Cutaneous Human Papillomaviruses and squamous cell carcinoma of the skin: Nested case-control study

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Abstract

Background Cutaneous Human Papillomavirus (HPV) types have been associated with non-melanoma skin cancer (NMSC), including a previous nested case-control study using HPV serology with bacterially derived fusion proteins with the major HPV capsid protein L1 (GST-L1). However, HPV serology using conformationally intact pseudovirions has been shown to correlate better with natural infection. Prospective studies using a more valid marker of infection are therefore warranted.

Methods Cancer registry follow-up of large Nordic biobanks identified prediagnostic serum samples from 633 subjects who later developed SCC, 1990 subjects who developed BCC. The samples from cases and matched controls were tested for IgG to pseudovirions to 16 different HPV types (3**, 5**, 6, 11, **15**, 16, 18, 31, 32, 33, **38**, 45, 52, 58, 68 and **76**) and two polyomaviruses (MCPyV and JCPyV).

Results Baseline seropositivity was not associated with SCC risk and there were only weak associations with BCC risk (HPV-5 (OR=1.1 95%CI 1.0-1.3), HPV-15 (OR=1.2 95%CI 1.0-1.4), HPV-38 (OR=1.2 95%CI 1.0-1.3) and MCPyV (OR=1.1 95%CI 1.0-1.3)). Acquisition of HPV-5 seropositivity during follow-up was associated with SCC risk (OR=3.2 95%CI 1.3-7.6). Persistent seropositivity for HPV-15 was weakly associated with BCC (OR=1.4 95%CI 1.0-1.9) and HPV-6 antibody persistence was weakly associated with SCC (OR= 2.2 95% CI 1.0-4.8).

Conclusion Considering the large number of viruses tested, the weak associations found do not support any strong links between studied HPV and NMSC, with the possible exception of HPV-5 seroconversion and SCC.

Impact Known alpha and beta papillomaviruses do not appear to be risk factors for NMSC.

Introduction

Immunosuppression greatly raises the risk for non-melanoma skin cancer. Activation of oncogenic skin viruses has been proposed as a possible explanation. Cutaneous papillomaviruses infect healthy skin and are found in skin lesions such as actinic keratosis (AK) and squamous cell carcinoma of the skin (SCC) (1). Prospective HPV seroepidemiology has been instrumental in providing prospective evidence supporting the causal association between HPV and cervical, anogenital and oropharyngeal cancers (2).

Previously, we reported weak associations between HPV types 3, 15, 38 and 76 and future risk of SCC (3). The previous study was carried out using an HPV serological method (GST-L1 fusion proteins) that has only weak association with HPV infection (4). Using a conformational HPV antigen (pseudovirions), HPV serology shows a better correlation to HPV infection (4). To use the improved HPV serology for a large prospective study is therefore likely to be more informative regarding any possible role of HPV in skin cancer.

Materials and methods

Cohorts and study design

The cohorts and the study design are previously described (3). One matched control was selected for each case. We could include 633 SCC cases with 3115 samples and 1990 BCC cases with 6145 samples and the same numbers of controls. In the serial-samples analysis, there were 531 BCC and 256 SCC cases (and the same numbers of controls) that had at least 2 pre-diagnostic samples,

HPV serology using Pseudovirions

Serology was performed as described (5). Pseudovirions of HPV 3, **5**, 6, 11, **15**, 16, 18, 31, 32, 33, **38,** 45, 52, 58, 68, **76** and Human polyomaviruses Merkel Cell polyomavirus (MCPyV)

and JC polyomaviruses (JCPyV) were included(4). Cut-off values to define seropositivity were calculated independently for each HPV type by analysing the mean fluorescence intensity unit (MFI) values obtained from 141 childrens' sera (average 4 years old). The cut-off algorithm recommended by the global HPV LabNet (6) (mean MFI value of a negative control serum panel plus 3 standard deviations) was used, except that the cut-off had to be at least 250 MFI.

