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Human Papillomavirus Vaccination and Actinic Keratosis Burden
The VAXAK Randomized Clinical Trial

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IMPORTANCE The substantial morbidity and socioeconomic costs associated with actinic keratosis (AK) management represent major public health concerns. Anecdotal evidence suggests that human papillomavirus (HPV) vaccination may offer therapeutic and preventive effects against AK and keratinocyte carcinomas (KCs).

OBJECTIVE To investigate the effect of HPV vaccination on burden of disease in immunocompetent patients with high numbers of AK.

DESIGN, SETTING, AND PARTICIPANTS The VAXAK trial was a parallel-design, double-blind, randomized sham-controlled clinical trial with 12 months' follow-up. This single-center trial was conducted at the Department of Dermatology, Bispebjerg University Hospital in Copenhagen, Denmark, between May 2021 and June 2024. Eligible participants were immunocompetent adults with 15 or more clinical AK lesions in a 50 cm^2 to 100 cm^2 test area on the head, trunk, or extremities.

INTERVENTIONS Participants were randomized 1:1 to blinded, 9-valent alphapapillomavirus vaccine or sham vaccine (isotonic sodium chloride solution), each administered intramuscularly at 0, 2, and 6 months. Thick AKs (Olsen grade II-III) received cryotherapy at months 6 and 9; test areas were otherwise untreated during the study.

MAIN OUTCOMES AND MEASURES The preselected primary outcome was the percentage reduction in baseline AKs assessed 2, 6, 9, and 12 months after first vaccination. Secondary outcomes included total AK number, thick lesions, new AKs, and rate of incident KCs over 12 months.

RESULTS Participants were selected by consecutive sampling of 163 screened patients following exclusion of 93 individuals due to ineligibility or patients opting out. Among 70 enrolled participants (median [IQR] age, 75.50 [69.00-79.00] years; 47 [67%] male), 69 completed the study. Median (IQR) AK reductions were higher in the HPV-vaccinated vs sham group, shown consistently over the study period (month 2: 35% [25%-44%] vs 25% [18%-33%]; $P = .03$; month 6: 47% [33%-53%] vs 29% [16%-44%]; $P = .01$; month 9: 58% [37%-63%] vs 42% [33%-56%]; $P = .09$; month 12: 58% [47%-69%] vs 47% [32%-65%]; $P = .05$). Total AK numbers were correspondingly lower in the HPV-vaccinated group (median [IQR] at month 6: 14.00 [11.00-16.00] vs 17.00 [12.00-23.00]; $P = .01$; month 12: 10.00 [6.00-24.00] vs 16.00 [8.50-21.00]; $P = .02$). Coincidingly, fewer thick AKs were observed in the HPV-vaccinated group (median [IQR] at month 6: 5.00 [3.00-7.00] vs 6.50 [3.75-10.00]; $P = .02$; month 12: 3.00 [2.00-5.00] vs 5.00 [2.50-8.50]; $P = .049$). In contrast, no significant differences in rates of new AKs (1-2 AK[s] per month) or KC numbers overall or per participant were identified during the 12-month trial.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, standard alphapapillomavirus vaccination was found to reduce AK burden in immunocompetent individuals with multiple lesions. HPV-targeted vaccines may be useful for management of AK, a chronic, relapsing disease and the most common precancer in fair-skinned populations.

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Supplemental content

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Actinic keratosis (AK) is the most prevalent precancer in fair-skinned populations, affecting an estimated 14% of persons worldwide.[1] In the US, AKs are the most commonly diagnosed skin condition at dermatology visits, and with increases of 232 000 visits per year,[2] annual management costs now exceed $1 billion.[3] Primarily caused by chronic exposure to UV radiation, AKs are typically identified as rough, scaly, and erythematous patches on sun-exposed skin areas.[4] Understood to be a precursor on a disease continuum,[5] lesions consist histologically of intraepidermal proliferations of atypical keratinocytes. As such, AK has a well-known potential to progress to invasive squamous cell carcinoma (SCC). Although the progression rate per lesion is thought to be low (<1% per year),[6] individuals with multiple AKs,[7] field-cancerized background skin,[8] or a history of skin cancer are at elevated risk.[7,9] Accordingly in 2023, a cohort study of more than 500 000 Medicare beneficiaries found absolute risks of skin cancer of 18% and 29% 3 and 5 years after a first AK, respectively.[10] It follows that the substantial morbidity and rising socioeconomic costs associated with AK care[11] represent major public health concerns.[1]

