Actas Dermosifiliogr. 2007;98:583-93

REVIEW ARTICLE

Cutaneous squamous cell carcicoma and human papillomavirus

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Abstract. The relationship between mucosal human papillomavirus (HPV) and cervical carcinoma or anogenital squamous cell carcinoma (SCC) is becoming increasingly evident, whereas a link between HPV and other cutaneous SCCs is less clear. Recent studies have reported links between epidermodysplasia-verruciformis-associated HPV and extragenital cutaneous SCC, particularly in immunosuppressed patients, although immunocompetent patients have also been affected. Mucosal HPV could also be linked to some types of Bowen disease and certain SCCs of the fingers, oropharyngeal mucosa, etc. We review the possible oncogenic mechanisms involving mucosal HPV and epidermodysplasia-verruciformis-associated HPV. Most SCCs could be explained by the combined action of HPV, immunosuppression, and the oncogenic and immunosuppressive effect of UV radiation. HPV might be associated with worse prognosis of SCC, with implications for clinical practice including greater risk of metastasis.

Key words: human papillomavirus, HPV, epidermodysplasia verruciformis, squamous cell carcinoma, skin

CARCINOMA ESPINOCELULAR CUTÁNEO Y PAPILOMAVIRUS (VPH)

Resumen. La relación entre los virus papilomas humanos (VPH) de tipo mucoso (VPH-muc) y el carcinoma de cérvix o los carcinomas espinocelulares (CE) de la región ano-genital es cada vez más evidente. Sin embargo, la relación del VPH con el resto de los CE cutáneos es más controvertida. Recientes publicaciones relacionan los VPH tipo epidermodisplasia verruciforme (VPH-EV) con los CE cutáneos extra-genitales, sobre todo en los pacientes inmunodeprimidos, aunque también en los inmunocompetentes. Los VPH-muc también se podrían relacionar con algunas enfermedades de Bowen y determinados CE: dedos de manos, mucosa oro-faríngea, etc.

Revisamos los posibles mecanismos oncogénicos de los VPH-muc y los VPH-EV. La mayoría de los CE podrían explicarse por la acción conjunta de los VPH, la inmunodepresión y los efectos oncogénicos e inmunosupresores de las radiaciones ultravioleta. Los VPH podrían implicar un peor pronóstico de los CE, con más posibilidades de producir metástasis, entre otras implicaciones en la práctica clínica.

Palabras clave: virus papiloma humano (VPH), epidermodisplasia verruciforme, carcinoma espinocelular, piel.

Introduction

Human papillomaviruses (HPV) are DNA viruses that belong to the Papovaviridae family and more than 95 different genotypes have been characterized in humans. HPV can be classified into 3 basic groups[1,2]:

1. *Cutaneous HPV (HPV-cut)*. This group includes HPV subtypes 1, 2, 3, 4, 7, 10, 26 to 29, 41, 49, 57, 60, 63, 65, and 75 to 77, among many others.
2. *Mucosal HPV (HPV-muc)*. HPV-muc are further classified as high risk (subtypes 16 and 18), intermediate risk (subtypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, and 83), and low risk (subtypes 6, 11, 26, 30, 32, 40, 42 to 44, 53 to 55, 62, 66, 70, 72, and 81) according to their oncogenic potential.
3. *Epidermodysplasia verruciformis-associated HPV (HPV-EV)*. This group especially includes HPV subtypes 5, 8, 9, 10, 12, 14, 15, 17, 19 to 25, 36 to 38, 47, and 50. It tends also to include certain HPV-cut which are very frequent in epidermodysplasia verruciformis, such as subtypes 3 and 10. New HPV-EV have been characterized thus increasing the HPV-EV list.[3,4]

Some studies have correlated the histological signs attributable to the cytopathic effects of HPV with the

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Accepted June 5, 2007.

