Table 2.27. Studies of HPV and skin cancer

Reference, study location	No. of cases	No. of controls	Method of detection	HPV prevalence (%)		Odds ratio (95% CI)	Comments/ adjustments
				Cases	Controls		
Stark *et al.* (1994), Scotland	Keratoses; Intra-epidermal carcinomas; SCC	Uninvolved skin	Low-stringency Southern blot, PCR for 8 types, used biopsies	Keratoses 25 Intradermal carcinomas 23 SCC 22	Ctls 8		Higher prevalence with Southern blot indicated that additional types not assayed by PCR were involved
Boxman *et al.* (2000), Australia	64 NMSC 51 BCC 25 SCC	1:1 matched on age	PCR for EV types on plucked hairs, sequencing of amplimers	63 61 56	67 71 44	0.8 (0.3–1.8) 0.6 (0.2–1.5) 2.0 (0.5–8.0)	Fair agreement between plucked hairs and lesions in a subset
Wieland *et al.* (2000), Germany and Poland	61 BCC	31 matched biopsies from BCC patients, from unaffected skin 200 controls without skin cancer compared with 40 cases by serology	6 different PCR primer systems for DNA VLP serology for alpha HPV 16, beta-1 HPV 8, 36, beta-2 HPV 15	31 matched DNA: 7 BCC neg/ Ctl neg 3 pos/ neg 1 neg/pos 20 neg/neg *Serology* HPV8 17.5 HPV15 5.0 HPV36 12.5 HPV16 5.0	 15.5 4.5 12.5 10.7	DNA: 3.0, based on 3 vs. 1 among discordants *Serology* 1.2 1.1 1.0 0.4	DNA 32% in BCC, 26% in paired healthy skin, combined with serological findings, interpreted as null association between HPV and BCC
O'Connor *et al.* (2001), Ireland	12 SCC in immuno-competent patients	Undefined skin samples from 20 general population ctls.	CP65-70 primer PCR	83.3	15.0	28.3	Study mainly showed null association with p53 codon 72 polymorphism

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Iftner *et al.* (2003), Germany and U.S.	71 keratoses 20 Bowen's 72 SCC 18 BCC	106 normal	CP4-CP5 and PPF1-CP5 primer PCR on biopsies, sequencing of amplimers, to detect at least 64 types	*SK/Bowen's* Any 60.4 Alpha 11.0 Beta 6.6 *SCC* Any 59.7 Alpha 12.5 Beta 95.6 *BCC* Any 27.8 Alpha 16.7 Beta 0.0	*Ctl* Any 4.7 Alpha 0.9 Beta 0.9	*SK/Bowen* 26 (7.3–91) n.a. 9.2 (1.0–80) 32 (10–100) n.a. 9.6 (0.9–100) 7.3 (1.7–30) 26 (21.1–318) n.a.	Adjusted for age, sex, and sun exposure, leading to some missing OR estimates
Forslund *et al.* (2003), Australia	Lesional biopsies from 19 BCC 12 SCC 10 SCC	Swabs of perilesional skin and buttock skin from same patients	FAP PCR primers, TS-primers for HPV 38 and 92, with sequencing of amplimers		Peri Buttk BCC 21 52 SCC 33 92 63 SK 70 80 60	n.a., paired	Concluded that normal skin is often infected with beta types
Masini *et al.* (2003), Italy	46 SCC	84 age and sex matched controls hospitalized for unrelated dermato-logical conditions	VLP serology for beta-1 HPV 8 and 36, beta-2 HPV 15 and 23	HPV 8 56.5 HPV 15 34.8 HPV 23 15.2 HPV 36 19.6	32.1 47.6 11.9 8.3	3.2 (1.3–7.9) 0.4 (0.2–0.9) 1.0 (0.3–3.3) 2.8 (0.8–10.0)	Adjusted for age, sex, history of sun exposure, eye colour
Struijk *et al.* (2003), The Netherlands	155 SCC	371 ophthalmology clinic controls, dark-skinned persons excluded	General nested and TS PCR for HPV alpha HPV 2 and 16, beta-1 HPV 5, 8, 20, 24, beta-2 HPV 15, 38 on 8-10 plucked eyebrows	General 74.8 Any TS 71.0 HPV5 23.2 HPV8 17.4 HPV15 16.8 HPV20 32.9 HPV24 25.2 HPV38 32.3	58.2 55.2 12.8 10.3 8.2 24.2 15.2 24.7	1.7 (1.1–2.7) 1.7 (1.1–2.6) 1.9 (1.0–3.4) 1.8 (0.9–3.4) 2.5 (1.3–4.8) 1.7 (1.0–2.9) 1.4 (0.8–2.6) 1.5 (0.9–2.6)	Adjusted for age and sex HPV DNA positivity increased with age and among males, but not related to sun exposure No HPV 16 found, only 1 HPV 2

