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Disparities in Uveal Melanoma: Patient Characteristics

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Abstract

Uveal melanoma is the most common intraocular malignancy in adults. Despite excellent rates of local control, half of all patients with uveal melanoma ultimately go on to develop fatal metastatic disease. This review focuses on disparities and differences in the underlying characteristics of the patients, and how these patient characteristics impact the development of metastasis and subsequent patient survival. Specifically, we detail disparities in epidemiology and risk factors as they relate to the development of primary uveal melanoma, to the development of metastasis, and to patient survival following metastasis.

Keywords

Disparities; epidemiology; metastasis; ocular tumors; ophthalmology; prognosis; risk factors; survival; uveal melanoma

INTRODUCTION

Uveal melanoma is the most common intraocular tumor in adults.[1–3] The annual incidence of uveal melanoma has been stably estimated at 6–7 cases per million over the past few decades.[1–3] Though there have been advances in eye-preserving approaches for local tumor control, the five-year survival rate has remained stable between 72–84%.[4–7] Despite effective local control with radioactive plaque brachytherapy or enucleation, as many as 50% of patients develop metastases, sometimes more than 15 years following the initial diagnosis of uveal melanoma.[3,8,9] Tumors metastasize hematogenously and involve the liver as much as 96% of the time.[3] Mounting evidence suggests that hepatic micrometastases are already present at the time of initial diagnosis. However, by the time macrometastases are

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identifiable by currently available imaging modalities, uveal melanoma metastases are uniformly fatal, with average survival less than six months after clinical diagnosis of metastatic disease.[3,5,6,9]

This review focuses on disparities in the epidemiology, risk factors, morbidity, and mortality associated with uveal melanoma. More specifically, we detail the mounting evidence supporting the significant impact of patient characteristics on the risk of uveal melanoma and disease-related morbidity.

PATIENT CHARACTERISTICS

Age

Uveal melanoma is not only increasingly common with age (peaking in the 80s), but also carries a worse prognosis in older individuals.[6,7,10–12] Damato and colleagues conducted a prospective study of 3,072 choroidal melanoma patients in Liverpool, England. They found that choroidal melanomas diagnosed in younger patients tended to have better prognostic features, including smaller size, less common extraocular extension or ciliary body involvement, maintenance of two copies of both chromosome 3 and 8, and lower TNM stages. Notably, the lifespans of patients who died of choroidal melanoma metastasis did not correlate with risk factors for developing metastasis. In their discussion of their findings, Damato and colleagues directly address the possibility that their age-related findings may, in fact, reflect diagnostic delays. These diagnostic delays may allow for the accumulation of malignant features and increased metastatic potential, suggesting a role for uveal melanoma management in the differential survival amongst uveal melanoma patients.[13] Additionally, Rietschel et al. conducted a retrospective analysis investigating factors that correlated with survival in 119 stage IV patients treated at a single referral center. Their findings showed that age <60 correlated significantly with prolonged survival (>4 years) in patients with metastatic uveal melanoma.[14] Consistent with the observed inverse relationship between age and survival, increased age is associated with class 2 (higher-metastatic-risk) tumors.[15,16]

Gender

Gender has been a debated topic with respect to uveal melanoma. There is currently mounting evidence in support of an increased age-adjusted incidence of uveal melanoma in men.[6,17] Bishop and colleagues conducted a retrospective analysis of the Surveillance, Epidemiology and End Result (SEER) database, including 7,069 cases of ocular melanoma from 1988 to 2010, and found a significantly lower age-adjusted incidence of ocular melanoma in women than in men.[6] Singh and associates used the SEER database to look at all patients with uveal melanoma between 1973–2008. They found that, among the 4,070 patients included in their study, the US age-adjusted incidence is again significantly higher in men than women (5.8% vs. 4.4%).[4] Similarly, McLaughlin and colleagues conducted a retrospective descriptive analysis of the North American Association of Central Cancer Registries, which included 4,885 ocular melanomas from 1996–2000. Again, they found ocular melanoma to be significantly more common in men than women, with 6.8 cases per million in men versus 5.3 cases per million in women.[17]