An association between human papillomavirus (HPV) and cutaneous dysplasia has long been recognized, but the relationship dynamics remain controversial.[12-15] Unclear whether causal or merely correlative, detection of betapapillomavirus (β-HPV) and gammapapillomavirus (γ-HPV) DNA in keratinocyte carcinoma (KC) and particularly AK lesions is reported in epidemiological studies and systematic reviews.[12,15-18] The association is especially striking in immunosuppressed populations where, coinciding with a 65-fold to 250-fold increase in AK and skin cancer risk,[19-21] up to 85% of KC and precursor lesions are positive for particularly β-HPV DNA.[22,23] HPV is furthermore reported to be a predictor of SCC risk, with a recent prospective cohort study finding an up to 4 times higher SCC rate among immunocompetent patients with a β-HPV DNA-positive forearm swab.[24] While cutaneotropic HPVs have not been shown to directly cause skin cancer, the wealth of evidence linking these 2 entities is compelling, leading some researchers to propose an HPV-directed approach to tackling the expanding burden of KC disease.[25-29]

Intriguingly, emerging evidence suggests a beneficial impact of alphapapillomavirus (α-HPV) vaccination for KC and precursor lesions.[25,30,31] Reflecting a potential preventive effect in high-risk individuals, reduced SCC and basal cell carcinoma (BCC) incidences following HPV vaccination are described in case reports of both immunocompetent and immunosuppressed patients.[27,32] A small retrospective study similarly noted a significant reduction in dermatologic interventions (ie, biopsies, curettages, or excisions) after standard HPV vaccination in 38 immunosuppressed patients (hazard ratio, 0.27 [95% CI, 0.14-0.51]).[33] Off-label HPV vaccination has also been used to treat existing KC and precursor lesions. Indeed, several reports describe clearance of SCC in situ,[30,34,35] SCC variants,[31,36] keratoacanthoma,[37] and reduced AK burden[28,38] following intramuscular and/or intralesional administration of HPV vaccine. At present, however, most evidence indicating utility of α-HPV vaccination in the context of AK and KC is anecdotal. Further, the underlying mechanisms behind vaccine's potential utility remain unknown.

Key Points

Question Does human papillomavirus (HPV) vaccination affect the burden of disease in patients with actinic keratosis (AK)?

Findings In this randomized clinical trial of 70 immunocompetent adults with multiple AKs, consistently greater reductions in median (IQR) lesion count were shown after HPV vaccination vs sham, reaching statistical significance at month 2 (35% [25%-44%] vs 25% [18%-33%]) and month 6 (47% [33%-53%] vs 29% [16%-44%]).

Meaning Standard HPV vaccination may reduce AK burden in immunocompetent individuals with multiple AKs.

Prompted by the notable human and economic cost of AK and KC management, the link between HPV, AK, and skin cancer; approved HPV vaccines' strong safety profile[39]; and initial reports indicating potential efficacy against KC and precursors, this randomized clinical trial (RCT) investigated the effect of HPV vaccination on burden of disease in immunocompetent patients with multiple AKs.

Methods

Trial Design and Participants

The VAXAK study was a nonindustry investigator-initiated, parallel-design double-blind, randomized sham-controlled trial with 12 months' follow-up, conducted at Copenhagen University Hospital-Bispebjerg from May 2021 to June 2024 in Copenhagen, Denmark. Prior to initiation, the study protocol (Supplement 1) was approved by the Capital Region's Committee on Health Research Ethics (H-21047863), the Danish Medicines Agency (EudraCT 2021-003895-15), the Danish Data Protection Agency (2021-P-776), and registered on clinicaltrials.gov. The study was monitored by the University of Copenhagen's Good Clinical Practice unit and conducted in accordance with the Declaration of Helsinki. Before inclusion, written informed consent was obtained from all participants. Reporting adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[40]

Patients attending regular outpatient care at the Department of Dermatology, Copenhagen University Hospital-Bispebjerg, Denmark, were screened for trial eligibility by consecutive sampling. Eligible participants were immunocompetent adults (≥18 years) with a 50 cm^2 to 100 cm^2 skin site on the head, trunk, or extremities that presented with a high AK burden, herein defined as 15 or more clinically diagnosed AKs. Exclusion criteria were known or suspected immunosuppression due to disease or medication, other dermatological disease in the skin area at baseline, history of HPV vaccination, keloids, any vaccine-related allergy, known allergy to yeast, pregnancy, or lactation. Participants must also have been willing to refrain from non-protocol-outlined AK treatments in the skin area for the duration of the trial.

Interventions

Interventions consisted of 3 doses of a commercially available, recombinant 9-valent α-HPV vaccine, 0.5 mL (Gardasil-9 [MSD]) or sham vaccine (isotonic sodium chloride solution, 9 mg/mL [Fresenius Kabi]), administered intramuscularly (deltoid) at baseline, month 2, and month 6 according to the approved vaccination schedule for adults. Due to ethical concerns about leaving AKs untreated for the duration of the study, both groups underwent lesion-directed cryotherapy (10 seconds ×2) of any Olsen grade II to III AK in the test area at months 6 and 9.

