Epidemiology of Cutaneous Human Papillomavirus Infections

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Introduction

Human papillomaviruses (HPV) are small epitheliotropic DNA viruses. HPV infect keratinocytes in the skin as well as the mucosa. More than 100 different human papillomaviruses have been sequenced so far. Some HPV are involved in cancer development. HPV infection is particularly associated with anogenital cancer, most notably cervical cancer, but likely also with nonmelanoma skin cancer (NMSC). The beta papillomaviruses (beta-PV) are the most likely candidates to be involved in skin carcinogenesis.

In this chapter, the role of beta-PV in the etiology of NMSC is discussed. The prevalence of beta-PV in lesions and unaffected skin from immunosuppressed organ transplant recipients (OTR) and immunocompetent individuals is outlined, as well as the epidemiological association between beta-PV infection and NMSC.

Papillomaviruses

Papillomaviruses are small DNA viruses that can induce a wide variety of hyperproliferative lesions (papillomas, warts, carcinomas) in the skin and mucosa of mammals (rabbit, horse, dog, sheep, deer, elk, cattle, primates, and humans) and birds.

In 1933, the etiological agent of cutaneous warts in cottontail rabbits was identified by Richard Shope [1]. It was identified as a transmissible virus and was later called the cottontail rabbit papillomavirus (CRPV). In 1949, the nature of the infectious agent of human warts was investigated by Strauss and Shaw [2]. They were the first to detect viral particles in human warts by electron microscopy. In total, almost 100 different full-length HPV genomes have been described [3, 4]. A new papillomavirus (PV) isolate is recognized as such if the complete genome has been cloned and the DNA sequence of the L1 open reading frame (ORF) differs by more than 10% from the closest known PV type [4].

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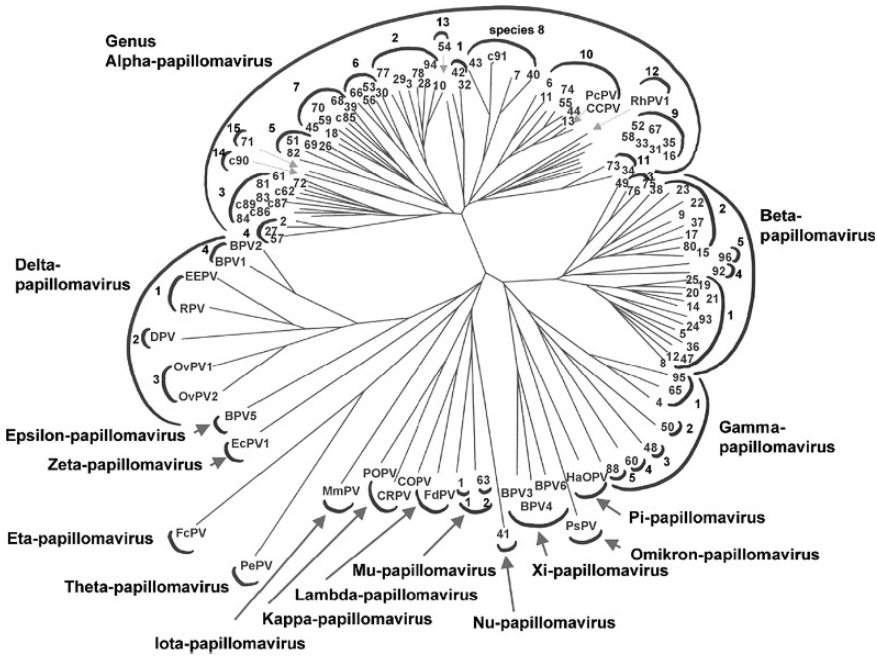

Fig. 1 Phylogenetic tree containing the sequences of 118 papillomavirus types. The numbers at the ends of each of the branches identify a human papillomavirus (HPV) type; "c" numbers refer to candidate HPV types. All other abbreviations refer to animal papillomavirus types. The *outermost semicircular symbols* identify papillomavirus genera, e.g., the genus alpha-papillomavirus. The number at the *inner semicircular symbol* refers to papillomavirus species. This figure is reprinted from reference 4 (De Villiers et al.) with permission from the publisher

Papillomaviruses are subdivided into different genera (Fig. 1). The alpha papillomaviruses (alpha-PV) are primarily mucosal types that include high-risk types such as HPV16 and HPV18, which are known to cause cervical cancer, and low-risk alpha-PV types such as HPV6 and HPV11, known to cause condylomata acuminata. The other HPV types belong to the genera beta, gamma, mu, and nu. The beta-PV types are exclusively cutaneous types, a subset of which probably plays a role in the development of cutaneous squamous cell carcinomas (SCC).

