Predictors of Squamous Cell Carcinoma in High-Risk Patients in the VATTC Trial

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Invasive squamous cell carcinoma (SCC) of the skin is one of the most common cancers in the United States, with no proven means for prevention other than systemic retinoids, which have significant toxicity, and sunscreen. We sought to determine the risk factors for invasive SCC on the face or ears in a high-risk population comprising 1,131 veterans in the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial. Participants were required to have been diagnosed with at least two keratinocyte carcinomas (KCs) in the 5 years prior to enrollment. The median duration of follow-up was 3.7 years. Twenty-three percent of the participants developed a new invasive SCC, and the cumulative risk of invasive SCC was 30% at 5 years. The following factors independently predicted for new invasive SCCs: number of invasive SCCs and number of *in situ* SCCs in the 5 years prior to enrollment, actinic keratoses count at enrollment, a history of ever use of topical 5-fluorouracil, and total occupational time spent outdoors. In contrast, the use of angiotensin-convering enzyme inhibitors or angiotensin receptor blockers during the study and a history of warts anywhere on the body were found to protect against new invasive SCCs. These independent predictors remained the same for all SCCs (invasive and *in situ* combined). The number of basal cell carcinomas in the 5 years prior to enrollment, sunburns, sun sensitivity, and recreational sun exposure were not associated with new SCCs. These findings identify key risk factors for additional SCCs in patients with multiple prior KCs, and suggest that a history of warts may be associated with reduced SCC risk.

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INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common malignancies in the United States (Rogers *et al.*, 2010). In particular, invasive SCC is a significant health concern with no proven means for prevention other than systemic retinoids (Kraemer *et al.*, 1988; Bavinck *et al.*, 1995; DiGiovanna, 1998; Kovach *et al.*, 2006), which have significant toxicity, and sunscreen (Green *et al.*, 1999). Although less common than BCCs, SCCs account for the majority of deaths due to nonmelanoma skin cancer (Weinstock, 1993; Lewis and Weinstock, 2004). The incidence of SCC has continued to increase over the past several decades, especially for older age groups (Weinstock, 1993; Miller and Weinstock, 1994; Karagas *et al.*, 1999), a trend that is also being seen worldwide (Gray *et al.*, 1997; Staples *et al.*, 1998; Hannuksela-Svahn *et al.*, 1999; Iversen and Tretli, 1999). However, the exact incidence of SCC in the United States is unknown because it is not reported to cancer registries. The cumulative 3-year risk of subsequent SCC in patients with a prior SCC is 18% (Marcil and Stern, 2000). Predisposing risk factors for SCC have been well established, including increased sun exposure (Armstrong and Kricker, 1996, 2001; English *et al.*, 1998a; Suarez *et al.*, 2007), populations closer to the equator, occupational exposure outdoors (Schmitt *et al.*, 2011), and a history of precancerous lesions, along with other factors (Kricker *et al.*, 1991, 1994; Gallagher *et al.*, 1995; Grodstein *et al.*, 1995; Elwood and Gallagher, 1997; English *et al.*, 1998b). Although there is evidence demonstrating an enhanced risk of BCC among individuals exposed to ionizing radiation, this does not appear to be the case with SCC (Karagas *et al.*, 1996; Ron *et al.*, 1998; Yoshinaga *et al.*, 2005; Levi *et al.*, 2006).

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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BCC, basal cell carcinoma; CI, confidence interval; HPV, human papilloma virus; HRR, hazard rate ratio; KC, keratinocyte carcinoma; SCC, squamous cell carcinoma; VATTC, Veterans Affairs Topical Tretinoin Chemoprevention

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Evidence for predictors of future SCCs in high-risk populations have not been firmly established (Marcil and Stern, 2000). To better define risk factors for future SCCs in a high-risk population, we investigated predictors of SCC among participants in the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial, who had at least two keratinocyte carcinomas (KCs) in the 5 years before enrollment.

RESULTS

A total of 1,131 participants were enrolled, most of whom were men (97%). The median age of participants was 72 years. Participants in the study tended to have a history of heavily sun-damaged skin, with an average of 3.6 KCs in the 5 years before randomization and an average of 7.3 actinic keratoses (AKs) at baseline examination at start of the study.

The median duration of follow-up in years from the date of randomization to the end of study or death, or withdrawal in the cohort, was 3.7 years; 23% of study participants developed at least one new invasive SCC during the study period. The 1, 3, and 5-year Kaplan–Meier estimates for development of new invasive SCCs were 8, 22, and 30% respectively.

