The role of HPV in keratinocyte skin cancer development: A systematic review

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Funding information
The authors received no financial support for the research, authorship and/or publication of this article.

Abstract

Keratinocyte skin cancers are the most frequent malignancy, accounting for approximately 30% of all cancers. Although beta genus HPV are the main etiologic agents for squamous cell carcinoma development in patients with epidermodysplasia verruciformis and organ transplant recipients, their role in non-melanoma skin cancer (NMSC) progression in the general population remains controversial. The aim of our review is to summarize current scientific data and to systematically analyse evidence regarding the role of HPV in keratinocyte skin cancers. A total of 2284 patients were included, of which 724 with actinic keratoses, 290 with Bowen's disease, 949 with cutaneous squamous cell carcinomas and 321 with keratoacanthomas. In the case of actinic keratoses, the majority were positive for beta ($n = 372$, 58.49%) and gamma HPV ($n = 256$, 40.25%) and only a few ($n = 6$, 0.94%) were positive for alpha subtypes. Similarly, most of the cutaneous squamous cell carcinomas were positive for beta ($n = 248$, 55.98%) and gamma HPV ($n = 172$, 33.82%) and 23 cases (2.42%) were positive for alpha subtypes. Bowen's disease lesions were mostly positive for beta ($n = 43$, 55.84%) and alpha HPV ($n = 30$, 38.96%), in contrast to the gamma genus ($n = 4$, 5.19%). Keratoacanthomas showed a high distribution among beta genus ($n = 79$, 50.31%) and an equal proportion between alpha ($n = 39$, 24.84%) and gamma ($n = 39$, 24.84%) genera. Studies published so far identifying HPV in keratinocyte skin cancers reflect the difference in detection methods rather than a type-specific tendency towards either actinic keratoses, Bowen's disease, squamous cell carcinoma or keratoacanthoma. On the other hand, recent evidence regarding the role of HPV vaccination in patients with non-melanoma skin cancer brings into perspective the idea of a beta-HPV vaccine or a combined alpha and beta-HPV vaccine that could be used as an adjuvant treatment measure in patients with recalcitrant non-melanoma skin cancer.

Nicoleta Neagu and Caterina Dianzani equally contributed to this study.

INTRODUCTION

Keratinocyte skin cancers (KC), also known as non-melanoma skin cancers (NMSC), are the most frequent malignancy, accounting for approximately 30% of all cancers. They are preferentially located in sun-exposed areas, especially in the head and neck region (80%–90%).[1–3] One of the most important risk factors for the development of keratinocyte skin cancers is ultraviolet (UV) exposure, notably UV-B, augmented by the length of exposure and a lighter skin phototype. Also, immunosuppression is a well-known risk factor for squamous cell carcinoma, as seen in patients with epidermodysplasia verruciformis and organ transplant recipients.[2–4] In fact, 30%–60% of epidermodysplasia verruciformis patients develop squamous cell carcinomas and human papillomavirus (HPV) types 5 and 8 have been isolated in 90% of the cases.[2] Organ transplant recipients have up to 100-fold increased risk of developing keratinocyte skin cancers, mainly squamous cell carcinomas, as compared to the general population.[5–7]

Although beta-HPVs are the main etiologic agent of squamous cell carcinomas in patients with epidermodysplasia verruciformis and in organ transplant recipients, their role in non-melanoma skin cancer progression in the general population remains controversial.[8] Beta-HPVs are distributed throughout the human body and may be considered as part of the commensal flora.[9] However, data from epidemiological studies has shown that patients with squamous cell carcinomas have been associated with beta-HPV infections more often than the general population.[8] The aim of our review is to summarize current scientific data and to systematically analyse evidence regarding the role of HPV in keratinocyte skin cancers.

MATERIALS AND METHODS

We systematically searched the literature for studies published between 2011 and 2021, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed database using the term *human papillomavirus* in combination with the following terms: *actinic keratoses, Bowen's disease, cutaneous squamous cell carcinoma, keratoacanthoma*.