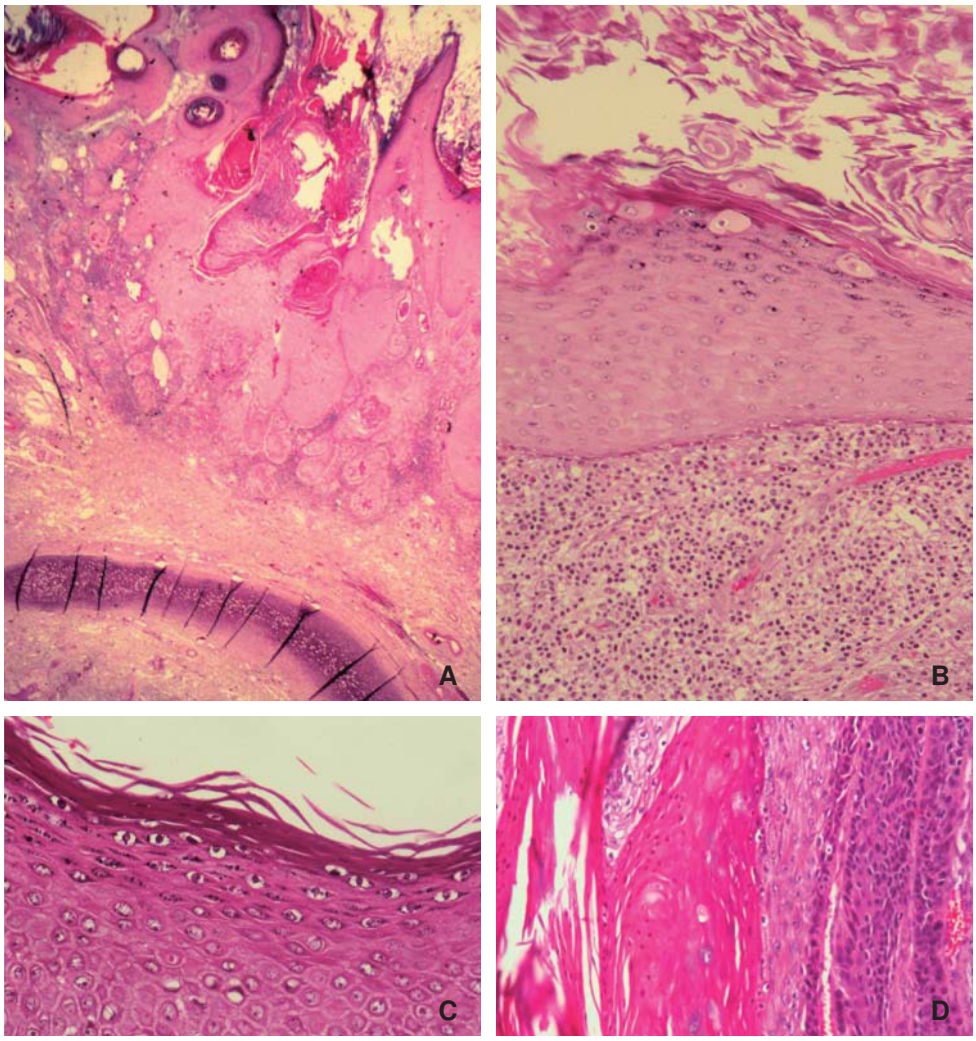

Figure 1. (A) Common wart in the surface layer and underlying squamous cell carcinoma (Hematoxylin-eosin ×16). (B) Epidermodysplasia verruciformis-type cells in the granular layer of the epidermis (Hematoxylin-eosin ×100). (C) Detail of the epidermis next to a squamous cell carcinoma. Increase in the size and quantity of keratohyalin granules, "bird's eyes," and other indirect signs of human papillomavirus (HPV). (Hematoxylin-eosin ×400.) (D) Pseudoparakeratosis among other signs attributable to HPV (Hematoxylin-eosin ×200).

different HPV subtypes (detected through polymerase chain reaction [PCR]), and thus, it would be possible to establish the HPV subtype for each lesion according to the indirect histological signs that are observed, at least approximately.[5-8] The histological signs attributable to HPV infection include the following: the keratohyalin granules are more numerous and larger, with different shapes and sizes, and can be seen not only in the cytoplasm but also in the nucleus; koilocytes; papillomatosis; pseudoparakeratosis (rounded nuclei instead of flat ones in the stratum corneum) is occasionally observed; and cells like those seen in epidermodysplasia verruciformis (large globular cells with cytoplasmic granules) [9,10] (Figure 1).

