Comparative effectiveness of treatment of actinic keratosis with topical fluorouracil and imiquimod in the prevention of keratinocyte carcinoma: A cohort study

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Background: The effectiveness of 5-fluorouracil compared with that of imiquimod for preventing keratinocyte carcinoma is unknown.

Objective: To compare the effectiveness of 5-fluorouracil and that of imiquimod in preventing keratinocyte carcinoma in a real-world practice setting.

Methods: We identified 5700 subjects who filled prescriptions for 5-fluorouracil or imiquimod for treatment of actinic keratosis in 2007. An intention-to-treat analysis controlling for potential confounding variables was used to calculate 2- and 5-year cumulative risk differences for subsequent keratinocyte carcinoma overall and in field-treated areas.

Results: 5-Fluorouracil was associated with a statistically significant decreased risk of any keratinocyte carcinoma compared with imiquimod (adjusted hazard ratio [aHR], 0.86; 95% confidence interval [CI], 0.76-0.97), but there were no significant differences in risk by tumor subtype (for squamous cell carcinoma: aHR, 0.89; 95% CI, 0.74-1.07; for basal cell carcinoma: aHR, 0.87; 95% CI, 0.74-1.03) or site-specific keratinocyte carcinoma (aHR, 0.96; 95% CI, 0.81-1.14). There were no significant differences in 2- or 5-year cumulative risk of keratinocyte carcinoma among those treated with 5-fluorouracil versus with imiquimod.

Limitations: Generalizability to other practice settings may be limited.

Conclusions: Whereas 5-fluorouracil was more effective in reducing keratinocyte carcinoma risk overall, we found no differences in the short- or long-term risk of subsequent site-specific keratinocyte carcinoma in a real-world practice setting. (J Am Acad Dermatol 2019;80:998-1005.)

Key words: actinic keratosis; basal cell carcinoma; comparative effectiveness; 5-fluorouracil; imiquimod; keratinocyte carcinoma; skin cancer; squamous cell carcinoma.

Actinic keratoses (AKs) are precancerous keratinocyte-derived cutaneous neoplasms caused by chronic sun exposure. AKs are prevalent and costly, arising in nearly 40 million Americans per year[1-3] and accounting for more than $1 billion in health care expenditures annually in the

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United States.[3] AKs are one of the most common reasons why patients visit a dermatologist,[4] and they are responsible for more than 3.7 million ambulatory care office visits in the United States each year.[5] A natural history study of AKs has shown that they can progress to both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which are collectively termed *keratinocyte carcinomas* (KCs).[6] Estimates of lifetime progression rates range from as low as 0.1% to as high as 20%.[6-9] Data from a prospective trial showed that the rate of malignant transformation of an untreated AK over a 5-year period was 5.58% (95% confidence interval [CI], 4.54-6.86).[6] One of the primary goals of AK treatment is to prevent progression to KC, which not only can become locally invasive, destructive, and deforming but can also metastasize.

CAPSULE SUMMARY

- 5-Fluorouracil and imiquimod are frequently prescribed treatments for actinic keratosis, but no studies have compared their effectiveness at preventing keratinocyte carcinoma in a real-world setting.
- Whereas 5-fluorouracil was more effective in reducing risk of keratinocyte carcinoma overall, we found no differences in the short- or long-term risk of site-specific keratinocyte carcinoma.

If a patient has multiple AKs on an anatomic unit, field treatment is often recommended to reduce AK burden and risk of subsequent AKs and KCs in the treated area. Multiple modalities, including various topical agents and light-based treatments, are used clinically for field treatment of AKs. Two commonly prescribed topical field-based treatments for multiple AKs are 5-fluorouracil (5-FU) and imiquimod.

There is no agreement on the best AK field treatment,[10] and there are insufficient data to guide clinicians as to which topical AK field treatment is most effective in preventing KCs.[11] A recent Cochrane review of AK treatments concluded that more direct comparisons of AK treatment strategies are needed to determine the best therapeutic approach.[11] A recent randomized controlled trial suggested that 5-FU could reduce SCC risk at 1 year.[12] However, previous studies have not compared the effectiveness of 5-FU with that of imiquimod in preventing KCs. The goal of this study was to compare the effectiveness of 5-FU and imiquimod in preventing subsequent KC with use of a real-world setting to help inform treatment selection.

