Human Papillomavirus Load in Eyebrow Hair Follicles and Risk of Cutaneous Squamous Cell Carcinoma

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Abstract

Background: Beta-human papillomavirus (betaPV) may play a role in the development of cutaneous squamous cell carcinoma (SCC). However betaPV is highly prevalent, and it may only be people with a higher viral load who have increased risk of SCCs. We therefore examined the association between betaPV load and SCCs.

Methods: We recruited 448 immunocompetent cases with SCCs and 464 controls from Italy and Australia and 497 immunosuppressed organ transplant recipients (OTR; 179 cases and 318 controls) from Europe. We used reverse hybridization to genotype 25 betaPV types in eyebrow hair follicles and determined the viral load for eight selected types using quantitative PCR. We used logistic regression to assess associations between type-specific and cumulative viral load and SCCs.

Results: Australian and OTR participants in the highest cumulative load tertile were at significantly higher risk of SCCs than those in the lowest tertile. Those with more than four betaPV types in the high load tertile were at approximately three-fold increased risk of SCCs. In Australia, HPV23 and 36 loads were significantly associated with SCCs, with borderline associations for HPV5 and 38. In OTR, HPV8 and 36 loads were significantly associated and HPV20 and 36 were borderline. We found little evidence for an association between load and SCCs in Italy.

Conclusions: High viral load may be associated with risk of cutaneous SCCs, with total load seemingly more important than the load of any specific type.

Impact: Our findings lend weight to the hypothesis that HPV plays a role in skin carcinogenesis.

Introduction

Keratinocytic cancers, predominantly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most frequently occurring cancers in Caucasians. The primary environmental cause of both BCCs and SCCs is exposure of the skin to solar ultraviolet radiation. However evidence is accumulating to suggest that infection with human papillomaviruses (HPV), particularly those of the beta genus (betaPV), may play a synergistic role (1). This is particularly apparent in patients with a rare genetic disorder that predisposes to high viral load betaPV infection, epidermodysplasia verruciformis, where 2 beta types, HPV5 and 8, have been classified by the International Agency for Research on Cancer as possibly carcinogenic (2). Patients who are immunosuppressed following organ transplantation are also at substantially increased risk of keratinocyte cancers, particularly SCCs (3), suggesting the involvement of an infectious agent in people without epidermodysplasia verruciformis.

The bulge area of the outer root sheath of the hair follicle has been suggested as a reservoir for cutaneous HPV, and comparative studies have shown reasonable concordance in prevalence and type multiplicity between eyebrow hair follicles and normal skin, hair follicles from other body sites, perilesional skin, and actual skin lesions (4, 5). Viral DNA in hair follicles has thus been used as an indicator of cutaneous infection in a number of epidemiologic studies.
In our multicentre case–control study in immunocompetent populations, the presence of betaPV DNA in hair follicles was associated with a significant 3-fold increased risk of SCCs in the Netherlands but no significant overall association in Australia or Italy (6). In our study, in people who had been organ transplanted, there was a nonsignificant 2-fold increase in risk in people with evidence of betaPV infection in hair follicles (7). Earlier studies using older laboratory techniques were largely supportive of an association, although the data were somewhat inconsistent (8–10).

The challenge in identifying causal associations between HPV and skin disease is that it appears to be part of the commensal flora of the skin. In our recent studies more than 90% of both organ transplant recipients (OTR) and immunocompetent people were betaPV-positive (6, 7, 11). Finding markers of increased viral activity may help to elucidate the role of HPV in cutaneous carcinogenesis. HPV antibodies, present in about half of those who have evidence of eyebrow hair infection, have been associated with SCC risk in several case–control studies (12–16), possibly indicating the presence of more active virus. However, it is also possible that presence of skin cancer causes the generation of HPV antibodies and that reverse causality is responsible for this finding (17). An attempt to highlight biologically relevant betaPV infections by looking for betaPV DNA and antibody directed against the same type identified a significant association between SCCs and the concordant detection of antibodies and DNA for at least one betaPV type but no association with antibodies without concordant DNA (7). Similarly, a recent study found several type-specific associations between antibodies and SCCs in people who were DNA-positive for the same HPV type in tumor tissue but not in those whose tumor was DNA-negative (18).

