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Nail Squamous Cell Carcinoma: A Hidden High-risk HPV Reservoir for Sexually Transmitted Infections

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Abstract

Human papillomavirus (HPV) causes cervical cancer, anal cancer, vulvar cancer, vaginal cancer, penile cancer and oropharyngeal cancer. SCC in the genital region in particular is recognized to be caused by HPV infection, and intraepithelial lesions of the penis and vulva are termed penile intraepithelial neoplasia (PIN) and vulvar intraepithelial neoplasia (VIN), respectively. Although SCC of the nail apparatus is recognized as being associated with high-risk HPVs, it is not well-known in general medicine, and its analysis has been insufficient. In this article, we reviewed 136 cases of HPV-associated nail SCC and SCC in situ and delineated their clinical characteristics. We found that half of the cases were high-risk HPV-associated. Almost all of the types were high-risk α-HPVs. This disease had male dominance and left digit 3 and right digits 1-3 were typically affected. In this review, 24% of the cases of nail SCC had a history of other HPV-associated diseases, suggesting the possibility of genito-digital transmission. We propose that nail SCC is a hidden high-risk HPV-associated reservoir and should be recognized as a sexually transmitted infection.

Squamous cell carcinoma (SCC) of the skin can develops from preceding lesions, such as actinic keratosis, Bowen's disease, burn scars and chronic radiation dermatitis. Bowen's disease is SCC *in situ* and is sometimes induced by high-risk human papillomavirus (HPV) infection. [1, 2] We previously reported that genital SCC and nail SCC *in situ* (Bowen's disease) are HPV-associated diseases. [3, 4] SCC in the genital region in particular is recognized to be caused by HPV infection, and intraepithelial lesions of the penis and vulva are termed penile intraepithelial neoplasia (PIN) and vulvar intraepithelial neoplasia (VIN), respectively. [5] Although 60% to 80% of cases of SCC of the nail apparatus have been reported to be associated with high-risk HPVs (mainly HPV 16) [6-8], this fact is not widely known in general medicine, and systemic analyses have not been performed.

In this article, we reviewed 136 cases of HPV-associated nail SCC and SCC *in situ* and delineated their clinical characteristics. Based on analyses of HPV types reported in the literature, we propose that nail SCC is a hidden high-risk HPV-associated reservoir site for sexually transmitted infection (STI).

Anatomy of the nail apparatus and clinical classification of nail SCC

The nail apparatus consists of the nail plate, nail matrix, nail bed, hyponychium, grooves and fold surrounding the nail plate. The nail matrix is located at the ventral surface of the proximal portion of the nail and forms the nail plate (Figure 1A). The most proximal portion of the nail matrix lies proximal to the nail root, which is embedded beneath the proximal nail fold (Figure 1B).

We previously reported on cases of nail Bowen's disease (Figure 1C). [3, 4] In these cases, numerous HPV-positive cells were seen around the nail fold, especially in the nail matrix (Figure 1D, E). Of note, HPV-positive cells were distributed even in the epithelial cells of the proximal nail fold, suggesting that the HPV infection spreads beyond the clinically visible lesion. The HPV-positive areas were plotted in a schematic illustration shown in Figure 1F.

In this article, we classified nail lesions of SCC into two types: periungual type (PUT), defined as lesions occurring in the periungual area, such as the nail fold and nail groove (Figure 1G); and subungual type (SUT), defined as lesions located beneath the nail plate. “Longitudinal melanonychia type (LMT)” is clinically characterized by a pigmented streak of the nail plate and is included in SUT (Figure 1H).

Search strategy and selection criteria

We searched the English literature of HPV-associated nail SCC from 1983 to 2017 by PubMed using the following keywords: human papillomavirus, HPV, nail, nail bed, nail matrix, digits, fingers, SCC, Bowen disease, Bowen's disease and skin cancer.

Patient demographics

We found 136 patients with nail SCC (53 patients) and SCC *in situ* (83 patients). Since multiple lesions were seen in 11 patients, the number of tumors on the fingers and toes was 140 and 16 tumors, respectively (Table 1, 2). We used the term "nail SCC" for both invasive SCC and SCC *in situ* unless otherwise specified. The patients' ages ranged from 12 to 85 years (average age 52.2 years and median age 50; 5 cases were unknown) and sex ratio was 2.3:1 (92 males and 39 females; 5 cases were unknown). Right fingers were affected in 61 cases and left fingers in 54 cases: right f-1,17; f-2, 17; f-3 17; f-4, 6; f-5, 4 (Figure 2A) and left f-1, 1; f-2, 12; f-3, 19; f-4, 13; f-5, 9 (Figure 2B). The most frequently affected digits were the left middle finger (f-3) followed by the right middle finger (f1-3). Five cases had toe lesions. Clinically, 46 (34%) of the tumors were classified as PUT, 35 (26%) as SUT/LMT and 7 as both types (5%) (Table 1).

