Nail squamous cell carcinoma: A hidden high-risk human papillomavirus reservoir for sexually transmitted infections

Akira Shimizu, MD, PhD,[a] Yuko Kuriyama, MD,[a] Michiko Hasegawa, MD,[b] Atsushi Tamura, MD, PhD,[b] and Osamu Ishikawa, MD, PhD[a]
Maebashi and Isesaki, Japan

Human papillomavirus (HPV) causes cervical cancer, anal cancer, vulvar cancer, vaginal cancer, penile cancer, and oropharyngeal cancer. Squamous cell carcinoma (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 and vulvar intraepithelial neoplasia, 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 a male dominance and left hand digit 3 and right hand 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 genitodigital transmission. We propose that nail SCC is a hidden high-risk HPV-associated reservoir and should be recognized as a sexually transmitted infection. (J Am Acad Dermatol 2019;81:1358-70.)

Key words: Bowen disease; human papillomavirus; nail apparatus; sexually transmitted infections; squamous cell carcinoma.

Squamous cell carcinoma (SCC) of the skin can develop from preceding lesions, such as actinic keratosis, Bowen disease, burn scars, and chronic radiation dermatitis. Bowen 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 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 and vulvar intraepithelial neoplasia, respectively.[5] Although 60%-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. On the basis of 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.

ANATOMY OF THE NAIL APPARATUS AND CLINICAL CLASSIFICATION OF NAIL SCC

The nail apparatus consists of the nail plate, nail matrix, nail bed, hyponychium, and grooves and nailfold 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 (Fig 1, *A*). The most proximal portion of the nail matrix lies proximal to the nail root, which is embedded beneath the proximal nailfold (Fig 1, *B*).

From the Department of Dermatology, Gunma University Graduate School of Medicine, Maebashi[a]; and Isesaki Municipal Hospital, Isesaki.[b]

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Reprint requests: Akira Shimizu, MD, PhD, Department of Dermatology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. E-mail: shimizuakira@gunma-u.ac.jp.

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

In this article, we classified nail lesions of SCC into 2 types: periungual type (defined as lesions occurring in the periungual area, such as the nailfold and nail groove; Fig 1, *G*)[9] 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 (Fig 1, *H*).[3]

CAPSULE SUMMARY

- Nail squamous cell carcinomas are often human papillomavirus (HPV)—associated skin tumors.
- 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.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed for HPV-associated nail SCC articles published during 1983-2017 and written in English using the following key words: "human papillomavirus," "HPV," "nail," "nail bed," "nail matrix," "digits," "fingers," "SCC," "Bowen disease," "Bowen's disease," and "skin cancer."

PATIENT DEMOGRAPHICS

We found a total of 136 patients with nail SCC (53 patients) and SCC in situ (83 patients). Multiple lesions were seen in 11 patients, resulting in a total of 140 tumors on the fingers and 16 tumors on the toes (Tables I and II).[1-4,6,8-65] We used the term nail SCC for both invasive SCC and SCC in situ, unless otherwise specified. The patients' ages ranged 12-85 years (average 52.2 years, median 50 years [5 cases were of unknown age]), and the sex ratio was 2.3:1 (92 males, 39 females, 5 unknown). Fingers on the right hand were affected in 61 cases (1st digit, n = 17; 2nd digit, n = 17; 3rd digit, n = 17; 4th digit, n = 6; 5th digit, n = 4; Fig 2, *A*) and on the left hand in 54 cases (1st digit, n = 1; 2nd digit, n = 12; 3rd digit, n = 19; 4th digit, n = 13; 5th digit, n = 9; Fig 2, *B*). The most frequently affected digit was the left-hand middle finger, followed by the right-hand digits 1-3. Five cases included lesions on the toes. Clinically, 46 (34%) of the tumors were classified as periungual type, 35 (26%) as SUT and LMT, and 7 (5%) as both types (Table I).

