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Research Article

The Association between Cutaneous Squamous Cell Carcinoma and Betapapillomavirus Seropositivity: a Cohort Study

Elsemieke I. Plasmeijer[1], Nirmala Pandeya[2], Peter O'Rourke[3], Michael Pawlita[4], Tim Waterboer[4], Mariet C.W. Feltkamp[1], Adele C. Green[3], and Rachel E. Neale[3]

Abstract

Background: It is currently unclear whether betapapillomaviruses (betaPV) play a role in the etiology of cutaneous squamous cell carcinoma (SCC). We investigated the association between betaPV antibodies and subsequent SCC in a population-based cohort study.

Methods: Serum samples were collected in 1992 and/or 1996 from 1,311 participants of the community-based Nambour Skin Cancer Study. These were tested for the presence of L1 antibodies against 21 different betaPV types. Histologically diagnosed SCCs were ascertained through three full-body skin examinations and linkage with the local pathology laboratories. We used age- and sex-adjusted Cox proportional hazards models to analyze the relationship between betaPV antibodies and SCC occurrence from 1992 until 2007.

Results: SCC was newly diagnosed in 150 people. No associations were found between the presence of any betaPV L1 antibodies and the occurrence of SCC (HR = 1.0), and stratification by sex, skin color, and sunburn propensity did not affect these results. However, among people who were less than 50 years old in 1992, the presence of betaPV antibodies was associated with a two-fold increased risk of SCC. There was no significant association between antibodies to any individual betaPV type examined and the later development of SCC.

Conclusions: Whether betaPV infection of the skin, and indirectly betaPV antibodies, are involved in the oncogenic process in the general population remains unclear, and this longitudinal study provides only limited support.

Impact: This study emphasizes the need for additional longitudinal studies of HPV (human papilloma virus) and SCC, to avoid the possibility of reverse causality in case–control studies. *Cancer Epidemiol Biomarkers Prev; 20(6); 1171–7. ©2011 AACR.*

Introduction

Cutaneous squamous cell carcinoma (SCC) is among the most commonly diagnosed cancers in people with fair skin. Human papilloma viruses (HPV) of the beta-genus (betaPV) are nonenveloped cutanotropic DNA viruses that have been associated with the development of SCC (1). At present, 31 different betaPV types have been fully sequenced (2–4).

Epidemiologic studies have shown that antibodies against the betaPV major capsid antigen, L1, can be found not only in the serum of patients with SCC or the precursor lesion actinic keratosis (AK) but also in people unaffected by these lesions (5–10). BetaPV L1 antibodies have been associated with both SCC and AK in case–control studies (6, 10–20), although the findings are somewhat inconsistent (reviewed in ref. 14). The most recent and largest case–control study found an association between betaPV antibodies and SCC, with an increasing risk for antibodies to multiple betaPV types as well as in people using glucocorticoids (20). It is difficult to assess the independent effect of specific viruses, due to the very high frequency of multiple infection (21), but to date, associations have mostly been identified between HPV8 and HPV38 and prevalent SCC (11–13, 16, 17, 19) A more recent study also found associations with HPV15 and HPV17 as well as with gammaPV types (18).

Case–control studies assess betaPV exposure at the same time as, or even after, diagnosis of the skin cancer. This prevents assessment of temporality, so the direction of any observed association cannot be determined.

Authors' Affiliations: [1]Leiden University Medical Center, Leiden, the Netherlands; [2]School of Population Health, University of Queensland; [3]Cancer and Population Studies, Queensland Institute of Medical Research, Queensland, Australia; and [4]Division of Genome Modifications and Carcinogenesis, German Cancer Research Center (DKFZ), Heidelberg, Germany

Corresponding Author: Rachel E. Neale, Cancer and Population Studies, QIMR, Locked Bag 2000, Royal Brisbane Hospital, Brisbane, QLD 4029, Australia. Phone: 61-7-3845-3598; Fax: 61-7-3845-3502. E-mail: Rachel.Neale@qimr.edu.au

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Longitudinal studies overcome this issue, but there has been only 1 report of a prospective pilot study published, in which there was no association found between baseline HPV antibodies and subsequent SCC in 39 patients (14). However, as the authors of this article pointed out, their study did not have adequate power to assess the association.

