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Celecoxib, Sirolimus, and Acitretin are Associated With Decreased Non-Melanoma Skin Cancer in the General Population

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INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common malignancy in the United States, and a growing public health concern.[1] While a variety of prevention strategies exist for high-risk groups such as organ transplant recipients, few systemic agents have been evaluated for NMSC prevention in the general population.[1] Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has demonstrated antitumor effects through antiangiogenic and proapoptotic mechanisms, and studies in high-risk patients found that celecoxib significantly reduced the incidence of NMSC.[2] In addition, the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, inhibits keratinocyte proliferation, angiogenesis, and oncogenic signaling, with randomized controlled trials in organ transplant populations demonstrating sirolimus's association with significant reduction in NMSC incidence.[3] Similarly, retinoids have also been studied as chemopreventive agents, with trials demonstrating acitretin decreases risk for squamous cell carcinoma (SCC) in high-risk populations.[4] This large-scale retrospective cohort study evaluated the real-world impact of celecoxib, sirolimus, and acitretin use on the risk of NMSC development and related procedural interventions in the general population.

MATERIALS AND METHODS

Within the TriNetX Research Network, we queried codes from the 10th revision of the International Classification of Diseases (ICD-10), Current Procedural Terminology (CPT), and RxNorm from August 1, 2015 to August 1, 2025. Three individual studies were conducted of adults (≥18) with ≥2 documented encounters for celecoxib (RxNorm: 140587), sirolimus (RxNorm: 35202), or acitretin (RxNorm: 16818) use were included and compared with a cohort without study medication exposure after propensity score matching (PSM). PSM was performed 1:1 on patient characteristics documented prior to study medication initiation, including demographics, comorbidities, and immunosuppressive medications/conditions (Table 1). Patients with inherited or acquired risk factors for NMSC, organ transplantation, previous or current systemic malignancy, exposure to multiple study medications or documentation of the target outcomes prior to study medication initiation were excluded. Primary outcomes included risk of NMSC development. Secondary outcomes included risk of Mohs micrographic surgery (MMS) (CPT: 17311-17315) and excision of malignant skin lesions (CPT: 1003243). Outcomes were evaluated using risk ratios (RR) and 95% confidence intervals (CI) at 5- and 10-year follow-up, with significance defined as *P*-value <0.05.

RESULTS

After PSM, the celecoxib, sirolimus, and acitretin cohorts included 15,415, 2,288, and 5,915 patients per group, respectively (Table 2). Celecoxib use was associated with a significantly lower risk of developing NMSC at both 5 years (RR 0.83; $P<0.001$) and 10 years (RR 0.77; $P<0.001$), as well as reduced risk of MMS at 5 years (RR 0.81; $P=0.0002$) and 10 years (RR 0.77; $P<0.001$), and lower risk of excision for malignant skin lesions at 5 years (RR 0.73; $P<0.001$) and 10 years (RR 0.75; $P<0.001$). Similarly, sirolimus exposure was associated with a reduced risk of NMSC at 5 years (RR 0.49; $P=0.018$), with this protective effect persisting at 10 years (RR 0.49; $P=0.01$); however, ≤10 MMS and excision events were reported at both time points, and exact counts were suppressed by TriNetX privacy policies, precluding statistical analysis of these outcomes. Acitretin use was also associated with a significantly lower risk of NMSC at 5 years (RR 0.58; $P<0.0001$) and 10 years (RR 0.66; $P<0.0001$), along with markedly reduced risk of MMS at 5 years (RR 0.27; $P<0.0001$) and 10 years (RR 0.31; $P<0.0001$), and lower risk of excision for malignant skin lesions at 5 years (RR 0.35; $P<0.0001$) and 10 years (RR 0.41; $P<0.0001$).

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TABLE 1.