MATERIALS AND METHODS

We conducted a retrospective longitudinal cohort study of all Kaiser Permanente Northern California (KPNC) health plan members age 18 years or older in whom an AK had been diagnosed (*International Classification of Diseases, Ninth Revision* [ICD-9], code 702.0) in 2007 and who subsequently filled a prescription for 5-FU (n = 5062) or imiquimod (n = 638) for AK treatment. Cohort members were followed for subsequent KC (any KC, any BCC, any SCC, and site-specific KC arising in the treated field).

Study setting

KPNC is a prepaid, integrated health care delivery system that provides comprehensive health care and pharmaceutical benefits to more than 4 million members in Northern California. KPNC maintains a computerized record system with detailed information on members' demographic characteristics; clinical visits; pharmacy dispensed medications; laboratory, pathology, and radiology results; and other medical services.

Study population

The study cohort has been described previously[13] and consists of adult KPNC members in whom AK was diagnosed (ICD-9 code 702.0) between January 1, 2007, and December 31, 2007, and who received subsequent topical AK field treatment with 5-FU or imiquimod (N = 8556) (Fig 1). The year 2007 was selected because imiquimod was not available before 2007 and doing so allowed for electronic review of all outpatient ambulatory notes, which facilitated abstraction of information on treatment indication, anatomic site of application, and site of subsequent KC.

Subjects were excluded if 5-FU or imiquimod was prescribed for any indication other than AK (such as skin cancer or warts), as determined by chart review, or if they had a history of (1) any ultraviolet light treatment, (2) infection with HIV, (3) chronic lymphocytic leukemia, (4) solid organ transplant, or (5) bone marrow transplant ever recorded in the KPNC database (due to the associated increased risk of skin cancer in those subpopulations).[14-18]

Exposure

Exposure was defined as pharmacy dispensation of 5-FU or imiquimod associated with an AK diagnosis in 2007. Clinic notes and medication orders were reviewed to ensure that the treatment was for AK and to abstract information on anatomic site of drug application, as categorized in 3 anatomic

Abbreviations used:

aHR:	adjusted hazard ratio
AK:	actinic keratosis
BCC:	basal cell carcinoma
CI:	confidence interval
5-FU:	5-fluorouracil
HR:	hazard ratio
ICD-9:	*International Classification of Diseases, Ninth Revision*
IPW:	inverse probability weighting
KC:	keratinocyte carcinoma
KPNC:	Kaiser Permanente Northern California
RD:	risk difference
SCC:	squamous cell carcinoma

groupings: (1) head and neck, including the face (forehead, nose, cheek, chin, and temple), scalp, ear, and neck; (2) trunk, including abdomen, back, shoulders, and buttocks; and (3) extremities, including ankle, arm, calf, finger, foot, forearm, hand, knee, leg, palm, thigh, and wrist.

Outcome

The four outcomes were specified as time to first KC (SCC or BCC), time to first KC within the treated field, time to first BCC, and time to first SCC, as identified through review of all KPNC pathology records. We abstracted tumor site in granular categories that were then grouped into categoric anatomic sites for analytic purposes to mirror the exposure categories as we have already defined. For each outcome definition, patients were followed up through the earliest of the following: outcome occurrence, health plan disenrollment, death, or end of the study period.[13]

Covariates

Information on patient demographics, including age (date of birth), sex (male, female, transgender, or other), and race/ethnicity (white-non-Hispanic, white-Hispanic, black, Asian, or Native-American) were obtained from KPNC databases. Data were also obtained on KC risk factors, including cigarette use (current smoker, former smoker, never-smoker, or unknown), body mass index ($\leq$24.9 kg/m^2 [normal weight], 25-29.9 kg/m^2 [overweight], or $\geq$30 kg/m^2 [obese]), comorbidities (Charlson comorbidity index of 0, 1, 2, or $\geq$3), baseline health care utilization (average number of any health care provider emergency department or outpatient visits in the 2 years before baseline), baseline skin surveillance measure (average annual number of dermatology visits in the 2 years before baseline), prior KC (yes versus no within the 5 years before cohort entry), prior AK (yes versus no within the 5 years before cohort entry), history of 5-FU treatment before cohort entry, and use of photosensitizing medication within 2 years before baseline. A previously published list of photosensitizing medications was used as the basis for categorizing photosensitizing medications.[19]