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Reference, study location	No. of cases	No. of controls	Method of detection	HPV prevalence (%)				Odds ratio (95% CI)	Comments/ adjustments
				Cases		Controls			
Feltkamp *et al*. (2003), The Netherlands	160 SCC 291 nBCC 141 sBCC 84 melanoma	333 ophthalmology clinic controls, dark-skinned persons excluded	VLP serology for alpha HPV 16, beta-1 HPV 5, 8, 20, 24, beta-2 HPV 15, 38	*SCC*		*Ctl*			134 of NMSC had multiple types of cancer, were included in each category that applied
				Any	19.4	Any	12.3	1.4 (0.8–2.5)	
				HPV5	1.3	HPV5	0.3	2.6 (0.2–31.9)	
				HPV8	4.4	HPV8	0.3	14.7 (1.6–135)	
				HPV15	4.4	HPV15	2.1	1.8 (0.6–5.6)	
				HPV20	5.0	HPV20	2.1	2.2 (0.8–6.7)	Adjusted for age and sex
				HPV24	13.1	HPV24	6.6	1.5 (0.8–2.9)	
				HPV38	5.6	HPV38	2.7	3.0 (1.1–8.4)	No risk for melanoma, no risk for HPV 16
				nBCC					
				Any	16.8			1.3 (0.8–2.1)	
				HPV5	1.0			3.7 (0.4–38.4)	
				HPV8	2.4			9.2 (1.1–78.2)	
				HPV15	2.4			1.2 (0.4–3.6)	
				HPV20	6.9			3.2 (1.3–7.9)	
				HPV24	10.7			1.5 (0.8–2.7)	
				HPV38	2.1			0.9 (0.3–2.6)	
				sBCC					
				Any	18.4			1.6 (0.9–2.7)	
				HPV5	0.0			n.a.	
				HPV8	5.0			17.3 (2.1–143)	
				HPV15	2.8			1.5 (0.4–5.3)	
				HPV20	6.4			3.4 (1.2–9.5)	
				HPV24	12.1			1.9 (0.9–3.6)	
				HPV38	2.8			1.2 (0.4–3.9)	

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Reference, study location	No. of cases	No. of controls	Method of detection	HPV prevalence (%)		Odds ratio (95% CI)	Comments/ adjustments
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Harwood *et al.* (2004), U.K.	19 NMSC	38 with no history of NMSC	Multiple PCR primers to detect HPV types broadly	63	25	1.6	Study investigated sunlight, immunosuppression, combined SCC and BCC. No difference in HPV DNA prevalence by habitual sun exposure of site Poor concordance of lesion and normal skin in same patients No risk for alpha HPV types Another group of immunosuppressed renal transplant patients were 87% HPV positive 6.4 (1.8-22.9) is OR estimate for all patients including transplant patients in adjusted model, taking into account multiple specimens as well
Gustafsson *et al.* (2004), Sweden	53 SCC	Normal tissues from same SCC cases	GP5+/GP6+ for alpha; type-specific PCR for beta-1 HPV 5, 8, 20, 24 and beta-2 HPV 38; sequencing of PCR products	Alpha: 53 Beta: 3	30 17	1.8 0.2	Comparison of tumour to normal tissue, by microdissection of SCC cases. No effect modification by p53 codon 72 genotype.