Eligibility was restricted to studies with human immunocompetent participants where the association between HPV and KC was investigated on the basis of biopsy samples, either frozen or formalin-fixed and skin swabs, using PCR-based methods for HPV detection. Keratinocyte skin cancer included tumours recorded as actinic keratoses, Bowen's disease, cutaneous squamous cell carcinoma and keratoacanthoma. Reviews, meta-analyses, cohort studies, case series and case reports were eligible for inclusion. Only articles in English were selected. Studies investigating patients with mucosal, digital, ungual keratinocyte skin cancer or studies that exclusively used serology, immunohistochemistry or plucked eyebrow hairs for HPV detection were excluded. Other potentially relevant articles were identified by manually checking the references of the included literature. The last search was run on 25th November 2021. Two investigators independently selected relevant articles according to predefined inclusion and exclusion criteria, as described above. Disagreements were resolved by discussion, with a prior arrangement that any unsettled discrepancy would be determined by a third author.

Limitations of this review lie in study heterogeneity, especially due to different HPV DNA detection methods. In order to limit bias in reporting, we objectively summarized relevant data from the literature, according to each keratinocyte skin cancer subtype. Pertinent data were selected in the form of: number of patients with HPV-positive keratinocyte skin cancer, keratinocyte skin cancer location, HPV types detected and the number of detections for each HPV type, HPV genera and the HPV detection methods employed. Data were objectively summarized in Table 1 and in Tables S1–S4 and where absent, it was mentioned as 'N/A'. Only known HPV sequences were considered. Additionally, the results for each study were interpreted and bias was discussed by an expert virologist according to the HPV detection methods employed.

RESULTS

A total of 583 articles were initially identified in the literature search, of which 49 were duplicates and 479 did not meet the inclusion criteria so were consequently excluded (Figure 1). A total of 2284 patients were included, of which 724 with actinic keratoses, 290 with Bowen's disease, 949 with cutaneous squamous cell carcinomas and 321 with keratoacanthomas. From a total of 1313 HPV sequences determined, the majority belonged to the beta ($n = 742$, 56.51%) and gamma ($n = 471$, 35.87%) genera and a small proportion ($n = 98$, 7.46%) were alpha HPV types.

Actinic keratoses

From our literature search we found a total number of 724 actinic keratoses investigated for the presence of HPV. The majority was represented by the beta ($n = 372$, 58.49%) and gamma ($n = 256$, 40.25%) genera and only a few actinic keratoses ($n = 6$, 0.94%) were positive for alpha subtypes (Table S1). The methodologies employed in these studies introduce a bias in the results and we cannot extrapolate a more frequent presence for any particular type of HPV in actinic keratoses. On the other hand, it is common knowledge that the same large spectrum of HPV can be found in healthy skin. However, a study by Galati et al.[10] that was comparing HPV detection in actinic keratoses by next generation sequencing (NGS) versus healthy skin in the same patient, showed that gamma HPV types were more frequent in actinic keratoses compared to healthy skin, thus suggesting a possible role of gamma HPV in the development of actinic keratoses.

TABLE 1 HPV detection in keratinocyte skin cancers

	Total lesions evaluated	Number of lesions positive for HPV(%)	Number of HPV types detected
Actinic Keratoses	724	90 (12.43%)	Alpha = 6 Beta = 372 Gamma = 256 Unknown = 2 Total: 636 HPV types detected in 90 actinic keratoses
Bowen's disease	290	72 (24.82%)	Alpha = 30 Beta = 43 Gamma = 4 Total: 77 HPV types detected in 72 Bowen's disease lesions
Squamous cell carcinomas	949	208 (21.91%)	Alpha = 23 Beta = 248 Gamma = 172 Total: 443 HPV types detected in 208 squamous cell carcinoma lesions
Keratoacanthomas	321	37 (11.52%)	Alpha = 39 Beta = 79 Gamma = 39 Total: 157 HPV types detected in 37 keratoacanthoma lesions
Total	2284	407 (17.82%)	Alpha = 98 Beta = 742 Gamma = 471 Unknown = 2 Total: 1313 HPV types detected in 407 keratinocyte skin cancer lesions