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 these reports, 47% (49/104) of nail SCC cases were positive for high-risk HPVs (Table III).[4,11,23,27,30,43,66] This value was similar to those found in other HPV-associated cancers.[67]

Next, we assessed 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 16 in 80 cases (57%), HPV 56 in 12 cases (9%), HPV 73 in 8 cases (6%), HPV 33 in 7 cases (5%), and HPV 58 in 6 cases (3%). As expected, HPV 16 accounted for more than half of the lesions. When the lesions were classified into invasive and in situ lesions, HPV 16 accounted for 50% of nail SCC in situ cases and 73% of invasive nail SCC cases (Fig 2, *C* and *D*). Although our sample size was limited, the detection rates of minor HPV types were also different between invasive and in situ lesions. For example, HPV 56 was observed in 12% (11 cases) of in situ lesions and 0% of invasive lesions (Fig 2, *D*). 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]

Last, we compared the HPV types between the 2 clinical types. In periungual type, the HPVs detected were as follows: HPV 16 in 24 cases (45%); HPV 73 in 6 cases (11%); HPV 33 in 5 cases (9%); HPV 58 in 4 cases (9%); HPV 35 in 3 cases (6%); HPV 34 in 3 cases (6%); HPV 51 in 3 cases (6%); HPV 18 in 2 cases (4%); HPV 26 in 2 cases (4%); and HPVs 9, 11, 17, 21, 49, and 82 in 1 case each (Fig 2, *E*). In SUT and LMT, the HPVs detected were as follows: HPV 16 in 15 cases (47%); HPV 56 in 11 cases (34%); HPV 59 in 3 cases (9%); HPV 18 in 2 cases (6%); and HPVs 6, 26, 33, 39, 45, 52, 68, and 84 in 1 case each (Fig 2, *F*). HPV 16 was the most frequent in both types, and other HPVs were detected at various frequencies. Of note, HPV

Abbreviations used:

HPV: human papillomavirus
LMT: longitudinal melanonychia type
NIN: nail apparatus intraepithelial neoplasia
SCC: squamous cell carcinoma
SUT: subungual type

56 was associated with LMT and was detected in 10 out of 15 of these cases. HPV 56, a minor contributor to cervical cancer, might have a specific affinity for the subungual epithelium.