Another possible indicator of increased viral activity is the betaPV DNA load. Exceptionally high loads of up to more than 400 viral DNA copies per cell were detected in eyebrow hair follicles of patients with epidermodysplasia verruciformis, who have a high risk of SCC development (19). The viral loads in eyebrow hair follicles from the general population and from OTR span 7 orders of magnitude and are mostly extremely low but OTR are more likely to have higher loads (20). This is consistent with a hypothesis that higher viral DNA loads may indicate an enhanced activity of betaPV, contributing to the strongly enhanced risk of SCC development seen in this patient group. However, the association between viral load and skin cancer has not been formally evaluated.

To explore the role of viral load in skin cancer development, we used a case–control study design to determine the association between the load of 8 different betaPV types and risk of SCCs in immunocompetent and immunosuppressed people from different geographical locations. The 8 types were selected because they are relatively prevalent in hair bulbs (11) and have been implicated in skin malignancies in patients with epidermodysplasia verruciformis (HPV5, 8, 20; ref. 21) in some previous epidemiology studies (HPV8, 36, 38; refs. 7, 13) and in studies of transgenic mice (HPV8, 38; refs. 22, 23).

Materials and Methods

Study participants

Immunocompetent participants. Selection and characteristics of participants have been reported previously (6). The immunocompetent participants (ICP) included in this study were recruited from Queensland, Australia and Rome, Italy. In Australia, cases were recruited from primary care skin cancer clinics and controls from several sources (150 from the federal electoral roll on which enrolment is compulsory; 75 from primary care skin screening clinics or dermatology clinics and 85 from community-based volunteer groups). In Italy, both cases and controls were recruited from the outpatient dermatology department of a major hospital in Rome. However, only 27 controls had a dermatological condition (actinic keratoses, psoriasis, seborrheic warts) with the potential to influence betaPV positivity or load, with the majority having conditions such as lipoma, cysts, and other problems requiring minor surgical procedures. In both countries, cases had a histologically-confirmed incident cutaneous SCC and controls, who were matched to the cases by sex and age in 5-year age groups, had no history of squamous cell carcinoma.

Organ transplant recipients. The selection processes have been reported previously (7). Cases had a history of histologically-confirmed posttransplant primary cutaneous SCCs (excluding in situ carcinoma) and were recruited from outpatient dermatology and transplant clinics in the Netherlands, the United Kingdom, France and Italy. Controls had no history of skin cancer and were selected from the same clinics. We attempted to match controls to cases by sex, age, and time since transplantation (2–7, 8–12, 13–17, 18–22, 23, and more years) in a 2:1 ratio. Patients with brown or black skin (Fitzpatrick skin type V and VI) were excluded, as were patients with only liver, lung, and pancreas transplants.

All studies had local human research ethics approval.

Data and sample collection

All participants completed a questionnaire in which information was elicited about skin type, hair and eye color, sun exposure on weekends and weekdays, sunburns, smoking, education, and alcohol consumption. Medical charts of OTR were reviewed to document the timing and number of transplants and immunosuppressive medications used.

Eight to 10 eyebrow hairs were plucked from each participant and snap-frozen in liquid nitrogen. They were stored at −80°C until analysis.

DNA extraction, HPV typing, and quantitative PCR

DNA from plucked eyebrow hair samples was isolated with the Qiamp DNA Mini Kit (Qiaegen; ref. 24). The presence or absence of individual betaPV types was determined with the skin (beta) PV prototype research...
HPV Load and Risk of Cutaneous Squamous Cell Carcinoma

We classified participants first according to the presence or absence of DNA of each of the 8 specific HPV types tested and for positivity to at least one of these types. For each type and for cumulative viral load, we then divided those positive into tertiles, using the viral load distribution of cases and controls combined for each study group to identify the tertile cutoff points. For each participant, we calculated the number of types, where the viral load was in the highest tertile.