Statistics

Relative risks were estimated as odds ratios and 95% confidence intervals by means of conditional logistic regression with SAS 9.4 software (SAS Institute, Inc., Cary, NC). If the asymptotic model did not converge, median unbiased estimates of ORs were estimated by exact conditional logistic regression. Heterogeneity in the OR estimates was assessed with a likelihood ratio test.

Results

Seropositivity at baseline showed no association to future risk for SCC for any of the tested viruses and only weak association to BCC for HPV-5 (OR=1.1 95%CI 1.0-1.3), HPV-15 (OR=1.2 95%CI 1.0-1.4), HPV-38 (OR=1.1 95%CI 1.0-1.3) and MCPyV (OR=1.1 95%CI 1.0-1.3) (Table 1.). All beta-2 HPV types together had a weak association with future BCC (OR=1.2 95%CI 1.1-1.4) (Table 1.). In analyses restricted to multiple samples, HPV3 and the alpha-7 HPV group had weak associations with SCC at baseline (OR=1.8 95 % CI 1.0-3.1 and OR=2.2 95 % CI 1.0-4.9 respectively) (Table 2a.). HPV-5 associated with SCC, if seropositivity was acquired during follow-up (OR=3.2 95%CI 1.3-7.6) (Table2a). Persistent HPV-6 seropositivity was weakly associated with SCC (OR= 2.2 95% CI 1.0-4.8) (Table2a) and persistent seropositivity to HPV-15 and the HPV beta-2 group was weakly associated

with BCC risk (OR=1.4 95%CI 1.0-1.9) and (OR=1.4 95%CI 1.1-2.0), respectively) (Table 2b).

Discussion

We report a large, prospective HPV serological study with improved methodology to assess possible associations between HPV infections and future non-melanoma skin-cancer, as has been reported previously (3). In the present study, we found exactly the same result for HPV-15 and the HPV beta-2 group as in the previous study regarding association with BCC development if seropositive at baseline and for HPV-15 if persistently seropositive. The previously reported associations between HPV-3, 38, 76 or the beta-2 group and SCC (3) were not found in the present study.

All statistically significant associations were very weak and, considering the large number of viruses analysed, might thus be attributable to chance. The strongest association was seen for acquired HPV-5 seropositivity and future SCC risk. In 2012, IARC classified HPV-5 as having "limited evidence" for carcinogenicity, mostly based on data from the *epidermodysplasia verruciformis* disease (7). We find that HPV-5 may be involved in skin SCC, also in the general population.

A majority of studied HPV types were genital/mucosal and were included as negative controls. Persistent seropositivity for HPV-6 was weakly associated with future SCC, most likely attributed to chance. As we only studied four different HPV types in the beta group, we cannot conclude that all cutaneous HPV are harmless. For example, a recently discovered HPV type (HPV-197) has been reported in a rather large proportion of SCC (8). Continued

analysis of possible association between cutaneous HPV and skin cancer, using extended panels with additional pseudovirions from new HPV types may be warranted.

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Tables

Table 1. Seropositivity at baseline among cases and risk for non-melanoma skin.