Randomization and Blinding

In a parallel-group design, patients were randomized (1:1) to receive HPV or sham vaccine. The allocation sequence was generated by computer-based block randomization (fixed block size of 8) using MATLAB software (MathWorks) without stratification. As described in detail in Supplement 2, both patients and investigators (ie, outcome assessors and data analysts) were blinded to the treatment allocation.

Procedures

The 12-month trial period had 5 scheduled visits at months 0, 2, 6, 9, and 12. During visits, AKs in the selected 50 cm^2 to 100 cm^2 test area were counted, labeled, and graded according to their clinical Olsen grade (grades I-III) based on degree of hyperkeratosis: grade I, mild (slightly palpable); II, moderate (moderately thick); and III, severe (very thick).[41] AK locations and numbers were mapped on a transparent template enabling reidentification of baseline lesions and new AKs at subsequent visits. Test areas were furthermore documented with standardized digital photography (Canon 750D). At every visit, patients also underwent a full-body skin examination for any incident KC lesions. Throughout the trial, AK assessments and skin examinations were performed by the same blinded investigator without exception.

Outcomes

The preselected primary outcome was percentage change from baseline in number of clinical AK lesions in the test area, evaluated at months 2, 6, 9, and 12. Preselected secondary AK-related outcomes were total AK count and new AKs at months 2, 6, 9, and 12, as well as partial (75%) and complete (100%) clinical patient clearance of AKs at 12 months. To assess response specifically in thick lesions, the number of grade II to III AKs at months 0, 2, 6, 9, and 12, as well as the number of thick lesions receiving cryotherapy at months 6 and 9, were added as additional outcomes at the time of data analysis.

Preselected secondary outcomes related to KC were the number of histologically verified tumors diagnosed during the 12 months. This yearly rate was compared to the average yearly KC rate 3 years prior to inclusion (based on pathology results in each patient's electronic medical record). Nonsystematic assessment of adverse events (AEs) and systematic determination of serious adverse events (SAEs) were also performed during the trial.

Sample Size and Statistics

Sample size calculation was based on data from a previously published case series of 12 patients with high AK burden who underwent HPV vaccination as an adjunct to standard AK therapies.[38] From these data, the sample size calculation set a minimal relevant difference of 10%, a power of 80%, an α level of 5%, and a variance of 14%, resulting in a minimum of 32 patients per group. Accounting for potential dropout (10%), the trial aimed to include 35 individuals per group, resulting in a total of 70 participants.

Because Shapiro-Wilk tests did not confirm normal distribution of the data, nonparametric tests were applied. Accordingly, descriptive statistics are presented as medians and IQRs. AK response, KC lesion rates, AEs and data on field treatments performed outside test areas in HPV vaccine and sham groups were compared using Mann-Whitney U tests for 2 unpaired groups. For the primary outcome specifically, both per-protocol and intention-to-treat populations were analyzed with missing data imputed as last observation carried forward only in the latter analysis. For secondary outcomes, per-protocol analyses were performed. Binominal data were compared with Fisher exact test. To assess associations between the primary outcome and participant age and sex, Spearman correlation and Mann-Whitney U tests were performed, respectively. Intraindividual comparisons of KC rates prevaccination and postvaccination were assessed using Wilcoxon signed rank tests for 2 paired groups. *P* values were exact, 2-sided, and considered statistically significant when less than .05. Analyses were performed using SPSS statistical software, version 29 (IBM Corporation).