The replication cycle is divided into two stages. First, the virus is maintained at low copy numbers within the initially infected, but still replicating, cells. The viral proteins E1 and E2 are essential for this basal DNA replication. When the basal cells are pushed to the suprabasal compartment, they lose their ability to divide and instead initiate the terminal differentiation program. Papillomaviruses replicate in this compartment, and for their release into the environment, take advantage of the disintegration of the epithelial cells that occurs as a consequence of their natural turnover at the superficial layers [reviewed in reference [5].

The carcinogenic role of high-risk mucosal HPV in cervical cancer is well established and was first proposed in 1976 [6]. After initial infection, viral particles reach the basal layer of the epithelium, where they bind to and enter into cells [5].

It has been suggested that for maintenance of the infection the virus has to infect an epithelial stem cell [7]. It is known that persistence of the virus is necessary for development of cervical cancer [8]. Integration of the HPV genome into the DNA of the host cell is an important event of alpha-PV-induced carcinogenesis. Integration appears to be a random event, where expression of parts of the genome is usually lost, whereas expression of the viral genes E6 and E7 is maintained. As a result of uncontrolled expression the viral proteins E6 and E7, which normally secure viral replication in the differentiated keratinocyte compartment, can turn into oncoproteins by neutralizing the action of the tumor suppressor proteins p53 and pRb, respectively. The affinity of E6 and E7 for p53 and pRb, respectively, correlates in general with the oncogenicity (high-risk/low-risk) of the HPV type in question.

Cutaneous HPV

Warts are very common in the healthy population, with a prevalence of about 20% [9]. Most persons develop warts at some time in life, but they occur most frequently in children and adolescents 12 to 16 years of age [10]. HPV types associated with warts are HPV1, -2, -3, -4, -7, -10, -26, -27, -28, -29, -41, -57, -60, -63, and -65, belonging to the genera alpha and gamma [4]. HPV1 is believed to cause myrmecia warts, mainly on the plantar site of the foot. A study showed HPV1 in 19.5% of plantar warts. HPV2 was detected in 21.5% and HPV4 in 7.8% of the plantar warts [11]. Verrucae vulgaris, localized mainly on the hands, are caused by HPV2, -4, -7, and -57. HPV2 is the most often detected HPV type in Europe and the United States [12]. In a Taiwanese population, however, in only 7% of verrucae vulgares was HPV2 or -3 found [13]. HPV types 1 and 4 were the most frequent types, in 13% and 16% of the warts, respectively. HPV7 is associated with butcher's warts, which are verrucae vulgares on the hands of slaughterhouse workers or meat handlers. HPV7 was found in 30% of butchers [14]. Verrucae planae are associated with HPV3, -10, and -41. They are located on the dorsum of the hands and in the face. Intermediate warts have clinical characteristics of verrucae vulgares, but also resemble verrucae planae. They are located mostly on the dorsa of the hands, but in immunosuppressed patients, they may be widely disseminated. The HPV types mainly found are HPV10, -26, -27, -28, and -29. Cystic warts are plantar warts, with different characteristics when viewed under the microscope, and are associated with HPV types 60, 63, and 65 [15].

It should be noted that HPV in some of these studies was typed with polymerase chain reaction (PCR). It cannot be excluded that the distribution and frequency of HPV infections in verrucae vulgares and planae will change when more sensitive techniques are applied.

