Melasma Risk Factors: A Matched Cohort Study Using Data From the All of Us Research Program

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PRACTICE **POINTS**

- Treatment options for melasma are limited due to its poorly understood pathogenesis.
- Depression and hypothyroidism and/or history of exposure to radiation and hormonal therapies may increase melasma risk.
- We recommend that patients with melasma be screened for depression and thyroid dysfunction. Patients undergoing radiation therapy or starting estrogen and/or progesterone therapy should be counseled on the increased risk for melasma.

To the Editor:

Melasma (also known as chloasma) is characterized by symmetric hyperpigmented patches affecting sun-exposed areas. Women commonly develop this condition during pregnancy, suggesting a connection between melasma and increased female sex hormone levels.[1] Other hypothesized risk factors include sun exposure, genetic susceptibility, estrogen and/or progesterone therapy, and thyroid abnormalities but have not been corroborated.[2] Treatment options are limited because the pathogenesis is poorly understood; thus, we aimed to analyze melasma risk factors using a national database with a nested case-control approach.

We conducted a matched case-control study using the Registered Tier dataset (version 7) from the National Institute of Health's All of Us Research Program (https://allofus.nih.gov/), which is available to authorized users through the program's Researcher Workbench and includes more than 413,000 total participants enrolled from May 1, 2018, through July 1, 2022. Cases included patients 18 years and older with a diagnosis of melasma (*International Classification of Diseases, Tenth Revision, Clinical Modification* code L81.1 [Chloasma]; concept ID 4264234 [Chloasma]; and Systematized Nomenclature of Medicine [SNOMED] code 36209000 [Chloasma]), and controls without a diagnosis of melasma were matched in a 1:10 ratio based on age, sex, and self-reported race. Concept IDs and SNOMED codes were used to identify individuals in each cohort with a diagnosis of alcohol dependence (concept IDs 433753, 435243, 4218106; SNOMED codes 15167005, 66590003, 7200002), depression (concept ID 440383; SNOMED code 35489007), hypothyroidism (concept ID 140673; SNOMED code 40930008), hyperthyroidism (concept ID 4142479; SNOMED code 34486009), anxiety (concept IDs 441542, 442077, 434613; SNOMED codes 48694002, 197480006, 21897009), tobacco dependence (concept IDs 37109023, 437264, 4099811; SNOMED codes 16077091000119107, 89765005, 191887008), or obesity (concept IDs 433736 and 434005; SNOMED codes 414916001 and 238136002), or with a history of radiation therapy (concept IDs 4085340, 4311117, 4061844, 4029715; SNOMED codes 24803000, 85983004, 200861004, 108290001) or hormonal medications containing estrogen and/or progesterone, including oral medications and implants (concept IDs 21602445, 40254009, 21602514, 21603814, 19049228, 21602529, 1549080, 1551673, 1549254, 21602472, 21602446, 21602450, 21602515, 21602566, 21602473, 21602567, 21602488, 21602585, 1596779, 1586808, 21602524). In our case cohort, diagnoses and exposures to treatments were only considered for analysis if they occurred prior to melasma diagnosis.

Multivariate logistic regression was performed to calculate odds ratios and *P* values between melasma and

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each comorbidity or exposure to the treatments specified. Statistical significance was set at $P<.05$.

We identified 744 melasma cases (mean age, 55.20 years; 95.43% female; 12.10% Black) and 7440 controls with similar demographics (ie, age, sex, race/ethnicity) between groups (all $P>.05$ [Table 1]). Patients with a melasma diagnosis were more likely to have a pre-existing diagnosis of depression (OR, 1.87; 95% CI, 1.51-2.31 [$P<.001$]) or hypothyroidism (OR, 1.31; 95% CI, 1.04-1.65 [$P<.05$]), or a history of radiation therapy (OR, 19.08; 95% CI, 10.20-35.69 [$P<.001$]) and/or estrogen and/or progesterone therapy (OR, 2.01; 95% CI, 1.69-2.40 [$P<.001$]) prior to melasma diagnosis. A diagnosis of anxiety prior to melasma diagnosis trended toward an association with melasma ($P=.067$). Pre-existing alcohol dependence, obesity, and hyperthyroidism were not associated with melasma ($P=.98$, $P=.28$, and $P=.29$, respectively). A diagnosis of tobacco dependence was associated with a decreased melasma risk (OR, 0.53, 95% CI, 0.37-0.76)[$P<.001$])(Table 2).

Our study results suggest that pre-existing depression was a risk factor for subsequent melasma diagnosis. Depression may exacerbate stress, leading to increased activation of the hypothalamic-pituitary-adrenal axis as well as increased levels of cortisol and adrenocorticotropic hormone, which subsequently act on melanocytes to increase melanogenesis.[3] A retrospective study of 254 participants, including 127 with melasma, showed that increased melasma severity was associated with higher rates of depression ($P=.002$)[2]; however, the risk for melasma following a depression diagnosis has not been reported.