Cutaneous HPV

HPV-cut is normally found in benign lesions such as common warts, flat warts, plantar warts, some epidermal cysts, etc.[11] The high prevalence of common, flat, and plantar warts in the healthy population (especially during childhood and adolescence) and the mechanisms of HPV infection (by personal contact and following minor injuries or skin damage) are epidemiological data suggesting that HPV may be present asymptomatically, and is probably symbiotic on the mucocutaneous surfaces of most immunocompetent adults and children.[11,12]

In benign lesions, HPV DNA is located in the cell nucleus, although outside the chromosomes. In contrast, in serious dysplasias and in carcinomas caused by HPV, viral DNA is fully integrated in the cellular genome of the keratinocytes.[13] On the other hand, cases of squamous cell carcinoma (SCC) arising from common warts[14-19] or plantar warts[11] have been described, suggesting that nononcogenic HPV, such as HPV-cut, could favor the development of malignant processes when occurring with other factors, such as immunosuppression.

Mucosal HPV

HPV-muc is normally detected in genital warts and in premalignant and malignant lesions in the anogenital region, and also in some patients (eg, those infected by the human immunodeficiency virus [HIV]) who apparently do not present clinical lesions.[20] HPV-muc has also been detected in lesions caused by genital lichen sclerosus, although the pathogenic role played by HPV in this process remains unclear.[21]

The oncogenic role of HPV-muc (especially some subtypes such as 16, 18, 31, 33, and 35) has been well characterized in uterine cervical carcinoma; similarly, the possible oncogenic role of these HPV-muc subtypes in cutaneous SCC of the anogenital region (including SCC of the vulva, penis, anus, or perineum) is increasingly clear.[22-24] On the other hand, HPV-muc has also been associated with the following:

1. Benign lesions such as oral papillomas[25,26] (especially subtypes 6 and 11) or some types of seborrheic keratosis.[27]
2. Some studies have observed classic oncogenic HPV-muc (such as subtype 16), with almost symbiotic behavior on the skin and mucous membranes of children and immunocompetent adults.[12,28]
3. Extragenital Bowen disease. Clavel et al[29] detected HPV-muc in 83% of patients with Bowen disease (78 cases out of 94). While some studies have found similar percentages of HPV-muc in Bowen disease of the hands,[30,31] others have found much lower percentages[32-38] or a predominance of HPV-EV.[3,39,40] Some recent publications support a possible relationship between HPV-muc and some cases of Bowen disease.[41,42]
4. SCC of the area around the nails or of the fingers[43-45] (a possible explanation would be autoinoculation or hand-genital transmission).
5. SCC of the oropharyngeal mucous membrane, by acting synergistically or potentiating other oncogenic factors such as tobacco.[25,26,46-48] According to some recent studies, HPV-muc could also be involved in carcinomas of the larynx, esophagus, tonsils, etc.[49-54]

In conclusion, HPV-muc could be involved in SCC of the anogenital region,[22-24] SCC of the fingers,[43-45] in some cases of Bowen disease,[29-42] and in carcinomas of the oropharyngeal mucosa[25,26,46-48] (also in carcinomas of the larynx, esophagus, tonsils, etc, as reported in several studies[49-54]).

