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Table SI. Differences between patients with AK who developed cSCC and patients who did not. AK cohort (n=84) includes patients who did not develop cSCC during 5-year observation period and AK to cSCC cohort (n=37) patients who developed cSCC during the observation period. Same microlocation means that initial lesion and subsequent cSCC were located within 30mm proximity

Characteristics	Total	AK	AK to cSCC	P value
Patients in total, n (%)	121 (100)	84 (100)	37 (100)	
Age at initial AK diagnosis				
Median, y	73.3	72.0	75.9	
Mean, y (SD)	72.6 (10.1)	71.3 (10.3)	75.6 (9.1)	0.031
Range, y	38-89	38-89	49-89	
Occupation				
High UV-exposure, n (%)	17 (14.0)	7 (8.3)	10 (27.0)	0.023
Low or moderate UV-exposure, n (%)	70 (57.9)	51 (60.7)	19 (51.4)	0.023
Missing, n (%)	34 (28.1)	26 (31.0)	8 (21.6)	
Sex				
Male, n (%)	67 (55.4)	36 (42.9)	31 (83.8)	<0.001
Female, n (%)	54 (44.6)	48 (57.1)	6 (16.2)	<0.001
Smoking				
Yes, n (%)	11 (13.9)	10 (16.9)	1 (5.0)	0.273
No, n (%)	68 (86.1)	49 (83.1)	19 (95.0)	0.273
Missing, n (%)	42 (34.7)			
Immunosuppression				
Yes, n (%)	14 (11.6)	6 (7.1)	8 (21.6)	0.031
No, n (%)	107 (88.4)	78 (92.9)	29 (78.4)	0.031
SOTR, n (%)	6 (5.0)	1 (1.2)	5 (13.5)	0.010
HIV, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Immunosuppressive medication, n (%)	12 (9.9)	4 (4.8)	8 (21.6)	0.007
Hematologic malignancy				
CLL, n (%)	3 (2.5)	1 (1.2)	2 (5.4)	0.221
Non-Hodgkin lymphoma, n (%)	2 (1.7)	2 (1.7)	0 (0.0)	1.000
Comorbidities				
Hypertension, n (%)	60 (49.6)	42 (50.0)	18 (48.6)	1.000
MCC, n (%)	24 (19.8)	14 (16.7)	10 (27.0)	0.219
Heart failure, n (%)	8 (6.6)	6 (7.1)	2 (5.4)	1.000
AF/AFL, n (%)	15 (12.4)	9 (10.7)	6 (16.2)	0.378
Earlier stroke, n (%)	6 (5.0)	3 (3.6)	3 (8.1)	0.368
Dyslipidemia, n (%)	10 (8.3)	7 (8.3)	3 (8.1)	1.000
Depression, n (%)	4 (3.3)	3 (3.6)	1 (2.7)	1.000