Betapapillomaviruses (Beta-PV)

There is increasing evidence for a carcinogenic role of beta-PV in NMSC, especially in SCC of the skin. At present, 25 beta-PV types are fully sequenced (HPV5, -8, -9,

-12, -14, -15, -17, -19, -20, -21, -22, -23, -24, -25, -36, -37, -38, -47, -49, -75, -76, -80, and cand92, -93, and cand96). Based on partial sequences, probably more than 35 new types have to be added to this list of beta-PV types [4, 16] (see Fig. 1). Because of the relationship between the rare genetic disease epidermodysplasia verruciformis (EV) and HPV, beta-PV types were formerly called EV-associated HPV types. Since the new taxonomic classification of papillomaviruses, these types are called beta-PV types [4].

Not much is known yet about the natural history of beta-PV infections. Beta-PV infections are very common in most people [17], but the clinical picture of cutaneous beta-PV infection is not clear. OTR often develop extensive warts and other hyperkeratotic lesions, which have been linked to beta-PV infection [18]. In contrast, infection with beta-PV in immunocompetent individuals probably remains subclinical. It is likely that beta-PV infection is transmitted through skin and hair derivates, as proposed in a study describing that children are infected with the same cutaneous HPV types as their parents within months after birth [19]. Beta-PV DNA is found in skin swabs of the forehead [20], the arms and legs, and in hairs from eyebrows, arms, and legs [17] of both healthy individuals and OTR.

The HPV life cycle is closely linked to the biology of the specific host cells, the keratinocytes, which are responsible for the renewal, cohesion, and barrier function of pluristratifying epithelia [21]. It is thought that beta-PV target stem cells are located in the basal layer of the epidermis and in the bulge of the hair follicles [17, 22]. The hair bulge is considered as an immune privileged region [17].

Persistence is considered an important aspect of mucosal infections in relation to cervical carcinogenesis. Recent studies indicate that beta-PV infections also persist. In a small cohort of healthy adults it was demonstrated that the majority of detected beta-PV infections persisted [23]. Another recent study showed persistent beta-PV DNA positivity in 48% of the healthy individuals and 33% of the OTR after 7 years [24]. These data are in contradiction with the study by Berkhout et al., which shows more beta-PV DNA persistence in OTR than in healthy individuals during up to 5.6 years in 2 to 5 time points [25]. In the study by Berkhout, 77.5% of the hyperkeratotic papillomas were positive for a beta type or a selected population of alpha-PV types: 77.8% of the SCC, 67.9% of the actinic keratoses (AK), only 35.7% of the basal cell carcinomas (BCC), 38.5% of benign lesions, and 32.3% of clinically normal skin were positive. Whether beta-PV persistence is a factor in skin cancer carcinogenesis needs further research.

Beta-PV can be found on different parts of the skin. The reservoir of the virus is possibly within epidermal stem cells of the hair bulge. Beta-PV DNA can easily be isolated from plucked eyebrow hairs. The presence of beta-PV in plucked eyebrow hairs has frequently been used as a measure of beta-PV infection in several epidemiological studies. Detection of beta-PV DNA is usually performed with polymerase chain reaction (PCR) on DNA extracted from hairs, skin swabs, or biopsies by which preferential areas of the genome can be amplified.

Over the years, several broad-spectrum PCR methods have been developed suitable to detect cutaneous HPV types, species, or genera: CPI/IIs [26], FAP59/64 [20],

F/G [27], modified F/G (M^aH^a) [28], HPV type-specific PCR [29], degenerate and nested PCR [30], and PM-PCR RHA [31].

Using virus-like particle (VLP) enzyme-linked immunoassay (ELISA) or multiplex technology (Luminex), antibodies against beta-PV viral proteins can be detected, to determine a person's beta-PV serological status. Antibodies can be detected against the major capsid protein L1 and the nonstructural protein E6 using HPV virus-like particle (VLP) or GST-HPV fusion proteins in ELISA [32, 33] or with multiplex serology using GST-L1 fusion proteins, respectively [34]. The latter method (Luminex) is a new method based on fluorescent bead technology that allows simultaneous detection of antibodies against up to 100 different in situ affinity-purified recombinant HPV proteins [35].