In univariable analyses, the most important predictors of time to new invasive SCC ($P<0.001$) were the number of prior invasive SCCs, number of prior *in situ* SCCs, number of AKs at enrollment, history of ever use of 5-fluorouracil, occupational sun exposure between 1000 and 1500 hours at ages over 30 years, total occupational sun exposure between 1000 and 1500 hours, total occupational time spent working outside between 1000 and 1500 hours, and total lifetime sun exposure (Table 1). Those in the highest quintiles for prior invasive SCCs and AKs at baseline had hazard rate ratios (HRRs) that were 4.3 times higher (95% confidence interval (CI): 2.6–7.2) and 5.7 times higher (95% CI: 3.5–9.2), respectively, than those in the lowest quintiles. On the other hand, the use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) during the study was associated with reduced risk of invasive SCCs. Sun sensitivity, history of sunburns, recreational sun exposure, and latitude of residence after teenage years were not significantly associated with new SCCs based on univariable analyses.

For the multivariable model, we used backwards stepwise regression to include variables that had a P-value <0.15 in the univariable analyses (Table 2). In addition, a forwards stepwise regression analysis was performed to identify the strongest risk factors for invasive SCC. Results from the forwards model were identical to those of the backwards model. The most important independent predictors for time to new invasive SCC ($P<0.001$) were the number of invasive SCCs in the 5 years before enrollment (HRR: 3.04, 95% CI: 1.79–5.18) and number of AKs at the start of the study (HRR: 3.07, 95% CI: 1.84–5.10). Other positive predictors included history of ever use of 5-fluorouracil (HRR: 1.61, 95% CI: 1.10–2.22), a history of *in situ* SCCs in the prior 5 years (HRR: 2.23, 95% CI: 1.27–3.95), and total occupational time outside, defined as decades spent working outdoors between 1000 and 1500 hours (HRR: 1.23, 95% CI: 1.08–1.39). In contrast, the use of either ACE inhibitors or ARBs during the study was negatively associated with time to new invasive SCC (HRR: 0.58, 95% CI: 0.41–0.81). Collinearity tests revealed Pearson's r-values to be less than 0.29 (Table 3) and variance inflation factor values to be less than 1.21 (Table 4).

We had several representations of sun exposure, including total occupational time spent outdoors, total occupation sun exposure, occupational sun exposure for ages over and under 30 years, and total lifetime sun exposure. Total lifetime sun exposure was calculated as the sum of occupational, recreational, and vacation sun exposure. Although all of these risk factors were statistically significant in the univariable analyses, total occupational time outdoors was more strongly associated with invasive SCC risk than any other representation.

In addition, we had four representations of sunscreen use, including any sunscreen use on the face or ears 1 week before enrollment and 6 months before enrollment, as well as sun protection factor $\geqslant 15$ use on the face or ears 1 week before enrollment and 6 months before enrollment. As these variables were highly collinear (all had variance inflation factors >20), we only included the variable with the lowest univariable P-value into the multivariable analysis, which in this case was any sunscreen use on the face or ears 1 week before enrollment. Sunscreen use, however, was ultimately not retained in the multivariable model.

The results for all SCCs (invasive and *in situ* combined) were similar to those for invasive SCCs alone, in both the univariable and multivariable analyses (Tables 1 and 2).

DISCUSSION

We report a cohort study of a population at high risk of KCs, who were followed for a median duration of 3.7 years for occurrence of SCC on the face or ears. The most important independent risk factors in this group were number of invasive SCCs in the 5 years before enrollment, number of AKs at enrollment, and total occupational time spent working outdoors. In addition, the number of prior *in situ* SCCs and a history of ever use of 5-fluorouracil were also strongly associated with an increased risk of future SCCs. On the other hand, the use of ACEi/ARB during the study and a history of warts anywhere on the body were associated with reduced risk of developing subsequent SCCs. After 5 years, study participants had a 30% probability of developing a new invasive SCC on the face or ears.

Strengths of this study include a large sample size in a high-risk population from six locations in the United States, with a mean follow-up duration of almost 4 years. Endpoints were verified by electronic medical records for completeness of obtained biopsies, and by central reference dermatopathology reviews. Key predictor variables were also obtained by direct observations (AKs) or by recorded reviews (prior KCs).

