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Metformin Use and Risk of Non-Melanoma Skin Cancer: A Propensity-Matched Case-Control Study

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ABSTRACT

Background: There is literature that suggests metformin may play a protective role against the development of non-melanoma skin cancers. Given the significant burden of disease non-melanoma skin cancers represent, the possibility of a widely available and generally well-tolerated medication such as metformin as part of the prevention and treatment ladder warrants further research.

Objective: This study aims to evaluate the potential of metformin in reducing the risk of non-melanoma skin cancers, specifically squamous cell carcinoma and basal cell carcinoma, using the All of Us research database.

Methods: A retrospective case-control analysis was conducted using the All of Us database. Propensity score matching and multivariable regression analyses were performed to evaluate the impact of metformin on the incidence of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) while controlling for confounding variables.

Results: Our results indicate a reduced risk of non-melanoma skin cancer following exposure to metformin in individuals diagnosed with both SCC and BCC. Subgroup analyses revealed that metformin exposure was associated with a decreased risk of BCC across all sex and ethnicity groups. Metformin use was also associated with a significantly lower risk of SCC, with univariable and multivariable ORs consistently showing reduced odds. However, metformin exposure was not significantly associated with decreased SCC risk in African American patients.

Conclusion: Our study's findings indicate a potential protective effect of metformin against skin cancer, particularly in patients with skin of color. Further prospective research is necessary to substantiate metformin's role in skin cancer chemoprevention within these populations.

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INTRODUCTION

Non-melanoma skin cancers, comprising primarily of cutaneous basal (BCC) and squamous cell carcinomas (SCC), present a significantly higher mortality and morbidity risk in patients with skin of color as compared with their age-matched peers.[1,2] This disparity is partly attributable to later stages of diagnosis and pervasive cultural misconceptions about skin cancer risks in skin of color.[3] This may also be due to varied prevalence of subtypes amongst different populations, each with their discrete natural histories. For example, while sun-induced squamous cell carcinomas common in Caucasian populations typically carry a 1 to 4% risk of metastasis, squamous cell carcinoma arising in chronic scarring processes — more prevalent in African American patients — demonstrate a markedly higher metastasis risk of 20 to 40%.[2]

Given these alarming gaps, it is crucial to thoroughly explore accessible prophylactic and treatment options for non-melanoma skin cancer. Within this context, metformin, a commonly used diabetes medication, emerges as a potentially significant addition to the treatment ladder for skin cancer. Preliminary findings in Iceland suggest metformin's protective role against squamous cell carcinoma but not basal cell carcinoma.[4] Similar conclusions have been drawn from population-level studies in Taiwan and the United States, which reported a reduced risk of non-melanoma skin cancer associated with metformin use; however, they did not differentiate between SCC and BCC in their analyses.[5,6]

Despite these promising leads, there remains a significant gap in our understanding of the impact of metformin on squamous cell carcinoma and basal cell carcinoma risk, especially as it relates to patients with skin of color. Our study utilizes the All of Us research database, which captures other patients who have historically been underrepresented in biomedical research, to shed light on the potential benefits of metformin in the context of non-melanoma skin cancers while capturing these specific populations.

TABLE 1.

Sociodemographic and Clinical Traits of SCC and BCC Cases/Controls in the All of Us Research Program