Human Papillomavirus, Epidermodysplasia Verruciformis, and Skin Cancer

Epidermodysplasia Verruciformis

The association between HPV and SCC originated from patients with the rare hereditary disease epidermodysplasia verruciformis (EV). EV patients have an abnormal susceptibility to widespread beta-PV infections of the skin [36, 37]. EV patients develop pityriasis versicolor-like lesions and flat warts and get numerous SCC on sun-exposed sites. In the SCC of EV patients, mainly beta-PV types 5 and 8 are found [38]. Recent studies have shown two genes, EVER 1 and -2, to be related with EV. EVER mutations have been described in EV patients worldwide. EVER genes are members of a transmembrane channel-like (TMC) gene family. The function of TMC is still unknown. It has been proposed that TMC proteins could constitute a novel group of ion transporters, or channels or modifiers of such activities, and could be involved in signal transduction [reviewed in reference [21]].

Also, OTR have an increased risk of developing SCC on sun-exposed sites, often preceded by hyperkeratotic lesions (actinic keratosis) [39–42]. Because the situation in OTR to some extent resembles that of EV patients, it was investigated whether HPV was present in these patients [43, 44].

Prevalence of Papillomavirus in Nonmelanoma Skin Cancer

HPV DNA is found in NMSC and precursors of both immunocompetent and immunosuppressed individuals. The percentage of HPV DNA positivity varies with populations tested, immunocompetent or OTR, as well as the detection method.

Extensive research has been carried out in OTR to discover the association between warts, hyperkeratotic skin lesions, NMSC, and HPV infection in immunosuppressed individuals [17,18,25,39,40,44–46]. OTR are at a high risk of developing

NMSC in the years following transplantation and on immunosuppressive drugs. The risk of developing skin cancer increases from 10% in the first 10 years after transplantation to 40% 20 years after the transplantation [41]. In this patient group, several studies have been performed to determine the prevalence of HPV DNA in healthy skin, benign keratotic lesions, AK, BCC, and SCC (Table 1). Already in 1989, Barr et al. found HPV5/8 DNA in 60% of SCC from OTR [40]. de Jong-Tieben et al. found a prevalence of HPV DNA in 80% of SCC biopsies, 50% of BCC, and 93% of AK [47]. In warts of OTR patients, HPV DNA was detected in 66% [43] and 91% [46], respectively. In most warts, HPV1, -2, or -4 was found. In benign keratotic skin lesions of OTR, in 55% of the lesions HPV DNA was found. Meyer et al. found HPV DNA in 75% of the SCC from OTR, 38% in AK and 17% in healthy skin [46]. Berkhout et al. found HPV DNA in 77.8% of SCC, 77.5% of hyperkeratotic papillomas, 67.9% of AK, 35.7% of BCC, 38.5% of benign lesions, and 32.3% of healthy skin [25]. They also found more persistence of HPV DNA in OTR than in healthy individuals [25]. Also, in nonlesional skin the prevalence of HPV DNA infections measured in plucked hairs was very high in OTR, up to 92% [17], with predominantly beta-PV types present. Forehead skin swabs also are frequently positive for HPV DNA, in 71% to 90% of OTR [24]. In Table 1, the different HPV prevalence studies in NMSC and precursor lesions are listed, and the predominant HPV types and genera found are shown.

HPV prevalence in cutaneous lesions from immunocompetent individuals has been less studied and is generally lower than in OTR. HPV DNA was found in 47% of SCC biopsies, 36% of AK, and 16% in healthy skin [46]. In an English study in immunocompetent patients, HPV DNA was found in 35% of the normal skin biopsies [48]. Of the SCC cases in a Dutch study, 71% was positive for HPV DNA, and of the healthy controls, 55.2% [49]. In plucked hairs from different sites of the body of healthy individuals, HPV DNA was present in 45% of the samples [17]. HPV DNA, isolated from plucked eyebrow hairs of Australian individuals, was present in 54% of AK cases. In SCC cases and tumor-free controls, the percentage was 44% and 40%, respectively [50]. A study in AK in immunocompetent individuals showed a prevalence of beta-PV of 85% in frozen biopsies and 67% in formalin-fixed biopsies [51]. No difference was found in the prevalence of beta-PV DNA between high-risk or low-risk AK. In BCC of immunocompetent persons, HPV DNA is found in approximately 43.5% [48, 52].