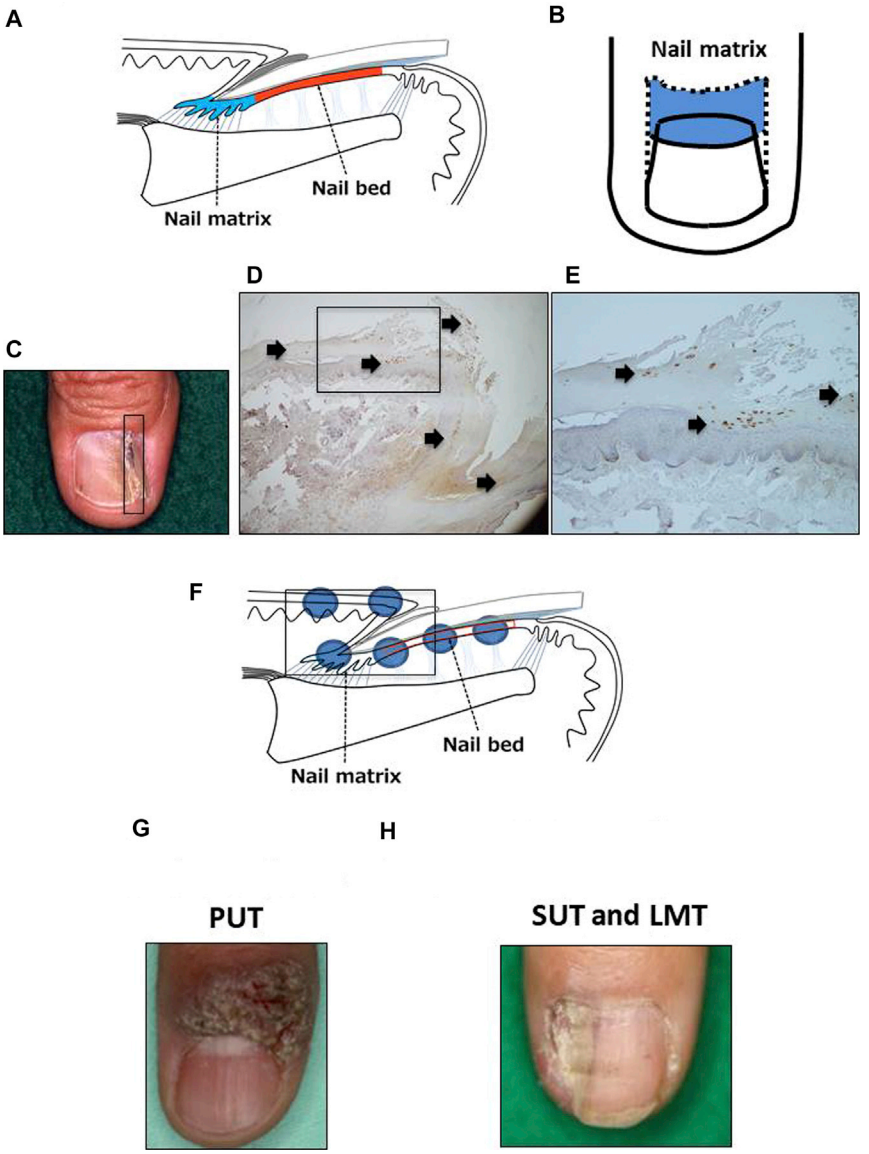

Fig 1. The distribution of human papillomavirus (HPV)–infected cells in the nail apparatus and the classification of nail squamous cell carcinoma (SCC). **A**, Side view of the nail apparatus. **B**, Top view of the nail apparatus. **C**, HPV 56–positive nail SCC (subungual and longitudinal melanonychia type [SUT and LMT]) and the area for surgical excision (*box*).[4] **D**, HPV antibody–positive cells (*arrows*) on the proximal nailfold. **E**, High-power view of inset in **D**. HPV antibody–positive cells (*arrows*) in the epidermis and stratum corneum. **F**, Distribution of HPV antibody–positive cells. *Circles* indicate the HPV-positive areas. **G**, Representative clinical manifestation of nail SCC (PUT); this HPV 58–positive case was previously reported.[9] **H**, Representative clinical manifestation of nail SCC (SUT and LMT); this HPV 56–positive case was previously reported.[3] *HPV*, Human papillomavirus; *LMT*, longitudinal melanonychia type; *PUT*, periungual type; *SCC*, squamous cell carcinoma; *SUT*, subungual type.

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

Category	Value
No. patients	136
Age, y, average (range)	52.2 (12-85)
Sex, male-to-female ratio	92:39*
Clinical findings, n (%)	
SCC	53
SCC in situ	83
Periungual type	46 (52)
SUT and LMT	35 (40)
Periungual type + SUT and LMT	7 (8)
Others or unknown	48
Multiple lesions	11 (8)
Other HPV-associated disease	
Male	18/92 (20)
Female	14/39 (36)
Immunocompromised	18 (13)

HPV, Human papillomavirus; *LMT*, longitudinal melanonychia type; *SCC*, squamous cell carcinoma; *SUT*, subungual type.
*Sex of 5 patients was unknown.

HPV SUSCEPTIBILITY OF THE NAIL MATRIX

All of the lesions included in this article involved the proximal nailfold (Fig 1, *G* and *H*), suggesting that HPV infection in the nail matrix cells occurs secondary to infection of the nailfold. Given that HPV infects cervical squamocolumnar junction cells in cervical cancer,[68-71] 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.[72] The immunologic characteristic of the nail matrix might account in part for its susceptibility to HPV infection. Further studies on this point are warranted.