HPV types associated with nail SCC

Although the number was limited, 7 case series of nail SCC were reported with analyses of

HPV types, in which 47% (49/104) of nail SCC cases were positive for high-risk HPVs (Table 3). This value was comparable to those of other HPV-associated cancers [9].

Next, we collected the HPV types described in the literature, irrespective of the methods used. In 21 patients, multiple HPVs were detected. The detection rates of HPV types were as follows: high-risk HPV type 16 in 80 cases (57%), HPV56 in 12 cases (9%), HPV73 in 8 cases (6%), HPV33 in 7 cases (5%) and HPV58 in 6 cases (3%). As expected, HPV16 accounted for more than half of the lesions. When the lesions were classified into invasive and *in situ* lesions, HPV16 accounted for 50% of nail SCC *in situ* cases and 73% of invasive SCC cases (Figure 2C, D). Although the number was limited, the detection rates of minor HPV types were also different between invasive and *in situ* lesions. For example, HPV56 was observed in 12% (11 cases) of *in situ* lesions and 0% of invasive lesions (Figure 2D). There is increasing evidence that, under certain circumstances, such as immunodeficiency, β-HPVs play a role in cutaneous carcinogenesis. β-HPVs are ubiquitous in normal hair follicles from early childhood. Almost all of the HPVs associated with nail SCC were α-HPVs; however, β-HPVs 9, 17, 21 and 49 were detected in 2 patients. [10, 11]

Finally, we compared the HPV types between the two clinical types. In PUT, the HPVs detected were as follows: HPV16 in 24 cases (45%), HPV73 in 6 cases (11%), HPV33 in 5 cases (9%), HPV58 in 4 cases (9%), HPV35 in 3 cases (6%), HPV34 in 3 cases (6%), HPV51 in 3 cases (6%), HPV18 in 2 cases (4%), HPV26 in 2 cases (4%) and HPVs 9, 11, 17,

21, 49 and 82 in 1 case each (Figure 2E). In SUT/LMT, the HPVs detected were as follows: HPV16 in 15 cases (47%), HPV56 in 11 cases (34%), HPV59 in 3 cases (9%), HPV18 in 2 cases (6%) and HPVs 6, 26, 33, 39, 45, 52, 68 and 84 in 1 case each (Figure 2F). While HPV16 was most frequent in both types, other HPVs were detected in varying degrees of frequency. Of note, HPV56 showed characteristics typical of LMT, as HPV56 was detected in 10 out of 15 cases. HPV56, a minor HPV for cervical cancers, may have specific affinity for subungual epithelium.

HPV susceptibility of the nail matrix

All of the lesions included in this article involved the proximal nail fold (Figure 1G, H), suggesting that HPV infection in the nail matrix cells occurs secondary to infection of the nail fold. Given that HPV infects cervical squamocolumnar junction cells in cervical cancer, [12-15] similar cells in the nail apparatus might be targeted by HPV. Furthermore, Ito et al. reported the absence of Langerhans cells in the nail matrix. [16] The immunological characteristic of the nail matrix may account in part for its susceptibility to HPV infection. Further studies on this point will be required.

Treatment and recurrence rate of HPV-associated nail SCC

Several treatments are available for nail SCC. In this review, we summarize the treatments

and recurrence rate of HPV-associated nail SCC invasive and SCC *in situ*. In SCC invasive, the Mohs micrographic technique was most frequently performed, with a recurrence rate of 23% among the 30 reported cases. The largest single-institution study was reported by Alam et al., who found that recurrence occurred in 6 (26%) out of 23 cases treated with Mohs surgery. Interestingly, the recurrence rate of nail SCC invasive after Mohs micrographic surgery (26%) was higher than the average recurrence rate for all cutaneous SCC after Mohs micrographic surgery (3%). [17, 18] It was reported that HPV-associated nail SCCs exhibited higher expression of $p16^{INK4a}$ and Ki67, suggesting that an increased cellular proliferation rate may be one of the factors underlying the aggressive behavior. [11] In addition, residual oncogenic HPV persisting in cells beyond the visible tumor margin (seen in Figure 1E) may be responsible for the high recurrence rate. [6] Although the detection of HPV was not routinely performed, several reports found that the recurrence rate of nail SCC after Mohs surgery ranged widely, from 0% [19] to 8% [20] to 22%[21]; however, these values are all lower than the 23% recurrence rate reported in this study. The outcome of HPV-positive and HPV-negative nail SCC after Mohs surgery needs to be studied further.