Concluding on the basis of these studies, HPV DNA is often found in biopsies of SCC, in both immunosuppressed and immunocompetent patients. Also in other NMSC biopsies and normal skin, as well as plucked hairs and skin swabs, HPV DNA is often found. Most frequently beta-PV types are found, but so far, no high-risk types were identified based on these HPV prevalence studies, possibly because the different PCR methods used in the different studies make it hard to compare results. Also, a study showed that stripping of the stratum corneum of SCC reduced the level of HPV DNA found in the tumor [53]. This finding might show that part of the HPV DNA found in tumor (biopsies) is contamination, or that HPV DNA is more present in the superficial layers and is not evenly distributed throughout the tumors.

Table 1 List of human papillomavirus (HPV) prevalence studies in nonmelanoma skin cancer (NMSC) and precursor lesions, and the predominant HPV types and genera present

Author (reference)	Patients	Lesions	Method	HPV types	Prevalence
Barr [40]	RTR	SCC	Southern blot	5, 8	60%
de Jong-Tieben [47]	RTR	SCC/AK/ BCC	Broad-spectrum PCR	Beta PV	80%/93%/50%
Meyer [46]	RTR	SCC/AK/normal skin	Degenerate PCR	Beta PV	75%/38%/17%
Berkhout [25]	RTR	SCC/papillomas/ AK/BCC/benign lesions/normal skin	MaHa PCR	Beta PV	77.8%/77.5%/ 67.9%/35.7%/ 38.5%/32.3%
Rudlinger [43]	RTR	Verrucae	PCR	1, 2, 4	66%
Meyer [46]	RTR	Verrucae	Degenerate PCR	1, 2, 4	91%
Harwood [54]	RTR	Normal skin	Degenerate/nested PCR	Beta PV	87%
Boxman [17]	RTR	Eyebrow/arm/leg hairs	Degenerate PCR	Beta PV	92%
Hazard [24]	RTR	Skin swabs (healthy skin)	FAP PCR	Beta PV/ gamma PV	71%–92%
Antonsson [65]	RTR	Skin swabs (healthy skin)	FAP PCR	Alpha/ beta/ gamma PV	94%
Meyer [46]	IC	SCC/AK/normal skin	Degenerate PCR	Beta PV	47%/36%/16%
Harwood [54]	IC	Normal skin	Degenerate/nested PCR	Beta PV	35%
Pfister [51]	IC	SCC/AK	Nested PCR	Beta PV	67% (formalin)/ 85% (frozen)
Struijk/Hall [33]	IC	AK/SCC/healthy skin	Type-specific PCR	5, 8, 15, 20, 24, 38	54%/44%/40%
Shamanim [66]	IC	SCC	Degenerate	HPV	
Wieland [52]	IC	BCC	Nested PCR	6, 8, 19, 20, 23, 24, 28, 34, 36, 37, 38	43.5%
Boxman [28]	IC	NMSC/eyebrow hairs	Nested PCR	Beta PV	39%/66%
Boxman [60]	IC	Eyebrow hairs (men/women)	Nnested PCR	Beta PV	49%/44%
Boxman [17]	IC	Eyebrow/arm/leg hairs	degenerate PCR	Beta PV	45%
Struijk [49]	IC	Eyebrow hairs	Type-specific PCR	2, 5, 8, 15, 16, 20, 24, 38	63.1%
de Koning [23]	IC	Eyebrow hairs	PM-PCR/RHA	Beta PV	96%
Termorshuizen [61]	IC	Eyebrow hairs (healthy/SCC)	Type-specific PCR	5, 8, 15, 20, 24, 38	44.8%/60.4%
Antonsson [65]	IC	Skin swabs (healthy skin)	FAP PCR	Alpha/ beta/ gamma PV	80%

RTR, renal transplant recipients; IC, immunocompetent; SCC, squamous cell carcinoma; AK, actinic keratosis; BCC, basal cell carcinoma; PCR, polymerase chain reaction.

Association Between HPV Infection and Skin Cancer

Case-control studies were initiated to investigate the association between markers of HPV infection, in particular, beta-PV infection and NMSC, in immunocompetent individuals.