Baseline Demographic Characteristics of the Celecoxib, Sirolimus, and Acitretin Cohorts After Propensity Score Matching (PSM)

	Celecoxib Cohort [n (%)][1] (n=15415)	No Celecoxib Cohort [n (%)] (n=15415)	*P*-value	Sirolimus Cohort [n (%)] (n=2,288)	No Sirolimus Cohort [n (%)] (n=2,288)	*P*-value	Acitretin Cohort [n (%)] (n=5,915)	No Acitretin Cohort [n (%)] (n=5,915)	*P*-value
Age at Index, Mean ± SD[2]	61.5 ± 13.5	61.6 ± 13.5	0.66	47.4 ± 18.6	47.5 ± 18.5	0.83	58.4 ± 16	58 ± 17	0.14
Male	5334 (34.60)	5351 (34.71)	0.84	1,033 (45.15)	1,035 (45.24)	0.95	3,045 (51.48)	3,138 (53.05)	0.09
Female	9037 (58.63)	9027 (58.56)	0.91	1,247 (54.50)	1,246 (54.46)	0.98	2,810 (47.51)	2,767 (46.78)	0.43
White	13396 (86.90)	13395 (86.90)	0.99	1,583 (69.19)	1,586 (69.32)	0.92	4,201 (71.02)	4,209 (71.16)	0.87
Black or African American	172 (1.12)	173 (1.12)	0.96	193 (8.44)	195 (8.52)	0.92	768 (12.98)	790 (13.36)	0.55
Asian	121 (0.79)	120 (0.78)	0.95	79 (3.45)	62 (2.71)	0.15	266 (4.50)	243 (4.11)	0.29
Hispanic or Latino	308 (2.00)	307 (1.99)	0.97	164 (7.17)	176 (7.69)	0.15	269 (4.55)	275 (4.65)	0.79
Not Hispanic or Latino	12482 (80.97)	12514 (81.18)	0.64	1,661 (72.60)	1,624 (70.98)	0.22	4,361 (73.73)	4,412 (74.59)	0.28
Overweight and Obesity	4793 (31.09)	4798 (31.13)	0.95	158 (6.91)	158 (6.91)	1.00	918 (15.52)	851 (14.39)	0.08
Smoking	1315 (8.53)	1329 (8.62)	0.78	70 (3.06)	67 (2.93)	0.79	667 (11.28)	653 (11.04)	0.68
TNF-alpha Inhibitor Use[3]	212 (1.38)	190 (1.23)	0.27	12 (0.52)	10 (0.44)	0.70	13 (0.22)	11 (0.19)	0.68
JAK Inhibitor Use[4]	29 (0.19)	23 (0.25)	0.41	10 (0.44)	10 (0.44)	1.00	10 (0.17)	10 (0.17)	1.00
Systemic Corticosteroid Use	381 (2.47)	376 (2.44)	0.85	32 (1.40)	28 (1.22)	0.60	48 (0.81)	58 (0.98)	0.33

[1]Percentages will not add up to 100% as certain patients did not have all demographics denoted comprehensively in their medical records.
[2]SD: Standard Deviation
[3]TNF-alpha: Tumor necrosis factor inhibitor
[4]JAK: Janus kinase

TABLE 2.

Risk of Non-Melanoma Skin Cancer (NMSC), Mohs Micrographic Surgery (MMS), and Excision for Malignant Skin Lesion Following Celecoxib, Sirolimus, or Acitretin Use in the General Population

	Number of eligible individuals (number of outcomes, 5 years)[1,2]	Number of eligible individuals (number of outcomes, 5 years)	Risk Ratio (95% Confidence Interval)	*P*-value	Number of eligible individuals (number of outcomes, 10 years)	Number of eligible individuals (number of outcomes, 10 years)	Risk Ratio (95% Confidence Interval)	*P*-value
	Celecoxib Cohort	No Celecoxib Cohort			Celecoxib Cohort	No Celecoxib Cohort		
NMSC	12070 (771)	12848 (988)	0.83 (0.76, 0.91)	<0.001	12070 (834)	12848 (1120)	0.77 (0.73, 0.86)	<0.001
MMS	14124 (521)	14608 (668)	0.81 (0.72, 0.90)	0.0002	14124 (568)	14608 (766)	0.77 (0.69, 0.85)	<0.001
Excision for malignant skin lesion	14258 (381)	14850 (541)	0.73 (0.65, 0.84)	<0.001	14258 (421)	14850 (587)	0.75 (0.66, 0.85)	<0.001
	Sirolimus Cohort	No Sirolimus Cohort			Sirolimus Cohort	No Sirolimus Cohort		
NMSC	2,247 (15)	2,256 (31)	0.49 (0.26-0.90)	0.018	2,247 (18)	2,256 (37)	0.49 (0.28-0.86)	0.01
MMS	2,276 (≤10)	2,281 (15)	Not available	Not available	2,276 (≤10)	2,281 (15)	Not available	Not available
Excision for malignant skin lesion	2,279 (≤10)	2,284 (≤10)	Not available	Not available	2,279 (≤10)	2,284 (12)	Not available	Not available
	Acitretin Cohort	No Acitretin Cohort			Acitretin Cohort	No Acitretin Cohort		
NMSC	5,771 (116)	5,208 (181)	0.58 (0.46-0.73)	<0.0001	5,771 (156)	5,208 (213)	0.66 (0.54-0.81)	<0.0001
MMS	5,875 (36)	5,598 (125)	0.27 (0.19-0.40)	<0.0001	5,875 (50)	5,598 (154)	0.31 (0.23-0.42)	<0.0001
Excision for malignant skin lesion	5.885 (32)	5,676 (88)	0.35 (0.23-0.52)	<0.0001	5,885 (43)	5,676 (102)	0.41 (0.29-0.58)	<0.0001