Results

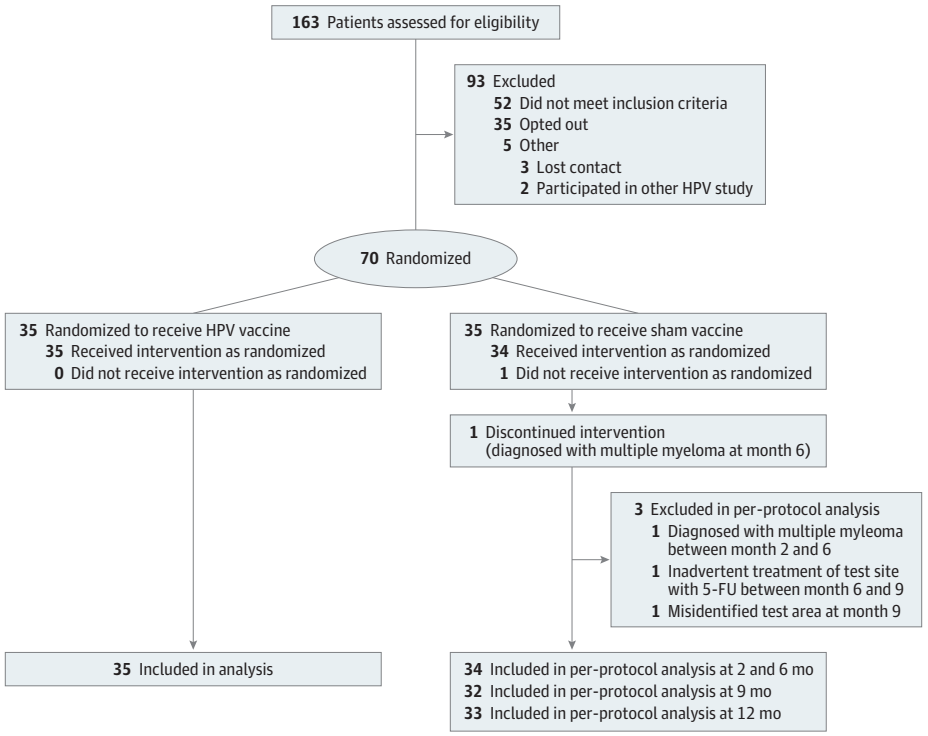
Baseline Characteristics

The trial's participant flow and baseline data are presented in **Figure 1** and **Table 1**, respectively. Participants were selected by consecutive sampling of 163 screened patients following exclusion of 93 individuals due to ineligibility or patients opting out. A total of 70 participants with a median (IQR) age of 75.50 (69.00-79.00) years (range, 58-95 years; 47 [67%] male) were included. Of these, 69 completed the 12-month follow-up following exclusion of 1 patient in the sham group due to a multiple myeloma diagnosis (Figure 1). Groups were generally similar based on demographic characteristics and skin cancer history (Table 1). One exception was Fitzpatrick skin type, in which a higher number of fair-skinned individuals was noted in the HPV vaccine group. In addition, the anatomic locations of test sites differed between groups, with a greater number of participants having facial/scalp sites in the sham vaccine group. Of note, median (IQR) baseline AK numbers were comparable between groups (20.00 [16.00-27.00] vs 19.00 [16.00-24.00] AKs) (Table 1).

Effect on AK Burden

Table 2 presents AK-related outcome results, with examples of clinical responses pictured in **Figure 2**. In the per-protocol analysis, median (IQR) percentage reduction in baseline AKs

Figure 1. CONSORT Flowchart



All patients (n = 35) allocated to human papillomavirus (HPV) vaccine completed the trial per protocol and were included in both the per-protocol and intention-to-treat analyses. Among patients allocated to sham vaccine, 1 patient received the second dose at month 3 rather than month 2. Because the timing of administration was within the approved window for HPV vaccination; however, the deviation was considered permissible, and the patient was not excluded from analyses. In the per-protocol analysis, 1 patient in the sham group was excluded from the trial (months 2-12) due to a multiple myeloma diagnosis. Actinic keratosis (AK) outcomes for a second patient were not evaluated in the per protocol analysis after month 6, due to inadvertent treatment of test area AKs with topical 5-fluorouracil (5-FU). Finally, a third patient's AK data at month 9 were not included in the per-protocol analysis due to test area misplacement. Thus, 34 patients in the sham group were included in the per protocol analysis at months 2 and 6; 32 patients at month 9; and 33 patients at month 12.

was higher in the HPV-vaccinated group, reaching significance at month 2 (35% [25%-44%] vs 25% [18%-33%]; P = .03) and month 6 (47% [33%-53%] vs 29% [16%-44%]; P = .01), and near-significance at month 12 (58% [47%-69%] vs 47% [32%-65%]; P = .05). These differences were supported by the intention-to-treat analysis, which showed greater AK reductions in HPV vaccinated group at all follow-up time points from months 2 to 12. Tests for associations between AK reductions and participants' age or sex did not reach significance. Further, rates of cryotherapy at months 6 and 9 were not significantly different between the 2 intervention groups.

Corresponding with the primary outcome findings, the median (IQR) total AK numbers were also lower in the HPV-vaccinated group, with differences growing more pronounced toward the end of the observation period (month 12: 10.00 [6.00-14.00] vs 16 [8.50-21.00] lesions; P = .02) (Table 2). Fewer thick AKs were likewise noted in the HPV-vaccinated group beginning at month 6 and continuing to the end of the trial (median [IQR] at month 12: 3.00 [2.00-5.00] vs 5.00 [2.50-8.50] lesions; P = .049). Numbers of new AK lesions however were not significantly different over the 12 months. Only 9 participants (13%) achieved partial 75% clearance by the end of the trial, 5 of which belonged to the HPV-vaccinated group. No participant demonstrated complete clearance.