Asthma, n (%)	6 (5.0)	6 (7.1)	0 (0.0)	0.176
Gout, n (%)	5 (4.1)	4 (4.8)	1 (2.7)	1.000
T2DM, n (%)	12 (9.9)	7 (8.3)	5 (13.5)	0.510
Hypothyroidism, n (%)	9 (7.4)	6 (7.1)	3 (8.1)	1.000
Psoriasis, n (%)	6 (5.0)	5 (6.0)	1 (2.7)	0.666
Atopic dermatitis, n (%)	5 (4.1)	4 (4.8)	1 (2.7)	1.000
Seborrheic dermatitis, n (%)	4 (3.3)	3 (3.6)	1 (2.7)	1.000
Medication				
ASA, n (%)	33 (27.3)	20 (23.8)	13 (35.1)	0.268
Thiazide diuretic, n (%)	14 (11.6)	7 (8.3)	7 (18.9)	0.123
Furosemide, n (%)	18 (14.9)	13 (15.5)	5 (13.5)	0.794
ACE/ARB, n (%)	36 (29.8)	24 (28.6)	12 (32.4)	0.829
Statin, n (%)	30 (24.8)	22 (26.2)	8 (21.6)	0.654
Thyroxin, n (%)	9 (7.4)	8 (9.5)	1 (2.7)	0.273
Trimethoprim, n (%)	5 (4.1)	3 (3.6)	2 (5.4)	0.641
Neuroleptics, n (%)	4 (3.3)	2 (2.4)	2 (5.4)	0.585
SSRI/SNRI, n (%)	6 (5.0)	4 (4.8)	2 (5.4)	1.000
Warfarin, n (%)	16 (13.2)	9 (10.7)	7 (18.9)	0.250
Dipyridamole, n (%)	6 (5.0)	4 (4.8)	2 (5.4)	1.000
Beta blocker, n (%)	39 (32.2)	26 (31.0)	13 (35.1)	0.677
Dihydropyridine, n (%)	14 (11.6)	9 (10.7)	5 (13.5)	0.759
Allopurinol, n (%)	6 (5.0)	5 (6.0)	1 (2.7)	0.666
Metformin, n (%)	5 (4.1)	3 (3.6)	2 (5.4)	0.641
5-alpha reductase inhibitor, n (%)	6 (5.0)	4 (4.8)	2 (5.4)	1.000
Alpha blocker (alfuzosine, tamsulosin), n (%)	8 (6.6)	2 (2.4)	6 (16.2)	0.010
In male patients, n (%)	8 (11.9)	2 (5.6)	6 (19.4)	0.131
Ciclosporin, n (%)	6 (5.0)	1 (1.2)	5 (13.5)	0.010
Azathioprine, n (%)	5 (4.1)	1 (1.2)	4 (10.8)	0.030
Prednisolon, n (%)	9 (7.4)	1 (1.2)	8 (21.6)	<0.001
Tretinoin, n (%)	7 (5.8)	4 (4.8)	3 (8.1)	0.436
Sulphonylurea, n (%)	5 (4.1)	2 (2.4)	3 (8.1)	0.166
Spirolactone, n (%)	6 (5.0)	4 (4.8)	2 (5.4)	1.000
Digoxin, n (%)	12 (9.9)	6 (7.1)	6 (16.2)	0.184
Isosorbide mono-/dinitrate, n (%)	20 (16.5)	11 (13.1)	9 (24.3)	0.182
Acitretin, n (%)	4 (3.3)	3 (3.6)	1 (2.7)	1.000
PPI, n (%)	10 (8.3)	6 (7.1)	4 (10.8)	0.492
Benzodiazepine, n (%)	12 (9.9)	8 (9.5)	4 (10.8)	1.000
Inhaled corticosteroid, n (%)	6 (5.0)	5 (6.0)	1 (2.7)	0.666
Antihistamine, n (%)	4 (3.3)	3 (3.6)	1 (2.7)	1.000
Co-malignancies				
BCC, n (%)	46 (38.0)	28 (33.3)	18 (48.6)	0.154
BCC before AK, n (%)	26 (21.5)	16 (19.0)	10 (27.0)	0.344

Other than cSCC or BCC, n (%)	45 (37.2)	31 (36.9)	14 (37.8)	1.000
Other than cSCC or BCC before AK, n (%)	22 (18.2)	14 (16.7)	8 (21.6)	0.610
Urothelial cancer, n (%)	4 (3.3)	2 (2.4)	2 (5.4)	0.585
Breast cancer, n (%)	11 (9.1)	10 (11.9)	1 (2.7)	0.113
Melanoma, n (%)	5 (4.1)	3 (3.6)	2 (5.4)	0.641
Prostate cancer, n (%)	10 (8.3)	6 (7.1)	4 (10.8)	0.492
Initial lesion characteristics				
Degree of dysplasia				
Low (I), n (%)	65 (53.7)	54 (64.3)	11 (29.7)	<0.001
Moderate (II), n (%)	10 (8.3)	2 (2.4)	8 (21.6)	<0.001
High (III), n (%)	27 (22.3)	12 (14.3)	15 (40.5)	<0.001
Missing, n (%)	19 (15.7)	16 (19.0)	3 (8.1)	<0.001
Location				
Head and neck, n (%)	104 (86.0)	77 (91.7)	27 (73.0)	0.014
Trunk, n (%)	10 (8.3)	5 (6.0)	5 (13.5)	0.014
Upper limb, n (%)	7 (5.8)	2 (2.4)	5 (13.5)	0.014
Lower limb, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Subsequent cSCC				
Same anatomical region, n (%)			26 (70.3)	
Other anatomical region, n (%)			11 (29.7)	
Same microlocation (<30mm), n (%)			11 (29.7)	

ACE/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; AF/AFL: atrial fibrillation/atrial flutter; AK: actinic keratosis; ASA: aspirin/acetylsalicylic acid; BCC: basal cell carcinoma; CLL: chronic lymphocytic leukemia; cSCC: cutaneous squamous cell carcinoma; cSCCIS: cutaneous squamous cell carcinoma *in situ*; HIV: human immunodeficiency virus; MCC: coronary artery disease; PPI: proton pump inhibitor; SOTR: solid organ transplant recipient; SSRI/SNRI: selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors; SD: standard deviation; T2DM: type 2 diabetes mellitus; UV: ultraviolet; y: years.

