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HPV Infections and Immunosuppression

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HPV Infections in Transplant Recipients

Human papillomavirus (HPV) infection can be considered as one of the most frequently occurring infections in transplant recipients.¹⁻⁴ Sooner or later most recipients will experience HPV infection (Fig 1 and 2). HPV infection is specifically important, because it can be considered as an exposure that poses a risk of several kinds of cancer.⁵ A wide diversity of HPV types can be detected in skin cancers and premalignant lesions of transplant recipients.⁶⁻⁸ The high prevalence of HPV DNA detected in squamous cell carcinomas and basal cell carcinomas of immunosuppressed patients suggests a potential role for HPV infection in the etiology of these lesions.⁹

Epidemiology

Incidence of Warts and Skin Cancer

Renal transplant recipients are at a highly increased risk for warts and nonmelanoma skin cancer, predominantly squamous cell carcinomas (Fig 3), and to a somewhat lesser extent basal cell carcinomas (Fig 4).^{1,3,10-12} The prevalence of viral warts rises steadily after transplantation.^{3,4,13-15} 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.² Skin cancer is particularly a problem in Queensland, Australia, where people have excessive exposure to sunlight,¹⁶ but it can also be a major problem in countries at higher latitudes and only a moderate amount of exposure to sunlight, such as the Netherlands and the United Kingdom.^{10,17,18} The cumulative incidence of skin cancer in a population of renal transplant recipients in Queensland increased from 7% after 1 year of immunosuppression to 16% after 3 years, 25% after 5 years, 33% after 7 years, 45% after 11 years, 59% after 15 years and 70% after 20 years of immunosuppression.¹⁹ The cumulative incidence of skin cancer in a comparable Dutch population at the same time

points was 0.2%, 0.7%, 3%, 6%, 16%, 24%, and 41%, respectively.^{10,19} Similar incidence data have been reported where the figures in the United Kingdom and the Nordic countries approach those in the Netherlands,^{18,20} and the figures in Spain approach those in Australia.²¹

The problem of skin cancer is not limited to recipients of renal transplants, but it is also eminent in recipients of heart transplants and of other organs.²²⁻²⁵

Association of HPV Infection with Nonmelanoma Skin Cancer

The first evidence that HPV infection is associated with squamous cell carcinoma of the skin was found in patients with the rare, genetically determined, condition epidermodysplasia verruciformis (EV). This syndrome is characterized by the presence of numerous flat warts, the occurrence of squamous cell carcinoma in 30 to 50% of patients, and possibly a defect in cell-mediated immunity.²⁶⁻²⁹ A large group of HPVs can be detected in skin lesions of patients with this condition. DNA of HPV 5 and HPV 8, and less frequently of HPV 14, 17, 20, and 47, has been detected in skin cancers of these patients.²⁶

The skin problems in recipients of renal transplants can mimic those seen in EV patients. DNA of HPV can be detected in more than 80% of biopsies from skin cancers and premalignant lesions from renal-transplant recipients.^{6,7} Other research groups also found a high percentage of HPV DNA in skin carcinomas of renal-transplant recipients;^{3,8,30-34} however, some groups, reported a lower percentage of lesions with HPV DNA or no HPV DNA at all.^{13,35-38}

What types of HPVs that are possibly implicated is a matter of controversy.^{7,39} Chiefly mucosal HPVs (type 6, 11, 16, and 18) were detected by some groups,^{31,34} but were not found by others.^{6,7} In sharp contrast, only HPVs belonging to the EV-related subgroup were detected by other groups,^{6,7,39} and still another group detected non-EV HPVs, such as HPV 41 or a HPV 29-related type, but also EV HPVs and mucosal HPVs.^{8,32}

The explanation for this phenomenon is probably largely attributable to differences in the techniques used.⁷ It is very likely that more than one HPV type is present in skin lesions; and depending on the technique used, one or another type can be picked up. The

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Figure 1. Extensive warts and solar keratoses on the hand of a renal transplant recipient.

existence of not yet established HPV types could be a second explanation for the obvious controversies in the literature.^{6-8,39} The role of HPV in cutaneous premalignant and malignant tumors is described more extensively in the chapter of Herbert Pfister and Jan ter Schegget (p. 335).