To further explore the issue, we aimed to assess the association between betaPV L1 antibodies and cutaneous SCC using data from a population-based cohort study in Nambour, Australia.

Material and Methods

Study population and sample collection

Participants were a subset of the study population of the Nambour Skin Cancer Study described in detail previously (22–24). Briefly, in 1986, 3,000 residents of Nambour, a subtropical township in Australia (latitude 26°S), who were aged 20 to 69 years were randomly selected from the Australian Electoral Roll (enrolment to vote is compulsory) and invited to participate in a skin cancer prevalence survey. From 1992 to 1996, 1,621 of the 2,095 participants of the 1986 survey took part in a trial of sunscreen application and beta-carotene supplementation for the prevention of skin cancer. All participants received full-body skin examinations by a dermatologist in 1992, 1994, and 1996 to ascertain the presence of actinic keratoses, skin malignancies, telangiectasia on the face, and elastosis of the neck. Skin lesions arising between these examinations, and from 1997 to 2007, were ascertained through the local pathology laboratories. Participants completed standardized questionnaires about sun exposure and other possible risk factors for skin cancer including past history of skin cancer. Blood was collected from a randomly selected subsample of participants in 1992 and from all consenting participants in 1996. A total of 1,388 participants had blood collected in either 1992 or 1996. Ethical approval for all aspects of the study was obtained through the Bancroft Centre Human Research Ethics Committee, Queensland Institute of Medical Research.

Multiplex serology

We tested serum samples for the presence of antibodies to the major capsid antigen L1 of HPV5, 8, 9, 14, 15, 17, 20, 21, 22, 23, 24, 36, 38, 47, 49, 75, 76, 80, 92, 93, and 96 by multiplex serology. This is an antibody detection method based on a glutathione *S*-transferase capture ELISA, in combination with fluorescent bead technology (25–27). Positive serology cutoff points were standardized at 200 MFI (mean fluorescence intensity; ref. 8).

Statistical analyses

Participants who had an SCC prior to their first serum measurement were excluded from this analysis ($N = 77$). We calculated the prevalence of betaPV antibodies for any betaPV type overall and for each of the 21 genotypes tested in 1992 and 1996. We estimated HRs for the association between SCC and the presence of any betaPV antibodies, the number of different antibody types, and selected specific antibody types (HPV5, 8, 9, 15, 20, 23, 24, 36, and 38) using a Cox proportional hazards model, adjusted for age and sex. The specific types were selected on the basis of their seroprevalence and also as they had been shown to be associated with SCC in previous studies. The date of entry into the cohort was the date at which serum antibodies were first measured (1992 or 1996), and the date of censoring was either the date of first SCC diagnosis, the date participant was lost to follow-up or 31 December 2007, whichever occurred first. If participants had both 1992 and 1996 serum measurements available, we used both records to allow for changing antibody status. A robust sandwich covariance matrix was used to account for intraperson correlation using the method described by Lin and Wei (28). We conducted additional analyses, within strata of age, sex, skin color, and tanning ability. Statistical analyses were performed using SAS 9.1.

Results

Baseline characteristics

After excluding people who did not have a blood sample collected in 1992 or 1996 and those who had SCC diagnosed prior to the start of the trial, 1,311 of the 1,621 people initially enrolled in the trial were included in this analysis, 176 with only a 1992 blood sample, 655 only a 1996 blood sample, and 480 with both 1992 and 1996 samples. Their mean age was 49 years (SD: 13, range: 25–75) and 44% were men (Table 1). SCC was diagnosed in 150 participants during follow-up. A single SCC developed in 97 people, and 53 participants developed more than 1 SSC (range: 2–20). Being aged over 50 years, having medium or fair skin color, a propensity to burn when exposed to the sun, and having a high degree of nuchal elastosis were significantly associated with the development of SCC (Table 1).

