
Leader

Human papillomavirus and the development of non-melanoma skin cancer

Catherine A Harwood, Jane M McGregor, Charlotte M Proby, Judith Breuer

Abstract

Human papillomaviruses (HPV) are increasingly recognised as important human carcinogens. The best established association with human malignancy is that of high-risk mucosal HPV types and anogenital cancer. HPV-induced transformation of anogenital epithelia has been the subject of intense research which has identified the cellular tumour suppressor gene products, p53 and pRB, as important targets for the viral oncoproteins E6 and E7 respectively. Certain HPV types are also strongly associated with the development of non-melanoma skin cancer in the inherited disorder epidermodysplasia verruciformis (EV). However, in contrast with anogenital malignancy the oncogenic mechanisms of EV-HPV types remain uncertain, and there appears to be a crucial additional requirement for ultraviolet radiation. Cutaneous HPV types in the general population are predominantly associated with benign viral warts, but a role in non-melanoma skin cancer has recently been postulated. Polymerase chain reaction based HPV detection techniques have shown a high prevalence of HPV DNA, particularly in skin cancers from immunosuppressed patients and to a lesser extent in malignancies from otherwise immunocompetent individuals. No particular HPV type has yet emerged as predominant, and the role of HPV in cutaneous malignancy is unclear at present. It remains to be established whether HPV plays an active or purely a passenger role in the evolution of non-melanoma skin cancer.

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Non-melanoma skin cancers are the most prevalent malignancies in fair skinned populations worldwide.¹ They account for up to one third of all cancers in the USA, and in Australia the estimated incidence is twice that for all other cancers combined.² While the mortality is low (545 deaths in the United Kingdom in 1991), the associated morbidity is significant, as is the burden on health care provision. Epi-

demiological and molecular data implicate ultraviolet radiation as the most important aetiological factor,^{3–5} but other agents—including the immune response, genetic predisposition, and viral infection—are also likely to be involved. Several viruses have been implicated in the development of non-melanoma skin cancer, but the most plausible evidence to date is that for human papillomavirus (HPV).

HPV are increasingly recognised as important human carcinogens: overwhelming evidence from both epidemiological and functional studies implicates high risk mucosal HPV types in cervical and other anogenital cancers.⁶ A role for HPV in cutaneous malignancy is also proposed in the rare inherited condition epidermodysplasia verruciformis, which is characterised by a predisposition to HPV infection and the development of cutaneous squamous cell carcinomas on sun exposed sites.⁷ However, until recently it has proved technically difficult to detect HPV DNA in skin cancers and this has hindered research in the area. With the introduction of polymerase chain reaction (PCR) based techniques, several groups now report a high prevalence of HPV DNA in non-melanoma skin cancers in both immunosuppressed and non-immunosuppressed patients, providing new impetus for research.^{8–12}

In this review we summarise the biology, epidemiology, and functional data on HPV that are potentially relevant to skin carcinogenesis.

HPV structure and life cycle

The papillomavirus family embraces a heterogeneous group of double stranded DNA viruses consisting of approximately 8000 nucleotide bases. The general organisation of the genome is the same for different HPV types and consists of three main regions: the “early” (E) region encoding viral regulatory, transforming, and replication proteins; the “late” (L) region encoding the structural capsid proteins L1 and L2; and the non-coding or upstream regulatory region. The HPV encoded early genes appear to have multiple functions including (E1) ATPase and helicase activity necessary for initiating viral replication, (E2) regulation of viral transcription and replication, and (E4) proteins involved in maturation and release of viral particles. E5 has some

Department of Academic Dermatology, Royal Hospitals NHS Trust, London E1 UK
C A Harwood
J M McGregor
C M Proby

Department of Virology, Royal Hospitals NHS Trust
J Breuer

Correspondence to:
Dr Judith Breuer,
Department of Virology, St Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, 37 Ashfield Street, London E1 1BB, UK.

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transforming potential but this is not fully characterised, while E6 and E7 are the major transforming proteins of genital HPV.