In the SCC *in situ* cases, surgical excision was most frequent in 15 cases with a recurrence rate of 33%. In two cases, wedge-shaped excision was performed, but recurrence was noted. PDT, [22] radiotherapy [23] and cryosurgery [24] have been reported; however, they were less effective than other approaches. Hunt et al. reported that radiotherapy was well tolerated

and less disabling than surgery to preserve the finger function and appearance. [25]

Prevention of nail SCC by vaccination

Recently, HPV vaccination through Cervarix (HPV 16 and 18), Gardasil (HPV 6, 11, 16, 18) and Gardasil 9 (HPVs 6, 11, 16, 18, 31, 33, 45, 52, 58), has become available in some countries. This review confirmed that HPVs 16, 33, 56 and 73 were prevalent in nail SCC with male predominance. Gardasil 9 may partially prevent nail SCC; however, HPV types 56 and 73 are not covered. To design a vaccine against HPV types, high-risk HPV infection in the skin should be taken into consideration.

Nail SCC in the global burden of cancer

The global burden of cancer caused by infectious agents has been reported. [9, 26] Plummer et al. calculated the number of cancer cases attributable to infections by combining the cancer incidence (from GLOBOCAN 2012) with the attributable fraction (AF) of infections. Martel et al. built on Plummer's report to clarify the annual incident of HPV-associated cancer by adding more detailed data (e.g. by country and cancer subsites). The reported respective number of incident cases, AF and number of HPV-associated cases for each cancer were as follows: cervical cancer (630,000, 100.0%, 530,000), anal cancer (40,000, 88.0%, 35,000), vulvar cancer (34000, 24.9%, 8,500), vaginal cancer (15000, 78.0% 12,000), penile cancer

(26000, 50.0%, 13,000) and oropharyngeal cancer (96000, 30.8%, 29,000). [9]

The lack of data concerning the annual incidence of nail SCC is an issue, so the number of SCC of extremities (C44.6 Malignant neoplasm: Skin of upper limb, including shoulder) was newly collected for the 10th version, ICD-10. Although the number is limited, an analysis of seven case series of nail SCC found that the AF was approximately 47% (Table 3). The average number of patients with HPV-associated nail SCC in our department is two cases/year. Gunma University Hospital is a tertiary hospital of Gunma Prefecture, which has a population of 2 million. We thus estimated the rate of nail SCC to be 1 per 1 million population per year. The global population is 7 billion, so about 7,000 people per year are estimated to be newly suffering from HPV-associated nail SCC. This number is comparable to that of vulvar cancer (8,500 per year).

Nail apparatus intraepithelial neoplasia (NIN)

Other HPV associated *in situ* lesions include intraepithelial neoplasia, such as cervical intraepithelial neoplasia (CIN), anal intraepithelial neoplasia (AIN), VIN and vaginal intraepithelial neoplasia (VAIN), all of which are HPV-associated lesions in ICD-10. In this context, we propose the term, “nail apparatus intraepithelial neoplasia (NIN)”. Based on a review of the previous cases, the characteristics of “NIN” are as follows: predominantly affects men, all fingers except the left small finger can be affected, young age of onset

compared to common cutaneous SCC *in situ* and lesion can be clinically classified into two types (PUT and SUT/LMT).

In contrast to other HPV-associated cancer, such as CIN and AIN, NIN can be self-assessed. In many cases, however, a delay from the first clinical manifestation noted by the patient to the first medical consultation has been reported. Perruchoud et al. reported that the mean delay was 5.7 years (range: <1 month to 20 years). They also checked the initial diagnosis and reported that viral warts and/or onychomycosis were most common. [27] The two phenotypes PUT and SUT/LMT should be widely recognized by doctors in order to facilitate the early correct diagnosis.

Sexual transmission of high-risk HPV between the nail apparatus and the genitals

The present data suggest that there is a high risk of HPV transmission through the nail apparatus. First, the age of the patients and sex were characteristic. As shown in Table 1, the average age was 52 years old (median: 50 years old), which is younger than that of ordinary SCC at other body sites, and this disease predominantly affects men. Second, we encountered 11 cases that had multiple finger lesions, suggesting that causative HPV is transmissible. Finally, as shown in Figure 2 in “Patient demographics”, the distribution of the affected digits was characteristic. This distribution strongly suggests that high-risk HPV transmission occurs via the genito-finger route. The distribution also suggested that the transmission of HPV from

men to their partners is likely to occur, strongly indicating nail SCC to be an STI.