Limitations include a study population of veterans who were primarily male, elderly Caucasians who had two or more prior KCs, which may limit the generalizability of our results to other groups. Index event bias may also be a limitation, as our requirement for participants to have had two or more pre-enrollment KCs will tend to shift results towards the null (Dahabreh and Kent, 2011). This may explain why some known risk factors for primary SCC, such as sun exposure,

Table 1. Univariable predictors of SCC risk on face or ears

		Invasive SCC			Invasive + *in situ* SCC		
Predictor	***n* (%)**	**HRR**	**95% CI**	***P*-value**	**HRR**	**95% CI**	***P*-value**
Sex		4.76	1.18–19.13	0.028	2.26	0.93–5.46	0.071
Male	1,097 (97)						
Female	34 (3)						
	1,131						
Age (in decades)		1.18	1.03–1.36	0.016	1.18	1.05–1.34	0.007
⩽59	158 (14)	1.00			1.00		
60–69	304 (27)	1.45			1.58		
70–79	505 (45)	1.90			1.90		
⩾80	164 (15)	1.48			1.66		
	1,131						
Education		0.94	0.74–1.21	0.648	0.91	0.73–1.14	0.415
No college	483 (43)						
Some college or higher	648 (57)						
	1,131						
BCCs in prior 5 years (0 to 1 scale)		1.05	0.71–1.55	0.813	0.99	0.69–1.41	0.962
0–1 (0)	204 (18)						
2 (0.25)	439 (39)						
3 (0.5)	200 (18)						
4–5 (0.75)	159 (14)						
⩾6 (1)	129 (11)						
	1,131						
SCCs invasive in prior 5 years (0 to 1 scale)		6.01	4.24–8.71	<0.001	5.22	3.72–7.33	<0.001
0 (0)	731 (65)	1.00			1.00		
1 (0.25)	222 (20)	2.08			2.28		
2 (0.5)	109 (10)	3.87			3.21		
3 (0.75)	34 (3)	1.07			1.66		
⩾4 (1)	35 (3)	4.31			2.17		
	1,131						
AKs at baseline (0 to 1 scale)		4.59	3.23–6.52	<0.001	3.96	2.89–5.42	<0.001
0 (0)	269 (24)	1.00			1.00		
1–2 (0.25)	252 (22)	2.29			2.18		
3–6 (0.5)	236 (21)	3.41			3.09		
7–14 (0.75)	181 (16)	4.86			4.39		
⩾15 (1)	193 (17)	5.70			4.71		
	1,131						
SCCs *in situ* in last 5 years (0 to 1 scale)		2.88	1.96–4.23	<0.001	3.06	2.16–4.34	<0.001
0 (0)	981 (87)	1.00			1.00		
1 (0.5)	103 (9)	2.20			2.28		
⩾2 (1)	47 (4)	2.42			2.56		
	1,131						
Family history of skin cancer (self-reported)[1]		0.92	0.70–1.21	0.555	0.95	0.74–1.21	0.667
Yes	307 (27)						
No	824 (73)						
	1,131						

Table 1 Continued on following page

Table 1. (continued)

		Invasive SCC			Invasive + *in situ* SCC		
Predictor	***n* (%)**	**HRR**	**95% CI**	***P*-value**	**HRR**	**95% CI**	***P*-value**
History of ever having eczema (self-reported)[1]		0.53	0.25–1.11	0.093	0.88	0.50–1.53	0.644
Yes	52 (5)						
No	1,079 (95)						
	1,131						
Current smoker		1.37	1.01–1.86	0.040	1.17	0.88–1.56	0.277
Yes	183 (16)						
No	948 (84)						
	1,131						
Current or former smoker		0.85	0.65–1.11	0.226	0.83	0.65–1.05	0.128
Yes	812 (72)						
No	319 (28)						
	1,131						
Sunburn causing pain at ages ⩽12		1.00	0.78–1.27	0.996	1.08	0.87–1.35	0.468
Yes	552 (49)						
No	550 (49)						
	1,131						
Sunburn causing pain at ages 13–17		1.01	0.79–1.29	0.925	1.09	0.88–1.37	0.420
Yes	477 (43)						
No	627 (57)						
	1,104						
Sunburn causing pain at ages ⩾18		1.03	0.80–1.31	0.837	1.09	0.87–1.36	0.446
Yes	477 (43)						
No	632 (57)						
	1,109						
Sunburn causing pain in prior 5 years		0.68	0.33–1.37	0.275	0.86	0.48–1.52	0.597
Yes	46 (4)						
No	1,066 (96)						
	1,112						
History of ever using 5-FU (self-reported)[1]		2.46	1.90–3.17	<0.001	2.20	1.73–2.78	<0.001
Yes	215 (19)						
No	916 (81)						
	1,131						
History of using ACEi/ARB during study[2]		0.65	0.51–0.84	0.001	0.60	0.48–0.76	<0.001
Yes	489 (47)						
No	562 (53)						
	1,051						
History of ever having warts anywhere on body (self-reported)[1]		0.70	0.54–0.89	0.004	0.70	0.56–0.88	0.002
Yes	726 (66)						
No	378 (34)						
	1,099						
Sun Sensitivity Index (0 to 1 scale, see Materials and Methods)		1.62	0.90–2.92	0.106	1.82	1.07–3.09	0.028
0.0–0.2 (0)	65 (6)						
>0.2–0.4 (0.25)	248 (22)						