In addition to gender differences in incidence, Damato et al. describe gender differences in intraocular location of uveal melanoma tumors. Their findings support a significant trend towards larger and more posterior tumors in men compared to women (largest basal diameter 12.2 mm vs. 11.9 mm and thickness 4.4 mm vs. 3.8 mm). Notably, women had greater involvement of the ciliary body (62% of ciliary body tumors found in women vs. 38% in men), which is associated with a worse prognosis. Interestingly, women also were more likely to have iris tumors (58.9% found in women vs. 41.1% in men), which is associated with better prognosis.[18] Zloto et al. carried out a retrospective analysis of 723 uveal melanoma patients at a single referral center in Jerusalem and evaluated for clinical and prognostic differences between genders. Although their findings did not reveal statistically significant gender differences in age at diagnosis, tumor size, intraocular location, or recurrence, they did support a statistically significant increase in the likelihood of developing metastases. In this study, men were found to have an increased rate of metastasis as well as shorter time interval between initial diagnosis and metastasis detection (one year following diagnosis: 26% of men vs. 13% of women and five years following diagnosis: 84% of men vs. 50% of women). Furthermore, their findings supported a melanoma-related mortality rate that was nearly twice as high in men in the 10 years following initial diagnosis.[19] Such gender differences in survival rates between men and women were corroborated by Rietschel et al.'s investigation into factors correlated with prolonged survival (>4 years) of patients with metastatic uveal melanoma. The authors found that female gender was independently correlated with prolonged survival in their patient cohort.[14] Notably, several studies have failed to demonstrate statistically significant gender differences in survival rates of patients diagnosed with uveal melanoma.[10,12] In fact, one study by Caminal et al., which evaluated five-year survival of 155 consecutive patients at a single center in Barcelona, Spain, actually showed women to have a 14% reduction in survival compared to men (92.5 % vs. 78.4%).[20]

Investigators have debated the effect of hormones and reproductive history on women's risk of uveal melanoma. Holly et al. conducted a case-control study of 186 women with uveal melanoma and 423 controls. Their findings indicated a statistically significant impact of parity on risk of uveal melanoma. Interestingly, they found no such impact of exogenous hormones such as oral contraceptives or hormone replacement therapy.[21] Notably, Hartge et al. conducted a case-control study of 238 patients diagnosed with intraocular melanoma and 223 controls; they found that previous pregnancy or use of replacement hormones *increased* risk of intraocular melanoma, but oral contraceptives did not have the same impact.[22] Egan and colleagues conducted a prospective study to investigate the effect of childbearing on survival of 1,818 patients with choroidal melanoma. They found that both female gender and history of having given birth were *protective* factors with respect to death secondary to metastasis, most notably in the early years (<3y) after diagnosis.[23] Specifically, they found that nulliparous women and men were at comparably *increased* risk of metastasis and death relative to parous women. Of interest, the number of children birthed had a dose-related protective impact, as did the number of years since first giving birth.[23] Schmidt-Pokrzywniak et al. investigated the impact of childbearing on five-year survival in a cohort of 459 women in Germany. In their study, the investigators found women to have lower five-year probability of death secondary to uveal melanoma (10.9% vs. 6.2%), even after

accounting for the impact of prognostic factors such as ciliary body involvement and tumor basal diameter. In addition, they found a reduced hazard ratio for women with at least one child compared to nulliparous women. Notably, they did not find that the number of children had an additional effect on the hazard ratio.[24] Both Egan and Schmidt-Pokrzywniak hypothesize that parous women may, in fact, benefit from an immunizing effect secondary to exposure to fetal antigens during pregnancy, which prove beneficial in the immune response to uveal melanoma. This expands on what Janerich refers to as the "fetal antigen hypothesis."[23–25] The "fetal antigen hypothesis" was first put forth as a potential explanation for the "crossover" phenomenon in which parous women are paradoxically at increased risk of breast cancer soon after giving birth, but are, in the aggregate, at lower risk of developing the disease in the long term, presumably due to increased immune surveillance in the wake of fetal antigen exposure during pregnancy.[25]