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 invasive nail SCC and SCC in situ. In invasive SCC, the Mohs micrographic technique was most frequently performed, and the recurrence rate was 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%) of 23 cases treated with Mohs surgery.[6] Of note, the recurrence rate of invasive nail SCC after Mohs micrographic surgery (26%) was higher than the average recurrence rate for all cutaneous SCC after Mohs micrographic surgery (3%).[73,74] It has been reported that HPV-associated nail SCCs exhibited higher expression of $p16^{INK4a}$ and Ki67, suggesting that an increased cellular proliferation rate might be a factor underlying this aggressive behavior.[11] In addition, residual oncogenic HPV persisting in cells beyond the visible tumor margin (Fig 1, *E*) might be responsible for the high recurrence rate.[6] Although assessing for HPV was not routinely performed, reports indicate that the recurrence rate of nail SCC after Mohs surgery ranged widely, from 0%[75] to 8%[76] to 22%[77]; 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 SCC in situ cases, surgical excision was the most frequent treatment, occurring in 15 cases; the recurrence rate was 33%. In 2 cases, wedge-shaped excision was performed, and recurrence was noted. Photodynamic therapy,[78] radiotherapy,[79] and cryosurgery[80] have been reported treatments of nail SCC in situ; 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 (GSK, Brentford, UK; HPV 16 and 18), Gardasil (Merck, Kenilworth, NJ; HPV 6, 11, 16, 18), and Gardasil 9 (Merck; HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58) has become available in some countries. This review confirmed that HPVs 16, 33, 56, and 73 were prevalent in nail SCC with a male predominance. Gardasil 9 might partially prevent nail SCC; however, HPV types 56 and 73 are not covered. When designing 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.[67,81] Plummer et al calculated the number of cancer cases attributable to infections by combining the cancer incidence (from GLOBOCAN 2012) with the attributable fraction of infections.[81] Martel et al built on Plummer's report to clarify the annual incidence of HPV-associated cancer by adding more detailed data (eg, by country and cancer subsite).[67] The reported number of incident cases, attributable fraction, and number of HPV-associated cases for each cancer were as follows: cervical cancer (630,000 cases, 100.0%, 530,000 HPV-associated), anal cancer (40,000 cases, 88.0%, 35,000 HPV-associated), vulvar cancer (34,000 cases, 24.9%, 8500 HPV-associated), vaginal cancer (15,000 cases, 78.0%, 12,000 HPV-associated), penile cancer

Table II. Nail SCC and Bowen disease as reported in the literature

No.	Reference	Tumor	Age, y/sex	Digit	HPV type	Clinical type	Therapy	Recurrence	Lesions of HPV	ICH
1	Ikenberg et al[1]	SCCis	74/F	NS	16	NS				
2	Kawashima et al[31]	SCCis	69/F	L3F	34	PUT			Warts, cervical cancer	
3	Stone et al[32]	SCCis	36/M	R4T	16	Other	Excision		GW	Silicosis
4	Ostrow et al[33]	SCCis	37/M	R1F	16	PUT				EV with SCC
5	Moy et al[2]	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]	SCCis	48/M	L2F	16	SUT	Mohs			
11	Rudlinger et al[35]	SCCis	42/F	R4F	35	PUT	Excision, radiation, cryo, IFN		BP with HPV35	PCC
12	Guitart et al[36]	SCCis	69/F	L3F	16, 18	SUT	Excision	yes	Cervical cancer with HPV16 and 18, warts	
13	Eliezri et al[37]	SCCis	NS	NS	16	PUT				
14	Kettler et al[38]	SCCis	36/M	NS	16	Other			Condyloma acuminatum with HPV11	
15		SCCis	60/M	NS	16	Other			BD of penis with HPV16	
16	Echt et al[39]	SCC	63/M	R2F	16, 18	PUT				
17	Ashinoff et al[30]	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]	SCC	71/F	R3F	16	Unknown	Mohs			
23	Rapini et al[41]	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 al[42]	SCCis	42/M	R2-4F	16	Other	Tretinoin, 5-FU, bleo		GW with HPV6	
27	Sau et al[43]	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]	SCCis	31/F	R3F	16	SUT/PUT	Excision	yes	VIN with HPV16	
32	Tosti et al[45]	SCC	28/M	R1F	16	SUT			Warts	AIDS