HPV infects basal epithelial cells, stimulating epithelial proliferation. In benign viral warts it is present as episomal DNA with low level replication of viral episome within basal keratinocytes maintained by E1 and E2 expression. The full vegetative life cycle of HPV is tightly linked to keratinocyte differentiation, and other viral early genes are not switched on until the infected keratinocyte leaves the basal layer. Late gene expression with production of virus particles can only take place in highly differentiated keratinocytes.

Classification, phylogeny, and detection of HPV

Until recently difficulties in producing adequate keratinocyte differentiation in vitro hindered development of culture systems for viral propagation, and serology proved less useful for HPV detection than for other viral infections. Consequently, improvements in HPV detection techniques coincided with the advent of recombinant DNA technology. Distinguished originally by its restriction enzyme map, a papillomavirus isolate is now classified exclusively by characterisation of its genome; a new type is one in which the nucleotide sequence of the most highly conserved part of the HPV genome, the L1 open reading frame (ORF), is shown to share less than 90% identity to the homologous sequences of established prototypes.¹³ Based upon this definition, 80 distinct HPV genotypes have now been described, but several groups have identified and partially characterised novel sequences predicting the existence of many more.⁶ Papillomaviruses show a marked host and epithelial cell specificity for infection and historically they have been grouped according to the location and clinical context from which they were initially isolated, hence the terminology "cutaneous," "mucosal," and "epidermodysplasia verruciformis" types. Subsequent phylogenetic analyses based on sequence information have broadly justified this clinical classification.¹⁴

The genomic diversity of the many different HPV poses a considerable challenge to HPV detection and genotyping. Methods based upon DNA hybridisation to specific HPV probes (Southern blot, slot blot, in situ hybridisation) have now largely been superseded by PCR based techniques using degenerate and nested primers to increase sensitivity and specificity. This has revealed a diverse range of HPV in skin and mucosal tissue, including HPV sequences which probably represent new, as yet uncharacterised types.⁸⁻¹²

Models of HPV associated skin carcinogenesis

EPIDERMODYSPLASIA VERRUCIFORMIS (EV)

In 1922, long before the association of HPV with cervical carcinoma was suspected, an association between warts and skin cancers was observed in patients with epidermodysplasia verruciformis.¹⁵ Epidermodysplasia verruciformis predisposes to widespread skin warts

with an average age of onset of six years. The warts are clinically unusual and include red-brown plaques and scaly pityriasis versicolor-like lesions, in addition to extensive plane and common warts.⁷ Squamous cell carcinomas develop on light exposed sites in 30–60% of affected patients by the fourth decade, and specific HPV types, predominantly HPV-5 and HPV-8, are found in over 90% of these tumours.¹⁶ The basis of this disorder is unknown but may involve alteration of viral regulatory pathways at the level of the keratinocyte. Partial defects in cell mediated immunity have been demonstrated but remain poorly defined.^{7, 17}

Despite the apparent strength of the association between HPV-5/8 DNA and epidermodysplasia verruciformis associated cutaneous squamous cell carcinoma, there are currently few data on mechanisms of viral transformation. Compared with high risk mucosal HPV, the transforming potential of EV-HPV in vitro is low.¹⁸ Although HPV-8 E6 transformed rodent fibroblasts cannot induce tumours in nude mice, morphological transformation, anchorage independence, and reduced serum requirement can be demonstrated and this activity is found to reside mainly in the E6 ORF.¹⁹ The E7 ORF, in marked contrast to HPV-16/18 E7, has little independent transforming activity. Similar results have been observed for HPV-47.²⁰ To date it has not been possible to immortalise human cells using EV-HPV. Interactions between E6 and p53 or E7 and pRB used by HPV16/18 cannot be demonstrated for the EV-HPV.²¹ A possible transforming mechanism is the trans-regulation function encoded by E2 which activates regulatory elements within the upstream regulatory region of oncogenic EV-HPV types.²² This may result in enhancement of gene transcription during early stages of malignant progression.²³ It is currently believed that EV-HPV may act only as co-carcinogens with an absolute requirement for ultraviolet light. This may explain the failure to date to show in vitro transformation of human keratinocytes using EV-HPV alone.