Impact on KC Burden

Table 3 presents annual KC rates observed during the study period. Over 12 months, at least 1 KC tumor was confirmed in 17 participants (49%) and 15 participants (44%) in the HPV vaccine and sham vaccine group, respectively (P = .81). Further, no significant difference in the number of patients who developed at least 1 SCC or BCC was shown between the 2 intervention groups. Regarding specific tumor counts, the numbers of KC overall, SCC, and BCC tumors were not significantly different between the 2 groups. In addition, when comparing these annual rates postvaccination to the annual rate assessed over 3 years prevaccination, a significant change in KC, SCC, or BCC rate was not detected in either group.

Adverse Events

Rates of AEs and SAEs were not significantly different between study groups. Thus, AEs were recorded in 12 (34%) and 15 (43%) participants in the HPV-vaccinated and sham groups, respectively (P = .47). Mild and transient AEs related to the study intervention were soreness at the vaccination site, headache, and dizziness, with no patients discontinuing the vaccination schedule due to AEs. Among the 8 participants experiencing SAEs (11%), 2 belonged to the HPV vaccine group and none were deemed related to the study intervention by investigators (ie, likelihood of a causal relationship and timing between vaccination and SAE occurrence).

Discussion

This RCT assessed the utility of standard 3-dose 9-valent α-HPV vaccination to reduce disease burden in immunocompetent patients with multiple AKs. Based on percentage reduction in baseline AK, a modest 10% to 18% difference was observed in the HPV-vaccinated vs sham-vaccinated group over the study

Table 1. Baseline Participant Characteristics

Characteristic	No. (%)	
	HPV group (n = 35)	Sham group (n = 35)
Demographics		
Sex		
Female	10 (29)	13 (37)
Male	25 (71)	22 (63)
Age, median (IQR), y	75.00 (67.00-79.00)	77.00 (72.00-80.00)
Fitzpatrick skin type		
I	18 (51)	9 (26)
II	12 (34)	11 (31)
III	5 (14)	15 (43)
IV-VI	0	0
Test site		
Area, median (IQR), cm^2	80.00 (72.00-96.00)	80.00 (66.00-96.00)
Anatomical location		
Scalp and face	7 (20)	16 (46)
Trunk	14 (40)	7 (20)
Proximal limb	11 (31)	7 (20)
Distal limb (ie, hands and feet)	3 (9)	5 (14)
No. of AKs (lesions), median (IQR)	19.00 (16.00-24.00)	20.00 (16.00-27.00)
Skin cancer history, median (IQR)		
No. of KC tumors in 3 y before inclusion	1.00 (0-5.0)	2.00 (0.00-4.00)
No. of KC tumors/y in 3 y before inclusion	0.30 (0-1.70)	0.70 (0.00-1.30)
No. of KC tumors detected at baseline visit	0.00	0.00 (0.00-0.25)

Abbreviations: AK, actinic keratosis; HPV, human papillomavirus; KC, keratinocyte carcinoma.

period. Correspondingly, total AK counts and numbers of thick lesions were significantly lower among HPV-vaccinated individuals, shown consistently at the 6-month and 12-month follow-ups. Taken together, our findings support the possibility that HPV-targeted vaccines could be used as an adjunctive therapy for patients with severe photodamage to reduce AK burden, although long-term impact, including on KC development, remains to be demonstrated. At present, efforts to develop a first-generation vaccine specifically against β-HPVs are underway.[42,43]

Several treatments are available to treat patients with AK, including field-directed therapies such as 5-fluorouracil (5-FU), imiquimod, photodynamic therapy (PDT), diclofenac, and tirbanibulin, as well as lesion-directed approaches, such as cryotherapy.[44] While these treatments can effectively clear AK in the short term, recurrence rates are high, and many patients eventually relapse (reportedly 39%-85% at ≥12 months).[45] Thicker, hyperkeratotic AKs pose a particular challenge due to their treatment resistance and higher recurrence rate.[46-48] Considering these clinical realities, the herein observed AK responses, seen also in thick lesions, make HPV vaccination of particular interest as a potential addition to conventional management.

Conflating AK clearance with KC prevention should be avoided.[49] To illustrate this point, 1 retrospective cohort study found that 5-FU was not superior to imiquimod based on SCC development beginning 1 year posttreatment, despite previously demonstrated superior AK destruction efficacy.[49] Another study failed to detect significant site-specific KC prevention 2 and 5 years after local 5-FU or imiquimod treatment.[50] In our study, the demonstrated effect of HPV vaccination on AK burden was not associated with development of significantly fewer new AKs, although in general, median new AK numbers were low throughout the trial. The study also found no difference in skin cancer rates in the first 12 months; both KC numbers overall and per participant were similar in the 2 groups. In addition, intraindividual comparison found no difference in patients' annual KC rates postvaccination vs 3 years prevaccination. We indeed expected little to no effect of vaccination for BCC, given BCC tumors have lower immunogenicity vs SCCs.[51] However, before concluding that α-HPV vaccination does not impact KC development generally, some factors should be considered. First, it is debatable that 12 months is adequate time to reveal impact on KC and SCC in particular,[45] considering that only 8 participants developed SCC during the observation period. Further, comparing annual KC rates from a period where patients underwent 5 or more skin examinations, with rates from a preceding period with conceivably less intensive monitoring, ignores the issue of detection bias. Definitive statements on the utility of α-HPV vaccination for KC and SCC prevention are therefore premature, and extended follow-up of our study population (up to 10 years postvaccination) using registry-based data outside the RCT framework is ongoing.