HPV type (genus, species)	SCC N pos (%)	SCC OR* (95% CI)	BCC N (%)	BCC OR† (95% CI)
32 (α1)	27 (4.3)	1.2 (0.7, 2.2)	80 (4.0)	0.8 (0.6,1.1)
3 (α2)	85 (13.4)	1.3 (0.9,1.8)	272 (13.7)	1.0 (0.9,1,2)
18 (α7)	29 (4.6)	1.2 (0.7,2.2)	119 (6.0)	1.0 (0.8,1.3)
45 (α7)	16 (2.5)	0.8 (0.4,1.6)	76 (3.8)	1.3 (0.9,1.8)
68 (α7)	23 (3.6)	1.1 (0.6,2.0)	85 (4.3)	0.9 (0.6,1.1)
16 (α9)	54 (8.5)	1.1 (0.8,1.7)	252 (12.7)	1.1 (0.9,1.4)
31 (α9)	29 (4.6)	0.9 (0.5, 1.6)	136 (6.8)	1.0 (0.8,1.3)
33 (α9)	17 (2.7)	1.1 (0.6, 2.3)	76 (3.8)	1.0 (0.8,1.5)
52 (α9)	7 (1.1)	0.9 (0.3,2.4)	45 (2.3)	1.1 (0.7,1.7)
58 (α9)	47 (7.4)	1.4 (0.9,2.1)	153 (7.7)	1.1 (0.9,1.4)
6 (α10)	57 (9.0)	1.1 (0.8,1.7)	247 (12.4)	1.0 (0.8,1.2)
11 (α10)	26 (4.1)	1.4 (0.8,2.6)	117 (5.9)	1.1 (0.9,1.5)
5 (β1)	170 (26.9)	1.1 (0.9,1.4)	458 (23.0)	1.1 (1.0,1.3)
15 (β2)	143 (22.6)	1.1 (0.8,1.4)	468 (23.5)	1.2 (1.0,1.4) ‡
38 (β2)	145 (22.9)	1.1 (0.8, 1.4)	412 (20.7)	1.1 (1.0,1.3)
76 (β3)	108 (17.1)	1.3 (0.9, 1.7)	276 (13.9)	0.9 (0.7,1.1)
MCPyV	460 (72.7)	0.9 (0.7,1.2)	1437 (72.2)	1.1 (1.0,1.3)
JCPyV	450 (71.1)	1.1 (0.9,1.5)	1530 (76.9)	1.0 (0.8,1.1)
Any α7 type	53 (8.4)	1.2 (0.8, 1.8)	227 (11.4)	1.0 (0.8,1.2)
Any α9 type	110 (17.4)	1.3 (0.9,1.7)	432 (21.7)	1.1 (0.9,1.3)
Any α10 type	68 (10.7)	1.2 (0.9, 1.8)	299 (15.0)	1.1 (0.9,1.3)
Any β2 type	189 (29.9)	1.1 (0.9, 1.4)	602 (30.3)	1.2 (1.1, 1.4) ‡

* Unadjusted ORs for 633 SCC cases and 633 controls.
† Unadjusted ORs for 1990 BCC cases and 1990 controls.
‡ $p<0.05$.
** $p<0.01$.

Table 2. Seropositivity among cases and risk for a) SCC or b) BCC for individuals with at least two samples[‡].

a)