Furthermore, in this review, 24% of the cases of nail SCC had a history of other HPV-associated diseases. Among female patients, 36% suffered from HPV-associated lesions, suggesting that self-inoculation was a possible route of infection. Forslund et al. reported two patients with nail SCC who had a history of genital dysplasia. They performed sequencing of HPV DNA and revealed that the nail and genital lesions were caused by patient-specific HPV16 strains. [28] Furthermore, they described five female patients diagnosed with genital dysplasia and Bowen's disease of the fingers who had the same HPV16 in both lesions. [29] In all cases, finger SCC was noted after the diagnosis of the genital lesion. It is of interest that the partners of five of the male patients had a history of gynecological diseases, suggesting genito-digital transmission in male patients. Alam et al. investigated 23 cases of nail SCC and found that the 2 female patients had suffered from cervical carcinoma, and the partners of 5 male patients had gynecological disease. [6] They suggested the genito-digital spread of HPV as a mechanism of nail SCC. [6]

Taken together, these findings suggest that high-risk HPV-associated nail SCC is not rare and should not be overlooked. The nail apparatus is another pivotal reservoir of high-risk HPV and should be recognized in the field of public health.

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445

Figure legends:

Figure 1. The distribution of HPV-infected cells in the nail apparatus and the classification of nail SCC.

(A) Side view of the nail apparatus.

(B) Top view of the nail apparatus.

(C) HPV56-positive nail SCC (SUT/LMT) and the area for surgical excision[4].

(D) Anti-HPV antibody-positive cells on the proximal nail fold.

(E) High-power view of the inset. Anti-HPV antibody-positive cells in the epidermis and stratum corneum.

(F) Distribution of anti-HPV antibody-positive cells. The circle indicates the HPV-positive area.

(G) Representative clinical manifestation of nail SCC (PUT); the HPV58-positive case was previously reported [30].

(H) Representative clinical manifestation of nail SCC (SUT/LMT); the HPV56-positive case was previously reported [3].

Figure 2. HPV-positive digital lesions and HPV types detected in nail SCC.

(A, B) The number of HPV-positive digital lesions.

(C, D) HPV types detected in nail SCC *in situ* and SCC invasive.

465 (E, F) HPV types detected PUT and SUT/LMT.

466

Table 1. Clinical summary of nail SCC (1983-2018)

No. of patients		136
Age (Average, range)		52.2years (12-85years)
Sex	Male:Female	92:39*
Clinical findings		
	SCC	53
	SCC *in situ*	83
	Periungual type (PUT)	46 (52%)
	Subungual/LM type (SUT/LMT)	35 (40%)
	PUT+SUT/LMT	7 (8%)
	Others/unknown	48
	Multiple lesions	11 (8%)
Other HPV-associated disease		
	Male	18/92 (20%)
	Female	14/39 (36%)
immunocompromised condition		18 (13%)

*Sex of Five patients' was unknown.

467

468

469 **Table 2. Nail SCC/Bowen's disease as reported in the literature**

No	Reference	Tumor	Age (years)/ Sex	Digit	HPV	Type	Therapy	Recur	Lesions of HPV	ICH
1	Ikenberg et al. [1] 1983	SCCis	74/F	ns	16	ns				
2	Kawashima et al. [31] 1986	SCCis	69/F	L3F	34	PUT			Warts, Cervical cancer	
3	Stone et al. [32] 1987	SCCis	36/M	R4T	16	other	Excision		GW	Silicosis
4	Ostrow et al. [33] 1987	SCCis	37/M	R1F	16	PUT				EV with SCC
5	Moy et al. [2] 1989	SCCis	47/M	L3F	16	PUT	Mohs			
6		SCCis	22/F	R4F	16	PUT	Mohs			
7		SCC	52/M	L2,3F	16	PUT	Mohs			
8		SCC	56/M	R2F	16	PUT	Mohs			
9		SCC	44/F	L3F	16	PUT	Mohs			
10	Ostrow et al. [34] 1989	SCCis	48/M	L2F	16	SUT	Mohs			
11	Rudlinger et al. [35] 1989	SCCis	42/F	R4F	35	PUT	Excision, radiation, Cryo, IFN		BP with HPV35	PCC
12	Guitart et al. [36] 1990	SCCis	69/F	L3F	16/18	SUT	Excision	yes	Cervical cancer with HPV16/18, Warts	
13	Eliezri et al. [37] 1990	SCCis	ns	ns	16	PUT				
14	Kettler et al. [38] 1990	SCCis	36/M	ns	16	other			CA with HPV11	
15		SCCis	60/M	ns	16	other			BD of Penis with HPV16	
16	Echt,	SCC	63/M	R2F	16,18	PUT				