NON-MELANOMA SKIN CANCER IN IMMUNOSUPPRESSED INDIVIDUALS *Organ transplant recipients*

For over 25 years, an association between virus warts and skin cancer has been suspected in renal transplant recipients.²⁴ Renal transplant recipients have a well documented 50- to 100-fold increased risk of cutaneous squamous cell carcinoma in particular,²⁵ and a reversal in the normal squamous cell to basal cell carcinoma ratio.^{24, 26} The cumulative incidence of skin cancer is 27–44% after 10–25 years of immunosuppression,²⁷⁻²⁹ and clinical and histological features of transplant squamous cell carcinoma indirectly support the progression of virus warts through increasingly dysplastic squamous lesions to invasive squamous cell carcinoma.³⁰⁻³³ Viral warts and cutaneous squamous cell carcinoma colocalise on sun exposed sites and ultraviolet light appears to be

an important factor in the development of both warts and cancers.³²

HPV DNA prevalence—In early studies of HPV in non-melanoma skin cancer from transplant recipients, detection of HPV DNA varied considerably both in overall prevalence (from 0–64%) and in the HPV types detected.³⁴ These discrepancies are likely to reflect the detection methods used.^{35–36} More recent studies using degenerate PCR consistently show a higher prevalence (65–81%) of HPV DNA in transplant tumours, although the spectrum of HPV types detected differs considerably.^{8–12} The nested PCR method developed by Berkhout *et al*^{10–11} detected epidermodysplasia verruciformis or EV related viruses in 49 of 61 squamous cell carcinomas (80%), four of eight basal cell carcinomas, 14 of 15 actinic keratoses, and two of five in situ carcinomas. In a separate study, Shamanin *et al* found identifiable HPV types in 13 of 20 squamous cell carcinomas and three of five basal cell carcinomas,⁹ but only 20% of the HPV types were EV associated; the majority consisted of either high risk mucosal types (HPV-16, -51, -54, -56, -61, and -69) or cutaneous types (HPV-41 and -60). Again these discrepancies are likely to reflect the PCR primers employed. Confirmation of this is provided in a recent study¹² in which lesions initially analysed using the PCR primer panel described by Shamanin *et al*⁹ were shown to contain predominantly cutaneous types. However, additional EV-HPV types were detected when the same lesions were reassessed using the nested primer pair of Berkhout *et al*.¹⁰

Our group has since extended the degenerate PCR methodology to include nested primer pairs for mucosal and cutaneous HPV as well as EV-HPV.³⁵ We have found a high prevalence of HPV in premalignant and malignant skin lesions from transplant patients (unpublished data): HPV DNA was detected in 39 of 47 squamous cell carcinomas (83%), 15 of 23 basal cell carcinomas, and 17 of 18 premalignant skin lesions. EV-HPV types were found in over 80% of cases of squamous cell carcinoma, and cutaneous types in approximately 50%. In contrast, mucosal types occurred in less than 15% of cases. Codetection of one or more distinct HPV types within a single squamous cell carcinoma was seen in almost 60% of tumours. A similar trend was observed in basal cell carcinomas and premalignancies. Indeed, a consistent observation to emerge from all recent studies is that such mixed infection of single lesions is common and no one HPV type predominates in malignancies.

PUVA treated patients

Psoralen and ultraviolet A (PUVA) photochemotherapy is associated with a dose dependent increase in the risk of non-melanoma skin cancer in patients treated for psoriasis.³⁷ Like ultraviolet B radiation, PUVA is both mutagenic and immunosuppressive and may thus act as a complete carcinogen.^{38–41} However, a cofactor role for HPV infection is suggested by the reversal of the usual basal cell to squamous cell carcinoma ratio observed in this group, just

as in renal transplant recipients. We have recently analysed a series of PUVA related benign and malignant lesions⁴² and found HPV DNA sequences in 15 of 20 non-melanoma skin cancers, seven of 17 dysplastic PUVA keratoses, four of five skin warts, and four of 12 PUVA exposed normal skin samples. The majority of HPV positive lesions contained EV related HPV including HPV-5, -20, -21, -23, -24, and -38. Possible novel EV types were identified in further lesions. Mixed infection with cutaneous and mucosal types of epidermodysplasia verruciformis was present in six of 30 HPV positive lesions. HPV-41 and HPV-16/18 have been found in other PUVA associated squamous cell carcinomas in smaller studies.^{43–46} Thus the prevalence and type of HPV infection in cutaneous lesions from PUVA treated patients is similar to that reported in renal transplant associated skin lesions.