Molecular Studies (Beta-PV DNA Detection)

In a case-control study performed with 155 immunocompetent individuals with a history of SCC and 371 controls without skin cancer, a statistically significant association was found between the overall prevalence of beta-PV DNA in plucked eyebrow hairs (types 2, 5, 8, 15, 16, 20, 24, and 38) and SCC [49]. The presence of beta-PV DNA was also significantly associated with increasing age and male sex. The odds ratio, adjusted for age and sex, to develop SCC in the presence of HPV DNA in eyebrow hairs was 1.7 [95% confidence interval (CI), 1.1–2.7]. HPV2 and HPV16 were only rarely present in eyebrow hairs in this study and were not associated with SCC. In an English study a significant association was found between the presence of beta-PV DNA in normal skin and NMSC status [odds ratio (OR), 6.41; 95% CI, 1.79–22.9] [54]. Both studies [49,54] showed that the presence of beta-PV DNA is associated with SCC and/or AK in immunocompetent individuals. Another study, also using plucked eyebrow hairs, found a significant association between beta-PV DNA and AK in males, with an odds ratio of 3.4 (95% CI, 1.8–6.5) [33]. For females, no such association was found in this study. Presence of beta-PV DNA was again associated with increasing age [33].

Serological Studies (Beta-PV Antibody Detection)

In a study among 540 immunocompetent cases with a history of skin cancer and 333 controls, seroreactivity to L1 virus-like particles (VLP) of beta-PV types 5, 8, 15, 20, 24, and 38 was measured [32]. Seroreactivity to HPV8 and HPV38 was significantly associated with SCC. The odds ratio (OR) for SCC adjusted for age and sex for HPV8 was 14.7 (95% CI, 1.6–135) and for HPV38, 3.0 (95% CI, 1.1–8.4) [32]. In another large study in immunocompetents, with 252 SCC cases, 525 BCC cases, and 461 controls [34], seroreactivity against L1 of HPV1, -2, -3, -5, -6, -8, -10, -15, -16, -20, -24, -32, -36, -38, and -57 was measured with multiplex Luminex technology [35]. Overall, HPV antibodies were statistically significantly associated with SCC (OR, 1.6; 95% CI, 1.2–2.3). Especially, beta-PV seropositivity was associated with an increased risk of SCC (OR, 1.5; 95% CI, 1.0–2.1) and particularly HPV5 (OR, 1.8; 95% CI, 1.0–3.1). The highest SCC risk was associated with positivity for multiple HPV types [34]. A third case-control study of immunocompetent individuals from Australia correlated HPV seroreactivity to L1 and E6 (HPV5, -8, -15, -16, -20, -24, and -38) and HPV DNA positivity with current AK and SCC [33].

The presence of seroreactivity to betaPV L1 was associated with AK (OR, 2.3; 95% CI, 0.85–4.9) and SCC (OR, 3.9; 95% CI, 1.4–10.7), and the presence of AK was inversely associated with seroreactivity to beta-PV E6 (AK: OR, 0.6; 95% CI, 0.29–3.0; SCC: OR, 0.45; 95% CI, 0.19–1.1). E6 and L1 antibodies were hardly ever found concomitantly, suggesting that antibody responses to the early (nonstructural, intracellular) and late (structural, also extracellular) beta-PV proteins take place at different times and phases during HPV infection or HPV-associated tumor development [33]. HPV DNA positivity and L1 seropositivity were correlated, and E6 seropositivity was inversely correlated with HPV DNA positivity, which might be in line with the hypothesis that E6 antibodies to some extent protect against SCC or that SCC patients have difficulties inducing immune responses to cutaneous HPV E6 proteins [33, 49].

A summary of the retrospective case-control studies available to date has been published recently (Fig. 2). This serological pilot study reported results on the first prospective data looking at the association between the L1 antigens of 38 HPV types and the development of SCC in immunocompetent patients with blood taken before diagnosis. Based on 39 patients with SCC and 80 controls, there was no statistically significant difference in seroprevalence of antibodies against any of the HPV types examined between cases and controls. Seroprevalence for many beta-PV types was higher among cases for whom blood was collected within 1.5 years of diagnosis than in those whom SCC was diagnosed more than 1.5 years after blood collection [55].