Statistical analysis

The comparative effectiveness of 5-FU and imiquimod was evaluated by using inverse probability weighting (IPW) to control for baseline covariates.[20] We conducted an intention-to-treat analysis given that differential noncompliance or surveillance between 5-FU and imiquimod was not expected, as their directions for application, duration of use, and side effect profiles are similar.[21] Logistic regression including all baseline variables was used to estimate the propensity score. The adjusted 2-year and 5-year cumulative risk differences (RDs) were estimated by linear regression using stabilized IPW weights calculated on the basis of propensity score estimates.[22] To estimate the adjusted 2-year RD, a complete case analysis was performed; outcomes from patients with no subsequent KC diagnoses and with less than 2 years of follow-up were treated as missing in the regression, and missingness was assumed to occur at random. A similar approach was used to estimate the adjusted 5-year RD. Conservative 95% CIs were derived on the basis of the robust variance estimator.[23] The distribution of the stabilized IPW weights was examined to detect extreme weight values; the maximum IPW weight value did not warrant weight truncation.[22] Results from the IPW estimation approach were compared with the results from (1) crude (unadjusted) estimates of the cumulative RD derived by unweighted linear regressions, (2) crude (unadjusted) Kaplan Meier estimates of the survival curves for the 2 exposure groups (data not shown), and (3) IPW estimates of the hazard ratios from Cox proportional hazard marginal structural models for a single-time point intervention.[23] All analyses were conducted with SAS software (version 9.3, SAS Institute Inc, Cary, NC). This study was approved by the institutional review board of the Kaiser Foundation Research Institute.

RESULTS

Of the 5700 cohort members, 5062 were exposed to 5-FU and 638 were exposed to imiquimod. Table I describes the baseline characteristics of cohort members. The average age at cohort entry was 66.6 years (standard deviation, 11.6 years). The majority of cohort members were non-Hispanic white (92.7%). Women constituted a larger proportion of those treated with imiquimod than with 5-FU (46.5% vs 39.9% [$P < .01$]). Cohort members treated