SCC (N=256) HPV type (genus, species)	**1st sample N pos[§] (%)**	**1st sample OR[**] (95% CI)**	**-/- [††] N (%)**	**-/- Ref.**	**-/+ N (%)**	**-/+ OR[††] (95% CI)**	**+/- N (%)**	**+/- OR[††] (95% CI)**	**+/+ N (%)**	**+/+ OR[††] (95% CI)**
32 (α1)	11 (4.3)	2.0 (0.7,5.9)	243 (94.9)	1.0	2 (0.8)	2.0 (0.2,22)	2 (0.8)	1.0 (0.1,7.1)	9 (3.5)	2.7 (0.7,10.1)
3 (α2)	36 (14.1)	1.8 (1.0,3.1)[*]	211 (82.4)	1.0	9 (3.5)	2.3 (0.7,7.6)	8 (3.1)	4.2 (0.9,20)	28 (10.9)	1.6 (0.9,2.9)
18 (α7)	10 (3.9)	2.0 (0.7,5.9)	244 (95.3)	1.0	2 (0.8)	0.3 (0.1,1.7)	4 (1.6)	5.3@ (0.9,∞)	6 (2.3)	1.2 (0.4,3.9)
45 (α7)	5 (2.0)	2.5 (0.5,13)	248 (96.9)	1.0	3 (1.2)	3.0 (0.3,29)	2 (0.8)	2.0 (0.2,22)	3 (1.2)	3.0 (0.3,29)
68 (α7)	8 (3.1)	2.0 (0.6,6.6)	244 (95.3)	1.0	4 (1.6)	1.3 (0.3,6.0)	1 (0.4)	1.0 (0.1,16)	7 (2.7)	2.3 (0.6,9.0)
16 (α9)	22 (8.6)	1.0 (0.5,1.9)	229 (89.5)	1.0	5 (2.0)	0.9 (0.3,3.0)	2 (0.8)	0.3 (0.1,1.7)	20 (7.8)	1.2 (0.6,2.4)
31 (α9)	9 (3.5)	0.9 (0.4, 2.2)	243 (94.9)	1.0	4 (1.6)	4.0 (0.4, 3.6)	4 (1.6)	5.3@ (0.9,∞)	5 (2.0)	0.5 (0.2,1.5)
33 (α9)	5 (2.0)	0.5 (0.2,1.5)	248 (96.9)	1.0	3 (1.2)	3.8@ (0.6,∞)	2 (0.8)	0.4 (0.1,2.1)	3 (1.2)	0.6 (0.1,2.5)
52 (α9)	2 (0.8)	0.7 (0.1,4.0)	252 (98.4)	1.0	2 (0.8)	2.4@ (0.3,∞)	1 (0.4)	0.5 (0.0,5.5)	1 (0.4)	1.0 (0.1,16)
58 (α9)	24 (9.4)	1.8 (0.9,3.6)	228 (89.1)	1.0	4 (1.6)	0.4 (0.1,1.7)	8 (3.1)	4.0 (0.8,19)	16 (6.3)	1.5 (0.7,3.1)
6 (α10)	24 (9.4)	1.5 (0.8,2.9)	226 (88.3)	1.0	6 (2.3)	0.6 (0.2,2.1)	3 (1.2)	0.5 (0.1,2.0)	21 (8.2)	2.2 (1.0,4.8)
11 (α10)	8 (3.1)	1.3 (0.5,3.8)	243 (94.9)	1.0	5 (2.0)	1.0 (0.3,3.5)	2 (0.8)	0.7 (0.1,4.0)	6 (2.3)	2.0 (0.5,8.0)
5 (β1)	64 (25.0)	1.2 (0.8,1.7)	169 (66.0)	1.0	23 (9.0)	3.2 (1.3,7.6)[#]	7 (2.7)	1.2 (0.4,4.0)	57 (22.3)	1.3 (0.8,1.9)
15 (β2)	53 (20.7)	1.2 (0.8,1.9)	187 (73.0)	1.0	16 (6.3)	1.4 (0.6,3.2)	5 (2.0)	1.0 (0.3,3.5)	48 (18.8)	1.3 (0.8,2.0)
38 (β2)	55 (21.5)	1.1 (0.7,1.7)	183 (71.5)	1.0	18 (7.0)	1.4 (0.7,3.0)	8 (3.1)	1.7 (0.5,5.2)	47 (18.4)	1.1 (0.7, 1.7)
76 (β3)	39 (15.2)	1.4 (0.8,2.4)	207 (80.9)	1.0	10 (3.9)	0.7 (0.3,1.7)	8 (3.1)	6.6 (0.8,55)	31 (12.1)	1.2 (0.7,2.1)
MCPyV	190 (74.2)	0.9 (0.6,1.3)	56 (21.9)	1.0	10 (3.9)	1.5 (0.5,4.6)	7 (2.7)	0.9 (0.3,2.5)	183 (71.5)	0.9 (0.6,1.4)
JCPyV	182 (71.1)	1.0 (0.7,1.6)	56 (21.9)	1.0	18 (7.0)	2.0 (0.8,4.8)	12 (4.7)	1.7 (0.7,4.5)	170 (66.4)	1.2 (0.7,2.0)