Our study raises the question but does not address, how a vaccine designed to prevent mucosal α-HPV infection might reduce established actinic skin lesions. Two points warrant attention here. First, there is a suggestion of overlapping utility, as improvement in β-HPV–related skin disease is reported following intramuscular α-HPV vaccination.[52-55] One study of treatment-recalcitrant plantar warts described complete clearance rates of 82% and 63% in 32 patients after intralesional or standard intramuscular α-HPV vaccination, respectively.[55] These responses may reflect nonspecific immune stimulation by the vaccine or adjuvant therapy, or as proposed by others, immunological cross-reactivity due to some antigenic similarity of L1 capsid proteins across HPV genera.[56-60] Second, heralding a paradigm shift in skin cancer, researchers' understanding of the interplay between the commensal skin virome, host immunity, and tissue homeostasis is evolving. In their seminal work, Strickley et al,[61] demonstrate that T-cell immune responses against skin tropic papillomaviruses suppress skin cancer development in immunocompetent hosts. Specifically, papillomavirus-specific CD8-positive T cells protect against the expansion of variant p53 clones by targeting keratinocytes that present increased viral antigens (due to the absence of functional p53).[62] Rather than papillomaviruses being a cofactor in skin carcinogenesis, it is the loss of this immunity that explains the greater prevalence of KC and cutaneous warts in immunosuppressed populations.[61,62] Although not their primary mechanism of action, α-HPV vaccine

Table 2. Impact of Human Papillomavirus (HPV) Vaccination on Actinic Keratoses (AKs) Over 12 Months

Variable	Median (IQR), %		
	HPV group (n = 35)	Sham group (n = 32-35)[a]	*P* value
Primary end point			
Per-protocol analysis			
Reduction in baseline AKs			
Month 2 (n = 69)	35.00 (25.00-44.00)	25.00 (18.00-33.00)	.03
Month 6 (n = 69)	47.00 (33.00-53.00)	29.00 (16.00-44.00)	.01
Month 9 (n = 67)	58.00 (37.00-63.00)	42.00 (33.00-57.00)	.09
Month 12 (n = 68)	58.00 (47.00-6.009)	4.007 (32.00-65.00)	.05
Intention-to-treat analysis			
Reduction in baseline AKs			
Month 2 (n = 70)	35 (25-44)	25 (18-33)	.03
Month 6 (n = 70)	47 (35-53)	29 (17-44)	.004
Month 9 (n = 70)	58 (37-63)	38 (33-56)	.04
Month 12 (n = 70)	58 (47-69)	41 (30-65)	.03
Secondary end points (per-protocol analysis)			
Total No. of AK with new AKs			
Month 0 (n = 69)	19.00 (16.00-24.00)	20.00 (16.00-27.00)	.31
Month 2 (n = 69)	15.00 (12.00-18.00)	16.00 (13.00-24.00)	.09
Month 6 (n = 69)	14.00 (11.00-16.00)	17.00 (12.00-23.00)	.01
Month 9 (n = 67)	11.00 (8.00-15.00)	13.50 (11.00-18.50)	.13
Month 12 (n = 68)	10.00 (6.00-14.00)	16.00 (8.50-21.00)	.02
Total No. of thick AKs (grade II-III)			
Month 0 (n = 69)	3.00 (1.00-6.00)	5.00 (2.00-8.00)	.12
Month 2 (n = 69)	3.00 (1.00-7.00)	4.50 (1.75-8.00)	.39
Month 6 (n = 69)	5.00 (3.00-7.00)	6.50 (3.75-10.00)	.02
Month 9 (n = 67)	4.00 (3.00-5.00)	5.00 (4.00-9.75)	.04
Month 12 (n = 68)	3.00 (2.00-5.00)	5.00 (2.50-8.50)	.049
New AKs only			
Month 2 (n = 69)	1.00 (1.00-2.00)	2.00 (1.00-3.25)	.16
Month 6 (n = 69)	2.00 (1.00-3.00)	2.00 (1.00-5.25)	.27
Month 9 (n = 67)	1.00 (0.00-3.00)	1.00 (0.00-2.00)	.65
Month 12 (n = 68)	1.00 (0.00-2.00)	1.00 (0.00-2.00)	.56
Total No. of AKs (grade II-III) that received cryotherapy			
Month 6 (n = 69)	4.00 (2.00-6.00)	6.00 (2.75-8.00)	.19
Month 9 (n = 69)	4.00 (3.00-5.00)	5.00 (2.75-9.00)	.10

[a] Depending on per-protocol or intention-to-treat analyses as detailed in Figure 1.