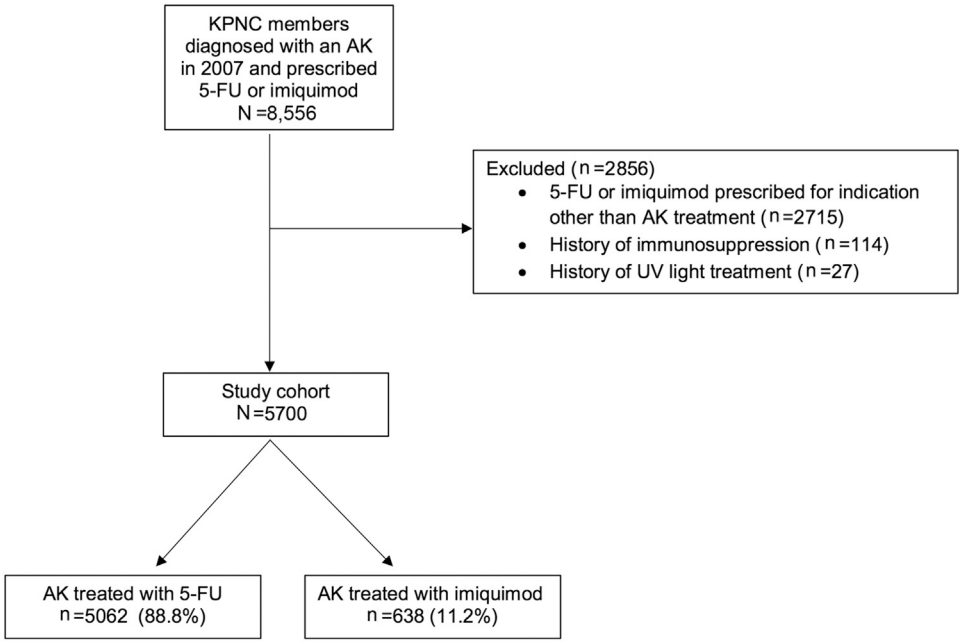

Fig 1. Study flow diagram. Diagram illustrates derivation of study cohort. *AK*, Actinic keratosis; *5-FU*, 5-fluorouracil; *KPNC*, Kaiser Permanente Northern California; *UV*, ultraviolet.

with imiquimod were more likely to have had a prior KC (52.2% vs 40.9% [$P < .01$]) but less likely to have had prior 5-FU treatment (39.0% vs 45.6% [$P < .01$]).

Fig 2 shows the 2- and 5-year cumulative RDs and hazard ratios (HRs) for KCs among those treated with 5-FU versus with imiquimod. The unadjusted 2- and 5-year RDs suggested a trend toward lower cumulative risk of KC following treatment with 5-FU than following treatment with imiquimod, with significantly lower risk observed for overall KCs at both 2 years (RD, −0.06; 95% CI −0.10 to −0.02) and 5 years (RD, −0.05; 95% CI −0.10 to −0.01), site-specific KCs at 2 years (RD, −0.05; 95% CI −0.08 to −0.02), and BCCs at 2 years (RD, −0.04; 95% CI −0.07 to −0.01). However, after adjustment for potential pretreatment confounders, there were no significant differences in 2- or 5-year cumulative risk of subsequent KC among those treated with 5-FU and imiquimod.

Cox proportional hazard modeling suggested a decreased risk of KCs following treatment with 5-FU versus following treatment with imiquimod (for any KC: HR, 0.79; 95% CI, 0.70-0.88; for site-specific KC: HR, 0.85; 95% CI, 0.73-0.99; for SCC: HR, 0.83; 95% CI, 0.70-0.99; and for BCC: HR, 0.81; 95% CI, 0.70-0.94). After adjustment for potential baseline confounders, 5-FU was associated with a statistically significant decreased risk of any KC compared with imiquimod (adjusted HR [aHR], 0.86; 95% CI, 0.76-0.97), but there were no significant differences in risk of site-specific KC (aHR, 0.96; 95% CI, 0.81-1.14), SCC (aHR, 0.89; 95% CI, 0.74-1.07), or BCC (aHR, 0.87; 95% CI, 0.74-1.03).

DISCUSSION

In this large cohort study performed within a community-based real-world setting, we did not find strong evidence that 5-FU and imiquimod have different short- or long-term effectiveness in the prevention of subsequent BCC, SCC, or site-specific KC. Although Cox proportional hazard modeling indicated that 5-FU was associated with a statistically significant (14.4%) decreased risk of any KC compared with imiquimod, there was no significant difference in risks of site-specific KCs.

Previous studies comparing the effectiveness of 5-FU and imiquimod for AK treatment have examined clearance of individual AK lesions as the primary outcome measure.[11] To our knowledge, no prior studies comparing 5-FU and imiquimod have examined subsequent KC as an outcome measure. However, one of the key goals of AK treatment is to prevent progression to malignancy,[10,24] which makes subsequent KC a key outcome to consider when comparing the efficacy of different AK treatments. Only 2 small, short randomized clinical trials have directly compared the efficacy of 5-FU with that of imiquimod for the treatment of AKs, and neither study examined subsequent KCs as an outcome. One small trial followed 36 subjects over 24 weeks and found that

Table I. Baseline characteristics of the KPNC cohort with AK diagnosed in 2007 and treated with 5-FU or imiquimod