33	Sanchez-Lanier et al[46]	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]	SCC	83/M	R4-5T	16	Other	Amp			
38		Verrucous condyloma acuminatum	79/M	R5T	16	PUT	Amp			
39	McHugh et al[48]	SCC	51/M	L1F	35	PUT	Mohs	yes		
40	Forslund et al[28]	SCCis	33/F	R1F	16	PUT	PDT		Genital dysplasia with HPV16 related HPV	
41	Forslund et al[28]	SCCis	38/F	L4F	16	SUT				
42	Downs et al[49]	SCC	35/M	R3F	16	SUT	Excision			Darier disease
43	Mitsuishi et al[50]	SCCis	53/M	R3F	16	PUT				
44		SCCis	34/F	L3F	73	PUT				
45	Forslund et al[28]	SCCis	57/F	L4F	16	PUT			CIN with HPV16	
46	Sass et al[8]	SCCis	67/M	L4F	16	SUT/LMT	Excision			
47	Theunis et al[51]	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]	SCCis	61/F	L3F	16	SUT			cervical cancer with HPV16	
51	Zabawski et al[52]	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]	SCCis	80/M	L2F	18	PUT				Formerly gynecologist
55	Alam et al[6]	SCC	50/F	R4F	16	SUT	Mohs	yes	Cervical cancer, hysterectomy	
56		SCC	78/M	R3F	16	PUT	Mohs	yes		
57		SCC	28/M	R2F, R4F	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		Condyloma acuminatum	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	

Continued

Table II. Cont'd

No.	Reference	Tumor	Age, y/sex	Digit	HPV type	Clinical type	Therapy	Recurrence	Lesions of HPV	ICH
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]	SCCis	25/M	R3F	56	SUT/LMT	Mohs			
79	High et al[55]	SCC	36/M	R2F	26	PUT				
80	Hara et al[56]	SCCis	46/F	NS	58	PUT			Vulva and cervical cancer with HPV68	
81	Sato et al[57]	SCCis	55/M	L4F	11, 16	PUT				
82	Weisenseel et al[58]	SCCis	49/M	L3F	73	PUT				
83	Handisurya et al[59]	SCC	28/M	All	26, 58	SUT	Unknown		BP with HPV26	AIDS with HAART
84	Ekeowa-Anderson et al[10]	SCCis	23/F	L3F	21, 34, 49, 58	PUT			VIN with HPV21, 31, 34	
85	Shimizu A et al[4]	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]	SCCis	32/M	R1F, L2F	73	PUT	Mohs	yes		HL
89	Depond et al[61]	SCC and SCCis	55/M	NS	58, 73	NS				
90	Inokuma et al[62]	SCCis	41/M	R2F	56	SUT/LMT				
91	Kreuter et al[11]	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]	SCCis	42/M	L1F, R4F, R5F	16	PUT	IQ + Mohs			
98		SCCis	44/M	R3F	High-risk HPV	PUT	Mohs + IQ			HIV
99	Tanese et al[64]	SCC	29/M	L1F	59, 84	SUT	Amp			RP
100	Nakajima et al[65]	SCCis	56/M	L3F	8, 16, 58	PUT				ATL
101	Aguayo et al[26]	SCCis	54/F		16, 6	SUT			CIN and hysterectomy	