Epidermodysplasia Verruciformis-Associated HPV

Epidermodysplasia verruciformis-associated HPV could be an important oncogenic factor in most cases of cutaneous SCC, especially in immunocompromised but also in immunocompetent patients.[55]

Cutaneous SCC and HPV-EV in Immunocompromised Patients

The increased incidence of SCC in immunocompromised patients (HIV-infected patients, transplant patients treated with immunosuppressive drugs, patients with cancer, etc) has been confirmed in numerous studies.[56-60] Some have found HPV-EV in approximately 80% of cases of SCC in immunocompromised patients,[4,61] an observation which would support a possible oncogenic relationship between HPV-EV and SCC in these patients. It should be pointed out that these figures are similar to those reported in cervical carcinoma, where HPV (albeit mucosal) is found in approximately 90% of cases.[23,62,63]

Some authors have pointed out striking parallels between immunocompromised patients and those affected by HPV-EV.[55] Immunocompromised patients often develop multiple actinic keratoses, Bowen disease, and SCC, especially in sunlight-exposed areas,[57] similar to the situation in patients with epidermodysplasia verruciformis.[64] Furthermore, immunocompromised patients have been described with lesions which are clinically and histologically indistinguishable from those in epidermodysplasia verruciformis.[65-68] Finally, some subtypes of HPV-EV are often detected in immunocompromised patients, such as HPV 5 and 8, which are usually found in tumors of patients with epidermodysplasia verruciformis.[55,56,66,69,70]

Thus, HPV-EV could play an important oncogenic role in immunocompromised patients, by acting synergistically and potentiating other oncogenic factors such as UV radiation.[55,70,71]

Cutaneous SCC and HPV-EV in Immunocompetent Patients

The possible oncogenic role of HPV-EV in immunocompetent patients is more debatable. HPV (predominantly HPV-EV) has been found in approximately 35%-45% of cases,[29,34,56,61,72-74] which are similar percentages to those in the healthy population; based on these data, some authors consider that HPV-EV are normal symbiotes of the skin.[12,75]

Thus, there may not be many differences between immunocompromised and immunocompetent patients. We consider that almost all patients with SCC are immunocompromised based on the fact that several studies discuss local or systemic immunosuppression caused by chronic exposure to UV radiation.[11,76-78] This would trigger

Table. Immunosuppressive Effects of UV Radiation

↓ Presentation of antigens (↓ number and function of Langerhans cells, among others)
↑ Immunosuppressive mediators and ↑ Th2 lymphocyte activity (inducing skin tolerance and lack of cellular response for antigens): • Increase in IL-10, IL-6, IL-15, TNF-a
↓ Th1 lymphocyte activity (directing cell-mediated immune activation): • Decrease in IL-12, IL-1, IL-7, IFN-g
↓ Number and function of natural-killer cells
Induction of T lymphocyte apoptosis
Other immunosuppressive effects that inhibit the cytotoxic and immune response: • Trans-urocanic acid changes to cis-urocanic acid • Free radical formation • Alterations in keratinocyte DNA • Alterations in surface receptors and adhesion molecules

Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; Th, T helper.

a cascade of interrelated biochemical and cellular alterations that would result in immunosuppressive effects[11,76-78] (Table). Another study has shown that old age itself is a strong immunocompromising factor.[79] If we take into account the immunosuppressive effects of UV radiation and old age, and given that most patients with SCC have also undergone chronic exposure to solar radiation, are older, or both, these patients could be considered immunocompromised, at least with local or cutaneous immunosuppression.

On the other hand, several studies have reported an increase in the quantity of HPV-EV residing in hair follicles compared to the rest of the skin,[80,81] in sunlight-exposed areas,[3,70,75] in patients with psoriasis receiving psoralen-UV-A (PUVA) therapy,[70,82-85] and in elderly patients,[70,75] all of which may give an indication of what occurs in the general population after chronic exposure to the sun.

Despite these studies, several authors have expressed doubt regarding the possible involvement of HPV in extragenital SCC, especially in immunocompetent patients.[12,75] There could be several reasons for this:

1. As discussed later, the oncogenic mechanisms of HPV-EV are not as well characterized as those of HPV-muc. HPV-EV has low oncogenic potential in vitro and requires the synergistic action of solar radiation to induce oncogenesis. Unlike in cervical carcinoma (where HPV could be the main oncogenic factor),[23,63] in skin cancers HPV would require other oncogenic factors, such as UV radiation or immunosuppression.[71]
2. In many cases it is not possible to demonstrate the presence of HPV through in situ hybridization or PCR. If we review recent publications, there is wide variability regarding the prevalence of HPV or which HPV subtypes predominate (cutaneous, EV or mucosal),[55] especially in studies conducted with immunocompetent patients, both those investigating SCC[29,33-35,56,61,72-74,86] and those studying actinic keratosis or Bowen disease.[33,35-40,56,72,73,86] Some have investigated the same lesions using different PCR techniques (with the aim of comparing them) and have obtained totally different results depending on the PCR technique used.[87-89] Frequently, larger or smaller quantities of HPV are found depending on the PCR technique used.[56,89] On the other hand, some studies have only investigated HPV-muc or some specific HPV serotypes.[35,36,38,40,86] Furthermore, viral DNA could be degraded and not detected when the sample lesions have been in paraffin for a long period or if they are in formalin for more than 24 hours, which is usually the case in most skin lesions.[90,91] A modified in situ hybridization method has recently been introduced that may have greater sensitivity and specificity.[92,93]
3. Finally, HPV may be eliminated (thus making its DNA undetectable) once the process of oncogenesis is initiated; that is, HPV could disappear having left its fingerprint.[94,95]

Association Between Cutaneous SCC and HPV-EV

Several relatively recent studies have found a statistically significant relationship between the presence of HPV-EV and greater risk of acquiring SCC in immunocompromised and immunocompetent patients:

1. Stark et al[70] found a statistically significant association between positive serological findings for HPV-8 and the presence of nonmelanoma skin cancer (NMSC) in immunocompetent patients. Serological findings were positive for HPV-8 in 45.6% of immunocompetent patients with NMSC (36 out of 79), whereas in people without NMSC this figure was lower: 7.6% (16 out of 210) in immunocompetent patients and 21% (39 of 185) in immunocompromised patients.
2. More recently, Masini et al[96] reported a similar statistically significant association between positive serological findings for HPV-8 and the presence of SCC in immunocompetent patients.
3. Feltkamp et al[97] also found a relationship between positive serological findings for HPV-EV (especially for HPV-8 and HPV-38) and a greater risk of acquiring SCC.
4. In an Australian study, Boxman et al[32] reported that the presence of HPV-EV in hair follicles was related to the

risk of acquiring NMSC (statistically nonsignificant association).
5. Harwood et al[98] studied a group with SCC and one without SCC using PCR and found a statistically significant relationship between the presence of HPV-EV in normal skin and the risk of acquiring SCC (in immunocompetent and immunocompromised patients).
6. Karagas et al[99] reached similar conclusions, finding a relationship between positive serological findings for HPV-EV, particularly for HPV-5, and a greater risk of SCC.
7. With respect to the precursor lesions, Bouwes Bavinck et al[100] found a relationship between positive serological findings for HPV-8 and the presence of actinic keratosis. Boxman et al[101] also found an association between the presence of HPV-EV in hair follicles and the presence of actinic keratosis, although this association was significant only in men.

In conclusion, HPV-EV is involved in cutaneous SCC in immunocompromised and immunocompetent patients,[55,96,98,102] as shown by Purdie et al.[102]