Figure 2. Extensive warts and solar keratoses on the shin.

Figure 3. Squamous cell carcinoma in a renal transplant recipient.

Besides the presence of HPV DNA in skin cancers, there are several epidemiological arguments that HPV infection is an important risk factor for the development of skin cancer in renal-transplant recipients. Firstly, the number of warts is highly associated with skin cancers;^{1,2,11} and, secondly, renal-transplant recipients with impaired antibody response against the L1 capsid protein of the EV-related subgroup of HPV are at an increased risk of skin cancer.⁴⁰

The epidemiological data and the serological findings, together with the presence of HPV DNA in at least a part of the squamous cell carcinomas, makes an etiologic role of HPV in nonmelanoma skin cancer oncogenesis in renal-transplant recipients very likely; however, the exact mechanism still has to be delineated. The demonstration that HPV infection is causally related to skin cancer awaits rigorous epidemiologic investigations.⁹

Association of HPV Infection with Carcinoma of the Lip
Renal-transplant recipients have an increased, prevalence of leukoplakia, dysplasia, and cancer of the lip

Figure 4. Basal cell carcinoma in a renal transplant recipient.

(Fig 5).⁴¹⁻⁴³ Exposure to the sun and smoking are risk factors for dysplastic and malignant lip lesions.⁴¹ The presence of HPV DNA (HPV 16) has been shown in 1 out of 25 carcinomas of the lip from non-immunosuppressed patients,⁴⁴ but studies in renal-transplant recipients are lacking. It is not unlikely that HPV DNA may be present in these lesions in a similar way as in squamous cell carcinomas of the skin.

Association of HPV Infection with Anogenital Lesions and Cervix Carcinoma

A number of studies have been conducted to estimate the prevalence of anogenital and cervical lesions and/or HPV infection among groups of women who are immunosuppressed following renal transplantation.^{5,45-48} The prevalence of cervical HPV infection in transplant recipients has been estimated at between 20 and 45%, while condylomata have been reported in 2 to 30% of women.^{5,48} Two cohort studies have followed large groups of patients following renal transplantation.^{20,49} In an Australian cohort of 7605 transplant recipients, a standardized incidence ratio for cervical cancer of 3.3 was calculated compared with the normal population,⁴⁹ and in a Nordic cohort of 2369 women, a standardized incidence ratio of 8.6 was found.²⁰ A recent French study consisting of 1002 kidney-, lung-, liver-, and heart-transplant recipients (302 women and 700 men) reported a prevalence of 3.6% external anogenital lesions in women and 1.7% in men.⁴⁸ Using molecular in situ hybridization on frozen or deparaffinized tissue sections or immunohistochemistry for HPV antigen, HPV DNA (mainly HPV 6 and 11, and less frequently, HPV 16 and 18) was found in 90% of the lesions, 68% was positive using in situ hybridization and 63% using immunohistochemistry.⁴⁸

Association of HPV Infection with Melanoma

Renal transplant recipients are also at an increased risk of developing malignant melanoma, with relative risks