Table SII. Differences between patients with cSCCIS who developed cSCC and patients who did not. cSCCIS cohort (n=85) includes patients who did not develop cSCC during 5-year observation period and cSCCIS to cSCC cohort (n=14) patients who developed cSCC during the observation period. Same microlocation means that initial lesion and subsequent cSCC were located within 30mm proximity.

Characteristics	Total	cSCCIS	cSCCIS to cSCC	P value
Patients in total, n (%)	99 (100.0)	85 (100.0)	14 (100.0)	
Age at initial AK diagnosis				
Median, y	75.3	75.7	74.7	
Mean, y (SD)	74.6 (10.8)	74.6 (10.5)	74.6 (12.8)	0.960
Range, y	40-91	40-90	55-91	
Occupation				0.464
High UV-exposure, n (%)	18 (18.2)	14 (16.5)	4 (28.6)	
Low UV-exposure, n (%)	54 (54.5)	48 (56.5)	6 (42.9)	
Missing, n (%)	27 (27.3)	23 (27.1)	4 (28.6)	
Sex				
Male, n (%)	52 (52.5)	42 (49.4)	10 (71.4)	0.156
Female, n (%)	47 (47.5)	43 (50.6)	4 (28.6)	0.156
Smoking				
Yes, n (%)	7 (7.1)	6 (7.1)	1 (7.1)	1.000
No, n (%)	70 (70.7)	65 (76.5)	5 (35.7)	1.000
Missing, n (%)	22 (22.2)	14 (16.5)	8 (57.1)	
Immunosuppression				
Yes, n (%)	15 (15.2)	10 (11.8)	5 (35.7)	0.036
No, n (%)	84 (84.8)	75 (88.2)	9 (64.3)	0.036
SOTR, n (%)	4 (4.0)	1 (1.2)	3 (21.4)	0.008
HIV, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Immunosuppressive medication, n (%)	14 (14.1)	10 (11.8)	4 (28.6)	0.108
Hematologic malignancy				
CLL, n (%)	3 (3.0)	2 (2.4)	1 (7.1)	0.370
Non-Hodgkin lymphoma, n (%)	1 (1.0)	1 (1.2)	0 (0.0)	1.000
Comorbidities				
Hypertensio, n (%)	47 (47.5)	38 (44.7)	9 (64.3)	0.249
MCC, n (%)	21 (21.2)	15 (17.6)	6 (42.9)	0.070