Table 1 Continued on following page

Table 1. (continued)

		Invasive SCC			Invasive + *in situ* SCC		
Predictor	***n* (%)**	**HRR**	**95% CI**	***P*-value**	**HRR**	**95% CI**	***P*-value**
>0.4–0.6 (0.5)	354 (32)						
>0.6–0.8 (0.75)	330 (30)						
>0.8–1.0 (1)	118 (11)						
	1,115						
Latitude of residence at ages ⩽12		0.97	0.94–0.99	0.011	0.97	0.95–0.99	0.011
<25	8 (1)						
25–35	304 (28)						
>35	784 (72)						
	1,096						
Latitude of residence at ages 13–17		0.99	0.97–1.00	0.086	0.99	0.97–1.00	0.094
<25	24 (2)						
25–35	318 (30)						
>35	733 (68)						
	1,075						
Latitude of residence at ages ⩾18		0.98	0.96–1.01	0.152	0.99	0.96–1.01	0.300
<25	15 (1)						
25–35	504 (45)						
>35	594 (53)						
	1,113						
Latitude of residence in prior 5 years		1.00	0.98–1.02	0.679	1.00	0.98–1.01	0.932
<25	23 (2)						
25–35	731 (66)						
>35	357 (32)						
	1,111						
Total occupational decades outdoors[3] in sun		1.30	1.19–1.42	<0.001	1.25	1.16–1.37	<0.001
0	93 (8)						
⩽3	919 (83)						
>3	101 (9)						
	1,113						
Total occupational decades outdoors[3]		1.25	1.16–1.36	<0.001	1.22	1.14–1.31	<0.001
0	92 (8)						
⩽3	791 (71)						
>3	230 (21)						
	1,113						
Total occupational decades outdoors[3] in sun at ages <30		1.21	1.01–1.46	0.037	1.10	0.93–1.31	0.271
0	89 (9)						
⩽1	767 (76)						
>1	152 (15)						
	1,008						
Total occupational decades outdoors[3] in sun at ages ⩾30		1.38	1.20–1.58	<0.001	1.43	1.16–1.78	0.001
0	92 (11)						
⩽1	386 (48)						
>1	328 (41)						
	806						

Table 1 Continued on following page

Table 1. (continued)

Predictor	*n* (%)	Invasive SCC			Invasive + *in situ* SCC		
		HRR	95% CI	*P*-value	HRR	95% CI	*P*-value
Total weeks on vacation[4]		1.11	0.82–1.50	0.514	1.18	0.91–1.55	0.213
0	913 (82)						
⩾1	199 (18)						
	1,112						
Total days outside[3] on vacation[4]		1.11	0.82–1.50	0.514	1.18	0.91–1.55	0.213
0	913 (82)						
⩾1	199 (18)						
	1,112						
Total days in sun[3] on vacation[4]		1.11	0.82–1.50	0.514	1.18	0.91–1.55	0.213
0	913 (82)						
⩾1	199 (18)						
	1,112						
Total days in sun[3] on vacation[4] without wearing SPF 15 or greater		1.26	0.89–1.82	0.194	1.24	0.89–1.72	0.205
0	993 (89)						
⩾1	118 (11)						
	1,111						
Total recreational months outside[3] at ages ⩽12		1.00	0.98–1.02	0.861	1.00	0.99–1.02	0.660
0	64 (6)						
⩽12	669 (61)						
>12	357 (33)						
	1,090						
Total recreational months outside[3] at ages 13–17		0.96	0.91–1.02	0.152	0.96	0.92–1.01	0.156
0	127 (12)						
⩽12	955 (88)						
>12	4 (0)						
	1,086						
Total recreational months outside[3] at ages 18–40		0.99	0.97–1.01	0.357	0.99	0.97–1.01	0.188
0	171 (16)						
⩽12	713 (66)						
>12	196 (18)						
	1,080						
Total recreational months outside[3] in prior 5 years		0.99	0.95–1.03	0.525	1.00	0.96–1.03	0.812
0	244 (23)						
⩽12	801 (75)						
>12	23 (2)						
	1,068						
Ethnicity of grandparents		0.75	0.57–0.98	0.037	0.85	0.67–1.08	0.187
1 = Scandanavian/Celtic	1,183 (33)						
1.5	193 (5)						
2 = Northern European/Slavic	1,905 (53)						
2.5	48 (1)						
3 = Mediterranean/Middle Eastern/ Hispanic/Latin American/Native American/Asian	245 (7)						