Race

It is well appreciated that race has a significant impact on the incidence of uveal melanoma. Margo and colleagues investigated the incidence of uveal melanoma in 873 histologically confirmed cases of uveal melanoma amongst various races and ethnicities, utilizing the Florida Cancer Data System. They found that White men and women had 72 times and 22 times the incidence of uveal melanoma compared to their Black counterparts, respectively. Overall, the relative risks of uveal melanoma in Black and Hispanic individuals compared with non-Hispanic White individuals were 0.03 and 0.36, respectively.[26] Similarly, Neugut et al. utilized the SEER database to analyze differences in the incidence of ocular melanoma amongst White and Black individuals. Analyzing 1,587 cases, they found a relative risk of 7.4 and 53 for White men and women as compared to their Black counterparts.[27] Interestingly, similar ethnic trends in relative risk were found for cutaneous, but not visceral melanomas. Hu et al. conducted a cross-sectional study, also utilizing the SEER database to study racial and ethnic differences in the incidence and relative risk of uveal melanoma. They found the annual age-adjusted incidence to be 19-fold greater in non-Hispanic Whites than in Blacks, with a greater difference seen in men than in women (1:42 vs. 1:12). The ratio of uveal melanoma among Blacks, Hispanics, and non-Hispanic Whites was 1:5:19. Hu et al. also found a low relative risk of uveal melanoma among Asians, which did not differ significantly from that seen in Blacks (0.38 in Asians vs. 0.31 in Blacks). The authors further explored the low incidence of uveal melanoma in "Mongolian-type" Asians, referring here to Chinese, Korean, and Japanese, utilizing a melanoma: retinoblastoma ratio in New York versus Shanghai and the presumed equal incidence of retinoblastoma across races. They found an ~37-fold higher incidence of uveal melanoma in New York compared to Shanghai.[28] This evidence suggests a markedly reduced risk of uveal melanoma in East Asians as well as Blacks.

Researchers have also explored the relationship between iris color, a phenotype correlated with race and ethnicity, and uveal melanoma. As seen with other eye conditions (such as senile cataracts), there is a relationship between iris color and risk of ocular disease.[29] Weis et al. conducted a meta-analysis, ultimately focusing on 10 case-control studies, which addressed "host susceptibility factors" with respect to uveal melanoma.[30] They found a statistically significant relationship between light iris color and higher risk of uveal

melanoma relative to brown irides, with a collective odds ratio of 1.75. The authors suggested two hypotheses for this relationship. One possible explanation the authors proposed is that increased uveal melanin may have a protective effect. Alternatively, they suggested the possibility of a protective mechanism unrelated to the presence of increased melanin in darker irides, in which case light iris color may simply serve as a surrogate for those ethnicities with a higher risk of uveal melanoma.[30] Additionally, the authors detected a statistically significant relationship between skin color and risk of uveal melanoma. Consistent with previous studies demonstrating a protective effect in darker-skinned ethnicities, the authors showed a protective effect of darker skin tones within a single race, with a cumulative odds ratio of 1.80.[30] Vajdic et al. conducted a large-scale, case-control study analyzing the relationship between several host-susceptibility factors and ocular melanoma at various anatomic locations. They found that light eye color was a statistically significant risk factor for both choroidal and ciliary body melanomas. Interestingly, out of 25 iris melanomas, not a single case was identified in a brown-eyed individual. Notably, there was a trend toward *increased* risk for conjunctival melanoma among brown-eyed individuals.[31] Some researchers speculate that the reduced incidence of uveal melanoma among races and ethnicities with darker skin pigmentation could reflect pigmentation's protective effect, as darker irides have higher total melanin by weight and transmit less UV light.[26–28,32,33] This race-based trend is also seen in cutaneous melanoma.[28] Researchers also acknowledge traditional correlations between race and/or ethnicity and socioeconomic conditions, which themselves may impact uveal melanoma epidemiology.[26]