We compared the continuous viral load distributions of cases and controls for those HPV DNA-positive using Wilcoxon 2-sample tests. Participants who were completely negative for HPV DNA were not included in these analyses. For each type less than 1% of people who were positive using the Diassay BV were negative on quantitative PCR. These were also excluded from these continuous analyses. Cumulatively, 0.2% of people who were positive for at least one of the 8 types were load-negative.

Demographic characteristics of cases and controls, stratified by study group, are shown in Table 1. In all 3 groups, cases were more likely to have fair skin than controls. The matching by age and sex was successful in the Australian population, with only small differences in the distribution of cases and controls. In the Italian and the OTR datasets, the cases were somewhat older than controls. The matching by age and sex was successful in both cases and controls in the included sample than in the entire study population, but there was no difference in the mean age.

Statistical methods

We recruited 1,705 participants and included a total of 1,394 participants (82%) who had adequate cellular input in this analysis, 627 cases (232 ICP from Australia, 216 ICP from Italy, and 179 OTR) and 782 controls (241 ICP from Australia, 223 ICP from Italy, and 318 OTR). The proportion of men was 4% higher in both cases and controls in the included sample than in the entire study population, but there was no difference in the mean age.

Demographic characteristics of cases and controls, stratified by study group, are shown in Table 1. In all 3 groups, cases were more likely to have fair skin than controls. The matching by age and sex was successful in the Australian population, with only small differences in the distribution of cases and controls. In the Italian and the OTR datasets, the cases were somewhat older than controls (although this was statistically nonsignificant in Italy) and had a higher proportion of men (0.05 < P < 0.1).

The proportion of participants positive for at least one of the 8 HPV types tested for viral load ranged from 83% in Australian controls to 93% in Italian and OTR cases (Table 2). In all 3 groups, the proportion positive was higher in cases than in controls, although none of these differences was statistically significant. The prevalence of each individual HPV type is shown in Table 2. Although we observed few significant differences between cases and controls, in most cases, the prevalence was slightly higher in cases than in controls. We found a positive association between the number of HPV types positive and SCCs in Australia and OTR, although in OTR, those positive to 4 types did not follow the trend of increasing risk with increasing number of types (Table 3). For each additional type, there was approximately a 13% increased risk of SCCs (P < 0.05 for both groups). There was no apparent trend in Italy. The associations identified were almost identical when we included participants with low cellular input in the analyses (data not shown).
The median viral load of the selected 8 HPV types, cumulatively and for individual HPV types, was substantially less than one copy per cell (Fig. 1). In Australia, the median load was higher in cases than in controls for most types, but with P values greater than 0.05 (Fig. 1A). The median cumulative load was significantly higher in cases than in controls (Wilcoxon 2-sample test, \( P = 0.008 \)). A similar pattern was observed for OTR, with significant differences in the distribution for HPV8 (\( P = 0.02 \)) and cumulative load (\( P = 0.005 \); Fig. 1C). There were no significant differences between cases and controls for any type or for cumulative load in Italian participants (Fig. 1B).

