The Association Between Host Susceptibility Factors and Uveal Melanoma

A Meta-analysis

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Objective: To conduct a meta-analysis, using observational studies, to examine the association between host susceptibility factors and uveal melanoma.

Methods: A review of 132 published reports on risk factors for uveal melanoma revealed 10 case-control studies that provided enough information to calculate odds ratios (ORs) and standard errors for host susceptibility factors. Data from these studies were extracted and categorized. Summary statistics were calculated for all risk factors reported by at least 4 independent studies.

Results: Summary statistics using meta-analysis are presented as ORs and their 95% confidence intervals (CIs). Statistically significant risk factors include light eye color (OR, 1.75 [95% CI, 1.31-2.34]), using 10 studies (1732 cases); fair skin color (OR, 1.80 [95% CI, 1.31-2.47]), using 5 studies (586 cases); and ability to tan (OR, 1.64 [95% CI, 1.29-2.09]), using 6 studies (1021 cases). Blond or red hair color, using 7 studies (1012 cases), was not a statistically significant independent risk factor (OR, 1.02 [95% CI, 0.82-1.26]).

Conclusion: This meta-analysis yielded strong evidence associating the host susceptibility factors of iris color, skin color, and ability to tan with uveal melanoma.

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HOROIDAL MELANOMA IS the most common primary intraocular malignancy in white individuals in the United States and Europe.1 The choroid is the second most common site for melanoma after cutaneous melanoma.1 Cutaneous melanoma has an annual incidence of 12.2 to 48.1 persons per 100,000,2 whereas uveal melanoma has an annual incidence of 6 persons per million.3 Melanomas arise from neural crest–derived dendritic melanocytes found in the eye, skin, mucosal epithelium, and leptomeninges.4,5 Moreover, it has been suggested that both uveal and cutaneous melanoma can arise from nevi.6,8 Given these findings, many health care professionals and researchers have postulated an association between melanomas that arise in different tissues. The association between uveal and cutaneous melanoma has been well summarized,9 and results are somewhat inconsistent.10-12 From the cutaneous melanoma literature, it is well established that host susceptibility factors increase the risk of developing certain subtypes of melanoma. These phenotypic characteristics include blond or red hair, fair skin color, light eye color, skin freckling, presence of nevi, and sensitivity to sunlight.13-19 It has been postulated that these phenotypic associations are related to an altered response to UV light.20 Furthermore, the risk of cutaneous melanoma increases with the number and pathologic severity of cutaneous nevi.21 Not surprisingly, ethnicity is also implicated. Compared with black individuals in the United States, the incidence rate of cutaneous melanoma is 17.2 times higher in non-Hispanic white men and 2.8 times higher in Hispanic men.22 Over the past 2 decades, multiple observational studies, consisting primarily of case-control studies, have attempted to characterize the association between host susceptibility or UV exposure factors and melanoma of the uvea.23-41 Except for eye color, the relationship of most other factors has been inconsistent and oftentimes conflicting.

To help resolve these prior inconsistencies and to estimate the magnitude of association, we performed a meta-analysis of observational studies to examine host susceptibility factors and uveal melanoma.

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Methods

LITERATURE SEARCH AND ELIGIBILITY CRITERIA
Three researchers (E.W., C.P.S., M.L.) independently searched the literature and collec-
tively participated in the study selection. MEDLINE (with both OVID and PubMed), EMBASE, MD Consult, and the Web of Science were searched using the following keywords to identify articles examining all risk factors for uveal melanoma: UV, sun, sunlight, uveal melanoma, eye cancer, eye melanoma, uveal melanoma, nevus, and risk factor. MEDLINE was searched from 1966 through May 2003, whereas EMBASE was searched from 1988 through May 2003. Hand-searching bibliographies for relevant articles was carried out with all identified articles. An attempt to contact all leading authors via email was made in an effort to find unpublished data.

Inclusion and exclusion criteria were kept broad to maximize sample size. This meta-analysis included original observational studies that examined risk factors for uveal melanoma. Studies were excluded if they did not supply enough information from which to calculate odds ratios (ORs) or standard errors.