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Reference, study location	No. of cases	No. of controls	Method of detection	HPV prevalence (%)		Odds ratio (95% CI)	Comments/ adjustments
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Shimizu *et al.* (2004), Japan	27 biopsies from SCC of lip	30, by cotton swab	L1 primer PCR for alpha HPV 2, 3, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82; nested PCR to detect all types; sequencing of amplimers	18	33	0.6	A variety of types found by novel mix of standard and novel PCR methods.
**Termorshuizen *et al.* (2004), The Netherlands	156 SCC	320 non-cancer, non-dark-skinned patients, ophthalmology outpatient clinic	Type-specific PCR in 8-10 plucked eyebrow hairs for DNA of beta-1 HPV 5, 8, 20, 25; beta-2 HPV 15, 38; serology by VLP ELISA for same types	DNA 71.2 Serol 19.9	DNA 54.4 Serol 12.5	DNA 1.8 Serol 1.7	Risk associations for HPV DNA complicated by decreased HPV related to increased sun exposure, but increased HPV related to sunburn. Adjusted OR's not reported.
Alotaibi *et al.* (2006), Canada	12 AK 8 SCC	47	Skin swabs. PCR-sequencing directly and after FAP59/64 and HVP2/B5 primers All types in comparison with EMBL and GenBank	FAP59/64 SCC 88 AK 100 Median # Types: SCC 2.0 AK 3.5	 Ctl 87 Ctl 1.0	 1.0 n.a n.a.	Much higher prevalence with FAP primers shows importance of test method A greater number of types in AK or SCC than in healthy participants; due more to novel than EV types
Karagas *et al.* (2006), United States	252 SCC 525 BCC	461 age matched	Multiplex serology based on ELISA, full-length L1 proteins linked to fluorescent beads Alpha: HPV 2, 3, 6, 10, 16, 32, 57; Beta-1 HPV 5, 8, 20, 24, 36; Beta-2 HPV 9, 15, 38; Mu HPV 1	SCC Alpha 28.6 Beta 32.5	 29.1 24.7	 1.2 (0.8–1.7) 1.5 (1.0–2.7)	Sun-related factors more prominent among participants who were beta HPV positive OR adjusted for age, sex, skin sensitivity No risk for BCC (OR <1.0 for both alpha and beta)

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Reference, study location	No. of cases	No. of controls	Method of detection	HPV prevalence (%)		Odds ratio (95% CI)	Comments/ adjustments
				Cases	Controls		
Struijk et al. (2006), Australia	64 SCC, 126 AK from hospital and clinics	57 tumour-free controls from ophthalmology outpatient clinic	E6 type-specific PCR to test DNA from 6-8 plucked eyebrow hairs L1 and E6 serology by ELISA Alpha 16 (serology only); beta-1 HPV 5, 8, 20, 24; beta-2 HPV 15, 38	*L1* AK 26.5 SCC 37.0 *DNA* AK 54.0 SCC 44.4	Ctl 13.5 Ctl 40.3	Main finding of L1 VLP seropositivity for SCC vs. normal, adj. **OR** All 3.9 (1.4–10.7) HPV 8 9.3 (1.9–45.6) HPV 15 3.8 (0.9–15.8) HPV 20 ∞ HPV 24 2.6 (0.7–9.7) HPV 38 ∞ (rare) HPV 16 7.9 (0.8–81.7)	L1 seropositivity elevated in AK and especially SCC DNA positivity highest in AK, not elevated in SCC overall or specific types, some evidence against risk of HPV 38 E6 not related to risk
Casabonne *et al.* (2007), UK	Stored plasma from 15 prevalent SCC, 39 subsequent incident SCC	80 controls with no SCC	Multiplex serology based on ELISA, full-length L1 proteins linked to fluorescent beads 38 alpha, beta, gamma, and other types	Incident 1 12.8 2+ 66.7	Ctls 20.0 66.2	Incident 0.4 (0.1–1.9) 0.7 (0.2–2.1)	Prevalent cases had elevated seropositivity for many beta types (e.g., HPV 8) compared with controls, but incident cases did not. Incident cases with diagnosis closest to blood draw showed some elevation. Low power, but results suggest that seropositivity might rise with disease onset

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Forslund *et al.* (2007), Sweden	Lesional biopsy from 349 participants: 82 SCC, 126 BCC, 49 AK, 92 benign lesions.	1 control biopsy near each lesion from all 349 participants	PCR testing for DNA in triplicate (3 laboratories) followed by sequencing of 2-mm biopsies taken after stripping of skin surface with tape. All sequenced HPV types in GenBank. Positive for a type if found in 2/3 or 3/3 labs.	Benign 26.1 AK 22.5 BCC 17.5 SCC 25.6	Healthy 12.0	3.1 (1.7–5.8) 1.4 (0.6–3.1) 1.4 (0.8–2.6) 2.1 (1.1–4.0)	Adjusted for age, sex, skin type and eye colour, sun exposure and sunburn Beta species-2 types more common in SCC, Beta-1 types more common in benign lesions, than healthy skin HPV prevalence strongly associated with areas of skin exposed to sunlight (OR= 4.3, 95% CI 2.7-6.8, raising possibility of residual confounding of association found between lesions and HPV
Waterboer *et al.* (2008), Italy	43 SCC	77 hospital controls with unrelated skin conditions, frequency matched for age and sex	Multiplex serology based on ELISA, full-length L1 proteins linked to fluorescent beads. 31 types from 5 genera			Any beta-2 (OR 3.3, 1.2–8.7) Any gamma (OR 3.1, 1.1–8.6)	In multivariable models adjusting for all types, gamma HPV 95 and 50 were significantly associated with risk.