### Table 1. Demographic and skin type characteristics of cases and controls in each of the three study groups

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th></th>
<th>Italy</th>
<th></th>
<th>OTR</th>
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<tr>
<td></td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
</tr>
<tr>
<td></td>
<td>( N = 241 )</td>
<td>( N = 232 )</td>
<td>( N = 223 )</td>
<td>( N = 216 )</td>
<td>( N = 318 )</td>
<td>( N = 179 )</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>186 (77)</td>
<td>188 (81)</td>
<td>146 (65)</td>
<td>159 (74)</td>
<td>232 (73)</td>
<td>143 (80)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (23)</td>
<td>44 (19)</td>
<td>77 (35)</td>
<td>57 (26)</td>
<td>86 (27)</td>
<td>36 (20)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.30</td>
<td>0.06</td>
<td>0.08</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age (mean, range)</td>
<td>65 (37–96)</td>
<td>66 (31–91)</td>
<td>68 (31–90)</td>
<td>71 (34–95)</td>
<td>53 (23–77)</td>
<td>61 (34–80)</td>
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<tr>
<td>Age group, y</td>
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<tr>
<td>&lt;50</td>
<td>25 (10)</td>
<td>18 (8)</td>
<td>13 (6)</td>
<td>11 (5)</td>
<td>109 (34)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>50–59</td>
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<td>45 (19)</td>
<td>23 (10)</td>
<td>18 (8)</td>
<td>114 (36)</td>
<td>55 (31)</td>
</tr>
<tr>
<td>60–69</td>
<td>79 (33)</td>
<td>80 (34)</td>
<td>74 (33)</td>
<td>63 (29)</td>
<td>79 (25)</td>
<td>75 (42)</td>
</tr>
<tr>
<td>70+</td>
<td>86 (37)</td>
<td>89 (38)</td>
<td>113 (51)</td>
<td>124 (57)</td>
<td>16 (6)</td>
<td>24 (13)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.76</td>
<td>0.56</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Education</td>
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<tr>
<td>High school or less</td>
<td>107 (45)</td>
<td>119 (51)</td>
<td>146 (65)</td>
<td>144 (67)</td>
<td>163 (51)</td>
<td>106 (59)</td>
</tr>
<tr>
<td>Technical college</td>
<td>79 (33)</td>
<td>88 (38)</td>
<td>13 (6)</td>
<td>3 (1)</td>
<td>79 (25)</td>
<td>35 (20)</td>
</tr>
<tr>
<td>University degree</td>
<td>53 (22)</td>
<td>25 (11)</td>
<td>64 (29)</td>
<td>69 (32)</td>
<td>76 (24)</td>
<td>38 (21)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.004</td>
<td>0.04</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin phototype</td>
<td></td>
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<tr>
<td>Olive</td>
<td>82 (34)</td>
<td>52 (22)</td>
<td>118 (53)</td>
<td>71 (33)</td>
<td>157 (49)</td>
<td>70 (39)</td>
</tr>
<tr>
<td>Medium</td>
<td>139 (58)</td>
<td>129 (56)</td>
<td>96 (43)</td>
<td>140 (65)</td>
<td>110 (36)</td>
<td>78 (44)</td>
</tr>
<tr>
<td>Fair</td>
<td>19 (8)</td>
<td>51 (22)</td>
<td>9 (4)</td>
<td>5 (2)</td>
<td>51 (16)</td>
<td>31 (17)</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.07</td>
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</tbody>
</table>

The median viral load of the selected 8 HPV types, cumulatively and for individual HPV types, was substantially less than one copy per cell (Fig. 1). In Australia, the median load was higher in cases than in controls for most types, but with \( P \) values greater than 0.05 (Fig. 1A). The median cumulative load was significantly higher in cases than in controls (Wilcoxon 2-sample test, \( P = 0.008 \)). A similar pattern was observed for OTR, with significant differences in the distribution for HPV8 (\( P = 0.02 \)) and cumulative load (\( P = 0.005 \); Fig. 1C). There were no significant differences between cases and controls for any type or for cumulative load in Italian participants (Fig. 1B).