Table 1 Continued on following page

Table 1. (continued)

Predictor	*n* (%)	Invasive SCC			Invasive + *in situ* SCC		
		HRR	95% CI	*P*-value	HRR	95% CI	*P*-value
4 = African black	0 (0)						
	3,574						
Days spent outside[3] for ⩾30 mins in prior week (0 to 1 scale)		1.18	0.88–1.56	0.264	1.17	0.90–1.51	0.234
None (0)	352 (32)						
Some (0.5)	256 (23)						
All (1)	503 (45)						
	1,111						
Days spent outside[3] for ⩾2 h in prior week (0 to 1 scale)		1.18	0.89–1.57	0.246	1.18	0.92–1.53	0.199
None (0)	618 (56)						
Some (0.5)	213 (19)						
All (1)	280 (25)						
	1,111						
Days spent outside[3] for ⩾30 min in prior 6 months (0 to 1 scale)		1.03	0.75–1.43	0.843	0.99	0.74–1.33	0.969
None (0)	222 (20)						
Some (0.5)	437 (39)						
All (1)	450 (41)						
	1,109						
Days spent outside[3] for ⩾2 h in prior 6 months (0 to 1 scale)		0.99	0.72–1.35	0.927	0.99	0.75–1.32	0.965
None (0)	480 (43)						
Some (0.5)	390 (35)						
All (1)	239 (22)						
	1,109						
Sunscreen use[3] on face or ears in prior week (0 to 1 scale)		1.42	1.08–1.88	0.013	1.44	1.12–1.85	0.005
Never (0)	616 (56)						
Sometimes (0.5)	184 (17)						
Always (1)	291 (27)						
	1,091						
Sunscreen use[3] on face or ears in prior 6 months (0 to 1 scale)		1.21	0.89–1.63	0.219	1.23	0.94–1.62	0.129
Never (0)	522 (47)						
Sometimes (0.5)	320 (29)						
Always (1)	259 (24)						
	1,101						
SPF ⩾15 use[3] on face or ears in prior week (0 to 1 scale)		1.32	0.99–1.74	0.055	1.36	1.06–1.76	0.017
Never (0)	630 (58)						
Sometimes (0.5)	179 (16)						
Always (1)	282 (26)						
	1,091						
SPF ⩾15 use[3] on face or ears in prior 6 months (0 to 1 scale)		1.18	0.87–1.60	0.276	1.24	0.94–1.63	0.121
Never (0)	542 (49)						
Sometimes (0.5)	312 (28%)						
Always (1)	247 (22)						
	1,101						

Table 1 Continued on following page

Table 1. (continued)

Predictor	*n* (%)	Invasive SCC			Invasive + *in situ* SCC		
		HRR	95% CI	*P*-value	HRR	95% CI	*P*-value
Lifetime sun exposure in decades		2.47	1.67–3.66	<0.001	2.22	1.55–3.18	<0.001
⩽0.5	711 (64)						
>0.5	403 (36)						
	1,114						

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AK, actinic keratose; BCC, basal cell carcinoma; CI, confidence interval; HRR, hazard rate ratio; SCC, squamous cell carcinoma; SPF, sun protection factor; 5-FU, 5-fluorouracil.
[1]Data were self-reported, as records were not available beyond 5 years before study.
[2]Frequency is for invasive SCC. Similar frequency is seen for total SCC.
[3]During 1000–1500 hours.
[4]Between latitudes 25° N and 25° S.