Our results also showed that hypothyroidism was associated with an increased risk for melasma. On a cellular level, hypothyroidism can cause systemic inflammation, potentailly leading to increased stress and melanogenesis via activation of the hypothalamic-pituitary-adrenal axis.[4] These findings are similar to a systematic review and meta-analysis reporting increased thyroid-stimulating hormone, anti–thyroid peroxidase, and antithyroglobulin antibody levels associated with increased melasma risk (mean difference between cases and controls, 0.33 [95% CI, 0.18-0.47]; pooled association, $P=.020$; mean difference between cases and controls, 0.28 [95% CI, 0.01-0.55], respectively).[5]

Patients in our cohort who had a history of radiation therapy were 19 times more likely to develop melasma, similar to findings of a survey-based study of 421 breast cancer survivors in which 336 (79.81%) reported hyperpigmentation in irradiated areas.[6] Patients in our cohort who had a history of estrogen and/or progesterone therapy were 2 times more likely to develop melasma, similar to a case-control study of 207 patients with melasma and 207 controls that showed combined oral contraceptives increased risk for melasma (OR, 1.23 [95% CI, 1.08-1.41; $P<.01$).[3]

Tobacco use is not a well-known protective factor against melasma. Prior studies have indicated that tobacco smoking activates melanocytes via the Wnt/β-Catenin pathway, leading to hyperpigmentation.[7] Although exposure to cigarette smoke decreases angiogenesis and would more likely lead to hyperpigmentation, nicotine exposure has been shown to increase angiogenesis, which could lead to increased blood flow and partially explain the protection against melasma demonstrated in our cohort.[8] Future studies are needed to explore this relationship.

TABLE 1. Demographic Characteristics of Patients With Melasma and Control Group Matched on Age, Sex, and Self-Reported Race

	Matched controls (n=7440)	Melasma cases (n=744)	*P* value
Mean (SD) age, y	55.20 (12.93)	55.20 (12.94)	0.9994
Sex at birth, n (%)			1
Male	340 (4.68)	34 (4.68)	
Female and other[a]	7100 (95.43)	710 (95.43)	
Self-reported race/ethnicity, n (%)			1
White	2770 (37.23)	277 (37.23)	
Black	900 (12.10)	90 (12.10)	
Hispanic	2630 (35.35)	263 (35.35)	
Asian	520 (6.99)	52 (6.99)	
Other	620 (8.33)	62 (8.33)	

[a] Count and percentage withdrawn due to All of Us data policy: https://www.researchallofus.org/wp-content/themes/research-hub-wordpress-theme/media/2020/05/AoU_Policy_Data_and_Statistics_Dissemination_508.pdf

TABLE 2. Potential Risk Factors Associated With Melasma

Risk factor	Match controls, n (%)(n=7440)	Melasma cases, n (%)(n=744)	OR (95% CI)	*P* value
Tobacco dependence	428 (5.75)	39 (5.24)	0.53 (0.37-0.76)	<.001
Alcohol dependence	229 (3.08)	29 (3.90)	1.01 (0.66-1.54)	.98
Depression	973 (13.08)	203 (27.28)	1.87 (1.51-2.31)	<.001
Anxiety	1416 (19.03)	227 (30.51)	1.20 (0.99-1.46)	.067
Hypothyroidism	653 (8.78)	113 (15.19)	1.31 (1.04-1.65)	<.05
Hyperthyroidism	≤20[a]	≤20[a]	2.03 (0.55-7.51)	.29
History of radiation therapy	≤20[a]	36 (4.84)	19.08 (10.20-35.69)	<.001
History of hormonal medications containing estrogen and/or progesterone	1329 (17.86)	263 (35.35)	2.01 (1.69-2.40)	<.001
Obesity	1654 (22.23)	238 (31.99)	1.11 (0.92-1.33)	.28

[a]Count and percentage withdrawn due to All of Us data policy: https://www.researchallofus.org/wp-content/themes/research-hub-wordpress-theme/media/2020/05/AoU_Policy_Data_and_Statistics_Dissemination_508.pdf

Limitations of our study include lack of information about melasma severity and information about prior melasma treatment in our cohort as well as possible misdiagnosis reported in the dataset.

Our results demonstrated that pre-existing depression and hypothyroidism as well as a history of radiation or estrogen and/or progesterone therapies are potential risk factors for melasma. Therefore, we recommend that patients with melasma be screened for depression and thyroid dysfunction, and patients undergoing radiation therapy or starting estrogen and/or progesterone therapy should be counseled on their increased risk for melasma. Future studies are needed to determine whether treatment of comorbidities such as hypothyroidism and depression improve melasma severity. The decreased risk for melasma associated with tobacco use also requires further investigation.

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