BetaPVL1 antibody prevalence

The overall prevalence of betaPV antibodies in 1992 was 62%, and 46% of participants were positive for multiple types (Table 2). The type-specific seroprevalence was highest for HPV8 (34%), HPV38 (33%), and HPV49 (26%) and lowest for HPV14 (2%) and HPV93 (3%). In 1996, 66% of participants were betaPV seropositive and 48% were positive for more than 1 type (Table 2). Type-specific prevalence varied from 31% for HPV38 to 1% for HPV14. The overall and type-specific prevalences were similar among the 480 people with both 1992 and 1996 sera available (Table 2). The betaPV antibody prevalence of the 480 people with serum samples collected in 1992 and 1996 was generally stable in the intervening 5 years, with only 13% of people changing their antibody status between 1992 and 1996. Seroconversion occurred in 46 people (10%), whereas 17 people (3%) seroreverted between 1992 and 1996.

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Table 1. Baseline characteristics of participants of the Nambour Skin Cancer Study (n = 1,311) with betaPV antibodies measured in 1992 and/or 1996

	***N* = 1,311, *n* (%)**	**Person years**	**Number who developed SCC (%)**	**Incidence rate/100.000/ person years**	**Adjusted HR[a]**
Sex					
M	571 (44)	5,845	71 (12)	1,215	1.0
F	740 (56)	7,805	79 (11)	1,012	0.8 (0.6–1.1)
Age in 1992, y					
<50	730 (56)	8,190	38 (5)	464	1.0
50+	581 (44)	5,459	112 (19)	2,052	4.4 (3.1–6.4)
Skin color					
Olive	89 (7)	1,008	3 (3)	298	1.0
Medium	499 (38)	5,091	49 (10)	962	3.7 (1.2–11.6)
Fair	722 (55)	7,539	98 (14)	1,300	5.5 (1.8–17.0)
When exposed to sun					
Only tan	144 (11)	1,416	9 (6)	636	1.0
Burn than tan	911 (69)	9,627	88 (10)	914	1.3 (1.1–4.4)
Always burn, never tan	256 (20)	2,594	53 (21)	2,043	5.0 (2.5–9.8)
Occupational sun exposure					
Mainly indoors	584 (45)	6,264	57 (10)	910	1.0
Both indoor and outdoor	483 (37)	4,938	62 (13)	1,256	1.0 (0.7–1.5)
Mainly outdoors	244 (19)	2,436	31 (13)	1,273	1.1 (0.7–1.7)
Recreational sun exposure					
Mainly indoors	198 (15)	2,029	18 (9)	887	1.0
Both indoor and outdoor	573 (44)	5,944	64 (11)	1,077	1.4 (0.9–2.4)
Mainly outdoors	540 (41)	5,665	68 (13)	1,200	1.2 (0.7–2.1)
Nuchal elastosis					
Limited	292 (22)	3,322	7 (2)	211	1.0
Moderate	639 (49)	6,709	63 (10)	939	2.7 (1.2–6.0)
Extensive	376 (29)	3,598	78 (21)	2,168	4.3 (1.9–9.9)
Telangiectasia face					
Low	384 (29)	4,113	30 (8)	729	1.0
Moderate	628 (48)	6,529	71 (11)	1,087	1.1 (07–1.7)
Extensive	294 (23)	2,962	48 (16)	1,621	1.3 (0.8–2.2)
Smoker					
Life-long nonsmoker	800 (61)	8,171	78 (10)	955	1.0
Current smoker	148 (11)	1,508	15 (10)	995	1.6 (0.8–3.2)
Ex-smoker	363 (28)	3,970	57 (16)	1,436	1.0 (0.6–1.6)

[a]HR adjusted for age and sex.

