SKIN

RESEARCH LETTER

Drug-induced Photosensitivity and Malignant Melanoma in Latino Populations: A Case-control Study in the All of Us Research Program

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ABSTRACT

Background: Widely prescribed medications, such as anti-inflammatory agents, diuretics, and oral hormonal contraceptives, exhibit photosensitizing properties, heightening susceptibility to ultraviolet light and potentially escalating the risk of skin cancer. This risk is particularly notable for cutaneous malignant melanoma (CMM), a type of skin cancer on the rise among Hispanic/Latino individuals.
Objective: This study examines associations between various pharmaceutical agents and the onset of malignant melanoma in self-identified Hispanic/Latino individuals.
Methods: Through the All of Us health record database, 80 Hispanic/Latino individuals with diagnosed CMM were selected, forming the case cohort. Each case was age-, race-, and sex-matched to four Hispanic/Latino participants without CMM to compose the control cohort, and the use of numerous potential photosensitizing agents prior to the onset of CMM, if applicable, was documented.
Results: Compared to controls, Hispanic/Latino participants with CMM exhibited significantly higher odds of prior use of various pharmacologic agents, including histamine H1-receptor blockers, methotrexate, monoclonal antibodies, small-molecule inhibitors, tetracycline, and tricyclic antidepressants. Topical antifungals were also significantly associated with CMM onset, though the correlation with application sites remains unknown.
Conclusion: This study underscores the associations of potential photosensitizing agents with the development of CMM among Hispanic/Latino individuals, a population historically underrepresented in research. Raising awareness is crucial for counseling during prescription to reduce skin cancer incidence. Limitations of this study include unknown agent use duration, time between use and cancer onset, and potential disease influences, necessitating further research to better understand the contribution of these agents to CMM development in Latino populations.

INTRODUCTION

Certain commonly prescribed medications possess photosensitizing properties, which can induce cutaneous changes leading to increased sensitivity to ultraviolet light.[1] These medications, including anti-inflammatory agents, diuretics, and oral hormonal contraceptives (OCPs), may consequently raise the risk of skin cancer. The incidence of cutaneous malignant

melanoma (CMM), the most fatal type of skin cancer, is increasing among Hispanic/Latino individuals.[2] Furthermore, Latinos who present with melanomas often exhibit thicker tumors and reduced risk awareness and reduction behaviors compared to their non-Latino, white counterparts.[3,4] Considering the increasing prevalence and worse prognosis of CMM, it is crucial to investigate the role of drug-induced photosensitivity to enhance dermatological and health outcomes in Latino populations. This study examines associations between various photosensitizing pharmaceutical agents and the onset of malignant melanoma in self-identified Hispanic/Latino individuals.

METHODS

Through the *All of Us* health record database, 80 self-identified Hispanic or Latino participants with diagnosed CMM were selected to form the case cohort. Each participant was age-, race-, and sex-matched to four Hispanic/Latino participants without CMM to compose the control cohort. Participant demographics are displayed in **Table 1**. Based on retrospective chart review, use of the following drug classes prior to the onset of CMM were documented: anti-histamines, anti-rheumatics, anti-microbials (tetracycline or trimethoprim-sulfamethoxazole), non-steroidal anti-inflammatory drugs (NSAIDs), OCPs, phenothiazines, sulfonylurea, thiazide diuretics, topical antifungal agents, and tricyclic antidepressants (TCAs). The use of photosensitizing drug classes was compared between CMM and non-CMM participants, with odds ratios (OR) and 95% confidence intervals (CI) presented in **Table 2**.

RESULTS

Compared to the control cohort, Hispanic/Latino participants with CMM had significantly higher odds of prior use of histamine H1-receptor blockers (OR 3.056, 1.846-5.059 CI), methotrexate (OR 5.313, 1.644-17.168 CI), monoclonal antibodies (OR 7.891, 2.996-20.781 CI), small-molecule inhibitors (OR 28.948, 1.450-566.300 CI), tetracycline (OR 7.044, 1.647-30.132 CI), and TCAs (OR 3.036, 1.296-7.111 CI). Additionally, topical antifungals were significantly associated with the onset of CMM (OR 2.901, 1.595-5.279 CI), though it is unknown whether the site of antifungal application corresponds to the site of CMM development.

