

DOES IRIS COLOR MATTER IN UVEAL MELANOMA?



Research confirms that light eyes are a risk factor.

BY CHARLES DEYOUNG, BA; ALEXANDRA R. ZALOGA, BA; ROLIKA BANSAL, MD; AND CAROL L. SHIELDS, MD

Uveal melanoma (UM) is an ocular malignancy that most often affects individuals of European descent.¹ This tumor can arise de novo or via transformation of a benign nevus,^{2,3} and epidemiological risk factors include older age, male gender, White race, fair skin color, blond hair, light iris color, sunlight exposure, and history of cutaneous melanoma.⁴⁻⁶ Thus, the incidence of UM varies substantially worldwide, with individuals of lighter skin tone and with lighter irises being more at risk.⁷ In addition to higher UM rates in White individuals, there is a notable increase in the incidence of UM from southern to northern Europe.^{1,7}

The most common iris color globally is brown, accounting for approximately 70% to 80% of the world population,⁸ but many northern European countries demonstrate a majority of individuals with blue eyes (Figure).⁸ Moreover, populations with lighter irises, such as those in Northern Europe, exhibit higher rates of UM compared with populations with darker irises, such as those in Africa and Asia.⁶ Incidence rates of UM are greater than or equal to eight cases per one million in northern Europe, western Europe, and Oceania; two to eight cases per one million in North America, eastern Europe, and southern Europe; and more than two cases per one million in South America, Asia, and Africa.⁷

IRIS COLOR AND RISK OF UVEAL MELANOMA

Iris pigmentation is determined by the ratio of pheomelanin to eumelanin in the iris, with a higher pheomelanin to eumelanin ratio found in individuals with lighter irises.⁹ In contrast, eumelanin, which is photoprotective, is found to be elevated in darker irises. Pheomelanin is phototoxic, which can induce DNA damage

in pigmented tissues via prooxidant activity. This damage can also be exacerbated by UV radiation exposure,⁹ a phenomenon that may be a potential factor in the pathogenesis of UM.¹⁰

A meta-analysis by Weis et al that included 10 case-controlled studies assessed UM risk and reported that individuals with lighter irises are at a 1.75-times greater risk of developing UM compared with those with darker irises.¹¹ Other studies have shown an odds ratio (OR) ranging from 1.3 to 3.1 for green irises and 1.1 to 3.4 for blue irises when compared with brown irises.^{1,12-19} While the increased likelihood of developing UM in individuals with lighter irises is well-documented, there are little data available about outcomes in darker irises.^{12,13}

In 2020, Houtzagers et al analyzed UM rates based on iris color in a Dutch population.¹ This study included 412 patients who were matched with controls based on eye color. Unsurprisingly, the results indicated that individuals of White/European ancestry with green/hazel iris color (OR = 3.64) and those with blue/gray iris color (OR = 1.38) had a significantly higher risk of developing UM compared with those with brown irises, which supports prior reports.¹¹ While this study demonstrated a strong correlation between iris color and UM risk, the differences in clinical features or outcomes based on eye color were not explored.

IRIS COLOR AND CLINICAL OUTCOMES OF UVEAL MELANOMA

Zaloga et al sought to further explore the clinical characteristics and outcomes of UM based on iris color.¹⁹ They analyzed 7,245 patients with UM who were treated at a single ocular oncology center and observed that most patients were White (n = 7,075; 98%) and had blue