[‡] Results are based on serostatus at the first and the last serum sampling of 256 SCC cases and controls (*table a)* of 531 BCC cases and controls (*table b)*.
[§] N: Number, pos: positives
[*] p<0.05. [**] Unadjusted OR. [#] p<0.01
[††] -/- is both first and last sample negative, -/+ is first sample negative and last positive, +/- is first sample positive and last negative, +/+ is both first and last sample positive.
@Median unbiased estimate

Any α7 type	20 (7.8)	2.2 (1.0,4.9)*	228 (89.1)	1.0	8 (3.1)	1.0 (0.4,2.7)	7 (2.7)	7.0 (0.9,57)	13 (5.1)	1.6 (0.7,3.9)
Any α9 type	47 (18.4)	1.3 (0.8, 2.1)	202 (78.9)	1.0	7 (2.7)	0.8 (0.3,2.3)	11 (4.3)	1.4 (0.6,3.5)	36 (14.1)	1.3 (0.8,2.1)
Any α10 type	26 (10.2)	1.4 (0.8, 2.5)	223 (87.1)	1.0	7 (2.7)	0.5 (0.2, 1.4)	3 (1.2)	0.4 (0.1,1.7)	23 (9.0)	2.0 (1.0,4.1)
Any β2 type	71 (27.7)	1.2 (0.8,1.7)	164 (64.1)	1.0	21 (8.2)	1.2 (0.6,2.5)	8 (3.1)	1.4 (0.5,4.0)	63 (24.6)	1.2 (0.8,1.7)

b)