ranging from 2 to 9 times the incidence of melanoma in the normal population.^{19,50,51} Clinically atypical nevi and large numbers of acquired melanocytic nevi are the strongest known risk factors for melanoma (Fig. 6).^{52,53} Additional possible risk factors for the development of nevi in renal-transplant recipients are immunosuppressive therapy^{54,55} and infection with human papillomaviruses.⁵⁴⁻⁵⁶ HPV 38 has been reported once in a superficial spreading malignant melanoma of a renal-transplant recipient,⁵⁷ but since the patient had multiple keratotic skin lesions, contamination cannot be excluded. In contrast to earlier findings regarding squamous cell carcinomas and basal cell carcinomas,^{2,11,40} there was no association between nevi and the number of keratotic skin lesions in the same group of renal-transplant recipients;⁵⁸ in addition, no association was present with the humoral immune response against the fusion protein of β -galactosidase and the late antigen, L1 of human papillomavirus type 8.⁵⁸ Without epidemiological and immunological evidence, it seems unlikely that HPVs play a major role in influencing the numbers of either clinically atypical nevi or normal nevi in renal-transplant recipients, but the results of molecular biological studies should be awaited to definitively exclude a role for HPVs in the pathogenesis of malignant melanoma.

Association of HPV Infection with Kaposi's Sarcoma

Kaposi's sarcoma has been described in immunosuppressed organ-transplant recipients (Fig. 7).⁵⁹⁻⁶⁶ The incidence of Kaposi's sarcoma is increased 50- to 500-fold in transplant recipients compared with the normal population.^{61,67} Several studies have investigated the relationship between cytomegalovirus (CMV) and classic or AIDS-associated Kaposi's sarcomas by testing for either serologic evidence of CMV infection in patients with Kaposi's sarcoma or for the presence of CMV DNA in Kaposi's sarcoma tissue, but no consistent association was found.⁶⁰ Using the polymerase chain re-

Figure 5. Squamous cell carcinoma of the lip in a renal transplant recipient.

Figure 6. Clinically atypical nevi in a renal transplant recipient.

Figure 7. Kaposi's sarcoma in a renal transplant recipient.

action (PCR) HPV 16-related DNA fragments were found in 20% of Kaposi's sarcoma by one group, and HPV 18 in one AIDS-associated Kaposi's sarcoma, but other groups were not yet able to reproduce this finding.⁶⁸⁻⁷⁰ Recently, a new herpesvirus, provisionally termed human herpesvirus 8 (HHV 8) or Kaposi's sarcoma-associated herpes virus (KSHV) has been identified in biopsy specimens from patients with AIDS-associated Kaposi's sarcoma.⁷¹⁻⁷⁴ Soon after this publication, the DNA sequences of this agent were also detected in high frequencies in biopsies from classic Kaposi's sarcoma, African endemic Kaposi's sarcoma, and Kaposi's sarcomas from immunosuppressed organ-transplant recipients.⁷⁵⁻⁷⁸ In view of these recent findings, it is not likely that HPV plays a major role in the development of Kaposi's sarcomas.

Risk Factors For Warts and Skin Cancer

Risk factors for HPV infection are not very well studied. Most data refer to skin cancer. Well-known general environmental risk factors for nonmelanoma skin cancer are exposure to sunlight, ionizing radiation, and various chemical carcinogens.^{1,16,79-81} Host-related risk factors for skin cancer include genetic factors such as a fair complexion and an inability to tan, and nongenetic factors such as chronic scars and ulcers of the skin.^{80,82-84} Increasing age is also an important nongenetic, host-related, risk factor for the development of skin cancer.^{79,82,85,86} In transplant recipients, the most important factor is the immunosuppressive therapy.

Immunosuppressive Therapy

Transplant recipients receive continuous immunosuppressive drugs, initially azathioprine and prednisone, and more recently cyclosporine A and FK506. Immunosuppressive drugs exert a carcinogenic effect, and they may facilitate the further development of skin cancer.⁸⁷ The risk of skin cancer increases with time of immunosuppression that is obligatory after organ transplanta-

tion.^{10,85,86,88} Several studies did not observe significant differences in the risk of developing skin cancer between recipients on cyclosporine and recipients who were treated with azathioprine.^{19,89-91} In light of these findings, it is difficult to maintain that genesis of skin cancer in transplant recipients is solely or largely due to enhanced carcinogenesis due to azathioprine metabolites, as has been proposed.⁹² It is more likely that the increased risk of skin cancer following immunosuppression is independent of the agents used, but is a result of the immunosuppression per se; in addition, there appears to be no association between the cumulative doses of immunosuppressive drugs and the occurrence of nonmelanoma skin cancer.^{11,86,87} Perhaps in all renal-transplant recipients, the level of immunosuppression exceeds a certain threshold value, above which the risk of nonmelanoma skin cancer is not further increased by a higher dose of immunosuppression.

