# 5-fluorouracil decreases rates of persistent and reappearing actinic keratoses: The VAKCC Trial

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## Background

- Actinic keratoses (AKs) are known precursors of keratinocyte carcinoma (KC), which includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin.
- In a population with a history of multiple KCs, 60% of SCCs were found to arise from an AK.
- AK diagnosis and treatment costs are estimated at over 1 billion dollars per year in the U.S. An AK prevention strategy or long-lasting treatment may reduce the number of treatments needed over time and has potential to cut this cost.
- Topical 5-fluoruracil (5-FU) has been shown to decrease AK counts for at least 2 years but the specific effect on individual AKs is unknown.

## Purpose

- We examined the effect of 5-FU on individually tracked AKs in order to better understand how the response of individual AKs contributes to an overall decreased count.

## Methods

### Study Population

- We tracked individual AKs on the face/ears of 319 veterans enrolled in the Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) trial and randomized to apply topical 5-FU (n=153) or a vehicle control (n=166) to the face/ears twice daily for 2 to 4 weeks.
- Participants had a history of at least 2 KCs in the past 5 years, with at least one on the face/ears, and had not used topical 5-FU in the past 3 years. Demographics, KC history, and baseline AKs did not differ between the 5-FU and control groups.

### Data Collection/Measures

- Study dermatologists performed complete skin exams at baseline and every 6 months. Clinically diagnosed AKs were marked, photographed, and treated with cryotherapy (starting at 6 months). Photos were used to track the presence/absence of AKs over time.
- **Persistent AKs** were present at baseline and at 6 months with no recorded absence in between.
- **Reappearing AKs** were present at baseline, absent at 6 months, and present again in the exact same location at a later study visit.

### Statistical Analysis

- Student's T-tests were used to estimate differences in persistent AKs. Survival analyses and Cox proportional hazards models were used to assess differences in time-to-reappearance of baseline AKs.

## Results

**Figure 1.** Proportion of participants with ≥1 AK that persisted from baseline to 6 months

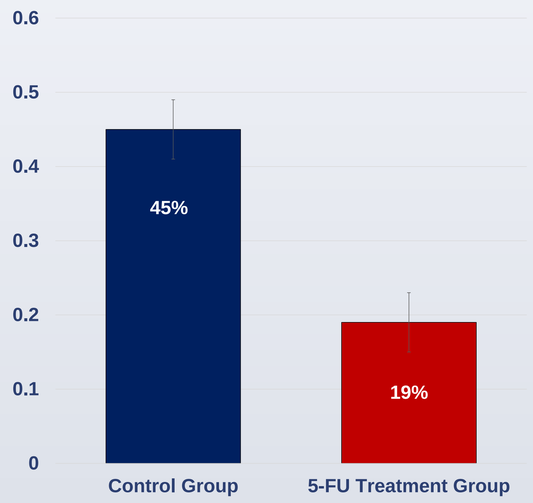



**Figure 2.** Proportion of AKs that persisted from baseline to 6 months

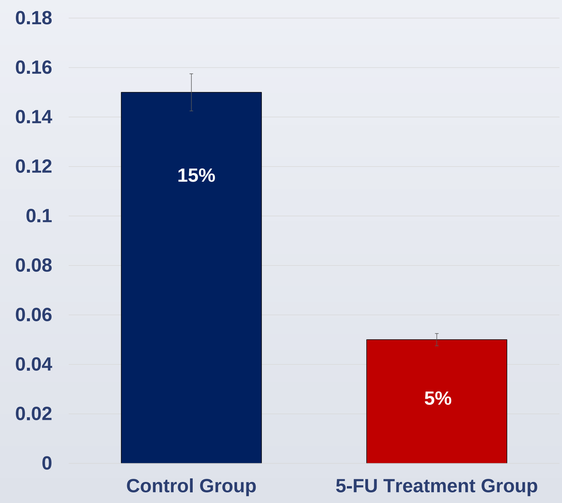
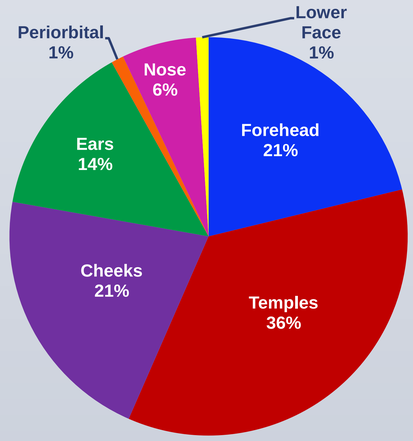
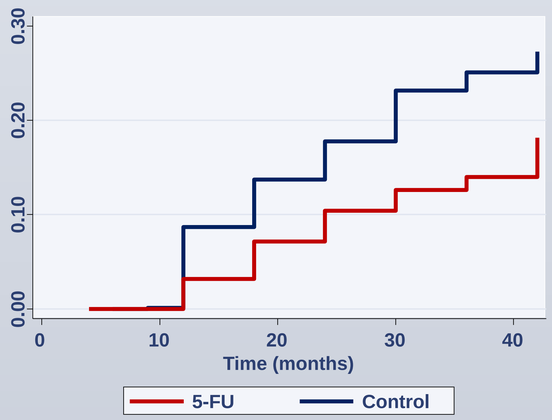



**Figure 3.** Distribution of AKs present at both baseline and 6 months in both study arms*




*There is no significant difference in anatomical distribution of baseline AKs between the 5-FU and control groups.

**Figure 4.** Nelson-Aalen cumulative risk curve of the reappearance of baseline AKs at a later study visit




### Persistent AKs

- Participants were almost all elderly men with extensive sun damage.
- In the 5-FU group, 19% of participants had ≥1 AK present at both baseline and 6 months, compared to 45% in the control group (Incidence rate ratio: 0.42, 95% CI 0.26 – 0.66, $p<0.001$; Figure 1).
- The mean number of persistent AKs was 0.39 in the 5-FU group and 1.09 in the control group (difference: 0.7, $p<0.001$).
- Only 5% (59/1177) of baseline AKs on participants in the 5-FU group persisted from baseline to 6 months, compared to 15% (174/1160) in the control group ($p<0.001$; Figure 2). Anatomical distribution of these AKs is shown in Figure 3.

### Reappearing AKs

- Baseline AKs in the 5-FU group were less likely to reappear than baseline AKs in the control group for the entire study (mean 0.12 vs. 0.19; hazard ratio: 0.57, 95% CI 0.46 – 0.71, $p<0.001$; Figure 4).
- However, the number of participants with ≥1 reappearing AK during the trial was not significantly different between the 5-FU and control groups.

Note: All analyses of persistent AKs exclude 6 participants who received cryotherapy before their 6-month visit.

## Conclusions

- Photographing, mapping, and tracking AKs allowed us to better understand AK response to treatment.
- A single course of 5-FU is effective in treating clinically apparent AKs, preventing them from persisting and lowering the likelihood of reappearance in the same location for at least 3.5 years.
- In the control group, 85% of AKs spontaneously resolved within 6 months without any treatment, but nearly half of this group had at least one AK persist to 6 months.
- Because many AKs spontaneously regress, they may not require immediate treatment.

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## Acknowledgments

This work was supported by Cooperative Studies Programs (CSP) 562 from the U.S. Department of Veterans Affairs. These contents do not represent the view of the U.S. Department of Veterans Affairs or the U.S. Government.

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