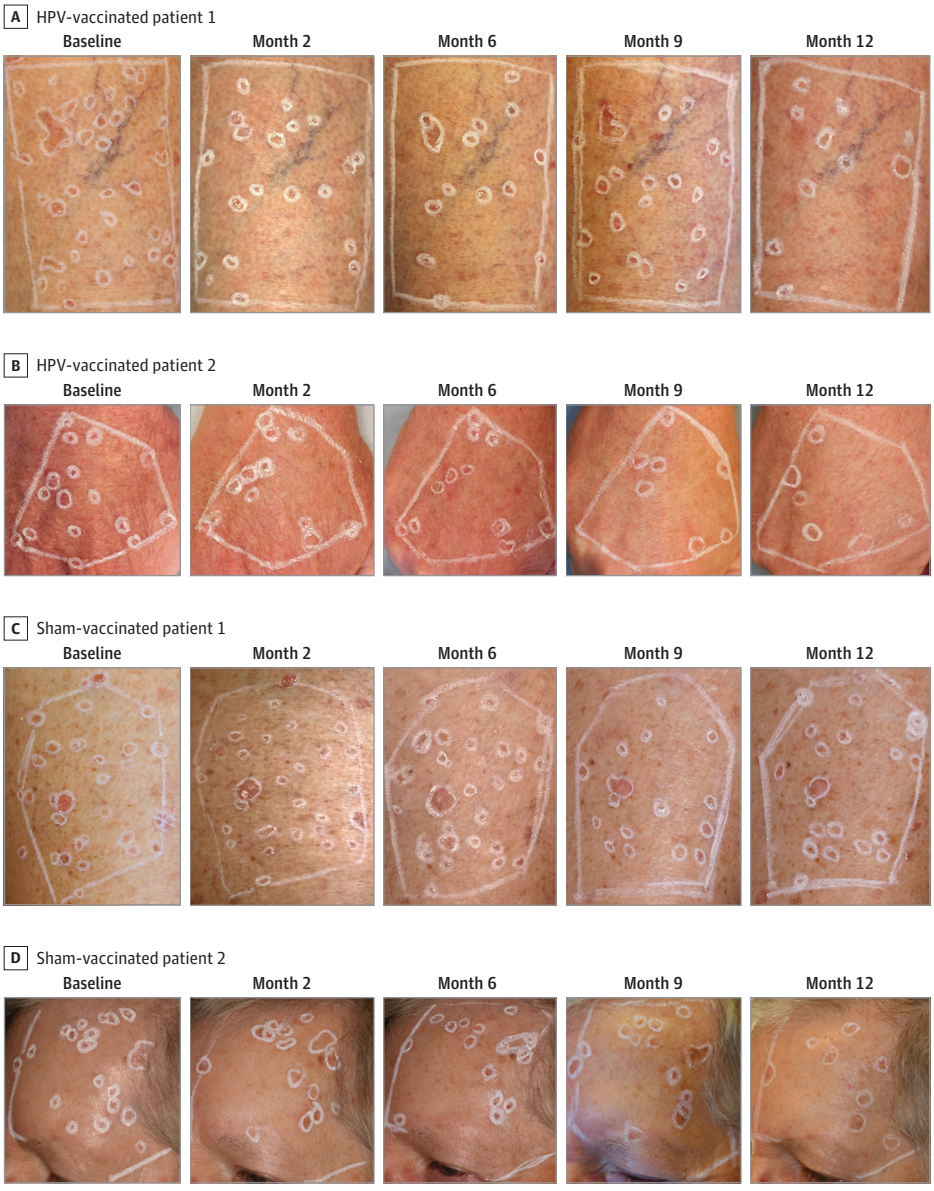
can induce cytotoxic T-cell immunity that may display greater cross-reactive potential than the corresponding antibody response.[58,63-65] Furthermore, increased CD8 T-cell infiltration is anecdotally described in SCCs from vaccinated patients.[66] Thus, a possible mechanism behind our clinical responses could be boosted T-cell immunity against variant keratinocytes in AK that demonstrate increased viral antigen expression.[62]