Exposure to Sunlight

Except for the immunosuppressive therapy, exposure to sunlight is believed to be one of the most important risk factors for the development of both nonmelanoma skin cancers and warts in renal-transplant recipients.^{1,2,11} Nonmelanoma skin cancers are thought to be the result of cumulative lifetime exposure to sunlight.⁸⁰ Age-specific exposure also may play a role. There is some evidence that exposure to sunlight at a younger age contributes more to the development of solar keratosis and the associated skin cancers later in life than exposure at an older age.^{79,93}

In a retrospective follow-up study, 36 renal-transplant recipients with and 101 without skin cancer were assessed to determine the risk of nonmelanoma skin cancer with exposure to sunlight during childhood and adolescence.² As could be expected, a strong association between exposure to sunlight and the occurrence of skin cancer was observed;² in addition, the majority of skin cancers and keratotic skin lesions was confined to sun-exposed skin. Exposure to sunlight before the age of 30 contributed more to the risk of developing skin cancer later in life than the period after the age of 30; however, given the long latency period for the development of skin cancer, and given the average age of our patients (45 years), the possibility that the period after the age of 30 is equally important for the development of skin cancer at an age older than 45 years cannot be excluded.

Specific p53 gene mutations (eg C to T and CC to TT mutations) are induced by ultraviolet (UV) radiation.⁹⁴ Measurement of these mutations may be useful as a biologically relevant measure of UV exposure in humans and as a possible predictor of risk for skin cancer.⁹⁵ P53 immunostaining was observed in 6 out of 14 transplant-associated squamous cell carcinomas, which could indicate p53 gene mutation in these lesions.³⁷ Us-

ing single-strand-conformation polymorphism (SSCP) analysis, mutations in p53 were found at similar frequency in both transplant and nontransplant skin cancers: in 7 (50%) of 14 posttransplant tumors and in 4 (57%) of 7 control tumors from nontransplant patients.⁹⁶ The majority of the mutations was consistent with damage caused by ultraviolet radiation. HPV DNA was detected in about half of the lesions; however, there was no relationship between HPV detection and p53 mutation.⁹⁶ No information is available about UV-induced mutations in other potentially important tumor suppressor genes, such as the p16 (CDKN2), and the ptc gene (patched).⁹⁷⁻⁹⁹

Except for its harmful effect by inducing DNA damage, UV light can also be harmful by inducing immunological unresponsiveness.^{100,101} Ultraviolet radiation is known to perturb many of the activities associated with normal cellular responses to mitogens and alloantigens.^{102,103} Epidermal Langerhans cells have a well-established role in the local processing and presentation of antigen to lymphocytes as a critical step in the initiation of immune responses against virus-infected cells and skin cancers.^{101,104} Low doses of UV radiation already affect the integrity of these cells, resulting in an impaired antigen-presenting capacity.^{100,104} In contrast to the mechanism of DNA damage, locally UV-induced immunological unresponsiveness does not show a linear dose-response relationship, but above a certain UV dose the local immune response is totally abolished.¹⁰³ Ultraviolet radiation also induces systemic immunosuppression, probably by generating *cis*-urocanic acid, a systemic immunosuppressive mediator close to the skin surface.^{101,105}

Cumulative exposure to sunlight was not associated with the development of keratotic skin lesions in the Dutch study;² however, the preferential localization of keratotic skin lesions on sun-exposed skin strongly suggests an important role of sunlight in the pathogenesis of these lesions. On the basis of these indirect data, it can be postulated that recent or present-day exposure to the sun is also important for the development of warts and other keratotic skin lesions and, consequentially, probably also of squamous cell carcinomas. The increased prevalence of warts and other keratotic skin lesions on sun-exposed skin may be the result of local immunological unresponsiveness, induced by UV radiation.