Characteristic	SCC Cases (n= 4111)	SCC Controls (n= 16444)	*P* value	BCC Cases (n= 8047)	BCC Controls (n= 32188)	*P* value
Age (SD)	75.29 (10.01)	75.29 (10.01)	>0.99	72.69 (10.64)	72.69 (10.63)	>0.99
No. %						
Sex	--	--	>0.99	--	--	>0.99
Male	2360 (57.41)	9440 (57.41)		4126 (51.27)	16504 (51.27)	
Female	1672 (40.67)	6688 (40.67)		3775 (46.91)	15100 (46.91)	
Other*	79 (1.92)	316 (1.92)		146 (1.81)	584 (1.81)	
Race/Ethnicity	--	--	>0.99	--	--	>0.99
White	3738 (90.93)	14952 (90.93)		7372 (91.61)	29488 (91.61)	
Black	70 (1.70)	280 (1.70)		69 (0.86)	276 (0.86)	
Hispanic	86 (2.09)	344 (2.09)		217 (2.70)	868 (2.70)	
Other*	217 (5.28)	868 (5.28)		389 (4.83)	1556 (4.83)	
Annual Income	--	--	>0.99	--	--	>0.99
≥ $50k	2392 (58.19)	8672 (52.74)		4925 (61.20)	17182 (53.38)	
$35k- $50k	355 (8.64)	1565 (9.52)		670 (8.33)	2929 (9.10)	
$25k- $35k	253 (6.15)	1155 (7.02)		439 (5.46)	2223 (6.91)	
$10k- $25k	305 (7.42)	1564 (9.51)		574 (7.13)	3038 (9.44)	
≤ $10k	113 (2.75)	562 (3.42)		179 (2.22)	1404 (4.36)	
Other*	693 (16.86)	2926 (17.79)		1260 (15.66)	5412 (16.81)	
Education	--	--	>0.99	--	--	>0.99
College graduate	2602 (63.29)	9596 (58.36)		5311 (66.00)	18253 (56.71)	
Attended college, no degree	896 (21.80)	3921 (23.84)		1684 (20.93)	8042 (24.98)	
12th Grade	452 (10.99)	2038 (12.39)		767 (9.53)	4194 (13.03)	
No HS degree	74 (1.80)	503 (3.06)		127 (1.58)	988 (3.07)	
Other*	87 (2.12)	386 (2.35)		158 (1.96)	711 (2.21)	
Other medications						
Hydrochlorothiazide	1196 (29.09)	3652 (22.21)	<0.001	2090 (25.97)	6620 (20.57)	<0.001
Photosensitizing medications	1945 (47.31)	4384 (26.66)	<0.001	3540 (43.99)	8289 (25.75)	<0.001
Statins	2648 (64.41)	8125 (49.41)	<0.001	4697 (58.37)	14775 (45.90)	<0.001
Tumor necrosis alpha inhibitors	98 (2.38)	215 (1.31)	<0.001	187 (2.32)	409 (1.27)	<0.001
Associated comorbidity						
Obesity	1198 (29.14)	5644 (34.32)	<0.001	2415 (30.01)	11527 (35.81)	<0.001
Ever smoker	2155 (52.42)	8012 (48.72)	<0.001	3891 (48.35)	15647 (48.61)	0.681
HPV	1069 (26.00)	1254 (7.63)	<0.001	1838 (22.84)	2320 (7.21)	<0.001
Metformin						
Ever use	370 (9.00)	2176 (13.23)	<0.001	519 (6.45)	4210 (13.08)	<0.001
Never use	3741 (91.00)	14268 (86.77)	--	7528 (93.55)	27978 (86.92)	--

*Includes participants with more than one indicated, no matching concept, other, or unknown
BCC: basal cell carcinoma, SCC: squamous cell carcinoma, SD: standard deviation.

MATERIALS AND METHODS

The All of Us (AoU) research program is a National Institutes of Health (NIH) initiative aimed at creating a diverse health database from >1,000,000 Americans, with a specific focus on underrepresented groups.. AoU seeks to address longstanding health disparities within the field of medicine by actively recruiting diverse populations, such as racial and ethnic minorities, individuals from low-income backgrounds, and rural communities. Inclusion criteria include participants 18 years and older and current residence in the United States (US) or a US territory. Exclusion criteria include those in prison and individuals unable to consent on their own.[7]

The data used in this study was collected by the AoU Research Program. The dataset comprises surveys, electronic health record (EHR) data, and physical measurements (PM). EHR data includes information consisting of clinical notes, vital signs, disease diagnosis, medications, and laboratory values.[7] After obtaining informed consent, enrolled participants provided survey responses regarding their health status and demographics, including ethnicity, race, age, sex, income, and education. The AoU Research Program collects participant EHR data through partnerships with healthcare organizations, hospitals, and clinics across the US, following participant consent and authorization.[7] Standardized coding systems (SNOMED and ICD-10) codes were used to classify and categorize medical conditions and procedures. SNOMED enables the alignment of data points across various EHR systems, while ICD-10 primarily focuses on diagnosis and disease classification.

