

Increased Odds of Multiple Primary Cancers in Merkel Cell Carcinoma Patients: A Large-Scale Propensity-Matched Analysis

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To the Editor:

Merkel Cell Carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer that primarily affects older adults and the immunocompromised.^{1,2} Studies have indicated that MCC has a higher propensity for metastasis and recurrence compared to other cutaneous malignancies, necessitating aggressive diagnostic and treatment strategies.³⁻⁵ This study examines the relationship between MCC and the risk of developing multiple primary cancers from the *TriNetX database*, a global health research network that aggregates de-identified electronic medical records.

A cohort of 7,472 patients diagnosed with MCC were enrolled in the study and compared to the same number of cases without MCC, propensity-matched by age, sex, and race/ethnicity for primary cancer comorbidities. The analysis included the computation of odds ratios (ORs) with 95% confidence intervals (CIs) using Wald's method (Table 1).

MCC patients demonstrated significantly higher odds of developing various skin cancers compared to the control group. Notably, the analysis revealed a substantially higher prevalence of neoplasms in general among MCC patients compared to the control group (OR, 2.202; 95% CI, 825.5-5,876.2; $P<0.0001$), and found a markedly increased prevalence of malignant melanoma (OR, 6.978; 95% CI, 5.779-8.427; $P<0.0001$), microcystic adnexal carcinoma (OR, 6.599; 95% CI, 3.496-12.457; $P<0.0001$), undifferentiated pleomorphic sarcoma (OR, 5.313; 95% CI, 3.842-7.349; $P<0.0001$), extramammary Paget's disease (OR, 5.122; 95% CI, 2.681-9.784; $P<0.0001$), atypical fibroxanthoma (OR, 4.016; 95% CI, 2.007-8.037; $P<0.0001$), dermatofibrosarcoma protuberans (OR, 6.599; 95% CI, 3.496-12.457; $P<0.0001$), squamous cell carcinoma (OR, 3.111; 95% CI, 2.449-3.951;

$P<0.0001$), and basal cell carcinoma (OR, 2.685; 95% CI, 2.184-3.3; $P<0.0001$).

Hematological malignancies showed varying associations with MCC. Non-Hodgkin lymphoma was significantly more prevalent in MCC patients (OR, 1.766; 95% CI, 1.3-2.398; $P=0.0002$), as was leukemia (OR, 1.827; 95% CI, 1.01-3.304; $P=0.043$).³ However, Hodgkin's lymphoma did not show a significant association (OR, 0.842; 95% CI, 0.433-1.638; $P=0.6117$).

It is worth noting that neoplasm comorbidities of the thyroid gland (OR, 1.685; 95% CI, 0.993-2.859; $P=0.0504$) liver and/or intrahepatic bile ducts (OR, 1.21; 95% CI, 0.893-1.64; $P=0.2171$), or kidney (OR, 1.053; 95% CI, 0.795-1.395; $P=0.7199$) did not have statistical significance with MCC. Neoplasms of the breast and sebaceous carcinomas did not have substantial cases to make significant claims.

These results suggest that MCC patients are at an increased odds of multiple primary cancers, potentially due to underlying genetic, environmental, or immunological factors.^{4,5} Limitations of this study include the retrospective nature of this study and reliance on de-identified electronic records which restrict the degree of detail available, such as family history or lifestyle influences, which could further elucidate these associations.^{4,5} Clinically, these findings highlight the need for consistent surveillance and tailored management strategies for MCC patients, emphasizing the role of early detection and monitoring for secondary malignancies.^{4,5} Future research should focus on the mechanisms underlying these associations and the development of targeted interventions to mitigate cancer risk in this vulnerable population.

TABLE 1.

Baseline Demographics in Merkel Cell Carcinoma Patients and Propensity-Matched Control Group (After Matching)

Characteristic	Cases (%) (n = 7,472)	Controls (%) (n = 7,472)	OR (95% CI) [†]	P value [†]
Average Age, SD (Years)	73.3, 11.6	73.3, 11.6	--	1.00
Male	4,610 (61.70%)	4,610 (61.70%)	--	1.00
Female	2,582 (34.60%)	2,582 (34.60%)	--	1.00
White	6,138 (82.10%)	6,138 (82.10%)	--	1.00
Not Hispanic or Latino	5,387 (72.1%)	5,387 (72.1%)	--	1.00
Hispanic or Latino	226 (3.00%)	226 (3.00%)	--	1.00
Black or African American	151 (2.00%)	151 (2.00%)	--	1.00
Asian	93 (1.20%)	93 (1.20%)	--	1.00
Native Hawaiian or Other Pacific Islander	69 (0.90%)	69 (0.90%)	--	1.00
American Indian or Alaska Native	18 (0.20%)	18 (0.20%)	--	1.00
Atypical Fibroxanthoma	40 (0.54%)	≤ 10**	4.016 (2.007-8.037)	<0.0001*
Basal Cell Carcinoma	334 (4.47%)	128 (1.71%)	2.685 (2.184-3.3)	<0.0001*
Dermatofibrosarcoma Protuberans	72 (0.96%)	11 (0.15%)	6.599 (3.496-12.457)	<0.0001*
Extramammary Paget's Disease	56 (0.75%)	11 (0.15%)	5.122 (2.681-9.784)	<0.0001*
Hodgkin's Lymphoma	16 (0.21%)	19 (0.25%)	0.842 (0.433-1.638)	0.6117
Leukemia	31 (0.41%)	17 (0.23%)	1.827 (1.01-3.304)	0.043*
Malignant Melanoma	816 (10.92%)	129 (1.73%)	6.978 (5.779-8.427)	<0.0001*
Microcystic Adnexal Carcinoma	72 (0.96%)	11 (0.15%)	6.599 (3.496-12.457)	<0.0001*
Neoplasm of the Breast	≤ 10**	≤ 10**	1 (0.416-2.404)	1.00
Neoplasm of the Kidney (no Renal Pelvis)	101 (1.35%)	96 (1.28%)	1.053 (0.795-1.395)	0.7199
Neoplasm of the Liver and Intrahepatic Bile Ducts	93 (1.24%)	77 (1.03%)	1.21 (0.893-1.64)	0.2171
Neoplasm of the Thyroid Gland	37 (0.50%)	22 (0.29%)	1.685 (0.993-2.859)	0.0504
Neoplasms	7468 (99.95%)	3428 (45.88%)	2202 (825.5-5876.2)	<0.0001*
Non-Hodgkin Lymphoma	114 (1.53%)	65 (0.87%)	1.766 (1.3-2.398)	0.0002*
Sebaceous Carcinomas	0 (0.00%)	0 (0.00%)	--	--
Squamous Cell Carcinoma	276 (3.69%)	91 (1.22%)	3.111 (2.449-3.951)	<0.0001*
Undifferentiated Pleomorphic Sarcoma	228 (3.05%)	44 (0.59%)	5.313 (3.842-7.349)	<0.0001*

*Statistically significant values between cases and controls, defined at P<0.05

**Per TriNetX data dissemination guidelines, participant counts ≤10 are suppressed from display.

[†]After propensity score matching

CI, Confidence Interval; OR, odds ratio; SD, Standard Deviation.

MCC: Merkel Cell Carcinoma; CI: Confidence Interval; OR: Odds Ratio

DISCLOSURES

Dr Tolkachjov is a speaker and investigator for Kerecis, CASTLE Biosciences, Boehringer Ingelheim. The remaining authors have no relevant conflicts of interest to declare.

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