HLA phenotype and HLA Homozygosity

There are several specific immunological and immunogenetic factors, such as human leukocyte antigen (HLA), that may play a role in the development of non-melanoma skin cancer in renal-transplant recipients.^{11,106} The non-specific immune surveillance against skin cancer is hampered in renal-transplant recipients because of a depressed natural killer-cell function.¹⁰⁷⁻¹⁰⁹

Recent studies lay more strain upon the functioning of the specific cellular immune response through cytotoxic T lymphocytes. Specific immunological and immunogenetic factors may therefore play a role in the development of nonmelanoma skin cancer in renal-transplant recipients.¹¹

HLA antigens play a pivotal role in the cellular immune response to viral and tumor antigens.^{106,110} The HLA class II antigens are involved in recognition of foreign peptides by CD4 positive regulatory T lymphocytes,¹¹¹ whereas the HLA class I antigens mainly serve as restriction elements for the reactivity of CD8 positive cytotoxic T lymphocytes.¹¹²

A group of investigators found that the occurrence of skin cancer is associated with the class II antigen HLA-DR7.^{113,114} We found the same trend, but statistical significance was not reached.¹¹⁵

Homozygosity for HLA antigens has been reported to be a risk factor for the development of several kinds of cancer.^{116,117} In homozygous individuals, the number of different polymorphic class I and class II products is less than in heterozygous individuals. As a result, there are fewer possibilities for interaction with antigenic peptides and therefore fewer possibilities for recognition of foreign antigens.¹¹⁶ Renal-transplant recipients who were homozygous for the HLA-DR antigen were also at an increased risk for skin cancer and keratotic skin lesions.¹¹ This finding provides additional, indirect evidence that an impaired response of CD4-positive regulatory T cells to HLA class II associated peptides might indeed be involved in the etiology of skin cancer. The high incidence of warts and squamous-cell carcinomas among renal-transplant recipients may reflect an impaired immune response to the antigens involved in HPV infections and the occurrence of squamous-cell carcinoma, which might be even more impaired in recipients who are homozygous for the HLA-DR antigens.

Besides the induction phase of the immune response, the effector phase may be important, because associations of HLA class I antigens with skin cancer have been found.¹¹⁸⁻¹²¹ HLA-A11 was reported to be negatively associated with the development of skin cancer in renal transplant recipients.^{118,119} The same trend of a negative association between HLA-A11 and nonmelanoma skin cancer was found by others,^{113,114,121,122} although in most studies some HLA-A11-positive patients with skin cancer were found; however, recently, we found a positive association between HLA-A11 and skin cancer in an Australian population consisting of 1098 renal-transplant recipients of whom 271 (25%) had developed skin cancer.¹²³ HLA-A11 was associated with an increased risk of skin cancer (hazard ratio, adjusted for sex and age of the patients was 1.7, 95% confidence interval: 1.3 to 2.4). This illustrates the fact that the association of specific HLA alleles with certain disease

states may vary considerably between different populations. This may be caused by differences in genetic background, environmental risk factors, and possibly immunological factors such as the HPV type causing the disease or immunosuppressive effects caused by excessive UV irradiation.

