Leading Article

Human papillomavirus and skin cancer

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Introduction

Established evidence suggests an important role for viruses in the development of some human malignancies. These include Epstein–Barr virus in Burkitt's¹ and post-transplant lymphoma² and human papillomavirus (HPV) types 16 and 18 in anogenital³ and cervical cancer.⁴ Oncogenic HPV types may be involved in the development of skin cancer in patients with epidermodysplasia verruciformis (EV), a rare inherited condition predisposing to virus warts and skin cancer,⁵ and perhaps also in patients immunosuppressed following organ transplantation, but support for this remains controversial. The majority of skin cancers in the general population do not appear to be associated with HPV.

Human papillomaviruses

Papillomaviruses are small DNA viruses that infect both epidermal and mucosal squamous epithelia. Transmission is by direct contact (person to person or object to person) and is enhanced if the skin is broken or macerated. Approximately 60 HPV types have now been characterized, all of which are trophic for squamous epithelia, although many show marked preference for one anatomical site over another. A small number of HPV types, including types 1, 2, 3, 4 and 10 typically infect keratinizing epithelia (the skin) and account for the majority of cutaneous warts in the general population.⁶ Other rare epidermotrophic HPV types including 5, 8, 14, 17 and 20^{7,8} have been identified in the skin of EV patients, but these types are rarely identified in the skin in the general population, even in immunosuppressed patients.^{9–11} HPV types 6, 11, 16 and 18 are trophic for genital mucosa⁴ and are rarely identified in skin.

Papillomavirus replication occurs in fully differentiated keratinocytes and usually results in benign squamous proliferation (a papilloma). Transform-

ing HPVs, which may be important in the development of some squamous cell carcinomas, include oncogenic types 5 and 8 (in the skin) and 16 and 18 (in genital mucosa).

Human papillomaviruses and cervical cancer

To date the most compelling evidence of a role for HPV is in the development of anogenital and cervical cancer. Oncogenic HPV types 16 and 18 are frequently identified in anogenital and cervical tumours whilst 'low-risk' HPV types 6 and 11 are more commonly associated with benign cervical lesions.⁴ The oncogenicity of HPV 16 and 18 resides, at least in part, in the ability of viral encoded E6 and E7 proteins to bind and inactivate host tumour suppressor proteins (p53 and retinoblastoma, respectively).¹² HPV-encoded E6 and E7 sequences, critical for the transformation of human keratinocytes *in vitro*,¹³ are specifically retained and expressed in cervical cell lines and genital tumours.^{14,15} Inactivation of p53 tumour suppressor protein, in this case through binding to viral oncoproteins rather than gene mutation, appears to be a critical step in the development of diverse malignancies,¹⁶ including anogenital and cervical carcinomas.^{17,18}

Human papillomavirus and skin cancer

Although *in vitro* studies¹³ and animal models¹⁹ suggest that skin cancers may be caused by HPV type 16 and 18 infection, this is not reflected in studies of human skin cancer in the general population. For example, unlike cervical cancer where HPV types 16 or 18 are found in up to 90% of tumours, HPV 16 has consistently been identified only in peri-ungual squamous cell carcinomas.^{20–23} This is an unusual site for tumour development and probably reflects genital transmission of HPV 16 and 18.

HPV has been found in approximately 10% of skin cancers at other sites but, of these, no parti-

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cular HPV type predominates. To date HPV type 16/18 has been identified in occasional keratocanthomas,^{24,25} types 2,16^{26,27} and 34²⁸ in Bowen's disease, types 36²⁸ and 41²⁹ in actinic keratoses, type 20²⁸ in basal cell carcinomas, and types 5,²⁸ 11,^{30,31} 16/18^{28,32-35} and 41²⁹ in squamous cell carcinoma. However, the detection of HPV in occasional tumours does not necessarily implicate them in tumorigenesis, since co-existent HPV may contaminate tumour material, especially benign HPV types. Of the skin HPV types only types 5, 8 and 41 are known to be oncogenic *in vitro* and they are very rarely identified in skin cancers in the general population, although they appear to play an important role in the development of squamous cell carcinomas in EV patients.⁵

Epidermodysplasia verruciformis

Two groups of immunosuppressed patients predisposed to skin cancer have been studied extensively in an attempt to establish a role for HPV in tumorigenesis. These are patients with epidermodysplasia verruciformis (EV)⁵ and organ transplant patients,³⁶ both of whom develop multiple cutaneous warts and squamous cell carcinomas on sun-exposed sites.

EV patients are not systemically immunosuppressed. Their predisposition to widespread HPV infection and cutaneous malignancy is presumed due to some specific, limited immunological defect, the nature of which is unknown. To date, a number of unusual HPV types have been consistently identified in both benign lesions and squamous cell carcinomas in EV patients, including transforming HPV types 5 and 8.^{7,8,37} Integration of subgenomic fragments of HPV, retained in primary and metastatic tumour, have recently been demonstrated in some skin cancers from these patients,³⁸ consistent with a role for HPV in the development of these tumours. EV is a rare condition, however, and studies are few. We need more research in these patients before a role for HPV can be fully established.

Organ transplant recipients

Organ transplant patients are a much larger cohort to study. They have a well-documented overall increased risk of malignancy,³⁹ but an exceptionally high risk of developing virus-associated tumours including non-Hodgkin's lymphoma⁴⁰ and cervical and anogenital carcinoma.⁴¹ Since they are also at

very high risk of developing cutaneous squamous cell carcinomas,³⁶ a role for HPV in the development of these is certainly plausible. Transplant recipients develop multiple cutaneous warts and squamous cell carcinomas, often in very close proximity to each other.³⁶ Furthermore, post-transplant squamous cell carcinomas demonstrate some features suggestive of viral infection on microscopic examination.⁴² Direct evidence in support of a viral aetiology is lacking, however. Unlike EV patients where oncogenic HPV types have been isolated from benign cutaneous lesions, presumably precursors to squamous cell carcinomas, cutaneous warts in transplant patients are most frequently caused by common HPV types.⁹⁻¹¹ Moreover, only approximately 10% of post-transplant tumours examined to date have contained HPV DNA⁴³⁻⁴⁹ (and often of benign HPV types^{10,44,49-51}), a figure which does not exceed that found in the general population with skin cancer. Since co-existent virus wart infection is extremely common in transplant patients with skin cancer, the demonstration of HPV DNA in some skin tumours may represent tissue contamination.

Oncogenic HPV types, including 5/8^{43,45,46,49} and 16/18,^{43,46,49} have been identified in occasional transplant-associated squamous cell tumours in some studies but many others^{47,48,52,53} have been unable to confirm these findings – even employing the polymerase chain reaction, the most sensitive technique currently available for the detection of single copy DNA. These data are insufficient to support a role for oncogenic HPV in the development of the majority of squamous cell carcinomas following renal allograft transplantation.

Conclusions

Available data do not support a role for oncogenic HPV in the development of the majority of skin cancers, either in the general population or in organ-transplant recipients. The exception to this may be peri-ungual squamous cell carcinomas where HPV 16 and 18 are consistently identified. It is possible that infection with benign HPV types may be a co-factor in the development of some cutaneous squamous cell cancers, particularly in transplant recipients, but this needs further investigation.

A role for HPV types 5 and 8 in the development of skin cancer in patients with EV seems more probable, although the mechanism by which these oncogenic papillomaviruses transform keratinocytes is not currently known.

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