### Table 2. Proportion positive [\( n \) (%)] and ORs describing associations between HPV positivity and cutaneous SCCs

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
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<th>Italy</th>
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<th>OTR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
</tr>
<tr>
<td></td>
<td>( N = 241 )</td>
<td>( N = 232 )</td>
<td>( N = 223 )</td>
<td>( N = 216 )</td>
<td>( N = 318 )</td>
<td>( N = 179 )</td>
</tr>
<tr>
<td>HPV pos ( a )</td>
<td>201 (83)</td>
<td>203 (88)</td>
<td>199 (89)</td>
<td>198 (93)</td>
<td>286 (90)</td>
<td>167 (93)</td>
</tr>
<tr>
<td>HPV5 pos</td>
<td>45 (19)</td>
<td>62 (27)</td>
<td>85 (38)</td>
<td>79 (36)</td>
<td>104 (33)</td>
<td>66 (37)</td>
</tr>
<tr>
<td>HPV8 pos</td>
<td>53 (22)</td>
<td>54 (23)</td>
<td>87 (39)</td>
<td>77 (36)</td>
<td>82 (26)</td>
<td>60 (34)</td>
</tr>
<tr>
<td>HPV15 pos</td>
<td>87 (36)</td>
<td>98 (42)</td>
<td>70 (31)</td>
<td>85 (39)</td>
<td>143 (45)</td>
<td>93 (52)</td>
</tr>
<tr>
<td>HPV20 pos</td>
<td>48 (20)</td>
<td>55 (24)</td>
<td>48 (22)</td>
<td>65 (30)</td>
<td>65 (20)</td>
<td>45 (25)</td>
</tr>
<tr>
<td>HPV23 pos</td>
<td>99 (41)</td>
<td>105 (45)</td>
<td>124 (56)</td>
<td>120 (56)</td>
<td>112 (35)</td>
<td>83 (46)</td>
</tr>
<tr>
<td>HPV24 pos</td>
<td>63 (26)</td>
<td>64 (28)</td>
<td>106 (48)</td>
<td>107 (50)</td>
<td>121 (38)</td>
<td>82 (46)</td>
</tr>
<tr>
<td>HPV36 pos</td>
<td>78 (32)</td>
<td>93 (40)</td>
<td>98 (44)</td>
<td>114 (53)</td>
<td>124 (39)</td>
<td>87 (49)</td>
</tr>
<tr>
<td>HPV38 pos</td>
<td>72 (30)</td>
<td>72 (31)</td>
<td>58 (26)</td>
<td>62 (29)</td>
<td>1.55 (1.00–2.98)</td>
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</tbody>
</table>

**NOTE:** Bolded values are significant at \( P < 0.05 \).

\( a \) Positive to at least one of the 8 types tested for viral load.

\( b \) The reference category is HPV-negative in each case.
The analyses of viral load tertiles are displayed in Fig. 2. We have also displayed ORs for type-specific HPV positivity for comparison purposes. We did not observe consistently increasing risk with increasing viral load in any group. However, in Australia, those in the highest load tertile for HPV23 and 36 were at significantly higher risk than participants negative for each type, respectively, and there were marginally significant associations for HPV5 and 38. There was a significant positive association for those in medium and high cumulative load tertiles (compared with those in the low tertile combined with those negative as the reference group). The associations in OTR were similar to those in Australia, with significant associations for the highest load tertiles of HPV8, 38 and cumulative load (Fig. 2B). For those types where load was associated with SCCs, the risk was higher than that observed for simply being positive. For cumulative load, the patterns observed were similar when we stratified by skin color (Supplementary Table). In OTR, the effect seemed to be stronger in people who had been transplanted less than 13 years ago than in those who had been transplanted for longer, but this difference was not significant (Supplementary Table).

Only a small proportion of participants had more than 4 types in the highest load tertile, but Australian and OTR participants in this category were at approximately 3-fold increased risk of SCCs (Table 3). There was a trend of increasing risk with increasing number of types with high load, which was particularly noticeable in OTR.

### Discussion

This case–control study focused on 8 betaPV types for which there is evidence of potential involvement in the development of skin malignancies. In OTR and Australian ICPs, the presence of high cumulative viral load was associated with increased risk of SCCs.

We have previously reported the prevalence of positivity to at least one of 25 betaPV types (11). In all participants, including those with beta-globin input of less than 400 copies/2 μL DNA, the proportion positive ranged from 90% to 94% across the 3 groups. Restricting the population to those with higher cellular input, the proportion positive to 1 of the 25 types ranged from 89% to 94%. As the 8 types selected for viral load analysis are the most frequently occurring, this was only slightly higher than overall positivity to one of these 8 types, which ranged from 83% to 90%.

The overall prevalence was slightly but not significantly higher in cases than in controls in all groups. This was also true for most individual types, but no one type was consistently significantly associated with increased risk in all groups, suggesting that overall betaPV burden may be more important than infection with any specific type. In contrast to our earlier studies of 25 betaPV types, we found a significantly positive association...
between the number of selected types of betaPV detected and SCC risk in Australia and OTR but again not in Italy.