Following extraction, data was transformed into Observational Medical Outcomes Partnership (OMOP) format. The collected data then underwent data standardization and harmonization, ensuring consistency across diverse healthcare settings. To ensure participant privacy, several data transformations were applied. These transformations involved suppressing codes with high identification risk, generalizing categories, and shifting dates by a random number of days (less than a year) consistently across each participant's records. For the race category, participants were classified into 4 groups: White, Asian, Black, Hispanic, and other. The other group included American Indians, Alaska Natives, and individuals not covered by the other categories, participants with more than one indicated value, no matching concept, or an unknown value.

A case-control study was performed using the AoU database. Following nearest neighbor propensity score matching, cases of SCC (SNOMED: 254651007) and BCC (SNOMED: 254701007) were selectively matched with 4 controls by age, race, ethnicity, and sex. SCC in the lungs, nasal passages, and genital regions, and BCC in the eyes and genital regions were not included in the analyses, respectively. Individuals were considered exposed to metformin if they had filled one prescription more than 2 years before SCC diagnosis, excluding prescriptions within 2 years of diagnosis. Univariable and multivariable logistic regression assessed the association of metformin with SCC with multivariable regression controlling for medications associated with increased risk of skin cancer.[4]

RESULTS

We identified a total of 4111 SCC cases and 8047 BCC cases, each matched with their respective controls (SCC: n=16444, BCC: n=32188). Age, sex, and race were well-matched with a *P*-value >0.99. The mean age of the participants was 75.29 years for SCC and 72.69 years for BCC. Among cases, 40.67% were female for SCC, while 46.91% were female for BCC. In Table 2 and

TABLE 2.

Univariable and Multivariable-Adjusted Associations of Metformin With BCC

Disease	Univariable OR (95% CI)	Multivariable aOR (95% CI)†	Multivariable aOR (95% CI)††
BCC	0.46 (0.42, 0.50)	0.37 (0.34, 0.41)	0.33 (0.29, 0.36)
Sex			
Male	0.49 (0.43, 0.55)	0.38 (0.33, 0.43)	0.34 (0.29, 0.38)
Female	0.40 (0.34, 0.47)	0.34 (0.29, 0.39)	0.30 (0.25, 0.35)
Race/Ethnicity			
White	0.47 (0.42, 0.52)	0.38 (0.34, 0.42)	0.33 (0.30, 0.37)
Black	0.29 (0.08, 0.73)	0.16 (0.04, 0.44)	0.09 (0.02, 0.26)
Hispanic	0.35 (0.20, 0.56)	0.27 (0.16, 0.45)	0.20 (0.12, 0.33)
Comorbidity*			
Obesity	0.48 (0.42, 0.54)	0.39 (0.34, 0.44)	0.33 (0.29, 0.38)
Ever smoker	0.42 (0.37, 0.48)	0.34 (0.29, 0.39)	0.30 (0.26, 0.34)
HPV	0.31 (0.23, 0.41)	0.30 (0.22, 0.40)	0.28 (0.20, 0.37)

aOR: multivariable-adjusted odds ratio, CI: confidence interval, BCC: basal cell carcinoma, HPV: Human papillomavirus
*Regression only including cases and controls with associated comorbidity
†aOR: Multivariable regression analysis controlled for hydrochlorothiazide, photosensitizing medications, and tumor necrosis alpha inhibitors.
††aOR: Multivariable regression analysis controlled for hydrochlorothiazide, photosensitizing medications, tumor necrosis alpha inhibitors, and statins.