BetaPV antibody–SCC associations

No association was found between the presence of L1 antibodies to at least 1 betaPV type and the development of SCC [relative risk (RR): 1.0, 95% CI: 0.7–1.4; Table 3]. Also, no association was found with antibodies to multiple types (RR: 1.0, 95% CI: 0.7–1.5 for 1–3 antibody types; RR: 0.9, 95% CI: 0.6–1.4 for 4 or more antibody types). However, among people who were less than 50 years old in 1992, the presence of betaPV antibodies was associated with a 2-fold increased risk of SCC. This association was not evident in those older than 50 years. Stratification by sex, skin color, and burning ability showed no differences in associations between betaPV risk factors and SCC risk. There was no significant association between any of the individual betaPV types examined (HPV5, 8, 9, 15, 20, 23, 24, 36, and 38) and the development of SCC (Table 4). Seroconversion between 1992 and 1996 was not associated with the development of SCC after 1996, but with small sample size, the power to detect an association was limited.

Discussion

The majority of previous studies finding associations between betaPV and SCC of the skin have been case–control studies (6, 11–13, 16, 17, 19, 20, 29). In this

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Table 2. Detection of betaPV antibodies overall and for specific betaPV types in 1992 and 1996, for the whole cohort and restricted to those people with both 1992 and 1996 sera available

	1992 antibodies ($n = 656$)[a] *N* (%)	1996 antibodies ($n = 1,135$)[b] *N* (%)	1992 antibodies ($n = 480$)[c] *N* (%)	1996 antibodies ($n = 480$)[c] *N* (%)
Any betaPV type	409 (62)	748 (66)	300 (63)	329 (69)
HPV5	61 (9)	109 (10)	43 (9)	46 (10)
HPV8	220 (34)	346 (30)	159 (33)	173 (36)
HPV9	109 (17)	179 (16)	79 (16)	93 (19)
HPV14	11 (2)	17 (2)	6 (1)	8 (2)
HPV15	155 (24)	253 (22)	112 (23)	119 (25)
HPV17	149 (23)	283 (25)	109 (23)	129 (27)
HPV20	97 (15)	134 (12)	69 (14)	61 (13)
HPV21	119 (18)	207 (18)	82 (17)	97 (20)
HPV22	82 (13)	137 (12)	60 (13)	60 (13)
HPV23	82 (13)	139 (12)	54 (11)	63 (13)
HPV24	107 (16)	174 (15)	77 (16)	84 (18)
HPV36	86 (13)	136 (12)	56 (12)	57 (12)
HPV38	214 (33)	347 (31)	160 (33)	176 (37)
HPV47	85 (13)	134 (12)	56 (12)	59 (12)
HPV49	170 (26)	269 (24)	130 (27)	138 (29)
HPV75	113 (17)	174 (15)	79 (16)	84 (18)
HPV76	103 (16)	149 (13)	75 (16)	72 (15)
HPV80	110 (17)	208 (18)	74 (15)	89 (19)
HPV92	84 (13)	142 (13)	60 (13)	66 (14)
HPV93	21 (3)	29 (3)	15 (3)	12 (3)
HPV96	126 (19)	199 (18)	92 (19)	98 (20)
Number of types				
0	247 (38)	387 (34)	180 (38)	151 (31)
1–3	214 (32)	416 (37)	156 (32)	167 (35)
4+	195 (30)	332 (29)	144 (30)	162 (34)

[a]All people with 1992 serum sample.
[b]All people with 1996 serum sample.
[c]All people with 1992 and 1996 serum sample.

longitudinal study of 1,311 adults followed over 10 to 15 years, we did not observe any association with overall antibody positivity, antibodies to multiple betaPV types or to specific types previously shown to be associated with SCC. There was, however, an association among younger adults. Those under 50 years showed a 2-fold increased risk of SCC in the presence of betaPV antibodies.