102	Gormley et al[24]	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	L2F, L4F	33, 51, 73	PUT				HIV
106		SCCis	50/F	R3F	33, 51	PUT				
107	Ohishi et al[23]	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/LMT				
113		SCCis	41/M	R5F	33	SUT/LMT				
114	Grundmeier et al[22]	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[21]	SCCis	60/F	R1F, R2F, L2-5F	16	SUT/PUT			VIN invasive, cervical cancer partner with GW	
118	Patel et al[20]	SCC	68/F	R1F	18,39,45,59,68	SUT	Amp			
119	Shimizu A et al[3]	SCCis	67/M	L2F	56	SUT/LMT	Excision			
120	Park et al[19]	SCCis	33/M	L1F	NS	SUT/LMT	Longitudinal excision			
121	Hunt et al[25]	SCC and SCCis	36/M	R2-4F	High-risk HPV	PUT	Amp, radiation	yes		AML, GvHD
122	Kato et al[9]	SCCis	36/M	R3F	58	PUT	Excision			
123	Nordin and Stenquist[18]	SCCis	57/M	R2F	16	PUT	Excision	yes		
124	Sohn et al[17]	SCCis	85/F	R3F	56	SUT/LMT	No treatment			
125	Shimizu A et al[16]	SCCis	84/M	R2F	67	SUT/LMT	Excision			
126	Nanba et al[15]	SCCis	51/M	L2F	16, 82	PUT			Genital BD	
127	Hyun et al[14]	SCCis	12/M	R2F	34	PUT	PDT			
128	Ogata et al[13]	SCC	46/M	L4F	16	SUT	Amp		Digital lesion with HPV90	
129	Perruchoud et al[27]	SCCis	58/M	R3F, L3F	73	Other	Cryo and surgery			
130		SCCis	44/M	L4F	16	Other	IQ			

Continued

Table II. Cont'd

No.	Reference	Tumor	Age, y/sex	Digit	HPV type	Clinical type	Therapy	Recurrence	Lesions of HPV	ICH
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 and 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[12]	SCCis	46/F	R4F	35	PUT	Excision			

5-FU, 5-Fluorouracil; *AIN*, anal intraepithelial neoplasia; *AML*, acute myeloid leukemia; *Amp*, amputation; *ATL*, adult T-cell leukemia; *AW*, anal warts; *BD*, Bowen disease; *Bleo*, bleomycin; *BP*, Bowenoid papulosis; *CIN*, cervical intraepithelial neoplasia; *Cryo*, cryotherapy; *EV*, epidermodysplasia verruciformis; *F*, finger; *GvHD*, graft-versus-host disease; *GW*, genital warts; *HAART*, highly active antiretroviral therapy; *HL*, Hodgkin's lymphoma; *HPV*, human papillomavirus; *ICH*, immunocompromised host; *IFN*, interferon; *IQ*, imiquimod; *L*, left; *LMT*, longitudinal melanonychia type; *NS*, not specified; *OW*, oral warts; *PCC*, pheochromocytoma; *PDT*, photodynamic therapy; *PIN*, penile intraepithelial neoplasia; *PUT*, periungual type; *PW*, penile warts; *R*, right; *RP*, relapsing polychondritis; *SA*, salicylic acid; *SCC*, squamous cell carcinoma; *SCCis*, squamous cell carcinoma in situ; *SUT*, subungual type; *T*, toe; *VIN*, vulvar intraepithelial neoplasia; *WS*, wedge-shaped.

(26,000 cases, 50.0%, 13,000 HPV-associated), and oropharyngeal cancer (96,000 cases, 30.8%, 29,000 HPV-associated).[67]

Data on the annual incidence of nail SCC were not available, so we assessed the number of SCCs of the extremities using the International Classification of Diseases, 10th Revision (C44.6 malignant neoplasm, skin of upper limb including the shoulder). Although the number of cases was limited, an analysis of 7 case series of nail SCC found that the attributable fraction was ~47% (Table III). The average number of patients with HPV-associated nail SCC in our department typically is 2 cases/year. Gunma University Hospital is a tertiary hospital of Gunma Prefecture, Japan, which has a population of 2 million. We thus estimated the rate of nail SCC to be 1 case/1 million person-years. The global population is 7 billion, so we estimate that ~7000 persons/year acquire HPV-associated nail SCC. This number is similar to that of vulvar cancer (8500 persons/year).