Table 2. Multivariable predictors of SCC risk on face or ears

Predictor	HRR	95% CI	*P*-value
Invasive SCCs			
SCCs invasive in prior 5 years[1]	3.04	1.79–5.18	<0.001
SCCs *in situ* in prior 5 years[2]	2.23	1.27–3.95	0.006
AKs at baseline[3]	3.07	1.84–5.10	<0.001
History of ever using 5-FU[4]	1.61	1.10–2.36	0.014
History of using ACEi/ARB during study	0.58	0.41–0.81	0.001
History of ever having warts anywhere on body[4]	0.69	0.49–0.97	0.034
Occupational time outdoors[5] in decades	1.23	1.08–1.39	0.002
All SCCs (invasive + in situ)			
SCCs invasive in prior 5 years[1]	2.90	1.82–4.62	<0.001
SCCs *in situ* in prior 5 years[2]	1.75	1.10–2.78	0.019
AKs at baseline[3]	2.60	1.72–3.94	<0.001
History of ever using 5-FU[4]	1.46	1.05–2.03	0.023
History of using ACEi/ARB during study	0.60	0.45–0.79	<0.001
History of ever having warts anywhere on body[4]	0.72	0.54–0.95	0.020
Occupational time outdoors[5] in decades	1.26	1.14–1.39	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AKs, actinic keratoses; CI, confidence interval; HRR, hazard rate ratio; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil.
[1]Categorical variable (0 to 1 scale): 0, no invasive SCCs; 0.25, 1 SCC; 0.5, 2 SCCs; 0.75, 3 SCCs; 1.0⩾4 SCCs.
[2]Categorical variable (0 to 1 scale): 0, no *in situ* SCCs; 0.5, 1 SCC; 1, ⩾2 SCCs.
[3]Categorical variable (0 to 1 scale): 0, no AKs at beginning of study; 0.25, 1–2 AKs; 0.5, 3–6 AKs; 0.75, 7–14 AKs; 1.0, ⩾15 AKs.
[4]Data were self-reported, as records were not available beyond 5 years before study.
[5]During 1000–1500 hours.

Table 3. VIFs for multivariable predictors

Predictor	VIF
SCCs invasive in prior 5 years[1]	1.21
SCCs *in situ* in prior 5 years[2]	1.10
AKs at baseline[3]	1.11
History of ever using 5-FU[4]	1.12
History of using ACEi/ARB during study	1.01
History of ever having warts anywhere on body[4]	1.00
Occupational time outdoors in decades[5]	1.02

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AKs, actinic keratoses; SCC, squamous cell carcinoma; VIF, Variance inflation factors; 5-FU, 5-fluorouracil.
[1]Categorical variable (0 to 1 scale): 0, no invasive SCCs; 0.25, 1 SCC; 0.5, 2 SCCs; 0.75, 3 SCCs; 1.0, ⩾4 SCCs.
[2]Categorical variable (0 to 1 scale): 0, no *in situ* SCCs; 0.5, 1 SCC; 1, ⩾2 SCCs.
[3]Categorical variable (0 to 1 scale): 0, no AKs at beginning of study; 0.25, 1–2 AKs; 0.5, 3–6 AKs; 0.75, 7–14 AKs; 1.0, ⩾15 AKs.
[4]Data were self-reported, as records not available beyond 5 years before study.
[5]During 1000–1500 hours.

were not found to be significant predictors in our model. In addition, overfitting of the multivariable model is a concern, as certain variables we tested, such as number of baseline AKs, are along the causative pathway. Nonetheless, overfitting seems unlikely to be substantial given our low variance inflation factor and Pearson's *r*-values, which are all less than 1.21 and 0.29, respectively (Tables 3 and 4). Finally, we cannot eliminate the possibility of error with assessments, which are dependent on recall. However, recall bias was minimized as many of the predictors, such as prior KCs and baseline AKs, were measured by dermatological examination or medical record review. Moreover, the prospective ascertainment of these variables further helps in preventing recall bias.