TABLE 3.

Univariable and Multivariable-Adjusted Associations of Metformin With SCC

Disease	Univariable OR (95% CI)	Multivariable aOR (95% CI)†	Multivariable aOR (95% CI)††
SCC	0.65 (0.58, 0.73)	0.52 (0.46, 0.58)	0.45 (0.40, 0.51)
Sex			
Male	0.73 (0.63, 0.84)	0.57 (0.49, 0.66)	0.50 (0.43, 0.58)
Female	0.51 (0.41, 0.62)	0.41 (0.33, 0.51)	0.36 (0.28, 0.44)
Race/Ethnicity			
White	0.66 (0.58, 0.74)	0.53 (0.46, 0.60)	0.46 (0.40, 0.52)
Black	0.61 (0.28, 1.22)	0.48 (0.21, 1.02)	0.22 (0.09, 0.52)
Hispanic	0.43 (0.21, 0.82)	0.30 (0.14, 0.59)	0.24 (0.11, 0.48)
Comorbidity*			
Obesity	0.68 (0.58, 0.81)	0.54 (0.45, 0.64)	0.47 (0.39, 0.56)
Ever smoker	0.65 (0.55, 0.76)	0.51 (0.44, 0.60)	0.45 (0.38, 0.53)
HPV	0.58 (0.45, 0.74)	0.54 (0.41, 0.69)	0.51 (0.39, 0.66)

aOR: multivariable-adjusted odds ratio, CI: confidence interval, SCC: squamous cell carcinoma, SOTR: solid organ transplant recipient, CLL: chronic lymphocytic leukemia
*Regression only including cases and controls with associated comorbidity
†aOR: Multivariable regression analysis controlled for hydrochlorothiazide, photosensitizing medications, and tumor necrosis alpha inhibitors.
††aOR: Multivariable regression analysis controlled for hydrochlorothiazide, photosensitizing medications, tumor necrosis alpha inhibitors, and statins.

Table 3, univariable and multivariable-adjusted associations of BCC and SCC following metformin exposure are presented, respectively. In our analyses, metformin use was significantly associated with a reduced risk of both BCC and SCC. For BCC, the univariable odds ratio (OR) was 0.46 (95% CI: 0.42-0.50), and the multivariable adjusted odds ratio (aOR) was 0.33 (95% CI: 0.29-0.36). Similarly, for SCC, the univariable OR was 0.65 (95% CI: 0.58-0.73), and the multivariable aOR was 0.45 (95% CI: 0.40-0.51). However, our findings also revealed that metformin exposure was not significantly associated with decreased SCC risk in African American patients (OR: 0.61, 95% CI: 0.28-1.22). Our analysis also investigated the relationships in cases and controls who were diagnosed with comorbidities known to be associated with non-melanoma skin cancer, including obesity, prior tobacco use, and a diagnosis of human papillomavirus (HPV). The observed trends remained consistent for both BCC and SCC.

DISCUSSION

Our results indicate a reduced risk of non-melanoma skin cancer following exposure to metformin in individuals diagnosed with both SCC or BCC (Tables 2 and 3). This study strengthens the evidence supporting metformin's potential as a protective agent against non-melanoma skin cancer, especially after adjusting for medications associated with increased risk of skin cancer. Subgroup analyses revealed that metformin exposure was associated with a decreased risk of BCC across all sex and ethnicity groups (Table 2). Metformin use was also associated with a significantly lower risk of SCC, with univariable and multivariable ORs consistently showing reduced odds (Table 3). However, our findings also revealed that metformin exposure was not significantly associated with decreased SCC risk in African American patients. This discrepancy could stem from the fact that SCC in these patients often develops in sun-protected areas and is strongly linked to chronic scarring and inflammation, factors that may not be influenced by metformin use.[1]