Although basal cell carcinomas (BCC) are the most common NMSC, its association with HPV infections in immunosuppressed individuals remains controversial [25, 47, 48]. The relative risk for superficial multifocal and nodular BCC was increased in persons positive for HPV8 (OR, 17.3; 95% CI, 2.1–143; and OR, 9.2; 95% CI, 1.1–78.2) and HPV20 (OR, 3.4; 95% CI, 1.2–9.5; and OR, 3.2; 95% CI, 1.3–7.9) in a study among immunocompetent individuals [32]. In another study, however, HPV seropositivity was not associated with BCC (OR, 0.8; 95% CI, 0.6–1.1) [34]. A third study found no significant association between HPV antibody prevalence of BCC patients and healthy individuals; as well, the serological data did not correlate with special types found in the tumors [52].

Association Between HPV Infection, Skin Cancer, and Sun Exposure

Individuals in subtropical areas have an increased risk of AK and NMSC because the principal causal factor is excessive exposure to solar UV radiation [56–58]. Because HPV is a possible cofactor in the development of AK and SCC, in Queensland, Australia, where reported incidence rates are the highest in the world [59], a number of studies have been performed to investigate the role of HPV in the development of NMSC [28, 33, 60]. A nested case-control study in patients with NMSC (not specified), SCC, or BCC showed a nonsignificant negative association between beta-PV and NMSC (OR, 0.77; 95% CI, 0.34–1.8) and BCC (OR, 0.58; 95% CI, 0.23–1.50) and a nonsignificant positive association between beta-PV and