[1]The number of eligible individuals from which the number of individuals with the target outcome is obtained (ie: "n") for each outcome differs slightly because each analysis was conducted independently. For each specific outcome (eg, NMSC, MMS, excision), only patients with that outcome documented prior to the sirolimus exposure were excluded.
[2]The number of eligible individuals differs from the overall matched cohort size because patients with documentation of the target outcome prior to the index date or with data outside the 20-year TriNetX lookback window were excluded from individual analyses.

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DISCUSSION

Our findings concur with prior studies and may reflect several mechanistic hypotheses. Celecoxib may reduce NMSC risk by suppressing UV-induced prostaglandin E_2 and immunomodulatory cytokines that promote keratinocyte proliferation, while directly inhibiting COX-2 activity in dysplastic epidermal cells, resulting in reduced epidermal hyperplasia, tumor burden, and markers of DNA damage.[2] Despite these potential chemopreventive effects, celecoxib use is limited by well-established risks, including cardiovascular events, gastrointestinal bleeding, renal toxicity, and hypersensitivity reactions, necessitating careful patient selection.[2] As for sirolimus, it appears to reduce skin cancer risk primarily by inhibiting mTORC1-dependent keratinocyte proliferation and disrupting NRF2-mediated antioxidant defenses, thereby enhancing oxidative stress-induced tumor cell death, an effect that is predominantly protective against SCC.[3] However, the drug's established immunosuppressive properties warrant careful patient selection.[3] Additionally, acitretin is thought to reduce NMSC risk by activating nuclear retinoic acid receptors to regulate gene transcription involved in keratinocyte differentiation, proliferation, and immune surveillance, though its use is limited by mucocutaneous toxicity, hyperlipidemia, hepatotoxicity, and strict teratogenic risk.[5] Our findings highlight the potential role of celecoxib, sirolimus, and acitretin as chemopreventive adjuncts to reduce NMSC risk in select patients who are not immunosuppressed. Limitations include reliance on ICD-10, CPT, and RxNorm coding, retrospective design, and lack of generalizability to patients with inherited or acquired skin cancer risk factors. Future studies incorporating prospective data and evaluation by NMSC subtype are needed.

DISCLOSURES

SNT is an investigator/speaker for Bioventus, Kerecis, Boehringer Ingelheim, Regeneron, and CASTLE. Other authors have no conflicts of interest to declare.

Ethics Approval/Statement:
Data accessible via TriNetX is presented in aggregate form and only contains anonymized data as per the deidentification standard defined by the US Health Insurance Portability and Accountability Act (HIPAA) in section 164,514(a). Given this study used only de-identified data and did not involve individually identifiable patient data, this study was exempt from Institutional Review Board Approval.

Data Sharing Statement:
The data that support the findings of this study were obtained from the TriNetX Research Network and are available to other researchers upon request and with appropriate access permissions. De-identified aggregate-level data, a data dictionary describing the variables used, and the statistical code used for cohort creation and outcome assessment can be shared upon reasonable request to the corresponding author. Data access requires institutional credentials or collaboration with an institution that maintains a TriNetX license. Analyses may be replicated or extended within the TriNetX platform. There are no additional restrictions on the use of the shared materials beyond those imposed by the TriNetX user agreement.

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