Previous SCCs (both invasive and *in situ*) have been shown to be a risk factor for developing a new invasive SCC, and the 3-year risk of 22% that we noted is similar to prior reports (Karagas, 1994; Marcil and Stern, 2000). There was no association between previous BCCs and development of new SCCs, whereas other studies have shown a weak association (Marcil and Stern, 2000). We also did not find an association between history of eczema and subsequent SCC risk, although prior studies have suggested a link

Table 4. Pearson's correlation coefficients for multivariable predictors

	SCCs invasive in prior 5 years[1]	SCCs *in situ* in prior 5 years[2]	AKs at baseline[3]	History of ever using 5-FU[4]	History of using ACEi/ARB during study	History of ever having warts anywhere on body[5]	Occupational time outdoors in decades[5]
SCCs invasive in prior 5 years[1]	1.00						
SCCs *in situ* in prior 5 years[2]	0.25	1.00					
AKs at baseline[3]	0.28	0.14	1.00				
History of ever using 5-FU[4]	0.29	0.20	0.19	1.00			
History of using ACEi/ARB during study	− 0.05	− 0.07	0.01	− 0.03	1.00		
History of ever having warts anywhere on body[4]	0.00	0.04	0.02	0.03	0.01	1.00	
Occupational time outdoors in decades[5]	0.10	0.03	0.09	0.02	0.05	− 0.03	1.00

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AKs, actinic keratoses; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil.

[1]Categorical variable (0 to 1 scale): 0, no invasive SCCs; 0.25, 1 SCC; 0.5, 2 SCCs; 0.75, 3 SCCs; 1.0, ⩾4 SCCs.

[2]Categorical variable (0 to 1 scale): 0, no *in situ* SCCs; 0.5, 1 SCC; 1, ⩾2 SCCs.

[3]Categorical variable (0 to 1 scale): 0, no AKs at beginning of study; 0.25, 1–2 AKs; 0.5, 3–6 AKs; 0.75, 7–14 AKs; 1.0, ⩾15 AKs.

[4]Data were self-reported, as records not available beyond 5 years prior to study.

[5]During 1000–1500 hours.

between eczema and noncutaneous SCC (Duk *et al.*, 1989; Heinz *et al.*, 2003), and cutaneous BCC (Dyer *et al.*, 2012). In addition, we did not find smoking to be associated with subsequent SCC risk. Although some studies have shown smoking to be a risk factor for SCC (Aubry and MacGibbon, 1985; Karagas *et al.*, 1992), other studies have not (Green *et al.*, 1996; Odenbro *et al.*, 2005).

The association between AKs at the start of the study and time to new invasive SCC is extremely strong; indeed, AKs are a precursor to SCCs (Marks *et al.*, 1988; Green and Battistutta, 1990; Chen *et al.*, 2005). Prior research has shown that SCCs are associated with cumulative lifetime sun exposure (Marks *et al.*, 1988, 1990; Salasche, 2000), and our data confirm this. Our multivariable model did not demonstrate any associations between incidence of new invasive SCCs and residential latitude, leisure time, or sun exposure during vacation (Elwood *et al.*, 1974) in this high-risk population, but it did find an association with occupational time spent outside. Previous studies have also demonstrated that the risk of SCC is related to total occupational sun exposure (Armstrong and Kricker, 2001), although these associations are not strong.

Being male and being older has been shown to increase the risk of developing a new SCC, and in our study they were significant on their own, but not when other factors were included in the regression model. Only 3% of participants were women.

We found the use of ACE inhibitors or ARBs to be associated with reduced risk of SCCs, which has been previously demonstrated (Christian *et al.*, 2008). Other studies have also suggested a link between ACEi/ARB use and reduced risk of several types of cancers in humans (Lever *et al.*, 1998), as well as renal cell carcinoma in animal models (Hii *et al.*, 1998).

The association between human papilloma virus (HPV) and cutaneous nongenital/nonperianal SCC is based, in large part, on inconsistent epidemiological studies on HPV–DNA serologies (Steger *et al.*, 1990; Stark *et al.*, 1998; Bouwes Bavinck *et al.*, 2000; Favre *et al.*, 2000; Masini *et al.*, 2003; Andersson *et al.*, 2008; Mammas *et al.*, 2008; Waterboer *et al.*, 2008; Andersson *et al.*, 2012). However, the link between a self-reported history of warts and SCC development has not been extensively studied. Kricker *et al.* (1991) found that a history of ever having warts protected against BCC (odds ratio: 0.66, $P = 0.02$) but not SCC. In another study, a history of warts (odds ratio: 0.87, 95% CI: 0.57–1.32, $P = 0.51$) showed little association with SCC (English *et al.*, 1998b). However, we found that the presence of a wart anywhere on the body at any time in a subject's life reduced the risk of a future SCC. Given the ubiquity of HPV subtypes, a low-risk HPV subtype may exist that also confers protection against SCC development. One plausible explanation for this occurrence is the existence of antagonistic interference between HPV subtypes, as has been previously shown in cervical cancer (Silins *et al.*, 1999). Our observation of a history of warts and lower SCC risk calls for independent confirmation.