DATA EXTRACTION AND OUTCOME DEFINITION

For each trial, the 3 researchers (E.W., C.P.S., M.L.) independently gathered the data into host susceptibility categories including: (1) eye color, (2) hair color, (3) skin color, and (4) ability to tan. The ORs and upper 95% confidence intervals (CIs), to calculate the standard error, were extracted from all studies. When not available, the OR and/or standard error were calculated with the raw data or from P values provided in the articles. Disagreements among us were resolved through consensus. To develop informative summary statistics that allowed assessment of publication bias and heterogeneity, at least 4 independent ORs were required for each risk factor before calculating summary ORs. Independent ORs were ensured by only using 1 OR per study in each analysis and only using 1 effect estimate per analysis, if different studies used the same participants. No separate studies in this analysis used the same subjects.

Five of the 6 studies examining ability to suntan either specifically assessed response to sun after multiple previous exposures39 or general ability to tan.28,32,36,37 One study19 assessed ability to tan with 2 separate variables, response to bright sun at the first summer exposure and ability to tan after repeat exposures. The latter variable was used in the meta-analysis to be consistent with the other 5 ORs assessing response to repeat sun exposure.

Of the 10 studies analyzing eye color, 6 studies reported blue eye color as the lightest eye color13,14,16,17,20,24,25 and 3 studies distinguished between blue and gray eye color.11,12,27 Because many health care professionals do not distinguish gray and blue iris color, no research was found that compared the pigment between these 2 eye colors, and the majority of the studies did not separate these 2 colors, gray and blue eye color were combined as a single “light” eye color category for this analysis.

Of the 7 studies analyzing hair color, 3 studies differentiated red and blond hair,16,24,27 2 studies combined red and blond hair,13,16 and 1 study only differentiated light and dark hair color.20 Previous research has shown that unlike mice coat color, which is highly correlated with both hair melanin biochemical characteristics and melanin type, the correlation in human hair is not as strong.42 Most notably, red hair color follicular melanosomes vary from being composed of primarily pheomelanosomes, eumelanosomes, or a mosaic,43 and blond hair color hair follicles are primarily composed of eumelanosomes.42 Because of the overlap in the melanosome characteristics between blond and red hair, and because most studies did not differentiate these 2 hair colors, red and blond hair color were combined into a single red-blond hair color category.

STATISTICAL ANALYSIS

All analyses used Stata version 8 (StataCorp, College Station, Tex). Summary statistics were calculated using inverse variance weighting and presented in forest plots. If provided by the original studies, adjusted ORs were preferred over crude estimates. The ORs derived from population-based controls were preferred over hospital-based or sibling controls. The ORs comparing the category hypothesized to be the most susceptible to the referent were used. All meta-analyses were assessed for heterogeneity as a preliminary test. A random-effects model was used if the test of heterogeneity was significant (P < .05); otherwise a fixed-effects model was used. An OR with a P value < .05 was considered statistically significant. Publication bias was assessed with the Begg funnel plot and Egger weighted regression for funnel plot asymmetry.44 Publication bias was considered significant if both the Egger test was significant (P < .05) and the Begg plot suggested bias.

Meta-regression was conducted on all summary statistics to further explore possible reasons for heterogeneity.45 The outcome was defined as the ORs. The predictors were defined as either the latitude of the study site, the anatomical location of tumors included in the studies (conjunctival, iris, ciliary body, choroid), or the type of controls used in the study. Control type was regressed because we felt that the use of hospital-based controls with cataracts may result in biased summary statistics because of the association between UV exposure and the development of cataract.46 Similarly, retinal detachment controls were also thought to likely bias the results since retinal detachment has been associated with myopia47 and myopia is associated with corrective lens use, a factor possibly related to UV exposure. Finally, analyses that used these potentially biased hospital controls were rerun without these studies to determine if they affected the overall summary statistic.

RESULTS

The initial search attempted to find all studies on host factors and UV exposure. Following a thorough literature search, 132 studies were identified. Of these, 17 case-control studies and 2 cohort studies satisfied all inclusion criteria (Figure 1).23–41 Of these, 10 case-control studies assessed host susceptibility factors.23–29,29,30,32,36,37,39 The remaining 9 studies examined other risk factors, such as UV light exposure.
HAIR COLOR

Seven studies (1012 cases) provided an overall summary OR of 1.02 (95% CI, 0.82-1.26) \((P = .83)\) when comparing individuals who were classified as having blond and/or red hair compared with the reference group of those with dark hair (Figure 3). The test of heterogeneity \((Q_s = 10.29; P = .11)\) was not significant, allowing the use of a fixed-effects model. Thus, based on the data, blond or red hair was not a statistically significant risk factor for the development of uveal melanoma.