Bowen's disease

Bowen's disease search was restricted to extragenital/ extraungual cases. 290 Bowen's disease lesions were analysed and the majority of HPV types belonged to beta (n = 43, 55.84%) and alpha (n = 30, 38.96%) genera, in contrast to the gamma genus (n = 4, 5.19%) (Table S2). The different types of HPV detected in Bowen's disease studies appear to reflect the difference in detection methods rather than in the presence of specific HPV types. However, NGS demonstrated that alpha papillomaviruses are rarely detected in extragenital/ extraungual Bowen's disease. Conforti et al.[11] retrospectively analysed 23 cases of extragenital/ extraungual Bowen's disease arising in the absence of field cancerisation. They found that none of the lesions were positive for HPV DNA, which supports the hit-and-run mechanism theory, where beta-HPVs have a role only in the initial stages of skin carcinogenesis and not in the maintenance phase.[12,13] However, the methodologies employed by this research group were more specific for alpha HPVs rather than for beta or gamma HPVs.

Squamous cell carcinoma

Cutaneous squamous cell carcinoma lesions were the most frequently investigated, with a total number of 949 cases. The majority of HPV types belonged to the beta (n = 248, 55.98%) and gamma (n = 172, 33.82%) genera. 23 cases (2.42%) were positive for alpha HPV types (Table S3). In some reported studies, high throughput sequencing of skin lesions was useful for an unbiased assessment of viral DNA in these lesions.[14,15] Studies utilizing less specific and sensitive assays were restricted to the HPV primers employed, thus providing an incomplete representation. Thus, we can only approximate that alpha, beta and gamma HPVs are detected in these tumours with different percentages, mostly related to the sensitivity of each detection method.

Keratoacanthoma

Three hundred and twenty-one keratoacanthomas were investigated for the presence of HPV. Keratoacanthomas showed a high distribution among beta genus (n = 79, 50.31%) and an equal proportion between alpha (n = 39, 24.84%) and gamma (n = 39, 24.84%) genera (Table S4). Specific HPV types belonging to alpha, beta and gamma genera were detected using technologies with different sensitivity levels. These findings might imply that they are uniformly represented even if we cannot extrapolate from the differences in frequencies, given the heterogeneity of methods. Noteworthy, the only report with no positivity for HPV utilized a method that could only amplify genital-mucosal HPV.[16]