Variable	Overall (N = 5700)	5-FU (n = 5062)	Imiquimod (n = 638)	*P* value
Demographics				
Mean age at index, y (±SD)	66.6 (11.6)	66.6 (10.6)	66.6 (12.3)	.962
Age at index, n (%)				.022
18-49 y	427 (7.5)	379 (7.5)	48 (7.5)	
50-65 y	2232 (39.2)	1968 (38.9)	264 (41.4)	
66-80 y	2322 (40.7)	2094 (41.4)	228 (35.7)	
>80 y	719 (12.6)	621 (12.3)	98 (15.4)	
Sex, n (%)				.001
Male	3383 (59.3)	3042 (60.1)	341 (53.5)	
Female	2317 (40.7)	2020 (39.9)	297 (46.5)	
Race/ethnicity, n (%)				.553
Non-Hispanic white	5283 (92.7)	4688 (92.6)	595 (93.3)	
Other	417 (7.3)	374 (7.4)	43 (6.7)	
Risk factors for AK and KC				
Cigarette use, n (%)				.925
Never	3534 (62.0)	3131 (61.9)	403 (63.2)	
Former	1809 (31.7)	1614 (31.9)	195 (30.6)	
Current	258 (4.5)	229 (4.5)	29 (4.6)	
Unknown/not asked/secondhand	99 (1.7)	88 (1.7)	11 (1.7)	
Body mass index, n (%)				.063
≤24.9 kg/m^2 (normal)	1850 (32.5)	1622 (32.0)	228 (35.7)	
25-29.9 kg/m^2 (overweight)	2263 (39.7)	2014 (39.8)	249 (39.0)	
≥30 kg/m^2 (obese)	1409 (24.7)	1273 (25.2)	136 (21.3)	
Unknown/missing	178 (3.1)	153 (3.0)	25 (3.9)	
Exposure to a photosensitizing drug,*† n (%)				.835
No	1300 (22.8)	1155 (23.6)	148 (23.2)	
Yes	4400 (77.2)	3869 (76.4)	490 (76.8)	
Prior AK,‡ n (%)				.959
No	1270 (22.3)	1155 (22.8)	145 (22.7)	
Yes	4430 (77.7)	3907 (77.2)	493 (77.3)	
Prior KC,‡ n (%)				<.001
No	3298 (57.9)	2993 (59.1)	305 (47.8)	
Yes	2402 (42.1)	2069 (40.9)	333 (52.2)	
Prior 5-FU treatment,§ n (%)				.002
No	3144 (55.2)	2755 (54.4)	389 (61.0)	
Yes	2556 (44.8)	2307 (45.6)	249 (39.0)	
Baseline health care utilization				
Charlson comorbidity score, n (%)				.540
0	3543 (62.2)	3139 (62.0)	404 (63.3)	
1-2	1549 (27.2)	1375 (27.2)	174 (27.3)	
≥3	608 (10.7)	548 (10.8)	60 (9.4)	
Health care utilization: mean outpatient visits (±SD)‖	10.9 (9.6)	10.9 (9.8)	11.4 (10.1)	.229
Surveillance measure: mean dermatology visits (±SD)‖	1.6 (1.8)	1.6 (1.8)	1.9 (1.8)	<.001
Prescriber type, n (%)				.016
Dermatologist	5386 (94.5)	4770 (94.2)	616 (96.6)	
Nondermatologist	314 (5.5)	292 (5.8)	22 (3.4)	

AK, Actinic keratosis; *5-FU*, 5-fluorouracil; *KC*, keratinocyte carcinoma; *KPNC*, Kaiser Permanente Northern California; *SD*, standard deviation.
*In the 2 years before cohort entry.
†Photosensitizing drugs included tetracyclines, sulfonamide antibiotics, fluoroquinolones, thiazide diuretics, loop diuretics, calcium channel blockers, potassium-sparing diuretics, α-adrenergic agonists, antiarrhythmics, sulfonylureas, antimetabolites, antiestrogens, salicylic acid derivatives, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, benzodiazepines, tricyclic antidepressants, and oral retinoids.[19]
‡In the 5 years before cohort entry.
§Ever in the pharmacy records going back to 1996. There is no prior imiquimod exposure in the cohort because it was not available before 2007.
‖Average annual number during the follow-up period.