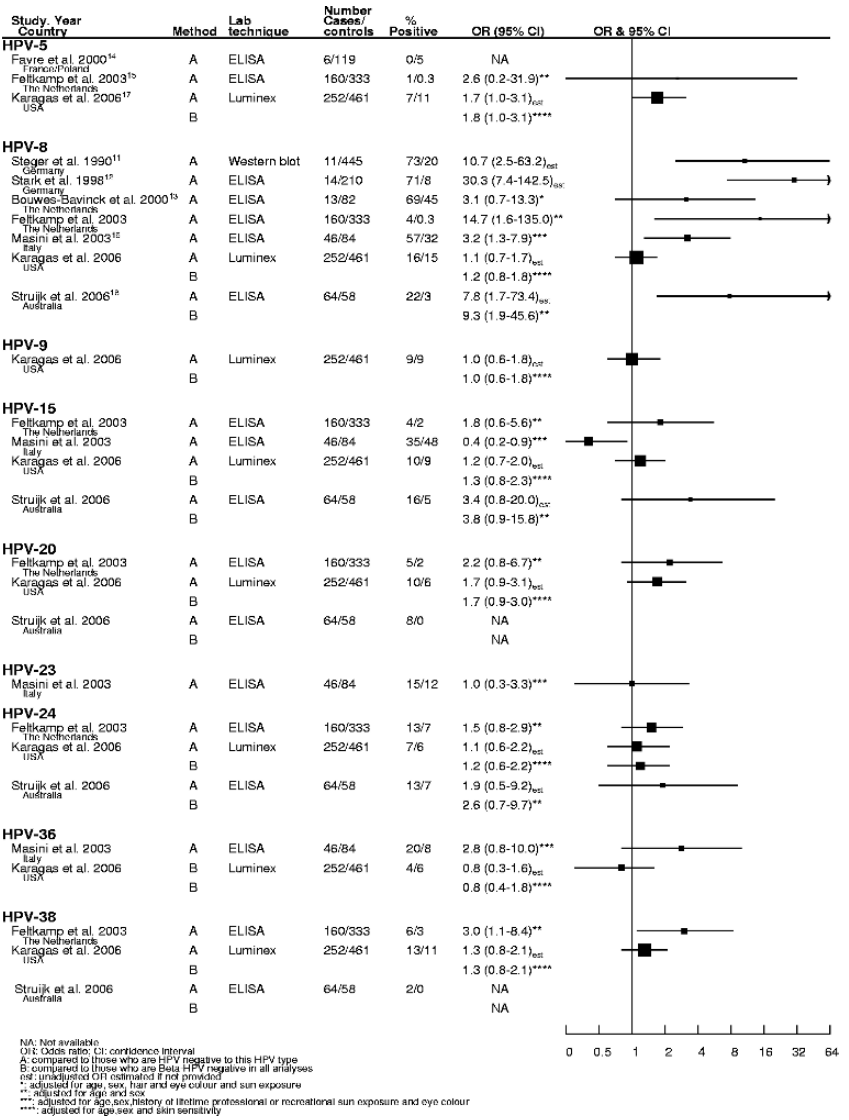

Fig. 2 Studies of cutaneous squamous cell carcinoma in relation to the detection of antibodies against capsid L1 protein of betaPV types. Odds ratio are presented by *squares*, the area of each square being proportional to the amount of statistical information for each study, and 95% CI are indicated by *lines*. Figure reprinted with permission from the publisher from Casabonne et al., Int J Cancer (2007) 121: 1862–68

SCC (OR, 2.00; 95% CI, 0.5–8.0) [28]. In the same population, a cross-sectional study was performed of the eyebrow hairs of individuals with AK [60]. There was a strong association between the presence of beta-PV and higher age and also between AK and higher age. Also, an association was found between male sex and beta-PV

(OR, 3.4; 95% CI, 1.77–6.53). A Dutch case-control study showed an association between sunburn in the past, especially at age 13–20 years, and higher beta-PV positivity [61]. A higher lifetime sun exposure, however, was associated with a lower risk of HPV infection. In the United States, a case-control study showed no significant relationship between HPV seropositivity and age, skin sensitivity, and number of sunburns [34]. However, SCC risk was elevated in beta-PV-positive individuals with a more sun-sensitive phenotype. SCC risk was also increased among those who reported 10 or more sunburns. In addition, an analysis was done to elaborate the possible joint effect of HPV and UV. The analysis, nested in an SCC case-control study in Queensland [33], showed that the combined effect of beta-PV seropositivity and presence of a susceptible phenotype or high lifetime sun exposure resulted in a greater risk of SCC than either risk factor alone [50].

Discussion

A role of beta-PV in the development of skin cancer has been proposed, and epidemiological evidence, as summarized in this chapter, was found in both immunocompetent and immunosuppressed individuals. The role that beta-PV potentially play in skin carcinogenesis, however, is far from clear, and seems to differ from known high-risk mucosal HPV types on essential points. So far, the beta-PV prevalence studies have not identified potentially high-risk beta-PV types in analogy to HPV16 and -18 in cervical cancer, although SCC case-control studies have suggested that HPV5, -8, and -38 are high-risk beta-PV types.

Further discrepancy between mucosal and potentially cutaneous high-risk HPV types lies in the viral load present in the tumors. In SCC, beta-PV DNA is found in approximately 1:100 cells [62]. This finding contrasts with the situation in cervical cancer, where high-risk HPV DNA is generally found integrated in the genome of every cancer cell. Apparently beta-PV are dispensable when it comes to maintenance of the transformed state of the cancer cells, and more likely play a role early in the carcinogenesis; this was also suggested by observations demonstrating that both the prevalence and the load of beta-PV are higher in early premalignant lesions such as actinic keratosis compared to malignant lesions [51, 62, 63]. Taken together, the role of HPV in skin carcinogenesis could be more important for tumor initiation than for tumor progression. Most experimental studies that investigated beta-PV-mediated cell transformation seem to support this notion. They indicated the ability of some beta-PV types to inhibit UVB apoptosis, which could be considered an early event in carcinogenesis, and the inability to inactivate the tumor suppressor proteins p53 and pRb, which can be considered important for transformation maintenance.

To summarize, the role of beta-PV in skin carcinogenesis is not understood yet. Exposure to UV radiation is the most important risk factor for the development of NMSC, and HPV infection might act as a cofactor in this regard. Recent epidemiological [34,50] as well as experimental studies [64] argue in favor of this hypothesis,

suggesting a possible synergetic effect between HPV infection and UV radiation in carcinogenesis of the skin.

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