	Hurwitz and Davis [39] 1990									
17	Ashinoff et al.1991	SCCis	26/M	R1F	16	other	Mohs			
18		SCC	46/M	R1F	16	other	Mohs			
19		SCCis	75/M	R5F	16	other	Mohs			
20		SCCis	29/M	L4F	16	other	Mohs			
21		SCC	84/M	R3F	16	other	Mohs			
22	Moy and Quan [40] 1991	SCC	71/F	R3F	16	Unknown	Mohs			
23	Rapini et al. [41] 1992	SCCis	66/F	R1F	16-related	PUT				
24		SCCis	42/M	L4F	16-related	PUT			Warts	
25		SCCis	76/M	R2F	16-related	PUT				
26	McGrae et a. [42] 1993	SCCis	42/M	R2,3,4F	16	other	Tretinoin, 5-FU, Bleo		GW with HPV6	
27	Sau et al. [43] 1994	SCCis	55/M	L3F	16	SUT/PUT	Mohs			
28		SCCis	61/M	L1F	16	SUT/PUT	Mohs	yes		
29		SCCis	39/M	L3F	16	SUT/PUT	Mohs			
30		SCCis	48/F	L4F	16	SUT/PUT	5-FU	yes		
31	Nordin et al. [44] 1994	SCCis	31/F	R3F	16	SUT/PUT	Excision	yes	VIN with HPV16	
32	Tosti et al. [45] 1994	SCC	28/M	R1F	16	SUT			Warts	AIDS
33	Sanchez-Lanier et al. [46] 1994	SCC	ns	ns	16	Other				
34		SCC	ns	ns	16	Other				
35		SCC	ns	ns	16	Other				
36		SCC	ns	ns	16	Other				
37	Sasaoka et al. [47] 1996	SCC	83/M	R4,5T	16	Other	Amp			

38		Verr Ca	79/M	R5T	16	PUT	Amp			
39	McHugh et al. [48] 1996	SCC	51/M	L1F	35	PUT	Mohs	yes		
40	Forslund et al. [28] 1997	SCCis	33/F	R1F	16	PUT	PDT		Genital dysplasia with HPV16 related HPV	
41	Forslund et al. [28] 1997	SCCis	38/F	L4F	16	SUT				
42	Downs et al. [49] 1997	SCC	35/M	R3F	16	SUT	Excision			Darier's disease
43	Mitsuishi et al. [50] 1997	SCCis	53/M	R3F	16	PUT				
44		SCCis	34/F	L3F	73	PUT				
45	Forslund et al. [28] 1997	SCCis	57/F	L4F	16	PUT			CIN with HPV16	
46	Sass et al. [8] 1998	SCCis	67/M	L4F	16	SUT/LMT	Excision			
47	Theunis et al. [51] 1999	SCCis	67/M	L4F	16	SUT				
48		SCCis	78/M	R1F	16	SUT				
49		SCCis	83/M	R1F	16	SUT				
50	Forslund et al. [29] 2000	SCCis	61/F	L3F	16	SUT			cervical cancer with HPV16	
51	Zabawski et al. [52] 2001	SCC	47/F	R3F	ns	SUT	Amp			
52		SCC	89/M	R4F	ns	SUT	Radiation			
53		SCC	72/M	L3F	ns	SUT	Radiation			
54	Ota et al. [53] 2002	SCCis	80/M	L2F	18	PUT				Formerly Gynaecologist
55	Alam et al.	SCC	50/F	R4F	16	SUT	Mohs	yes	Cervical	

	[6] 2003								cancer, hysterectomy
56		SCC	78/M	R3F	16	PUT	Mohs	yes	
57		SCC	28/M	R2,4F	16	ns	Mohs		
58		SCC	45/F	R2F	16	ns	Mohs		
59		SCC	52/M	R3F	16	ns	Mohs		
60		SCC	60/M	L1F	ns	ns	Mohs		CA	Heart transplant
61		SCC	82/M	L3F	31	ns	Mohs		Wife with hysterectomy	Organic chemical exposure
62		SCC	64/M	R3F	16	ns	Mohs		Wife with cervical cancer. hysterectomy	
63		SCC	37/M	R2F	16	ns	Mohs			
64		SCC	65/F	L2F	ns	ns	Mohs			Kidney transplant
65		SCC	80/F	R1F	ns	ns	Mohs			
66		SCC	67/M	R2F	ns	ns	Mohs	yes	Wife with hysterectomy	
67		SCC	62/F	R5F	ns	ns	Mohs		Hysterectomy	
68		SCC	63/F	R3F	16	ns	Mohs	yes		
69		SCC	76/M	L2F	16	ns	Mohs			
70		SCC	30/M	L2F	16	ns	Mohs		Wife with cervical dysplasia	
71		SCC	81/M	L5F	16	ns	Mohs			
72		SCC	45/F	R2F	16	ns	Mohs			
73		SCC	40/F	R5F	35	ns	Mohs			
74		SCC	52/M	L2F	16	ns	Mohs			
75		SCC	48/F	R2F	16	ns	Mohs			
76		SCC	68/F	R3F	16	ns	Mohs	yes		
77		SCC	47/F	L3F	16	ns	Mohs	yes		