BCC (N=531) HPV type (genus, species)	**1st sample N pos (%)**	**1st sample OR (95% CI)**	**-/- N (%)**	**-/- Ref.**	**-/+ N (%)**	**-/+ OR (95% CI)**	**+/- N (%)**	**+/- OR (95% CI)**	**+/+ N (%)**	**+/+ OR (95% CI)**
32 (α1)	12 (2.3)	0.6 (0.3,1.2)	513 (96.6)	1.0	6 (1.1)	0.6 (0.2,1.9)	4 (0.8)	1.3 (0.3,6.0)	8 (1.5)	0.4 (0.2,1.0)
3 (α2)	82 (15.4)	1.2 (0.9,1.7)	437 (82.3)	1.0	12 (2.3)	0.8 (0.4,1.8)	21 (4.0)	1.9 (0.9,4.0)	61 (11.5)	1.1 (0.7,1.6)
18 (α7)	21 (4.0)	1.1 (0.6,2.0)	501 (94.4)	1.0	9 (1.7)	1.3 (0.5,3.5)	3 (0.6)	0.7 (0.1,4.1)	18 (3.4)	1.1 (0.6,2.2)
45 (α7)	16 (3.0)	1.3 (0.6,2.8)	506 (95.3)	1.0	9 (1.7)	2.7 (0.7,10.1)	2 (0.4)	2.0 (0.2,22)	14 (2.6)	1.3 (0.6,2.8)
68 (α7)	12 (2.3)	1.0 (0.4,2.2)	508 (95.7)	1.0	11 (2.1)	1.3 (0.5,3.2)	4 (0.8)	0.8 (0.2,3.0)	8 (1.5)	1.1 (0.4,3.2)
16 (α9)	54 (10.2)	1.0 (0.7,1.5)	462 (87.0)	1.0	15 (2.8)	0.6 (0.3,1.2)	9 (1.7)	0.6 (0.2,1.3)	45 (8.5)	1.2 (0.7,1.8)
31 (α9)	26 (4.9)	0.8 (0.5,1.4)	493 (92.8)	1.0	12 (2.3)	1.3 (0.5, 3.3)	8 (1.5)	2.0 (0.6, 6.6)	18 (3.4)	0.6 (0.3,1.1)
33 (α9)	11 (2.1)	0.7 (0.3,1.5)	518 (97.6)	1.0	2 (0.4)	0.3 (0.1,1.2)	6 (1.1)	1.2 (0.4,3.9)	5 (0.9)	0.5 (0.2,1.3)
52 (α9)	10 (1.9)	2.5 (0.8,8.0)	515 (97.0)	1.0	6 (1.1)	1.0 (0.3,3.1)	2 (0.4)	2.0 (0.2,22)	8 (1.5)	2.7 (0.7,10.1)
58 (α9)	38 (7.2)	1.2 (0.7,1.9)	487 (91.7)	1.0	6 (1.1)	0.6 (0.2,1.9)	11 (2.1)	1.8 (0.7,5.0)	27 (5.1)	1.0 (0.6,1.7)
6 (α10)	58 (10.9)	1.1 (0.7, 1.7)	461 (86.8)	1.0	12 (2.3)	0.7 (0.3,1.4)	12 (2.3)	0.7 (0.3,1.5)	46 (8.7)	1.3 (0.8, 2.1)
11 (α10)	22 (4.1)	0.9 (0.5,1.6)	503 (94.7)	1.0	6 (1.1)	0.8 (0.3,2.2)	2 (0.4)	0.3 (0.1,1.4)	20 (3.8)	1.0 (0.6,2.0)
5 (β1)	112 (21.1)	1.2 (0.9,1.6)	385 (72.5)	1.0	34 (6.4)	1.1 (0.7,1.8)	18 (3.4)	1.2 (0.6,2.4)	94 (17.7)	1.1 (0.8,1.6)
15 (β2)	116 (21.8)	1.2 (0.9,1.7)	370 (69.7)	1.0	45 (8.5)	1.2 (0.8,2.0)	10 (1.9)	0.6 (0.3,1.4)	106 (20.0)	1.4 (1.0,1.9)
38 (β2)	93 (17.5)	1.0 (0.7, 1.4)	397 (74.8)	1.0	41 (7.7)	1.3 (0.8, 2.2)	7 (1.3)	0.5 (0.2, 1.2)	86 (16.2)	1.2 (0.8, 1.6)
76 (β3)	61 (11.5)	0.9 (0.6,1.3)	443 (83.4)	1.0	27 (5.1)	0.9 (0.6,1.6)	11 (2.1)	0.9 (0.4,2.0)	50 (9.4)	0.9 (0.6,1.3)
MCPyV	375 (70.6)	1.1 (0.9,1.5)	138 (26.0)	1.0	18 (3.4)	1.0 (0.5,1.9)	17 (3.2)	1.7 (0.8,3.7)	358 (67.4)	1.1 (0.8,1.5)
JCPyV	408 (76.8)	0.9 (0.7,1.2)	108 (20.3)	1.0	15 (2.8)	0.8 (0.4,1.6)	25 (4.7)	1.9 (0.9,4.2)	383 (72.1)	0.9 (0.6,1.2)
Any α7 type	42 (7.9)	1.2 (0.7,1.9)	467 (87.9)	1.0	22 (4.1)	1.9 (0.9,3.9)	7 (1.3)	0.9 (0.3,2.6)	35 (6.6)	1.3 (0.8,2.2)
Any α9 type	102 (19.2)	1.0 (0.8,1.4)	401 (75.5)	1.0	28 (5.3)	0.9 (0.5,1.5)	26 (4.9)	1.3 (0.7,2.4)	76 (14.3)	0.9 (0.7,1.3)
Any α10 type	69 (13.0)	1.1 (0.8,1.6)	449 (84.6)	1.0	13 (2.4)	0.8 (0.4,1.6)	13 (2.4)	0.8 (0.4,1.7)	56 (10.5)	1.2 (0.8,1.8)

Any β2 type	149 (28.1)	1.3 (0.9,1.7)	331 (62.3)	1.0	51 (9.6)	1.1 (0.7,1.7)	13 (2.4)	0.6 (0.3,1.2)	136 (25.6)	1.4 (1.1,2.0)*

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