Sham-vaccinated patients showed a reduction in AK lesions in the first 6 months, despite receiving no active vaccine or local test site treatment in that time frame. Spontaneous regression in clinical AKs is previously described and not uncommon. A 2022 systematic review and pooled analysis of 18 RCTs revealed a lesion-specific regression rate of 23% in placebo group populations, ranging from 13% at week 8 to 33% at week 12 posttreatment.[67] Furthermore, in our study, patients were encouraged to use daily sunscreen including on test sites, a practice that can lower AK counts and prevent new AK.[68,69] Finally, due to concerns about the ethics of leaving our severely photodamaged population untreated, most participants (53 of 70 [76%]) received field therapy with photodynamic therapy, 5-FU, or imiquimod in a non–test site anatomical locations in the first 6 months. The remote possibility that these treatments had an abscopal effect on test site AKs, as described by cryotherapy, cannot be excluded.[70] Importantly, however, treatment rates between the 2 groups were not significantly different based on patients having received any topical field treatment, the number of field treatments, or specific types of therapy (ie, photodynamic therapy, 5-FU, or imiquimod) received in the first 6 months.

Limitations

The main limitations of this study include the relatively small population size and the imperfect science of clinical AK

Figure 2. Digital Photography of Actinic Keratoses in Human Papillomavirus (HPV)-Vaccinated and Sham-Vaccinated Participants Over 12 Months



Test sites from 2 HPV-vaccinated participants are presented in the upper rows (A and B), while sites from 2 sham-vaccinated participants are depicted in the lower rows (C and D). Percentage reductions in baseline actinic keratoses of HPV-vaccinated patient 1 were 50% (month 2), 62% (month 6), 59% (month 9), and 74% (month 12) (A); for HPV-vaccinated patient 2, corresponding percentage reductions were 25% (month 2), 31% (month 6), 56% (month 9), 63% (month 12) (B). For sham-vaccinated patient 1, percentage reductions were 19% (month 2), 15% (month 6), 52% (month 9), and 41% (month 12) (C); corresponding percentage reductions for sham-vaccinated patient 2 were 33% (month 2), 39% (month 6), 33% (month 9), and 56% (month 12) (D). The uppermost, erythematous lesion noted in the test area of sham-vaccinated patient 1 was confirmed at month 2 to be a squamous cell carcinoma in situ and treated with curettage and electrodesiccation during the visit (C).

Table 3. Impact of Human Papillomavirus (HPV) Vaccination on Keratinocyte Carcinomas (KCs) Over the 12-Month Study Period

Variable	HPV group (n = 35)	Sham group (n = 34)	*P* value
Participants who develop cancer, No. (%)			
KC	17 (49)	15 (44)	.81
SCC	5 (14)	3 (9)	.71
BCC	14 (40)	14 (41)	>.99
No. of KC lesions/tumors, median (IQR)			
Total KC	0.00 (0.00-2.00)	0.00 (0.00-1.25)	.61
SCC	0.00 (0.00-0)	0.00 (0.00-0.00)	.64
SCC + SCC in situ/Bowen disease	0.00 (0.00-0.00)	0.00 (0.00-0.25)	.71
BCC	0.00 (0.00-2.00)	0.00 (0.00-1.25)	.87

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

assessment.[71] Although AKs are generally diagnosed clinically,[44] extended monitoring of multiple, individual le-

sions is notoriously challenging due to changing lesion morphologic characteristics, clustering, and distinguishing between similarly appearing lesions such as flat warts.[72] The method is furthermore prone to intraobserver and interobserver variability.[71,73] To mitigate these issues, the study used meticulous lesion mapping and eliminated the issue of interobserver variation by having the same evaluator perform all assessments. Histological confirmation of lesional clearance, counting AKs beyond the 50 cm^2 to 100 cm^2 test site, or assessing total test site surface area covered by lesions to achieve a more complete picture of clinical improvement, were not performed due to feasibility considerations. Also, although study randomization was predominantly successful, a higher number of fair-skinned patients with Fitzpatrick skin type I was identified in the HPV-vaccinated group, which may have influenced AK and KC outcomes. Relatedly, neither sun protection nor presence of HPV in participants' skin was assessed in the trial. Finally, longer follow-up may have been valuable since it is uncertain that herein observed AK effects wane over time; a scenario particularly likely if underlying immunological mechanisms are nonspecific. Still, key study strengths remain the quality of evidence provided by the trial's sham-controlled, double-blind design and relatively lengthy follow-up, as well as the minimal dropout rate and high fidelity to the study protocol.

Conclusions

In this RCT, standard α-HPV vaccination was shown to reduce AK burden in immunocompetent individuals with multiple lesions. Although the effect on skin cancer development remains uncertain, HPV-targeted vaccines might prove useful in the management of AK, a chronic, relapsing disease and the most common precancer in fair-skinned populations.

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