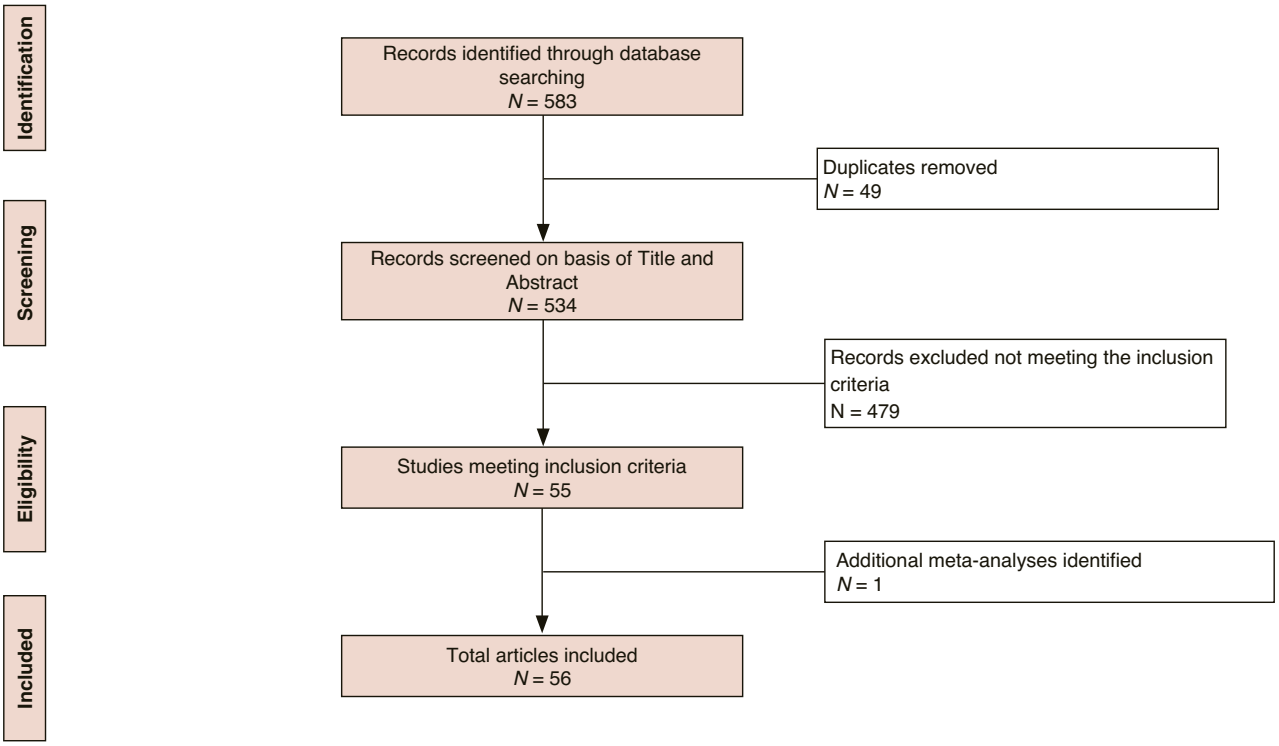

FIGURE 1 Literature search and article selection.

DISCUSSION

Papillomaviridae is a family of small non-enveloped viruses that contain double-stranded circular DNA. So far, more than 200 different human papillomaviruses (HPVs) have been indexed. From a total of 53 genera, only five include HPVs that can infect humans: alpha (n = 65 types), beta (n = 54), gamma (n = 99), mu (n = 3), nu (n = 1).[17,18] Based on epidemiological data, a subgroup of 12 mucosal alpha HPVs are considered high-risk HPV types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and have been classified as carcinogenic (IARC Group 1), being responsible for several cancers, involving the vulva, vagina, cervix, anus, penis and a subset of head and neck cancers. Other eight alpha HPVs (HPV 26, 53, 66, 67, 68, 70, 73, 82) have been classified as possibly carcinogenic (IARC Groups 2A and 2B). The alpha genus also includes low-risk HPV types, like HPV 6 and 11, that can induce benign genital warts or condyloma acuminata or HPV 2, 3, 7, 10, 27, 28, 57, that are responsible for common and plantar warts.[18] The genera beta, gamma, mu and nu are ubiquitously distributed on the cutaneous epithelia of the general population, while hair follicles are considered a reservoir of beta-HPV, with a prevalence as high as 90% reported in plucked hairs from different body sites.[9,19–21]

Beta-HPV might have a role only in the initial stages of skin carcinogenesis and not in the maintenance phase. One of the possible effects of beta-HPV seems to be the amplification of UV radiation-induced DNA breaks and somatic mutations, also known as the hit-and-run mechanism.[12,13] Evidence supporting this hypothesis consists in: beta-HPV E6 and E7 enhance UV mutagenic capacity via multiple cellular functions[2,22]; viral loads were higher in actinic keratoses than in squamous cell carcinomas[23]; not all keratinocyte skin cancers' neoplastic cells contain a copy of viral DNA[23]; when beta-HPV were detected in cutaneous squamous cell carcinomas, viral DNA copy numbers were low[24] and HPV mRNA was absent.[25] These findings support the rationale that beta-HPV are rather facilitators of non-melanoma skin cancers than causal agents.[9,18,22]