SKIN COLOR

Five studies (586 cases) provided a summary OR of 1.80 (95% CI, 1.31-2.47) \((P < .001)\) (Figure 4). There was no significant heterogeneity between the individual study ORs \((Q_s = 3.35; P = .50)\), allowing a fixed-effects model to be used. Thus, based on the data, fair skin color was a statistically significant risk factor for the development of uveal melanoma.

ABILITY TO TAN

Six studies (1021 cases) provided information on the association of the patient’s ability to tan and odds of developing melanoma. The overall summary OR was 1.64 (95% CI, 1.29-2.09) corresponding to a \(P\) value < .001 using a fixed-effects model (Figure 5). No significant heterogeneity was found \((Q_s = 4.17; P = .53)\). Thus, based on the data, ability to tan was a statistically significant risk factor for the development of uveal melanoma.

No evidence for publication bias was noted for eye color \((P = .91)\) (Figure 6), hair color \((P = .60)\), and ability to tan \((P = .50)\). There was a mild, yet insignificant, suggestion of publication bias in the skin-color Begg funnel plot \((P = .07)\) (Figure 7). Funnel plots for hair color and tanning ability were conducted but are not presented.

Three meta-regressions were conducted on each of the risk factors analyzed. Meta-regressing the host susceptibility factor on study-site geographic latitude as a continuous variable, tumor location (conjunctival, ciliary body, and choroidal), and control type (population and hospital based)
did not yield any significant results. Therefore, heterogeneity in the individual meta-analyses cannot be attributed to any of these variables. Geographic latitudes for 2 studies were not included because they were multicentric studies. One study defined their cases as “ocular” melanoma in the text; personal communication with the authors specified that only uveal tumors were included. When both studies using the potentially biased hospital controls were eliminated from the analysis, no changes in the significance of any of the ORs were noted.

**COMMENT**

In contrast to the consistent reports implicating “fair phenotype” as a risk factor for cutaneous melanoma, studies examining the association between host susceptibility factors and uveal melanoma have reported inconsistent results. This meta-analysis found evidence associating light eye color, light skin color, and ability to tan with the development of uveal melanoma. (Table).

In this analysis, there is strong evidence associating lighter (blue or gray) eye color with an increased risk for uveal melanoma. Lighter eye color is associated with a 75% increased odds of developing uveal melanoma compared with darker eyes. There are 2 likely explanations for this association. First, eyes with lighter irides generally have less melanin in their choroid and retinal pigment epithelium and thus may provide less protection from UV light. Second, lighter irides may be a predisposed phenotype unrelated to the amount of melanin. Unfortunately, this study was not able to distinguish between these 2 hypotheses.

It is well established that the incidence of uveal melanoma in darkly pigmented people is much lower than in lightly pigmented people. In the United States, white people have 8 times the risk of noncutaneous melanoma compared with black people. This study showed that even among white people, a lighter skin color is associated with greater odds of developing uveal melanoma. Light-skinned individuals have an 80% increase in the odds of developing uveal melanoma compared with people with dark skin. It is possible that white individuals with lighter skin have less or different types of melanin protecting their eyes, leading to increased risk of melanoma. Fair skin may also be a surrogate marker for a predisposed genotype unrelated to the amount and type of melanin.

This meta-analysis also found a statistically significant association between ability to tan and risk for uveal melanoma, reporting a 64% increase in the odds of developing uveal melanoma in people who sunburn easily compared with those who tan well. This relationship is likely similar to the theorized relationship between light skin color and uveal melanoma aforementioned.