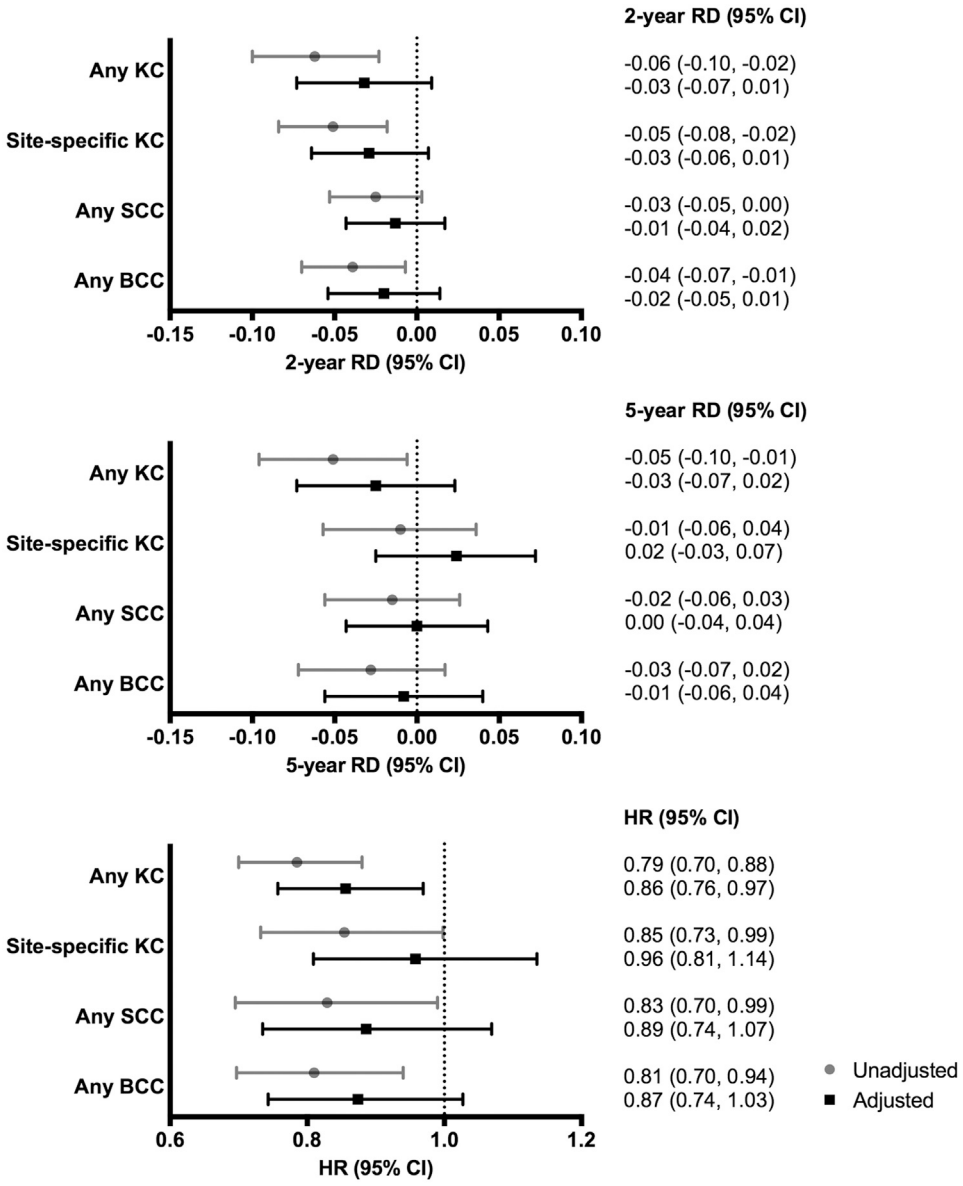

Fig 2. Cumulative 2- and 5-year risk differences (RDs) and hazard ratios (HRs) for subsequent keratinocyte carcinomas among cohort members treated with 5-fluorouracil (5-FU) versus with imiquimod. Gray circles and lines represent RDs and HRs (95% confidence interval [CIs]) from unweighted models, whereas black boxes and lines represent RDs and HRs (95% CIs) from weighted models. Imiquimod was used as the reference in all analyses. *BCC*, Basal cell carcinoma; *KC*, keratinocyte carcinoma; *SCC*, squamous cell carcinoma.