HPVs have been detected in different skin lesions such as squamous cell carcinomas, basal cell carcinomas, actinic keratoses, keratoacanthomas, as well as on healthy skin.[26] However, most of the HPV types detected in these skin lesions were actually multiple infections with different HPV types at very low viral loads (<1 copy/1000 cells), which raise the issue of relevance of these very low amounts of virus. HPV detection is highly dependent on the polymerase chain reaction (PCR) primers.[23,26] In the case of consensus primers, known HPV sequences are used, which makes this method biased to detect only HPV types with high similarity to the primers employed, while overlooking the others.[26]

Future perspectives

HPV detection in non-melanoma skin cancers might provide the groundwork for the development of alternative treatment measures. So far, HPV vaccination has been successfully used as a preventative measure among young,

sexually inactive girls[27] and it has shown promising results as a treatment measure in patients with cutaneous warts, recurrent respiratory papillomatosis, basal cell carcinomas and squamous cell carcinomas.[28]

Wenande et al.[29] successfully administered a nonavalent HPV vaccine on the basis of a three dose schedule at 0, 2 and 6 months, respectively, to a population of 12 immunocompetent patients with a mean age of 76.2 years and a median actinic keratoses burden of 56. They concomitantly administered topical therapies for actinic keratoses: cryotherapy, diclofenac, photodynamic therapy, 5-fluorouracil, imiquimod, ingenol mebutate. 12 months after the first dose of vaccine an average 85% reduction in total actinic keratoses burden was recorded, with median actinic keratoses burden decreasing from 56 (IQR: 44–80) to 13.5 (IQR: 1–18). Nichols et al.[30] administered quadrivalent HPV vaccine on the same three dose schedule to two patients with multiple basal cell carcinomas and squamous cell carcinomas and obtained partial remission: a reduction of 62.5% in the number of new squamous cell carcinomas and of 100% in new basal cell carcinomas for the first patient, while the second patient had a 66.5% reduction in new squamous cell carcinomas and a 100% reduction in new basal cell carcinomas.[31] Another case involved a woman with multiple, inoperable basaloid squamous cell carcinomas treated with a combination of systemic and intratumoral delivery of nonavalent HPV vaccine, with complete regression within 11 months of the first dose administration.

CONCLUSION

Evidence regarding environmental, as well as intrinsic risk factors for keratinocyte skin cancers is constantly growing. UV radiation, immunosuppression, skin phototype and genetic susceptibility have all been implicated at a certain point. Nowadays, there is increasing interest in the role that HPV plays in keratinocyte skin cancer tumorigenesis and establishing an association between HPV and keratinocyte skin cancers might have therapeutic implications.

Throughout the studies analysed, HPV diagnostic methods were highly heterogeneous and the findings were restricted by the primers used in each case, thus reflecting the difference in detection methods rather than a type-specific tendency towards either actinic keratoses, Bowen's disease, squamous cell carcinomas or keratoacanthomas. Furthermore, it is well known that a large spectrum of HPVs can be found even in healthy skin. Additionally, recent studies detecting HPV types at very low viral loads (<1 copy/1000 cells) raise the issue of relevance and suggest that HPV might act more as a facilitator of carcinogenesis than as a direct causal agent, which allows the accumulation of UV radiation-induced DNA breaks and somatic mutations. On the other hand, recent evidence regarding the role of HPV vaccination in patients with non-melanoma skin cancer brings into perspective the idea of a beta-HPV vaccine or a combined alpha and beta-HPV vaccine that could be used as an adjuvant treatment measure in patients with recalcitrant non-melanoma skin cancer. In order to be efficacious, the development of a beta-HPV vaccine should be based on both L1 and L2 capsid proteins.[4,32] However, one important limitation might be represented by the lower immunogenity of L2 compared to L1, which could produce insufficient antibody titres. Further research remains necessary in order to determine whether these types of vaccines could be used as a preventative measure or as an adjuvant treatment for keratinocyte skin cancers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data we included in this manuscript is openly available in a public repository that issues datasets with DOIs.

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