Oncogenesis and HPV

1. The tumor suppressor protein p16 inhibits tumor progression in cells whose DNA has been damaged through inhibition of the *retinoblastoma* (*Rb*) gene.[103,104] Greater expression of p16 induced by UV radiation[105-107] and oncogenic HPV has been reported.[104,108] Specific oncogenic HPV induce alterations in the *Rb* gene through E7 protein and thus trigger the suppressive mechanism of p16 protein.[104,108,109] Furthermore, these oncogenic HPV, through E6 protein, induce alterations in the *p53* gene,[55,104] and this would at least partly explain the alterations found in *p53* in areas not exposed to sunlight.[110]
2. The oncogenic mechanisms of HPV-muc in cutaneous SCC (for example, in some SCC of the fingers[44]) are comparable to those found in cervical and anogenital carcinomas. Mucosal HPV may produce alterations in the *p53* gene and *Rb* gene through proteins E6 and E7, respectively, inducing cellular immortality or tumor progression.[55,104] In addition, *p53* gene polymorphism should be taken into account; specific individuals with amino acid changes (arginine instead of proline) in codon 72 of the *p53* gene, especially homozygotes, would be more susceptible to the oncogenic action of this HPV-muc E6 protein.[111-113]
3. The oncogenic mechanisms of HPV-EV are less clear. On the one hand, HPV-EV E6 and E7 proteins, unlike those of HPV-muc, do not have the same affinity for the *p53* and *Rb* genes, respectively.[55,114] In addition, the in vitro oncogenic potential of these HPV-EV is low[115] and would require the combined action of UV radiation to be oncogenic, as occurs in epidermodysplasia verruciformis patients.[114] A possible oncogenic mechanism of these HPV-EV could be proapoptotic Bak protein inhibition.[114,116] UV radiation induces Bak protein activation, which then induces apoptosis, regardless of the p53 mechanism. The E6 protein of these HPV-EV (and of other HPV-cut such as HPV-10 and HPV-77) induces Bak protein degradation, thus inhibiting the apoptosis induced by UV radiation, independently of the state of p53.[114,116] Jackson et al[116] demonstrated that SCC without HPV had high levels of apoptotic Bak protein, whereas this protein was practically undetectable in SCC with HPV. In an in vitro model, Akgul et al[117] demonstrated how the E7 protein of HPV-EV type 8 could induce keratinocyte proliferation and, more importantly, favor the migration and invasion of these keratinocytes into the dermis. Nevertheless, more in vivo studies are needed to support this finding.
4. Furthermore, HPV uses immunosuppressive-type mechanisms to evade the immune system; these mechanisms could indirectly facilitate the escape of tumor cells.[94,118,119]

Taking all the above into account, HPV could play an important role as an initiator and promoter of SCC oncogenesis (Figure 2).

In short, in SCC oncogenesis, the main pathogenic factor seems to be solar radiation, especially chronic or continuous exposure.[120,121] Other individual factors, such as skin phototype, age, or changes in the *p53* suppressor gene, could increase individual susceptibility to SCC.[55]

Certain HPV, such as HPV-EV, could also be another synergistic or potentiating pathogenic factor in epithelial oncogenesis, especially in immunocompromised patients, but also in immunocompetent patients.[55,96,98] The significant immunosuppressive effects caused by UV radiation,[76-78] age,[79] or HPV itself[94,118,119] would induce immunosuppression (local, systemic, or both) in immunocompetent patients and would aggravate immunosuppression in immunocompromised patients. Alterations in the immune system (especially in its control functions and the elimination of cells with damaged DNA) could play as important a role as UV radiation.[71]

The interaction of these 3 pathogenic factors (UV radiation, alterations in the immune system, and HPV), together with other factors that may have an effect on these 3 (age, skin phototype, individual predisposition, etc) could explain most cases of SCC oncogenesis (Figure 3).

Practical and Clinical Implications

The possible role of HPV in SCC oncogenesis could have a strong impact on clinical practice and dermatological treatment:

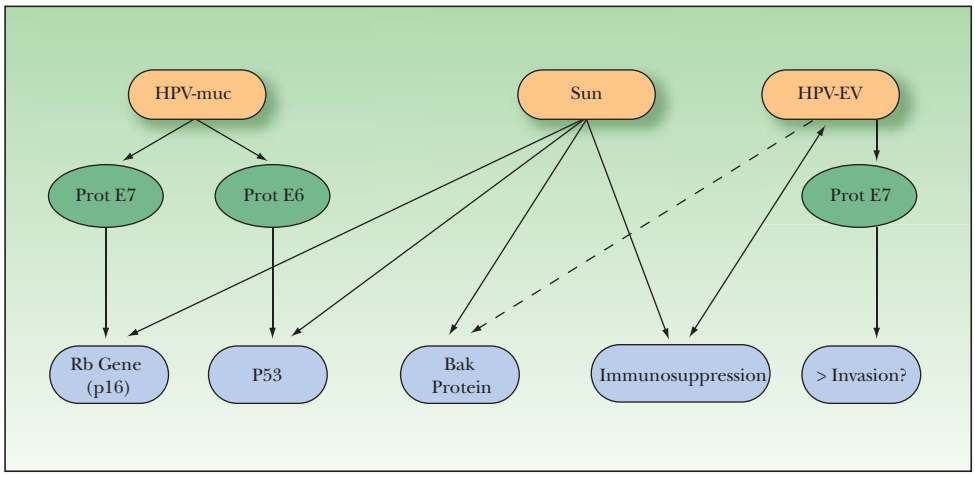

Figure 2. Oncogenic mechanisms of mucous-type human papillomavirus (HPV-muc) and epidermodysplasia verruciformis-type HPV (HPV-EV).

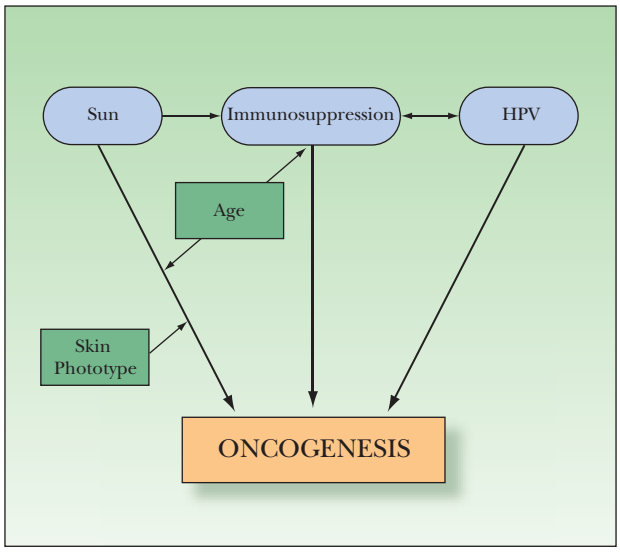

Figure 3. Summary of squamous cell carcinoma oncogenesis. HPV indicates human papillomavirus.

1. For example, HPV-muc vaccine[122,123] has recently been shown to have a strong prophylactic effect against cervical carcinoma, but also against SCC of the anogenital region, certain types of skin SCC, some cases of Bowen disease, and even other SCC such as those of the oropharyngeal region. These vaccines may also prove effective in men and so their use should not be restricted to young women. It may be possible to develop a vaccine against HPV-EV in the future (this would be very useful in immunocompromised patients, as well as in patients with a fair skin phototype or those who have undergone intense chronic exposure to the sun, etc).
2. The employment of early prevention campaigns similar to those against cervical carcinoma (some countries conduct these for SCC of the anus in patients at risk).[124,125]
3. Treatment with topical imiquimod for acuminate condylomata[126] could be indirectly useful as a prophylactic against certain SCC (for example, in the anogenital region).
4. Several publications have recently appeared stating that the presence of HPV in SCC would indicate worse prognosis with, for example, a greater probability of dissemination and a greater incidence of lymph node metastases.[127-130] Some authors attribute this to the changes caused by HPV-muc in the regulator gene *p53* through E6 protein, among other effects.[131-133] Another possible explanation is that E7 protein could induce greater invasiveness toward the dermis[117] (especially in the case of HPV-muc, since HPV-EV has only been studied in vitro[117]), thus encouraging the development of metastasis or greater aggressiveness in these tumors. Nevertheless, many more studies are needed to confirm or reject these hypotheses.
5. Some authors have shown that *Polypodium leucotomos* is useful in preventing SCC developing in patients receiving PUVA treatment.[134] Given that the pathogenesis of SCC in these patients is very similar to that in immunocompromised patients, this treatment could also be very useful in preventing SCC in the latter (we are aware that a multicenter study on this issue is currently taking place).
6. In any case, as occurs in epidermodysplasia verruciformis, HPV-EV requires the synergistic action of UV radiation to induce oncogenesis[55] (through apoptotic Bak protein inhibition,[116] for example). Thus, the best way to prevent cutaneous SCC continues

to be reduction of exposure to the sun or the use of topical or systemic sun filters.

Conflicts of Interest

The authors declare no conflicts of interest.

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