5-FU was more effective than imiquimod in exposing presumed subclinical AKs, reducing final AK count, and achieving complete AK clearance.[25] The other small trial compared the initial and 12-month clinical and histologic clearance of AKs after treatment with 5-FU (n = 24), imiquimod (n = 26), and cryosurgery (n = 25) and found that imiquimod was associated with superior sustained clearance compared with 5-FU.[21] A recent network meta-analysis that determined the relative efficacy of 8 AK treatments on the basis of the outcome "participant complete clearance" ranked 5-FU over imiquimod, leading the authors to conclude that 5-FU should be the treatment of choice for AKs to prevent progression to KC.[24] In agreement with this meta-analysis, in our previous study comparing the effectiveness of AK treatment with 5-FU and imiquimod, we found that 5-FU was significantly more

effective than imiquimod in preventing subsequent AKs at 2 years (RD, −4.54%; 95% CI, −7.91% to −1.17%), though not at 5 years (RD, −1.43%; 95% CI, −3.43% to 0.05%).[13] Although our present study revealed no differences in rates of subsequent site-specific KCs after topical field treatment with 5-FU or imiquimod at 2 or 5 years, we may have been underpowered to detect site-specific associations.

5-FU and imiquimod have distinct mechanisms of action that account for their efficacy in AK field treatment. 5-FU, which inhibits thymidylate synthetase, interferes with DNA and RNA synthesis and thus decreases cellular proliferation and induces cell death.[11] Imiquimod, which acts as an immune modulator through activation of Toll-like receptors, enhances both innate and acquired immune responses that have antitumor activity.[11] Our previous study showing that 5-FU is more effective than imiquimod at preventing subsequent AKs at 2 years suggested that the inhibitory effect of 5-FU on DNA and RNA synthesis may persist longer than imiquimod's immunomodulatory effects.[13] This distinct mechanism of action could lead to differential responses at nontreated AK sites and could explain the 14.4% decreased risk of any KC among those treated with 5-FU versus with imiquimod.

Strengths of this study include KPNC's closed, prepaid, integrated health care system, which enabled a real-world comparison of the efficacy of 5-FU and imiquimod in preventing KCs within a stable, well-characterized population. KPNC's computerized health system contains detailed records of the comprehensive care that patients receive, which allowed us to accurately assess potential pretreatment confounders, prescription details, and subsequent KC diagnoses. Limitations include the inability to control for unmeasured confounders, including physicians' perception of drug tolerability and differential physician counseling based on experience with each medication. Furthermore, we were unable to control for several known KC risk factors, including skin type, hair and eye color, and history of sun exposure. However, by limiting the cohort to members to whom field-based therapy for their actinic damage had been prescribed, we sought to make AK severity as similar as possible across the treatment groups, minimizing potential differences in skin type or history of sun exposure between the 2 treatment groups. We did not account for subsequent exposure to 5-FU or imiquimod during the follow-up period; multiple rounds of field treatment may have been prescribed to patients during the follow-up period, which would have affected risk of KC. Prescriptions filled served as a surrogate for medication use and exposure was inferred from directions at dispensing, which may not reflect patients' true exposure. However, this does reflect a real-world practice setting and enables measurement of effectiveness, rather than efficacy as in a clinical trial. Because treatment with 5-FU and imiquimod spans several weeks, there were many opportunities for noncompliance. Differential noncompliance between the 2 treatments was not expected because their directions for use, duration of application, and side effect profiles are very similar.[21] Finally, because the study cohort consisted of insured adults in Northern California, the results may not be completely generalizable to the uninsured or to other health care or geographic settings.

In summary, we found no difference in the effectiveness of 5-FU and imiquimod in preventing subsequent site-specific KCs in the short or long term in a real-life clinical setting, though we did see a statistically significant decreased risk of any (not site-specific) KC with 5-FU as compared to imiquimod. Given the burden that AKs pose to the health care system due to their high prevalence, significant cost, and potential for malignant progression, dermatologists should be aware of how available treatments compare in their effectiveness in preventing KCs.

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