HLA-B27 was reported to be positively associated with skin cancer, suggesting that susceptibility to skin cancer is associated with this class I antigen.^{113,118,119} This finding could be confirmed in the Australian population of renal-transplant recipients.¹²³

Humoral Immune Response

Patients without an apparent class switch from IgM to IgG to the fusion protein of the late antigen (L1) of HPV type 8 and β -galactosidase are at an increased risk of skin cancer as compared to the patients with a good humoral response to this fusion protein.⁴⁰ This indicates that the immune response against HPV antigens is relevant in these patients for the risk of developing skin cancer. The nature of this defect cannot be explained by factors that are related to transplantation, since the same association was also found when sera were considered that were collected before the transplantation.⁴⁰ The latter is a strong argument for a genetically determined predisposition for nonmelanoma skin cancer in patients who have a poor antibody response to the HPV 8 L1 fusion protein; moreover, this impaired antibody response is found mainly in patients who are HLA-DR7 positive, because a strong linkage between the absent class switch of antibody production to L1 of HPV 8 and HLA-DR7 was observed (relative risk: 26.2).⁴⁰ HLA-DR7 is also associated with the occurrence of nonmelanoma skin cancer in renal transplant recipients,^{19,113,114} therefore, this finding suggests that the development of nonmelanoma skin cancer is also genetically controlled by genes in the class II region of the major histocompatibility complex.

Strategies for Intervention and Treatment

Regular Surveillance

Regular surveillance of transplant recipients with skin problems and easy access of all patients to a dermatologist is advised, as well as early biopsy of suspicious lesions. This facilitates early removal of malignant and premalignant lesions to reduce the risk of skin cancer and metastasis in this patient population.

Protection Against Sun Exposure

Although we were not able to show a direct association between present-day exposure to sunlight and the occurrence of non-melanoma skin cancer, it is likely that present-day exposure increases the risk of warts and, consequentially, also the risk of non-melanoma skin cancer.² Because of the strong associations with chronic sun exposure, sun-protective measures are important to reduce the risk of nonmelanoma skin cancer in trans-

plant recipients. The use of long sleeves, long trousers, and a hat outdoors, especially in sunny climates, should be promoted. The protection against skin cancer by sunscreens is still controversial, though regular use of sunscreens may have some effect in slowing the development of solar keratoses in the nonimmunosuppressed population.¹²⁴ Indeed, it has been suggested that a false feeling of safety results from the use of sunscreens; while they are known to reduce sunburn, they may be less effective in preventing local immunosuppression.^{103,125} Perhaps it would be more advisable to warn transplant patients to avoid the midday sun when the UV B radiation from the sun is at maximum intensity.

Modulation of the Immunosuppressive Regimen

There is no association between the cumulative doses of immunosuppressive drugs and the occurrence of non-melanoma skin cancer;¹¹ therefore, reduction of the immunosuppressive therapy presumably will not decrease the risk of nonmelanoma skin cancer, unless the dose is lowered to a level that may lead to an increased risk of graft rejection. In addition, changing the immunosuppressive regimen from azathioprine to cyclosporine A or vice versa does not seem to relieve the skin problems.^{19,89-91}

Retinoids

Synthetic retinoids have been shown to be effective in the reduction of actinic keratoses and also to be potent inhibitors of cancer formation.¹²⁶⁻¹³⁰

Recent studies have suggested that etretinate or its main metabolite acitretin are also effective in reducing the number of keratotic skin lesions and in the prevention of skin cancer in renal-transplant recipients.¹³⁰⁻¹³⁴ Most patients experienced a considerable reduction of new squamous cell carcinomas during treatment.^{131,132} The response to treatment usually occurred during the first month of therapy and was maintained during the 6-month treatment period. Although the response to treatment was encouraging, patients tended to relapse when treatment was discontinued.¹³² This has also been noted in other studies.¹³¹

