1998, 2000; Harwood et al., 1999b, 2000) and EV-HPV infection in organ-transplant recipients may persist for many years, suggesting that organ transplant recipients are prone to persistent cutaneous HPV infection (Berkhout et al., 2000; de Jong-Tieben et al., 2000).
ARGUMENTS AGAINST A ROLE OF EV-HPV INFECTION IN SKIN CANCER ONCOGENESIS

There are several arguments against a direct causative role of EV-HPV infection in skin cancer oncogenesis. In a recent case-control study, the prevalence of EV-HPV DNA in benign keratotic skin lesions was equally high in organ transplant recipients with and without a history of skin cancer, i.e. 55 and 53% in the two groups, respectively (de Jong-Tieben et al., 2000) and the detection rate and spectrum of HPV infection in hyperkeratotic papillomas, actinic keratoses and squamous cell carcinomas is similar (Berkhout et al., 2000). The existence of one single or of a few oncogenic EV-HPV types seems unlikely (Berkhout et al., 2000).

In skin samples of patients with psoriasis and bullous diseases HPV5 DNA can also frequently be detected (Favre et al., 1998; Favre et al., 2000), and epidermal repair in patients with extensive second-degree burns is associated with the generation of anti-HPV5 antibodies (Favre et al., 2000). EV-HPV have also been detected in recurrent cutaneous and mucosal lesions of a stomacarrier (Wieland et al., 1998). Therefore, the frequent presence of EV-HPV in squamous cell carcinomas of organ transplant recipients does not indicate that these HPV types are necessarily causatively involved in cutaneous oncogenesis.

Recently, in the immunocompetent population no statistically significant differences could be detected between the presence of HPV DNA in basal cell carcinomas and normal skin nor between antibody prevalence in basal cell carcinoma patients and dermatologically healthy individuals (Wieland et al., 2000). This suggests that the occurrence of human papillomavirus-DNA in basal cell carcinoma does not reflect a major etiologic role of human papillomavirus in this specific skin cancer in immunocompetent hosts (Wieland et al., 2000).

INTERACTION BETWEEN EXPOSURE TO SUNLIGHT AND EV-HPV INFECTION IN RELATION TO SKIN CANCER

The oncogenic mechanisms of EV-HPV types remain uncertain in contrast to those of the HPV types involved in anogenital malignancy, but there appears to be a crucial additional requirement for UV radiation (Harwood et al., 1999a, b). A higher prevalence of EV-HPV DNA was found in benign skin lesions from sun-exposed sites, but only in patients with a history of skin cancer (de Jong-Tieben et al., 2000).

Ultraviolet light may exert its harmful effect by inducing DNA damage and/or by inducing local immunologic unresponsiveness (Kripke, 1994). Sun exposure might directly activate functions of HPV or sun exposure may enhance HPV replication in the host by inducing (local) immunosuppression and/or inactivating keratinocyte growth regulating host genes (e.g., p53). In this respect it is important to note that the E6 protein from a range of cutaneous HPV types effectively inhibits apoptosis in response to UV damage (Jackson and Storey, 2000). As EV-HPV is widely distributed it can be hypothesized that individuals who are infected by EV-HPV are at an increased risk of developing solar keratoses and squamous cell carcinomas by the inhibition of UV-induced apoptosis (Fig 3).
Inhibition of UV-induced apoptosis.

Finally, it cannot be excluded that HPV infection by itself is not a direct causative factor but, when present, it modifies the risk of UV-light-induced skin cancer.

THE POSSIBLE ROLE OF P53 IN HPV-RELATED ONCOGENESIS

The p53 tumor suppressor gene is a transcriptional activator involved in the control of the cell cycle (Brash et al., 1991). Like in the immunocompetent population, the high prevalence of p53 immunostaining in premalignant and malignant skin lesions of organ transplant recipients supports a role for p53 protein in skin cancer (McGregor et al., 1994, 1997; Ferrándiz et al., 1999; Hudson et al., 1999).

Degradation of the tumor suppressor gene p53 induced by the E6 protein of genital oncogenic HPV types is also an important mechanism for human papillomavirus-induced carcinogenesis (Storey et al., 1998). A common genomic polymorphism occurs at codon 72 of the p53 gene, and in vitro the codon 72 Arginine variant appears to be particularly susceptible to degradation (Storey et al., 1998). In a large study with organ transplant recipients, however, the p53 codon 72 Arginine allele did not confer susceptibility to the development of skin tumors after renal transplantation (Marshall et al., 2000). Also in the immunocompetent population no association was found between arginine homozygosity of codon 72 in the p53 gene and the development of cutaneous squamous cell carcinoma, basal cell carcinoma, or malignant melanoma (Bastiaens et al., 2001). In accordance with this observation it has been shown that the E6 protein of EV-HPV type 8 does not form a complex with p53 (Steger and Pfister, 1992).

SYNTHESIS/PROPOSED MECHANISM

It is conceivable that the development of squamous cell carcinomas in organ transplant recipients is the result of a complex interplay between EV-HPV infection, exposure to UV radiation, genetic predisposition, immune response, and possibly other factors, such as tobacco smoking, etc. The role of EV-HPV infection in the development of skin cancer in this complex interplay is still unclear. Although HPV infection may play a role in the development of squamous cell carcinomas, its role in the development of basal cell carcinomas remains highly speculative. HPV, no doubt, profit considerably from immunosuppression, as is indicated by the large number of warts in organ transplant recipients and, additionally, these HPV may profit from UV-light-induced immunosuppression.

The equally high prevalence of EV-HPV infection in patients with and without a history of skin cancer and the fact that, until now, no high-risk oncogenic EV-HPV types could be identified, are arguments against a direct causative role of EV-HPV infection in skin cancer oncogenesis and indicate that besides EV-HPV infection, other factors, such as sun exposure, may be crucial.

We hypothesize that EV-HPV infection is a (possibly necessary) cofactor in the complex interplay between environmental and genetic factors causing cutaneous squamous cell carcinoma. In this regard, inhibition of apoptosis in response to UV damage by the E6 protein from a range of cutaneous HPV types may play a key role in providing a survival advantage to genetically damaged keratinocytes, which cells otherwise would have been destroyed by apoptotic defense mechanisms.

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