For a large number of patients with a previous history of invasive SCCs, our findings further support the need to identify effective preventive measures in the high-risk population. Our finding of a protective effect on SCC development in patients with a history of warts demands further investigation.

MATERIALS AND METHODS

A full description of study methods is described in previously published reports from the VATTC Trial (Weinstock *et al.*, 2001; Jagdeo *et al.*, 2007; Christian *et al.*, 2008; Criscione *et al.*, 2009; Dore *et al.*, 2009; Geng *et al.*, 2009; Weinstock *et al.*, 2009a, 2009b; Lee *et al.*, 2010; Lee and Weinstock, 2011; Nunes *et al.*, 2011; Baibergenova *et al.*, 2012).

The VATTC was a randomized, double-blind, vehicle-controlled, multicenter study (ClinicalTrials.gov identifier: NCT00007631) with participants enrolled from six VA medical centers: Durham, North Carolina; Oklahoma City, Oklahoma; Chicago, Illinois; Long Beach, California; Miami, Florida; and Phoenix, Arizona.

The study population consisted of VA patients who had been diagnosed with at least two KCs (i.e., BCC or SCC) in the 5 years before enrollment, excluding KCs in the genital and perianal areas. Participants were required to be free of KCs at the beginning of the study, which was verified by a study dermatologist. Participants were excluded if they met any of the following criteria: systemic retinoid or chemotherapy treatment within the 6 months before enrollment; known allergy or severe past reaction to tretinoin; moderate to severe dermatitis on the face; severe medical problems with very high 3-year mortality risk, including but not limited to metastatic skin cancer, other invasive cancer, and AIDS; special conditions predisposing to KCs, including radiation therapy or scars from thermal burns to face or ears, psoralen plus UVA treatment, organ transplant recipient, arsenic exposure, basal cell nevus syndrome, mycosis fungoides, and xeroderma pigmentosum; pregnant or nursing; or unlikely to comply or not competent to give informed consent as judged by the study investigator. Moreover, participants were excluded if they obtained any of the following treatments 60 days before enrollment: topical 5-fluorouracil or masoprocol, calcipotriene on the face or ears, topical retinoids, or chemical peel or dermabrasion.

Participants were required to answer a baseline questionnaire to ascertain information related to sun exposure, skin characteristics, and other behaviors that have been linked to skin cancer development (Table 1). They were then followed for 2–6 years, and obtained a skin examination and interview every 6 months. Biopsies of any suspicious lesions were taken at these 6-month intervals. The diagnoses of all biopsies performed on study participants during the trial were reviewed centrally by one of two reference study dermatopathologists, whose diagnoses were considered definitive for study purposes. Ten percent of specimens were reviewed by both study dermatopathologists (Jagdeo *et al.*, 2007).

Univariable analyses and the 1-, 3-, and 5-year risk of developing a new invasive SCC were determined using Stata Version 8 statistical software package (StataCorp LP, College Station, Texas), which incorporates the Kaplan–Meier survivor function. The Cox proportional hazards model was used to do determine the HRRs and 95% CIs of a number of potential predictors of time to first new invasive SCC. A multivariable model was then employed using stepwise regression with those variables thought to be possible predictors of time to first invasive SCC (all variables that had a $P<0.15$ in univariable Cox regression), to determine whether they were independent predictors for future SCCs. We repeated the above analyses to determine the risk of developing all SCCs (both invasive and *in situ*). Finally, we tested for collinearity using variance inflation factor and Pearson's correlation analyses to assess the possibility of overfitting of the multivariable models.

This study was conducted in accordance with the Declaration of Helsinki Principles, and all participants gave written, informed consent. This study was approved by 17 committees: the Executive Committee of the VA Topical Tretinoin Chemoprevention Trial, the Study Data and Safety Monitoring Board, the Central Cooperative Studies Program Coordinating Center Human Rights Committee, as well as the institutional review boards and the research and development committees of the six participating medical centers and of the study chairman's medical center (VA Medical Center, Providence, Rhode Island). In addition, the Cooperative Studies Evaluation Committee approved this study at the outset and reviewed it at its midpoint.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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APPENDIX

Key personnel of the VATTC Trial

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