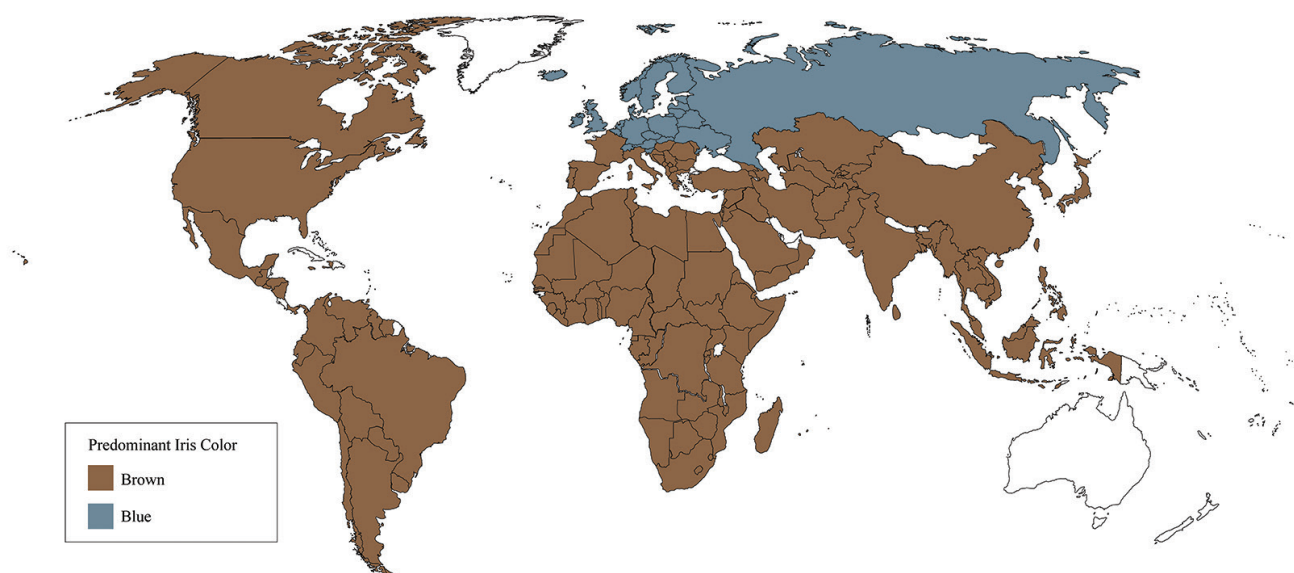


Figure. This world map shows the most common iris color by country.

Adapted with permission from: Eye color by country. World Population Review. Accessed June 14, 2024. worldpopulationreview.com/country-rankings/eye-color-by-country

irises (51%), followed by brown (29%) and green irises (20%).¹⁹ Initial treatment approaches included plaque radiotherapy (63%), enucleation (27%), partial lamellar sclerouvectomy (5.3%), and transpupillary thermotherapy (4.4%). The only difference in the initial treatment distribution based on iris color was a higher rate of primary enucleation in those with brown irises. No difference was noted in the presence of subretinal fluid or extraocular extension among the groups; however, patients with brown irises (brown irises vs blue irises vs green irises) were more likely to demonstrate Bruch membrane rupture (24% vs 19% vs 21%, $P < .01$) and subretinal and/or vitreous hemorrhage (12% vs 9% vs 9%, $P = .02$).

The researchers also found no difference in overall survival, globe salvage, or vision outcomes based on iris color.¹⁹ Although iris color did not consistently lead to differences in tumor features, outcomes, or death, independent risk factors for UM-related metastasis were tumor thickness (OR = 1.16) and subretinal and/or vitreous hemorrhage (OR = 1.52). The independent risk factors for UM-related death included patient age (OR = 1.01), tumor thickness (OR = 1.15), and subretinal and/or vitreous hemorrhage (OR = 1.59).¹⁹

A comparison of iris color revealed that green irises showed significantly greater risk of UM-related death than blue irises ($P = .02$), which was a bit surprising and unexplained. However, when comparing blue irises with brown irises, there was no significant difference in UM-related death. Despite similar proven risk factors for

metastasis and death (eg, tumor thickness, melanocytosis, heterochromia) between the blue and green iris groups, a difference in UM-related death persisted, suggesting eye color alone may play a role in UM-related outcomes. Therefore, iris color may be included as a risk factor for death, especially given that Sen et al found that individuals with lighter skin tones demonstrated greater UM tumor cytogenetic mutations that are known to be related to increased metastasis and death.²⁰

FUTURE DIRECTIONS

Iris color does appear to matter in UM. Individuals with lighter irises have higher rates of UM compared with those who have darker irises, which could influence screening, treatment, and overall outcomes of UM. Although Zaloga et al identified variations in tumor characteristics and mortality rates in UM patients based on iris color, further research is needed to better understand precisely how eye color affects the pathogenesis and disease course of UM. ■

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