78	Lambiase et al. [54] 2003	SCCis	25/M	R3F	56	SUT/LMT	Mohs			
79	High et al. [55] 2003	SCC	36/M	R2F	26	PUT				
80	Hara et al. [56] 2004	SCCis	46/F	ns	58	PUT			Vulva and cervical cancer with HPV68	
81	Sato et al. [57] 2004	SCCis	55/M	L4F	11, 16	PUT				
82	Weisenseel et al. [58] 2006	SCCis	49/M	L3F	73	PUT				
83	Handisurya et al. [59] 2007	SCC	28/M	ALL	26, 58	SUT	Unknown		BP with HPV26	AIDS with HAART
84	Ekeowa-Anderson et al. [10] 2007	SCCis	23/F	L3F	21,34,49,58	PUT			VIN with HPV21, 31, 34	
85	Shimizu A et al. [4] 2008	SCCis	34/M	L2T	56	SUT/LMT	WS- excision	yes		
86		SCCis	68/M	R1F	56	SUT/LMT	Excision			
87		SCCis	29/F	L1T	56	SUT/LMT	WS- excision	yes		
88	Guldbakke et al. [60] 2008	SCCis	32/M	R1F, L2F	73	PUT	Mohs	yes		HL
89	Depond et al. [61] 2009	SCC/SCCis	55/M	ns	58, 73	ns				
90	Inokuma et al. [62] 2009	SCCis	41/M	R2F	56	SUT/LMT				
91	Kreuter et al. [11] 2009	SCCis	62/M	R2F	26	PUT	5-FU		AW, PW, OW, AIN, PIN	HIV

92		SCC	71/M	L2F	51	other	Amp	PW	
93		SCC	62/F	R2F	16	other	Amp	PW	
94		SCCis	52/M	R1F	73, 81	other	Excision	AW	
95		SCC	71/M	L1F	33	other	Amp		
96		SCCis	59/M	L2F	56, 9, 17, 36	PUT	Excision	PW and CIN (Female partner)	
97	Turowski et al. [63] 2009	SCCis	42/M	L1,R4, 5F	16	PUT	IQ+Mohs		
98		SCCis	44/M	R3F	High-risk HPV	PUT	Mohs+IQ		HIV
99	Tanese et al. [64] 2009	SCC	29/M	L1F	59, 84	SUT	Amp		RP
100	Nakajima et al. [65] 2010	SCCis	56/M	L3F	8, 16, 58	PUT			ATL
101	Aguayo et al. [66] 2010	SCCis	54/F		16, 6	SUT		CIN and hysterectomy	
102	Gormley et al. [67] 2011	SCCis	47/M	R4F	33, 51	PUT			
103		SCCis	44/M	ns	16	PUT			
104		SCCis	42/M	R1F	33, 73	PUT			
105		SCCis	44/F	L2,4F	33, 51, 73	PUT			HIV
106		SCCis	50/F	R3F	33, 51	PUT			
107	Ohishi et al. [68] 2011	SCCis	50/M	L4F	56	SUT/LMT			
108		SCCis	36/M	L4F	16	SUT/LMT			
109		SCCis	41/M	L3F	59	SUT/LMT			
110		SCCis	32/M	L3F	56	SUT/LMT			
111		SCCis	43/M	R1F	56	SUT/LMT			
112		SCCis	66/M	L3F	52	SUT/L			

113		SCCis	41/M	R5F	33	MT SUT/L MT				
114	Grundmeier et al. [69] 2011	SCC	46/M	R2F	16	PUT	Amp			
115		SCCis	50/M	L1F	16, 31, 33	PUT	Micrographic entire nail unit excision+IQ			
116		SCCis	67/M	R2F	73	PUT	Tangential excision +LASER	yes		HIV
117	Hunt et al. [70] 2011	SCCis	60/F	R1,2F, L2-5F	16	SUT/PUT			VIN invasive, cervical cancer partner with GW	
118	Patel et al. [71] 2011	SCC	68/F	R1F	18,39,45,59,68	SUT	Amp			
119	Shimizu A et al. [3] 2012	SCCis	67/M	L2F	56	SUT/L MT	Excision			
120	Park et al. [72] 2012	SCCis	33/M	L1F	ns	SUT/L MT	Longitudinal excision			
121	Hunt et al. [25] 2013	SCC/ SCCis	36/M	R2,3,4F	High-risk HPV	PUT	Amp, radiation	yes		AML, GVHD
122	Kato et al. [30] 2013	SCCis	36/M	R3F	58	PUT	Excision			
123	Nordin et al. [73] 2013	SCCis	57/M	R2F	16	PUT	Excision	yes		
124	Sohn et al. [74] 2015	SCCis	85/F	R3F	56	SUT/L MT	no treatment			
125	Shimizu A et al. [75] 2015	SCCis	84/M	R2F	67	SUT/L MT	Excision			
126	Nanba et al. [76] 2015	SCCis	51/M	L2F	16, 82	PUT			Genital BD	

