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The effect of metformin on the risk of recurrent nonmelanoma skin cancers

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Dear Editor,

Metformin has recently been shown to have a protective effect on the primary development of nonmelanoma skin cancers (NMSCs) among a large population of type II diabetics in Taiwan.[1] This raises the question of whether metformin can reduce recurrences of NMSCs in patients with a history of NMSC. To answer this, we performed a preliminary retrospective cohort study of adult patients in the Minneapolis Veterans Affairs Health Care System with their first biopsy-confirmed NMSCs between January 1 and December 31, 2003. The patients' problems and medications were screened for exclusion criteria, including previous NMSCs, type I diabetes mellitus, immunosuppression, arsenic or radiation exposure, genetic predisposition to NMSCs, and use of oral retinoids, contraceptives, or nicotinamide. Of the 740 patients screened, 544 patients were excluded due to prior NMSCs, and 22 were eliminated due to other exclusion criteria. The remaining 174 patients were placed into three cohorts: nondiabetics ($n = 117$), type II diabetics on metformin ($n = 20$), and diabetics not on metformin ($n = 37$). Demographics, patient characteristics, exposure history, melanoma history, atherosclerotic cardiovascular disease, average of up to three hemoglobin A1c (HgbA1c) values after enrollment, and significant medication usage were collected for enrolled patients (Table 1). Dates of diagnosis and types and locations of initial and second NMSCs were obtained from pathology reports. The primary outcome for this study was the 3-year risk of developing a second NMSC. Secondary outcomes included the 3-year risk of developing a BCC or SCC, individually, the total number of NMSCs over 3 years, and the time to second NMSC. Statistical analysis

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methods included the chi-squared test for categorical items and the nonparametric Kruskal–Wallis or Wilcoxon rank sum tests for quantitative or ordered variables.

Our study did not reveal a decreased risk of developing a second NMSC over the 3-year period for type II diabetic patients on metformin compared to diabetics not on metformin (43.2 and 40.0%, respectively). Contrary to previous literature, we found an increased NMSC risk in nondiabetic patients compared to both diabetic cohorts ($P = 0.036$).[2] Additionally, our results failed to demonstrate a significant effect of metformin on secondary variables including time to second NMSC ($P = 0.573$) and total number of NMSCs over 3 years ($P = 0.127$) (Table 2). Radiation and agent orange exposure, tobacco use, and alcohol use were not significantly different among the three cohorts. Due to significantly higher daily aspirin use in diabetics without metformin compared to diabetics on metformin and nondiabetics (40.5, 20.0, and 15.3% respectively, $P = 0.005$), we re-analyzed the risk of developing a secondary NMSC while controlling for daily aspirin use. On post-hoc analysis, we found aspirin had a significant protective effect on the development of second NMSC among the diabetic cohorts ($P = 0.027$), consistent with previous data.[3] However, the nondiabetic group still had a significantly increased risk of NMSCs compared to diabetics, and controlling for aspirin did not change the lack of significant effect of metformin on secondary NMSC risk. Given that we found a protective effect of aspirin in our diabetic cohort in such a small sample size and did not see any trends associated with a protective effect with metformin, we wonder whether aspirin has a greater chemoprotective effect than metformin. However, the small sample size and lack of high-dose metformin usage may bias such a conclusion. Our study was limited by its small sample size, limited involvement of under-represented minorities, and retrospective nature. Furthermore, the finding that nondiabetic patients had a significantly increased risk of second NMSC may indicate that the data is not reproducible for the population at large. While metformin may be efficacious for primary NMSC prevention, its usage for secondary prevention remains a question that necessitates further study.