The overall prevalence of betaPV antibodies of 62% in 1992 and 66% in 1996 was slightly higher than the 51% previously found in a similar population where the same laboratory technique and cutoff point were used for ascertainment of antibodies (27) and was higher also than the 46% reported in New Hampshire in the United States (20). As betaPV seropositivity increases with age (8, 27), and the mean age was lower in this study than in the previous studies (20, 27), the relatively high seroprevalence here is not due to older age and remains unexplained. The betaPV antibody prevalence of the 480 people with serum samples collected in 1992 and 1996 was quite stable in the short term (5 years), with only around 10% of people changing their antibody status in that time.

This is the largest longitudinal study to evaluate the relationship between betaPV antibodies and SCC, and it is consistent with a small prospective pilot study (cases = 39) in the United Kingdom in that both found no association between baseline serology and incident SCC (14). However, we did find an association in people diagnosed with SCC who were less than 50 years at entry into the study. It is possible that SCC diagnosed at younger ages is less strongly related to cumulative ultraviolet radiation exposure with HPV more likely to play a role than in older people. No previous studies have reported results stratified by age, so we do not know whether stronger associations have been apparent in younger age groups in previous studies.

Apart from the association in younger people, our overall results are not in accordance with those from

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Table 3. Relative risks for SCC for the overall population as well as stratified by sex, age, skin type, and propensity to burn

betaPV AB	*N* (%)	Person years	Number of participants with SCC (% of total in the stratum)	Incidence rate/100,000/ person years	Adjusted HR
All[a] ($n = 1,311$)					
Absent	437 (33)	4,727	44 (10)	931	1.0
Present	874 (67)	8,894	106 (12)	1,192	1.0 (0.7–1.4)
Men[b] ($n = 571$)					
Absent	157 (27)	1,715	20 (13)	1,166	1.0
Present	414 (73)	4,118	51 (12)	1,238	0.7 (0.4–1.1)
Women[b] ($n = 740$)					
Absent	280 (38)	3,012	24 (9)	797	1.0
Present	460 (62)	4,776	55 (12)	1,152	1.3 (0.8–2.0)
<50 years[c] ($n = 730$)					
Absent	255 (35)	2,949	8 (3)	271	1.0
Present	475 (65)	5,224	30 (6)	574	2.1 (1.0–4.6)
50+ years[c] ($n = 581$)					
Absent	182 (31)	1,778	36 (20)	2,025	1.0
Present	399 (69)	3,670	76 (19)	2,071	0.8 (0.5–1.2)
Fair skin[a] ($n = 722$)					
Absent	238 (33)	2,650	25 (11)	943	1.0
Present	484 (67)	4,873	73 (15)	1,498	1.3 (0.8–2.0)
Medium/olive skin[a] ($n = 588$)					
Absent	199 (34)	2,078	19 (10)	914	1.0
Present	389 (66)	4,021	33 (8)	821	0.6 (0.3–1.1)
Always burn[a] ($n = 256$)					
Absent	79 (31)	892	11 (14)	1,233	1.0
Present	177 (69)	1,697	42 (24)	2,475	1.1 (0.6–2.1)
Burn-tan/only tan[a] ($n = 1,054$)					
Absent	358 (34)	3,836	33 (9)	860	1.0
Present	696 (66)	7,197	64 (9)	889	0.9 (0.6–1.3)

[a]HR adjusted for age and sex.
[b]HR adjusted for age.
[c]HR adjusted for sex.

recent large case–control studies which have showed generally positive associations (10–20). Understanding the relationship between HPV and skin cancer is hampered by lack of knowledge about the appropriate measure of infection. BetaPV are almost ubiquitous on the skin, with much higher prevalence of betaPV DNA than of antibodies, so some factor(s) other than simply the presence of betaPV on the skin must influence the development of antibodies. It has been hypothesized that the presence of SCC (or its precursor lesions, actinic keratoses) may result in increased viral load or local inflammation, resulting in presentation of the virus to the immune system and seroconversion (6, 10, 19). If this is the case, it is possible that the results of case–control studies using antibodies as a marker of infection do not indicate a causal association but are due to "reverse causality." In support of this, in the previous small longitudinal study in the United Kingdom, there was a tendency toward higher seroprevalence in 15 prevalent cases than in 39 incident cases, although this was not statistically significant. However, we did not find that a diagnosis of SCC between 1992 and 1996 increased the likelihood of seroconversion in our study, and there is also no evidence that the diagnosis of AK leads to seroconversion in people without a diagnosis of SCC (30). Furthermore, the lack of association between the presence of antibodies and BCC (basal cell carcinoma) in case–control studies argues against the reverse causality hypothesis (20).