127	Hyun et al. [77] 2016	SCCis	12/M	R2F	34	PUT	PDT	
128	Ogata et al. [78] 2016	SCC	46/M	L4F	16	SUT	Amp	Digital lesion with HPV90
129	Perruchoud et al. [27] 2016	SCCis	58/M	R3F, L3F	73	other	Cryo/Surgery	
130		SCCis	44/M	L4F	16	other	IQ	
131		SCCis	51/M	L1F	16	other	None	
132		SCCis	44/M	R1F	16	other	Cryo	
133		SCCis	50/F	L2F	16	SUT/PUT	Cryo/bleo	
134		SCCis	52/M	L2F	52	other	None	
135		SCCis	36/M	R1F, L3F	16	other	5-FU+SA+antimycotic	
136	Makino et al. [79] 2017	SCCis	46/F	R4F	35	PUT	Excision	

PUT: periungual type, SUT: subungual type, LMT: longitudinal melanonychia type, ns: not specified, ICH: immunocompromised host, BD: Bowen disease, PW: penile warts, AW: anal warts, OW: oral warts, GW: genital warts, BP: Bowenoid papulosis, PDT: photodynamic therapy, Cryo: cryotherapy, SA: salicylic acid, HAART: highly active anti-retroviral therapy, WS-excision: wedge-shaped excision, IQ: imiquimod, Amp: amputation, Bleo: bleomycin, HL: EV: epidermodysplasia verruciformis, Hodgkin's lymphoma, RP: relapsing polychondritis, PCC: pheochromocytoma, SCC: squamous cell carcinoma.

478

Table 3. Case series and attributable rate

Year	Author	SCC or *in situ*	AR*	Number of samples positive for HR**-HPV	Methods
1991	Ashinoff et al. [80]	Both***	71%	5/7 positive for HPV16	PCR and *in situ* hybridization
1994	Sau et al. [43]	SCC *in situ*	57%	4/7 positive for HR-HPV	*in situ* hybridization
2008	Shimizu et al. [4]	SCC *in situ*	60%	3/5 positive for HR-HPV	PCR
2009	Kreuter et al. [11]	Both	24%	6/25 positive for HR-HPV	PCR
2011	Ohishi et al. [68]	SCC *in situ*	100%	7/7 positive for HR-HPV	PCR
2016	Perruchoud et al. [27]	SCC *in situ*	75%	9/12 positive for HR-HPV	PCR
2017	Dika et al. [81]	SCC	37%	15/41 positive for HPV16	PCR
Average			47%	49/104	

AR*: attributable rate, HR**: high-risk, Both***: SCC *in situ* and invasive.