As observed before in controls (20), the viral loads in hair bulbs of cases spanned 7 orders of magnitude. The median loads for all types were below one viral DNA copy per 10 cells and usually did not differ significantly between cases and controls. The median cumulative load was significantly higher in cases than in controls in Australia and OTR but not in Italy. However, a comparison based on median load may not reflect the risk in the small number of people who have a much higher viral load. Low DNA loads probably reflect the commensal betaPV flora of the skin and have a negligible impact on skin cancer risk. When we grouped the viral loads into tertiles, we found a significantly higher risk of SCCs for those in the high cumulative load tertile both in ICPs from Australia and in immunosuppressed OTR. Australian and OTR participants with more than 4 HPV types in the high load tertile were at about a 3-fold increased risk of SCCs. Unfortunately, the sample size was too small to enable an analysis of the number of types in the highest load tertile independently of the number of types positive, but these results do suggest that the burden of HPV, possibly as a combination of the number of types positive and the load, is associated with risk of SCCs.
In analyses of type-specific viral loads, no particular type stood out as being consistently associated with risk of SCCs. In Australia, being in the highest load tertile for types HPV23 and 36 was significantly associated with risk of SCCs, with borderline associations for HPV5 and 38. In OTR, HPV8 and 38 were significantly associated and HPV20 and 36 were borderline. However, the high rate of co-infection makes it difficult to assess independent effects, and comparative laboratory studies are likely to be more informative. Viral DNA loads within the top decile are comparable with loads in patients with epidermodysplasia verruciformis highly predisposed to SCC development (19). An analysis of the proportion of cases and controls in the top load decile might reveal stronger associations, but the numbers are too small to enable a robust analysis.

We previously reported associations between antibody positivity and SCCs for Australia (6), and for OTR in the presence of concordant DNA positivity (7) but no association for Italy (6). A type-specific evaluation of these data shows significant associations for all 8 types except HPV23 in Australia and for HPV5 and 38 in OTR, with ORs between 1.5 and 2.0. Thus, there is little overlap in the types where associations were seen for antibodies and the types with associations for viral load. This may be due to the fact that it is total HPV burden rather than infection with a specific type that is more important or because a detectable seroreponse is not only dependent on the viral load but also on additional signals such as inflammation.

While the results from Australia and the OTR provide evidence for an association between viral load and cutaneous SCCs, results from Italy were largely null. We are unsure of the reasons for this. The source of controls varied according to centre, with all Italian controls being hospital-based and only a proportion of Australian controls being clinic-based. However, this is unlikely to explain the difference. We compared the overall prevalence and viral load of the Australian clinic-based controls with that of the non–clinic-based controls and found no difference (both \( P > 0.6 \)). Similarly, excluding the 27 Italian controls who presented specifically with dermatological conditions did not alter the results. While there were differences in the study groups according to sun exposure and skin type, adjustment for these factors made no difference to the results and stratifying by skin type did not reveal significantly different patterns. OTR controls were significantly younger than cases, which may have introduced bias despite adjustment in the analysis. However, we have previously shown no association between age and viral load in OTR, and the OTR results are supported by the Australian ICP results where age matching was successful.

Assuming that the findings from Australia and OTR are not due to chance or bias, the following explanations for the association should be considered. It is possible that skin cancer and high viral load independently have a common etiology, possibly UVR-induced immune suppression. However, the association may also point to an effect of viral load on cellular transformation. This
explanation is supported by data from HPV8 transgenic mice. Homozygous HPV8-E2 transgenic animals all spontaneously developed flat or polypous skin tumors during their first year of life in contrast to heterozygous mice (with half the viral DNA load and half viral mRNA levels), where only about 60% developed skin tumors in their second year of life (28).

This is the first time that the association between viral load and risk of cutaneous SCCs has been described. As no one particular type seems to be particularly oncogenic, it may be that total HPV burden is the most important etiologic factor. Our findings lend weight to the hypothesis that HPV plays a role in cellular transformation of human skin.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions


Writing, review, and/or revision of the manuscript: R.E. Neale, S. Weissenborn, A.C. Green, M. de Koning, T. Waterboer, U. Wieland, H. Pfister.

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.N.B. Bavinck, M. de Koning, U. Wieland.


References
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