An independent association between light hair color and melanoma was not found in this meta-analysis. This is a surprising result given that all other results point to the existence of a fair-phenotype predisposition to uveal melanoma. One possible explanation is that hair color is not a good surrogate marker for follicular melanin characteristics. Castanet and Ortonne reviewed the literature and concluded that follicular melanocytes and epidermal melanocytes...
cytes have several crucial differences, including a lack of response to UV light in the follicular melanocyte. Furthermore, human hair color is not highly correlated with either hair melanin biochemical characteristics or melanin types. It is also possible that some of the studies nondifferentially misclassified hair color, biasing the results toward the null. Hair color can gradually evolve over time; thus, hair color in adulthood might not be as strong a factor as childhood hair color. Of the 7 studies reporting on hair color, 4 asked about hair color at age 20 years or in the teenage years, 28,36,37,39 2 asked about adult hair color,25,32 and 1 was not specific.29 Additionally, artificial coloring of hair with dyes will alter the apparent color.

This study has several weaknesses and strengths. One weakness is that this meta-analysis combines data from observational studies. The quality of the results from this meta-analysis depends on the quality of each individual study that was included in the analysis. Observational studies are prone to biases and confounding factors when controls do not represent the base populations. This study examined the possibility of biased controls by meta-regressing on control type. Finding no significant biases suggests that the studies using potentially flawed controls23,26 did not significantly alter the summary OR. Furthermore, all meta-analyses were recalculated without these 2 potentially biased studies, and the resulting summary ORs varied by less than 5% without any change in significance.

Another weakness was the significant heterogeneity in meta-analyzing eye color. Therefore, a random-effects model was used, leading to a more conservative analysis. Despite trying to control for the geographic latitude of research center sites, the anatomical location of tumors, and the type of control population used, the significant heterogeneity for eye color was not explained. There are many possible explanations for this heterogeneity, including genetic differences between study populations likely still present despite controlling for study-site latitude.

This study was limited with regards to tumor location. The available data predominantly focused on uveal melanoma, which is far more common than conjunctival melanoma. 49 While most studies focused on uveal melanoma, Pane and Hirst36 combined data on both uveal and conjunctival melanoma. Of 313 melanoma cases in the Pane and Hirst article, 35, or 12%, were conjunctival. It would
be ideal to separately analyze uveal and conjunctival melanoma because there may be real differences between the 2. However, it was not possible to separate uveal and conjunctival melanoma using the published data, so the combined OR was used in meta-analysis to maximize total sample size. The 35 conjunctival melanoma cases represent a small portion of those analyzed: 1732 cases for eye color, 586 for skin color, 1021 for ability to tan, and 1012 for hair color. As expected by the small number of conjunctival melanoma cases, meta-regression on tumor size gave no evidence to suggest that inclusion of the Pane and Hirst data biased the results. Additionally, exclusion of the Pane and Hirst data in every individual meta-analysis did not alter the significance of the summary ORs.

Regarding the strengths of this meta-analysis, the combination of multiple studies afforded the opportunity to achieve the statistical power required for stable results, despite the rarity of uveal melanoma. Further, this meta-analysis combined studies examining white populations from around the world, allowing the results to be more generalized. Additionally, the included studies were critically examined to accurately compile comparable variables, and multiple attempts were made to minimize and explain any heterogeneity in summary statistics.

Uveal melanoma is the most common noncutaneous melanoma in the United States. Despite advances in treatment with enucleation, brachytherapy, charged particle irradiation, thermotherapy, and local eye wall resection, the mortality rate has not changed significantly. As such, it is important to elucidate the etiology of this lethal disease to help generate the knowledge necessary to develop preventive methods. This study’s findings associating host factors with uveal melanoma suggest that genetics likely play an important role in this disease. However, if this were the only etiological factor, stronger associations would be expected. This level of association points to the possibility of both polygenic and environmental factors playing an important role.

Because of the rarity of uveal melanoma, the identified risk factors will not likely change our current screening routine for detection of uveal melanoma. However, the highly significant results do help us in further understanding the etiology of uveal melanoma and are helpful in directing further research.

Meta-analysis is an ideal method for studying the epidemiologic risk factors of rare diseases such as uveal melanoma. This study found strong, reliable, and consistent associations between melanoma and the fair phenotype of light eye color, fair skin color, and propensity to burn, but not light hair color (Table). Further work is required to resolve the relative contributions of the genetic and environmental factors involved in the development of this complex disease.

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