Acitretin in a dose of 30 mg daily was especially effective in preventing the formation of new squamous cell carcinomas in renal-transplant recipients who have a history of previous skin cancers.¹³² The difference in efficacy of acitretin in the prevention of squamous cell carcinomas in the patients with a history of previous skin cancers as compared to those without this history is notable. It has been shown that retinoic acid is more effective to inhibit the growth of HPV 16 immortalized human keratinocytes than that of normal keratinocytes. This inhibition is probably due to the suppression of the early transcription by retinoic acid.^{135,136} If we postulate that HPVs play a role in the pathogenesis of skin cancer in renal-transplant recipients, this observation provides a potential biochemical basis for the effect of retinoic

acid in chemoprevention of HPV-induced squamous-cell carcinomas.¹³⁵

Despite theoretical concerns about possible allograft rejection associated with the immunopotentiating effects of etretinate,¹³⁷ no such side effects have as yet been described.^{132,133} Systemic retinoids are able to increase serum lipids.¹³⁸ Many renal-transplant recipients have elevated lipoprotein concentrations, either as part of their underlying disease, or as the result of the immune suppressive treatment with cyclosporine.^{131,139} Cardiovascular disease is common in renal-transplant recipients, so any increase in cholesterol and triglyceride levels may further increase this coronary risk. In our study, 3 out of 19 patients showed an increase in cholesterol and triglyceride levels.¹³² Possibly, this increase can be reduced by additional treatment with simvastatine. Chronic use of oral retinoids can cause skeletal changes with demineralization, refraction of bone, and cortical hyperostosis.¹⁴⁰

Topical treatment with 0.05% tretinoin cream for warts and keratoses in organ-transplant recipients has also been shown to be safe, and it showed some efficacy compared with placebo.¹⁴¹

Resurfacing

Resurfacing the back of the hand can be a successful treatment for patients with multiple skin cancers on the back of the hand, and this treatment can be used prophylactically in patients with severely actinically damaged skin;^{142,143} nevertheless, such surgery should be reserved for carefully selected patients, because it is an invasive procedure, recovery takes many months, and side effects are not negligible.¹⁴³

HPV Infections in HIV-Infected Patients

Nonmelanoma skin cancers are not uncommon in HIV-infected patients;^{144,145} however, Kaposi's sarcomas are more frequently found.^{145,146} Some patients also have widespread flat warts in which HPV 5 could be detected by Southern blot analysis, debilitating verruca vulgaris, and venereal warts.¹⁴⁷⁻¹⁴⁹ Squamous cell carcinomas in HIV-infected patients may occur in the anogenital area, other regions of the skin, cervix, the conjunctiva, and other sites.^{144,146,150-153} Occasionally, HPV DNA has been reported to be present in skin cancers of HIV-infected patients,^{151,153} but extensive studies have not yet been published.

HPV Infections in the Nonimmunosuppressed Population

It is interesting to speculate on a role of EV-related HPV types in the nonimmunosuppressed population.^{28,154} In 1983, Australian investigators showed virions resembling papillomaviruses in solar keratoses.¹⁵⁵ HPV DNA (HPV 36 and a not characterized HPV type) has been

detected in a low percentage of solar keratoses, and HPV 20 was seen in a basal cell carcinoma.⁴⁴ Still, the methods (Southern blot analysis and PCR) used might have not been sensitive enough to detect additional HPV types. Only very recently, a group of investigators were able to detect a wide spectrum of HPVs (mainly mucosal types) in skin cancers of non-immunosuppressed patients.⁸ With the help of a nested PCR, using degenerate primers,⁶ we were able to detect EV-HPV DNA in 50% of 40 skin cancers from nonimmunosuppressed patients, but also in about 40% of plucked hairs of normal controls (we refer to the chapter of Herbert Pfister and Jan ter Schegget, p. xxx). The latter finding strongly suggests that EV-HPV types (and maybe also other HPV types?) are latently or subclinically present in the skin of many subjects belonging to the normal population. Immunosuppression with immunosuppressive drugs or in patients with AIDS may lead to reactivation of the latent HPV infection and to higher HPV replication; and this would be important if a dose-response situation exists for the carcinogenic potential of HPV infection with an increased risk of skin cancer as a possible result.

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