DISCUSSION

Certain photosensitizing agents, specifically tetracycline and NSAIDs, have well-documented associations with non-melanoma skin cancer, while methotrexate is associated with both melanoma and non-melanoma skin cancer.[5] Photosensitizing agents raise CMM risk through several physiologic mechanisms. By absorbing UV light and generating reactive oxygen species (ROS), these agents cause DNA damage and impair the skin's DNA repair processes, leading to increased genetic mutations. The oxidative stress and resultant inflammation create a physiologic environment that promotes tumor growth and disrupts key signaling pathways involved in cell growth. However, research on the association between photosensitizing agents and cutaneous melanoma (CMM) has largely focused on predominantly white populations, often overlooking the context of Latino populations. Our study confirms these associations in Latinos and suggests that

Table 1. Demographics of Latin American individuals with cutaneous malignant melanoma and corresponding controls in the *All of Us* Database

Characteristics	Cases	Controls
n	80	320
Average age (SD)	53.02 (12.50)	53.02 (12.50)
Race/Ethnicity (%)		
Asian	0 (0.00)	0 (0.00)
Black or African American	1 (1.25)	4 (1.25)
None Indicated	63 (78.75)	252 (78.75)
White	16 (20)	64 (20)
Sex (%)		
Female	47 (58.75)	188 (58.75)
Male	33 (41.25)	132 (41.25)

SD, standard deviation

Table 2. Photosensitizing agents used by cases and corresponding controls in the *All of Us* Database

Photosensitizing agent	Cases	Controls	OR (95% CI)	*P* value	
Antihistamines (H1 receptor blockers)	42	85	3.056 (1.846; 5.059)	<0.0001	*
Anti-rheumatics					
Abatacept	0	1	1.323 (0.053; 32.782)	0.864	
Azathioprine	1	1	4.038 (0.250; 65.270)	0.326	
Etanercept	1	0	12.094 (0.488; 299.709)	0.128	
Hydroxychloroquine	1	4	1.000 (0.110; 9.072)	1	
Methotrexate	7	5	5.313 (1.644; 17.168)	0.005	*
Monoclonal antibodies†	12	7	7.891 (2.996; 20.781)	<0.0001	*
Small-molecule inhibitors‡	3	0	28.948 (1.450; 566.300)	0.027	*
Anti-microbials (systemic)					
Tetracycline	5	3	7.044 (1.647; 30.132)	0.009	*
Trimethoprim-sulfamethoxazole	8	23	1.435 (0.617; 3.340)	0.402	
NSAIDs	46	147	1.592 (0.971; 2.612)	0.065	
Oral hormonal contraceptives - *females only*	7	22	1.321 (0.527; 3.307)	0.553	
Phenothiazines	6	19	1.285 (0.496; 3.329)	0.606	
Sulfonylurea	2	13	0.606 (0.1334; 2.739)	0.515	

Thiazide diuretics	3	17	0.694 (0.198; 2.430)	0.568	
Topical antifungals	22	37	2.901 (1.595; 5.279)	0.001	*
Tricyclic anti-depressants	10	14	3.036 (1.296; 7.111)	0.011	*

CI, confidence interval; OR, odds ratio. *Denotes significance. †Examples include nivolumab, ipilimumab, rituximab, denosumab, etc. ‡Examples include dabrafenib, trametinib, vemurafenib, azathioprine, etc.

additional pharmacologic agents, including small-molecule inhibitors and monoclonal antibodies, may also be correlated with melanoma formation. Raising awareness of these connections is crucial to improve counseling on drug-induced photosensitivity and melanoma risk during prescription, aiming to reduce skin cancer incidence among Latinos.

This study emphasizes the urgent need to investigate drug-induced photosensitivity to improve dermatological and health outcomes in this population with a higher CMM prevalence and worse prognosis. However, due to this study's retrospective nature, a causal relationship between photosensitizing agents and CMM development in Latinos cannot be established. The wide-ranging confidence intervals observed in our odds ratios are likely due to several factors inherent in our study design. Primarily, the relatively small sample size of 80 cases may contribute to increased variability in the data, leading to broader confidence intervals. Variability in the exposure duration, dosage, and timing of photosensitizing agents among participants further contributes to the wide confidence intervals.

Other limitations include undetermined length of time between agent use and onset of CMM and potential influence of disease processes associated with agent use. For instance, diseases like rheumatoid arthritis or chronic infections could independently influence melanoma development through systemic inflammation or immune system alterations. While our study aimed to control for these factors by matching participants based on demographics and documenting drug use, the retrospective nature limits our ability to fully account for all disease-specific effects. To better understand these relationships, future research should focus on prospective studies with larger sample sizes and detailed records of underlying conditions and treatment regimens. Such studies could provide a more comprehensive view of how disease processes and photosensitizing agent use interact to influence melanoma risk.

CONCLUSION

While our study highlights significant associations between photosensitizing agents and cutaneous melanoma in Latino populations, it also underscores the need for further research to address confounding factors and establish clearer causal relationships. Future studies with larger sample sizes and prospective designs will be crucial in unraveling the complex interplay between pharmacologic agents, underlying diseases, and melanoma risk, ultimately guiding more effective prevention and management strategies for this high-risk population.

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