Previous population-level investigations have yielded inconclusive findings regarding the efficacy of metformin as an anti-cancer medication. An Icelandic study encompassing 6880 patients diagnosed with non-melanoma skin cancer found that metformin exposure was associated with a lower risk of developing BCC. However, this relationship was not maintained in patients diagnosed with SCC. Despite these findings, it's important to note that this study was limited by the usage of a largely white and genetically homogenous cohort.[4] Another study conducted in Taiwan using data from 16237 matched pairs of ever and never metformin users with new-onset type 2 diabetes between 1999 and 2005 found similar results. Skin cancer incidence was significantly lower among ever-metformin users, with hazard ratios showing a substantial reduction in risk. However, the study did not distinguish between basal cell carcinoma and squamous cell carcinoma during analyses.[5]

Metformin holds promise as a potential chemopreventive agent for skin cancer, with various proposed biological mechanisms supporting this role. These mechanisms encompass a spectrum of anti-cancer actions.[8-12] Firstly, metformin activates AMP-activated protein kinase (AMPK), which acts as a cellular energy sensor, regulating metabolic processes and impeding cancer cell growth by restricting their access to essential energy and nutrients. Simultaneously, metformin inhibits the mTOR (mammalian target of rapamycin) pathway, a pivotal regulator

of cell growth and proliferation. This dual action hinders the uncontrolled progression of cancer cells.[8] Metformin also influences the cell cycle, promoting cell cycle arrest, apoptosis, and autophagy, further curtailing unchecked cell division and tumor expansion. In addition to these direct effects, metformin enhances the body's immune response against cancer cells by increasing the number of tumor-infiltrating lymphocytes.[9] Furthermore, its anti-inflammatory properties mitigate chronic inflammation, a recognized contributor to carcinogenesis.[10] By reducing insulin and insulin-like growth factors, metformin tackles key drivers of cancer cell growth and survival. Lastly, metformin's potential to inhibit angiogenesis, the process of new blood vessel formation essential for tumor growth and metastasis, underscores its multifaceted approach to preventing skin cancer.[11] Preliminary studies in mice have also indicated that metformin can dose-dependently inhibit the development of squamous cell carcinomas (SCCs) and reduce tetradecanoylphorbol-13-acetate (TPA)-induced epidermal hyperproliferation. It was found that metformin, administered through drinking water, displayed a dose-dependent inhibition of papilloma and squamous cell carcinoma development in overweight and obese mice.[12]

Although our analyses provide valuable insights into the relationship between metformin and skin cancer risk, it is essential to acknowledge several limitations that may affect the interpretation of the results. Our study relies on electronic health records for prescription data, potentially missing cases of metformin obtained without prescriptions, which could introduce a selection bias. This limitation might underestimate the true extent of metformin exposure in the study population. The use of diagnostic codes to identify cases of skin cancer may introduce misclassification bias, as diagnostic codes can be subject to errors or variations in coding practices. This potential misclassification could affect the accuracy of the observed associations between metformin use and skin cancer risk. Furthermore, our analysis lacks clinical information on skin cancer cases, such as detailed clinical features, histopathological data, and the type of diagnosing healthcare provider. This absence of clinical details limits the depth of our understanding of the specific characteristics of skin cancer cases and the potential variations within the skin cancer cohort. Additionally, the study's reliance on retrospective data might introduce unmeasured confounding factors and biases, potentially impacting the accuracy of the results. Efforts have been made to account for these factors by adjusting for various potential confounders; however, some residual confounding may still exist.

While the findings suggest a potential protective role of metformin, further prospective studies are warranted to confirm these findings in skin of color (SOC) patients. If validated, metformin could offer a novel avenue for reducing SCC risk, particularly in skin of color patients who face higher burdens of SCC morbidity and mortality.[2] In conclusion, our results suggest that further research may be warranted to consider metformin as a chemopreventive agent. While previous population-level studies have yielded mixed results, the nuanced variations among racial groups found in our study underscore the need for personalized approaches in evaluating metformin's anti-cancer properties, emphasizing its potential significance in skin cancer prevention.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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