HIV infection

The gradual loss of immunity in AIDS produces increasing susceptibility to viral infection. HPV is perhaps the most common virus to produce mucocutaneous lesions in these patients, with a reported prevalence of between 5% and 27%.⁴⁷ Common and plantar warts are increased in frequency and may show histological evidence of dysplasia.⁴⁸ EV-like skin lesions have also been reported, and in two cases the presence of HPV-5 and HPV-8 was confirmed.⁴⁹

Non-melanoma skin cancer in AIDS patients has not been comprehensively studied but it remains likely that long term survivors will be at increased risk. One small study of non-melanoma skin cancer from HIV infected patients⁵⁰ found HPV DNA in two of 10 cutaneous squamous cell carcinomas using the suboptimal dot-blot method (with probes to mucosal genital types only) and three sets of consensus primers designed primarily for detection of mucosal HPV. We would anticipate finding a much higher prevalence of diverse HPV types in such lesions using a more comprehensive degenerate primer based method.

NON-MELANOMA SKIN CANCER IN THE GENERAL POPULATION

Most of the available data on the association of HPV and non-melanoma skin cancer in the general population are in the form of isolated case reports or small case series.^{34–35} These have invariably been undertaken using a limited number of HPV probes that are not informative for the majority of HPV types and have therefore underestimated the true prevalence of HPV in cutaneous lesions. This is frequently compounded by the use of paraffin embedded material which yields suboptimal results compared with fresh frozen tissue.³⁷

The most comprehensive studies to date using degenerate PCR detection methods have shown HPV DNA in up to 40% of fresh frozen tumours from immunocompetent individuals. Sixteen degenerate primer combinations were used in one study⁹ to identify HPV DNA in

eight of 25 squamous cell carcinomas, four of 11 basal cell carcinomas, and two of four keratoacanthomas. A broad spectrum of different HPV was found including EV associated types (8, 9, 23, and 25), common cutaneous types (4 and 7), and low risk mucosal types (6b, 32, 34, and 42). HPV 51 was the only high risk mucosal type detected. Two novel HPV types were detected, one related to HPV 48 and the other to HPV 68. In a second study (Berkhout RJM *et al*, unpublished), a nested PCR designed to detect EV types was used. With this approach, EV-*verruciformis* HPV DNA only was detected in one of three cases of Bowen's disease, 10 of 19 squamous cell carcinomas, and 10 of 31 basal cell carcinomas. Five EV-associated HPV types (HPV-15, -20, -23, -25, and -36) and nine putative novel EV related HPV types were identified.

Although the overall detection rate in these two studies is similar, the spectrum of HPV types clearly differs, again most likely reflecting differences in the specificities and sensitivities of the PCR primers used. Using our combined methodology^{36,42} capable of detecting a broader spectrum of cutaneous, EV, and mucosal HPV types to equivalent sensitivity, preliminary data on non-melanoma skin cancers from immunocompetent individuals indicate a similar HPV DNA prevalence: viral DNA was detected in 15 of 23 squamous cell carcinomas and 12 of 33 basal cell carcinomas. EV-HPV types predominated over cutaneous and mucosal types, and mixed infections were less common than in immunosuppressed patients (unpublished data).

Conclusions

The study of HPV in non-melanoma skin cancer has been limited by the detection methods available until very recently. With the development of degenerate PCR methods a high prevalence and a broad spectrum of HPV types has now been found in premalignant and malignant lesions from both immunosuppressed and non-immunosuppressed individuals. In anogenital cancer there is a specific association of certain high risk HPV types and malignancy. In addition epidemiological, molecular, and functional data fulfil the WHO criteria for viral carcinogenesis.⁵¹ These criteria are far from met in non-melanoma skin cancer; there is little on the epidemiology of cutaneous and EV associated HPV types and many HPV found in skin cancer have a low transforming potential *in vitro*. Nonetheless the high prevalence of HPV DNA in non-melanoma skin cancer is provocative despite a lack of mechanistic data. Future research may identify new cellular targets for HPV oncoproteins that prove to be relevant to skin cancer, either independently or in interaction with ultraviolet radiation.

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