479

480

Fig. 1

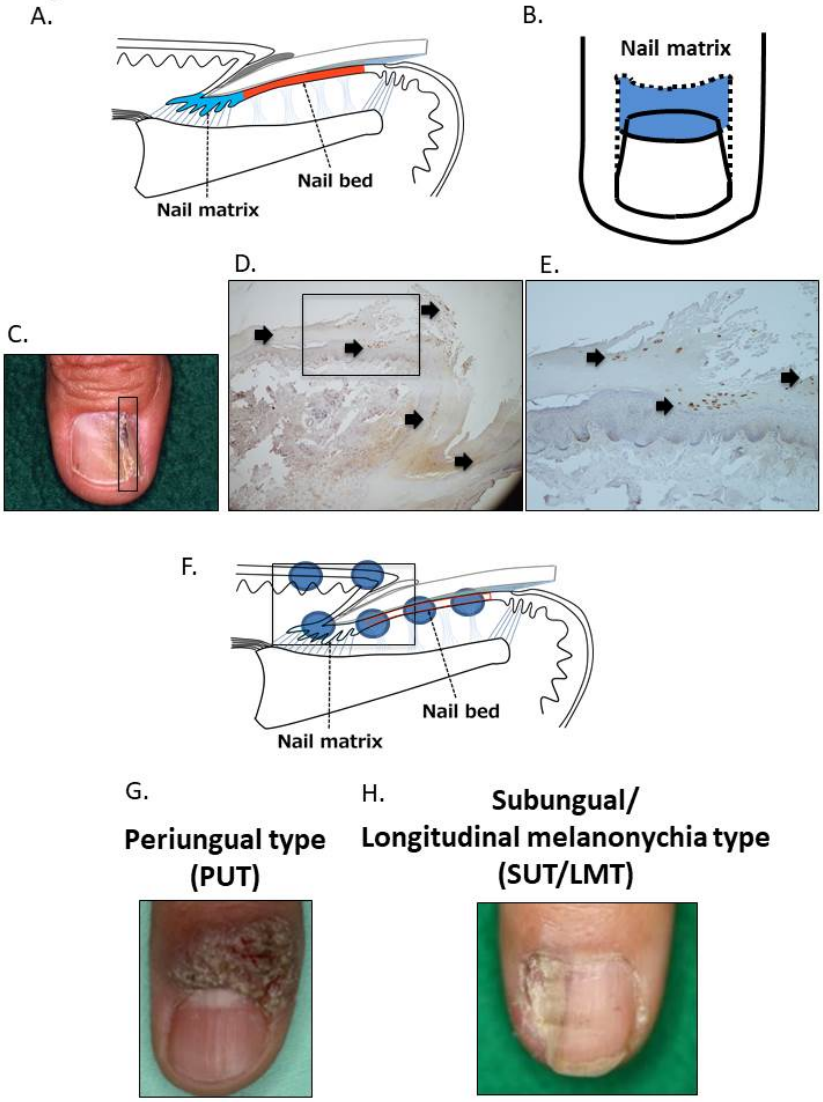
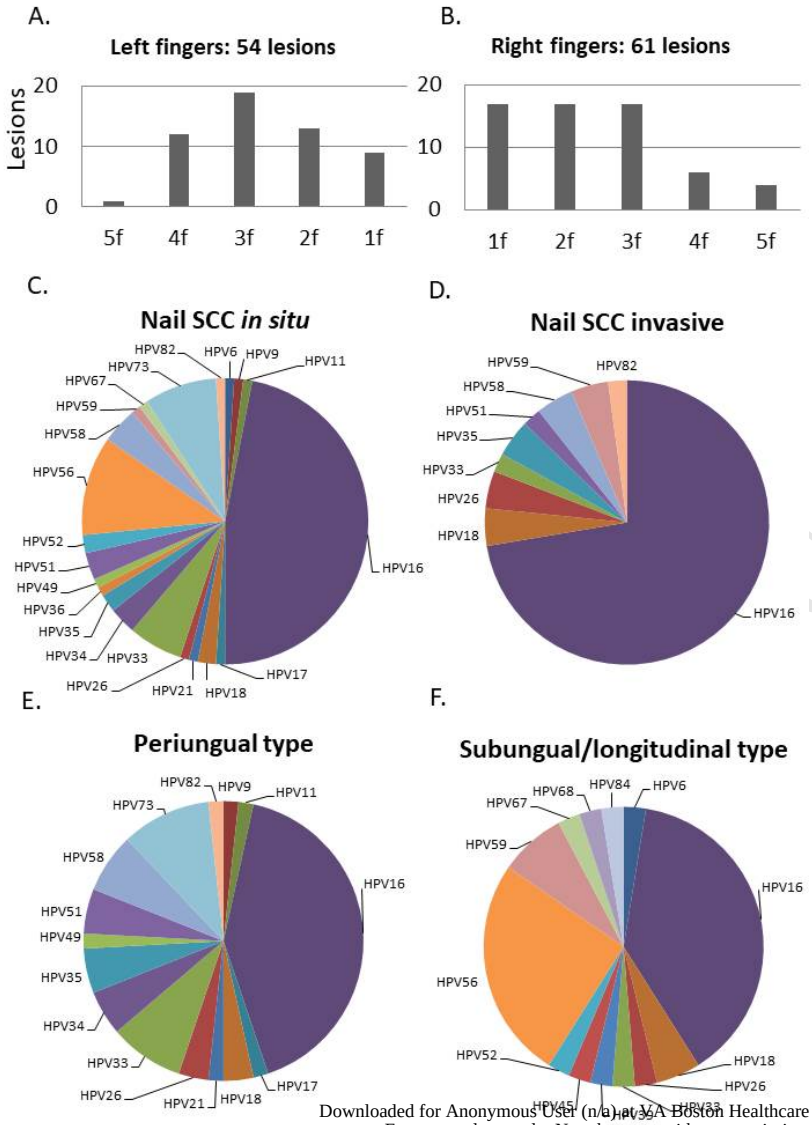


Fig. 2



Capsule summary

First bullet:

Nail squamous cell carcinomas are often HPV associated skin tumors.

Second bullet:

High-risk HPV-associated nail squamous cell carcinoma is not rare and should not be overlooked. The nail apparatus is another pivotal reservoir of high-risk HPV and should be recognized in the field of public health.