NAIL APPARATUS INTRAEPITHELIAL NEOPLASIA (NIN)

Other HPV-associated in situ lesions include intraepithelial neoplasias, such as cervical, anal, vulvar, and vaginal intraepithelial neoplasias, all of which are HPV-associated lesions in the International Classification of Diseases, 10th Revision. In this context, we propose the term, NIN. Based on a review of the previous cases, the characteristics of NIN are as follows: predominantly affects men, all fingers except the small finger of the left hand can be affected, young age of onset compared with that of common cutaneous SCC in situ, and lesions can be clinically classified into 2 types (periungual type or SUT and LMT).

In contrast with other HPV-associated cancers, such as cervical intraepithelial neoplasia and anal intraepithelial neoplasia, 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-20 years).[27] The authors also checked the initial diagnosis and reported that viral warts and onychomycosis were most common.[27] The 2 phenotypes periungual type and SUT with LMT should be widely recognized by doctors to facilitate the early correct diagnosis.

SEXUAL TRANSMISSION OF HIGH-RISK HPV BETWEEN THE NAIL APPARATUS AND GENITALS

The present data suggest that there is a high risk of HPV transmission through the nail apparatus. First,

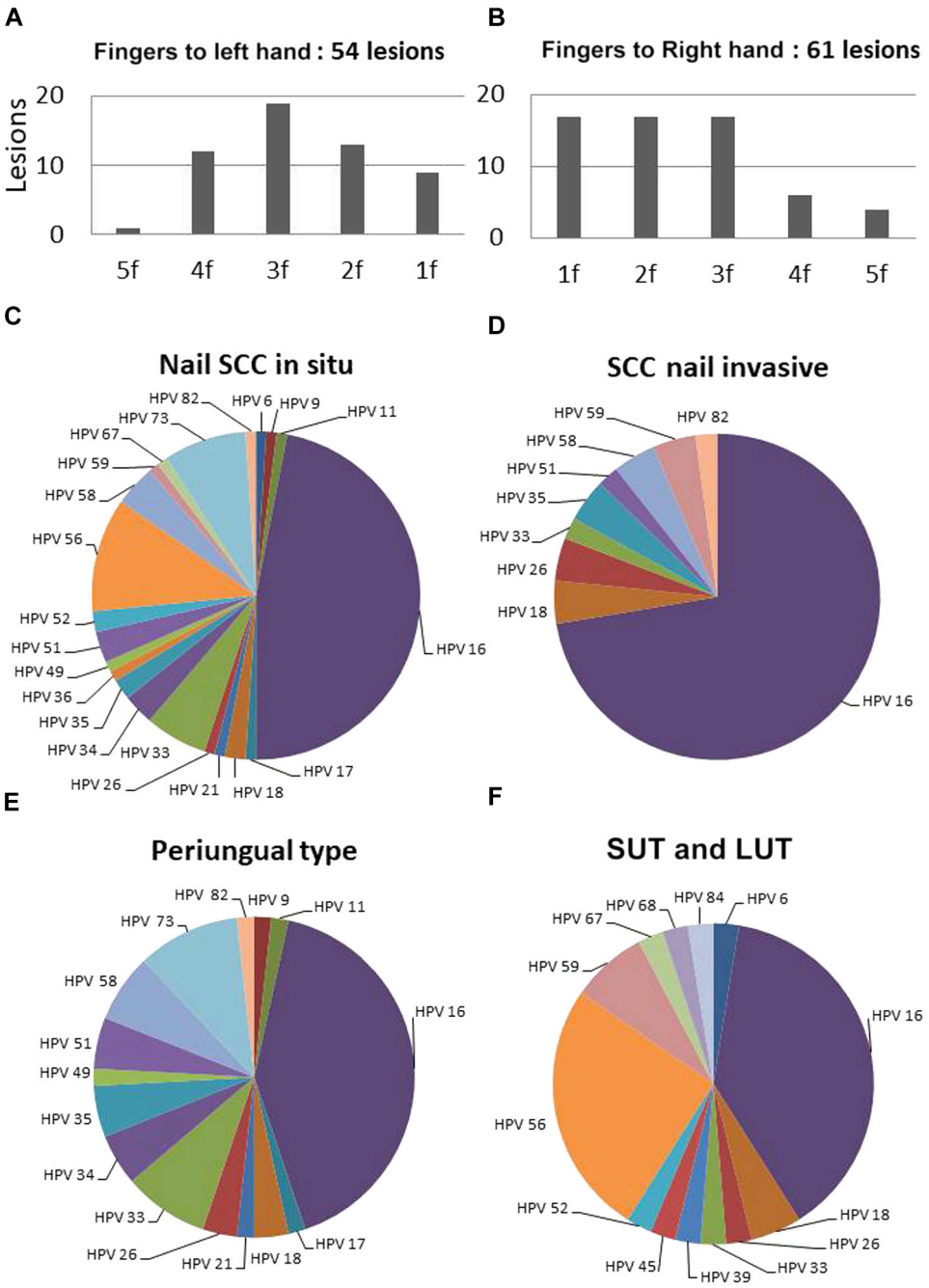

Fig 2. Human papillomavirus (HPV)–positive digital lesions and HPV types detected in nail squamous cell carcinoma (SCC). **A** and **B**, Number of HPV-positive lesions on finger digits. **C**-**F**, HPV types detected in nail SCC in situ (**C**), invasive nail SCC (**D**), periungual type (**E**) and SUT and LMT (**F**). *f*, Finger; *HPV*, Human papillomavirus; *LMT*, longitudinal melanonychia type; *SCC*, squamous cell carcinoma; *SUT*, subungual type.