There may be other biases or uncontrolled confounding that have led to the associations observed in case–control studies. However, assuming that neither bias nor reverse causality is responsible and that there is a

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Table 4. Associations between betaPV type-specific seropositivity and SCC

	N = 1,311, *n* (%)	Person years	Number of participants with SCC (%)	Incidence rate/100,000/ person years	Adjusted HR[a]
HPV5					
Absent	1,174 (90)	12,344	136 (12)	1,102	1.0
Present	137 (10)	1,278	14 (10)	1,095	1.0 (0.5–1.7)
HPV8					
Absent	888 (68)	9,329	95 (11)	1,018	1.0
Present	423 (32)	4,293	55 (13)	1,281	1.1 (0.8–1.5)
HPV9					
Absent	1,092 (83)	11,387	129 (12)	1,133	1.0
Present	219 (17)	2,235	21 (10)	940	0.7 (0.5–1.2)
HPV15					
Absent	1,002 (76)	10,522	112 (11)	1,064	1.0
Present	309 (24)	3,100	38 (12)	1,226	1.0 (0.7–1.5)
HPV20					
Absent	1,131 (86)	11,895	133 (12)	1,118	1.0
Present	180 (14)	1,727	17 (9)	984	0.6 (0.3–1.0)
HPV23					
Absent	1,138 (87)	11,973	136 (12)	1,136	1.0
Present	173 (13)	1,649	14 (8)	849	0.7 (0.4–1.1)
HPV24					
Absent	1,011 (77)	11,455	128 (13)	1,117	1.0
Present	300 (23)	2,167	22 (7)	1,015	0.8 (0.5–1.3)
HPV36					
Absent	1,133 (86)	11,887	134 (12)	1,127	1.0
Present	178 (14)	1,735	16 (9)	922	0.7 (0.4–1.1)
HPV38					
Absent	900 (69)	9,386	102 (11)	1,087	1.0
Present	411 (31)	4,236	48 (12)	1,133	0.9 (0.6–1.3)

[a]HR calculated using Cox proportional hazards model and adjusted for age and sex.

causal relation, the possible reasons for the overall lack of association in our longitudinal study need to be considered. It is possible that very high levels of sun exposure in Queensland overwhelm any detectable effect of betaPV. However, we have previously shown that the presence of persistent betaPV DNA in eyebrow hairs is associated with the development of AK in this population (31), providing support for an effect of long-term infection. We measured antibody status in mid-adulthood, and although antibodies appear to be relatively stable over a short time period, it is possible that this does not reflect the status at the time of initiation of SCC many years earlier (this limitation would also be true of case–control studies.) Finally, a high proportion of controls in this study had been diagnosed with AK. As these lesions are frequently not histologically diagnosed, we could not ascertain all AKs occurring during the follow-up period, so could not adjust for the presence of AKs. The fact that AKs are on the causal pathway between sun exposure and SCC, and possibly also between betaPV infection and SCC, may have made adjustment inappropriate even had it been possible. The complex interplay among betaPV, sun exposure, AK, and SCC therefore may be responsible for the lack of association between betaPV and SCC in people over 50 years of age at entry into this cohort.

In conclusion, whether betaPV infection of the skin, and indirectly betaPV antibodies, is involved in the oncogenic process in the general population remains unclear, and this study provides only limited support. Research incorporating measures of immune function and genotype, along with multiple measures of betaPV infection and sun exposure, may help to elucidate the role of betaPV in cutaneous carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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