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Table 1

Demographic information among diabetics on metformin, diabetics not on metformin, and nondiabetics

	DM on metformin (*n* = 20)	DM without metformin (*n* = 37)	No DM (*n* = 118)	*P*-value
Sex – no. (%)				
Male	20 (100)	36 (97.3)	116 (98.3)	0.754
Female	0 (0)	1 (2.7)	2 (1.7)	
Race – no. (%)				
White	20 (100)	35 (94.6)	112 (94.9)	NA
Black	–	–	–	
Native American	–	–	–	
Pacific Islander	–	–	1 (0.9)	
Asian	–	–	–	
Other	–	2 (5.4)	5 (4.2)	
Ethnicity – no. (%)				
Non-Hispanic	20 (100)	34 (91.9)	113 (95.8)	NA
Hispanic	–	1 (2.7)	–	
Average age at diagnosis of first NMSC				
Median	74.5	78.0	75.0	0.253
Interquartile range	62.5–79.0	70.0–80.0	65.0–79.0	
Initial NMSC – no. (%)				
Type				
BCC	11 (55.0)	22 (59.5)	73 (61.9)	0.835
SCC	9 (45.0)	15 (40.5)	45 (38.1)	
Location Head/neck	13 (65.0)	28 (75.7)	79 (67.0)	0.240
Trunk	2 (10.0)	5 (13.5)	27 (22.9)	
Upper extremities/hands	5 (25.0)	3 (8.1)	10 (8.5)	
Lower extremities/feet	–	1 (2.7)	2 (1.7)	
History of melanoma – no. (%)	–	–	6 (5.1)	0.223
History of previous coronary artery disease or cerebrovascular event – no. (%)	5 (25.0)	18 (48.7)	22 (19.0)	0.002 *
Daily aspirin – no. (%)	4 (20.0)	15 (40.5)	18 (15.3)	0.005 *
Daily NSAIDs – no. (%)	3 (15.0)	6 (16.2)	21 (17.8)	0.941

	DM on metformin (*n* = 20)	DM without metformin (*n* = 37)	No DM (*n* = 118)	*P*-value
Other diabetes medications – no. (%)	12 (60.0)	14 (37.8)	–	0.164
Sulfonylureas	12 (60.0)	14 (37.8)	–	0.164
Meglitinides	–	–	–	NA
Glitazones	–	1 (2.7)	–	NA
Insulin	2 (10.1)	10 (27.0)	–	0.182
Metformin dosage at time of initial NMSC – no. (%)				
<1,000	11 (55.0)	NA	NA	NA
1,001–2,000	8 (40.0)			
>2,000	1 (5.0)			

Statistical analysis methods included the chi-squared test for categorical items and the nonparametric Kruskal–Wallis or Wilcoxon rank sum tests for quantitative or ordered variables. Some of the subject characteristics do not add up to the total group sizes due to missing information. *P*-values < 0.05 were considered statistically significant (indicated by *). Zero values represented by "–" NA, not applicable.

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Table 2

Primary and secondary NMSC outcomes for diabetics on metformin, diabetics not on metformin, and nondiabetics

Outcomes	Type II diabetes on metformin (*n* = 20)	Type II diabetes without metformin (*n* = 37)	No Type II diabetes (*n* = 118)	*P*-value
Risk for developing second NMSC – no. (%)	8 (40.0)	16 (43.2)	74 (62.7)	0.036 *
95% confidence interval	19–64	27–61	53–71	
Risk for developing second NMSC based on metformin dosage – no. (%)				
<1,000 mg/day	4/11 (36.4)	NA	NA	0.795
1,001–2,000 mg/day	4/8 (50.0)			
>2,000 mg/day	0/1 (0)			
Risk for developing SCC after first NMSC – no. (%)	3 (15.0)	6 (16.2)	26 (22.0)	0.622
95% confidence interval	3–38	6–32	15–31	
Risk for developing BCC after first NMSC – no. (%)	5 (25%)	10 (27.0%)	48 (40.7%)	0.177
95% confidence interval	9–49%	14–44%	32–50%	
Total NMSCs over 3 years				
Median	1.5	2.0	2.0	0.127
Interquartile range	1.0–2.5	1.0–2.0	1.0–3.0	
Total SCC over 3 years				
Median	1.0	1.0	1.0	0.765
Interquartile range	0–1.0	0–1.0	0–2.0	
Total BCC over 3 years				
Median	1.0	1.0	1.0	0.215
Interquartile range	0.5–1.0	0–2.0	1.0–2.0	
Average time to second NMSC (days)				
Median	685.5	582.0	947.0	0.573
Interquartile range	366.5–1408.0	233.0–1545.5	329.0–2138.0	

NA, not applicable. *P*-values < 0.05 were considered statistically significant (indicated by *).