Heart failure, n (%)	5 (5.1)	4 (4.7)	1 (7.1)	0.541
AF/AFL, n (%)	12 (12.1)	7 (8.2)	5 (35.7)	0.012
Earlier stroke, n (%)	4 (4.0)	3 (3.5)	1 (7.1)	0.462
Dyslipidemia, n (%)	15 (15.2)	14 (16.5)	1 (7.1)	0.688
Osteoporosis, n (%)	6 (6.1)	5 (5.9)	1 (7.1)	1.000
Alzheimer, n (%)	5 (5.1)	3 (3.5)	2 (14.3)	0.145
COPD, n (%)	4 (4.0)	4 (4.7)	0 (0.0)	1.000
Asthma, n (%)	5 (5.1)	4 (4.7)	1 (7.1)	0.541
Rheumatoid arthritis, n (%)	6 (6.1)	5 (5.9)	1 (7.1)	1.000
Gout, n (%)	5 (5.1)	4 (4.7)	1 (7.1)	0.541
T2DM, n (%)	9 (9.1)	6 (7.1)	3 (21.4)	0.113
Hypothyroidism, n (%)	8 (8.1)	8 (9.4)	0 (0.0)	0.596
Medication				
NSAID, n (%)	5 (5.1)	5 (5.9)	0 (0.0)	1.000
ASA, n (%)	28 (28.3)	20 (23.5)	8 (57.1)	0.021
Thiazide diuretic, n (%)	8 (8.1)	7 (8.2)	1 (7.1)	1.000
Furosemide, n (%)	15 (15.2)	11 (12.9)	4 (28.6)	0.218
ACE/ARB, n (%)	23 (23.2)	17 (20.0)	6 (42.9)	0.086
Statin, n (%)	26 (26.3)	19 (22.4)	7 (50.0)	0.046
Thyroxin, n (%)	7 (7.1)	7 (8.2)	0 (0.0)	0.589
Neuroleptics, n (%)	6 (6.1)	4 (4.7)	2 (14.3)	0.200
Methotrexate, n (%)	4 (4.0)	3 (3.5)	1 (7.1)	0.462
Warfarin, n (%)	9 (9.1)	4 (4.7)	5 (35.7)	0.003
Dipyridamole, n (%)	5 (5.1)	5 (5.9)	0 (0.0)	1.000
Beta blocker, n (%)	36 (36.4)	27 (31.8)	9 (64.3)	0.033
Dihydropyridine, n (%)	11 (11.1)	7 (8.2)	4 (28.6)	0.047
Amlodipin, n (%)	5 (5.1)	3 (3.5)	2 (14.3)	0.145
Allopurinol, n (%)	4 (4.0)	3 (3.5)	1 (7.1)	0.462
Metformin, n (%)	5 (5.1)	2 (2.4)	3 (21.4)	0.019
5-alpha reductase inhibitor, n (%)	7 (7.1)	7 (8.2)	0 (0.0)	0.589
Alpha blocker (alfuzosine, tamsulosin), n (%)	6 (6.1)	5 (5.9)	1 (7.1)	1.000
Ciclosporin, n (%)	3 (3.0)	0 (0.0)	3 (21.4)	0.002

Azathioprine, n (%)	3 (3.0)	0 (0.0)	3 (21.4)	0.002
Prednisolon, n (%)	12 (12.1)	8 (9.4)	4 (28.6)	0.064
Sulphonylurea, n (%)	5 (5.1)	4 (4.7)	1 (7.1)	0.541
Digoxin, n (%)	7 (7.1)	5 (5.9)	2 (14.3)	0.257
Isosorbide mono-/dinitrate, n (%)	21 (21.2)	17 (20.0)	4 (28.6)	0.488
PPI, n (%)	8 (8.1)	7 (8.2)	1 (7.1)	1.000
Co-malignancies				
BCC, n (%)	28 (28.3)	21 (24.7)	7 (50.0)	0.062
BCC before AK, n (%)	14 (14.1)	12 (14.1)	2 (14.3)	1.000
Other than cSCC or BCC, n (%)	33 (33.3)	26 (30.6)	7 (50.0)	0.220
Other than cSCC or BCC before AK, n (%)	14 (14.1)	12 (14.1)	2 (14.3)	1.000
Breast cancer, n (%)	6 (6.1)	6 (7.1)	0 (0.0)	0.590
Colon cancer, n (%)	4 (4.0)	3 (3.5)	1 (7.1)	0.462
Prostate cancer, n (%)	10 (10.1)	6 (7.1)	4 (28.6)	0.033
Initial lesion characteristics				
Location				
Head and neck, n (%)	56 (56.6)	48 (56.5)	8 (57.1)	0.391
Trunk, n (%)	20 (20.2)	19 (22.4)	1 (7.1)	0.391
Upper limb, n (%)	17 (17.2)	13 (15.3)	4 (28.6)	0.391
Lower limb, n (%)	6 (6.1)	5 (5.9)	1 (7.1)	0.391
Subsequent cSCC				
Same anatomical region, n (%)			6 (42.9)	
Other anatomical region, n (%)			8 (57.1)	
Same microlocation (<30mm), n (%)			3 (21.4)	

ACE/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; AF/AFL: atrial fibrillation/atrial flutter; AK: actinic keratosis; ASA: aspirin/acetylsalicylic acid; ASO: arteriosclerosis obliterans; BCC; basal cell carcinoma; CLL: chronic lymphocytic leukemia; COPD: chronic obstructive pulmonary disease; cSCC: cutaneous squamous cell carcinoma; cSCCIS: cutaneous squamous cell carcinoma *in situ*; HIV: human immunodeficiency virus; IQR: interquartile range; MCC: coronary artery disease; NSAID: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitor; SOTR: solid organ transplant recipient; SSRI/SNRI: selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors; SD: standard deviation; T2DM: type 2 diabetes mellitus; UV: ultraviolet.