the age of the patients and sex were characteristic. As shown in Table I, the average age was 52 years (median 50 years), 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. Last, as shown in Fig 2, 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 a sexually transmitted infection.

Table III. Case series and attributable rate

Year	Author	SCC, SCC in situ, or both	Attributable rate, %	No. samples positive for high-risk HPV (type)	Methods
1991	Ashinoff et al[30]	Both	71	5/7 (HPV 16)	PCR and in situ hybridization
1994	Sau et al[43]	SCC in situ	57	4/7	in situ hybridization
2008	Shimizu et al[4]	SCC in situ	60	3/5	PCR
2009	Kreuter et al[11]	Both	24	6/25	PCR
2011	Ohishi et al[23]	SCC in situ	100	7/7	PCR
2016	Perruchoud et al[27]	SCC in situ	75	9/12	PCR
2017	Dika et al[66]	SCC	37	15/41 (HPV 16)	PCR
Total			47	49/104	

HPV, Human papillomavirus; *SCC*, squamous cell carcinoma.

Furthermore, in this review, 24% of the cases of nail SCC had a history of other HPV-associated diseases. Among female patients, 36% had other HPV-associated lesions, suggesting that self-inoculation was a possible route of infection. Forslund et al reported 2 patients with nail SCC who had a history of genital dysplasia.[28] The authors performed sequencing of HPV DNA and revealed that the nail and genital lesions were caused by patient-specific HPV 16 strains.[28] Furthermore, they described 5 female patients diagnosed with genital dysplasia and Bowen disease of the fingers who had the same HPV 16 in both lesions.[29] In all cases, finger SCC was noted after the diagnosis of the genital lesion. Also, 5 of the male patients' partners had a history of gynecologic diseases, suggesting genito-digital transmission to male patients. Alam et al investigated 23 cases of nail SCC and found that the 2 female patients had cervical carcinoma, and the partners of 5 male patients had gynecologic disease.[6] The authors suggested genitodigital 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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