EXPOSURES

UV Exposure

Although there is no shortage of literature supporting a role for UV exposure in cutaneous melanoma, the role of UV exposure in uveal melanoma remains controversial.[34,35] Racial and ethnic disparities in uveal melanoma incidence, as well as those intra-racial differences in incidence associated with differences in iris coloration, suggest a possible protective role of increased pigmentation. This protective role of increased pigmentation indirectly supports a possible causative role played by UV exposure. Importantly, such conclusions are predicated on the underlying assumption that lighter irides transmit more UV light to the posterior segment of the eye.

Exposure to UV irradiation, whether environmental or occupational, is inevitable but may vary with geography, use of protective garb, and occupation. The most "photocarcinogenic" form of UV irradiation is UV-B light. Importantly, only 2–17% of environmental UV irradiation is incident on the tissues of the eye. Even less irradiation is incident upon the choroid after filtering effects of the cornea, lens, and retinal pigment epithelium.[36] Since the aging lens filters greater and greater fractions of incident UV-B light, there may be greater exposure of the posterior pole of the eye of children to UV irradiation.[37] Of course, older patients are also more likely to have had their crystalline (UV-filtering) lenses removed via cataract surgery, and it is unclear the degree to which newer yellow-tinted, blue-light-filtering intraocular lens implants reduce UV light incident on the choroid, and the impact that this may have on choroidal melanoma formation. Over a nine-year period, Li et al.

investigated the pattern of estimated site of uveal melanoma tumor origin as it relates to the degree of UV irradiation exposure in 448 cases of uveal melanoma across the state of Massachusetts. They found that the greatest number of tumors originated in the macula, which is presumably the site of greatest UV exposure.[38] Schwartz et al. conducted a similar investigation comparing tumor location and estimated UV radiation exposure. Their results, based on 93 patients, did not support a relationship between tumor location and UV exposure.[39]

Much of the literature on the relationship between UV exposure and uveal melanoma is limited to often-conflicting case-control studies.[40–47] Shah et al. conducted a meta-analysis in which they reviewed 133 articles, ultimately focusing on 12 case-control studies, to investigate the relationship between UV exposure and uveal melanoma.[48] Upon reviewing five articles documenting 1,137 patients, they concluded that exposure to artificial UV irradiation due to welding had an odds ratio of 2.05. However, they found that occupational and geographic exposure to natural UV radiation did not have a statistically significant relationship to uveal melanoma.[48]

Given the inverse relationship between more darkly complected races and the incidence of melanoma, as well as the fact that more heavily pigmented complexions also correlate with more heavily pigmented choroids, Harbour et al. investigated the relationship between choroidal pigmentation among White individuals with light irides and the risk of uveal melanoma.[49] Conducting a cross-sectional study of 65 consecutive patients with uveal melanoma, they found that, relative to controls with similarly lightly colored irides, uveal melanoma patients had significantly more heavily pigmented choroids. This finding corresponded histologically with increased choroidal melanocytes in uveal melanoma patients. Interestingly, in the subset of patients with light-colored irides, increased choroidal pigmentation appears to increase the risk of uveal melanoma, rather than convey protection. This is particularly surprising in light of the comparatively low incidence of uveal melanoma among more darkly complected races, despite their having more heavily pigmented choroids. Harbour et al. suggest three possible explanations for the unexpected relationship between increased choroidal pigmentation and the risk of uveal melanoma: (1) The result of a risk-benefit balance between the protective characteristics of melanin and its previously described pro-oxidant effects, which may potentiate the deleterious effects of UV exposure. Evidence supporting the relative risks of higher density melanin within melanocytes includes the presence of increased reactive oxygen species proportional to greater amounts of melanin and the presence of greater amounts of UV-related DNA damage within more melanin-rich melanocytes. Harbour et al. further hypothesize that the relative risk reduction seen in more darkly complected races, known to have even more heavily pigmented choroids, may reflect a shift in the risk-benefit balance, such that the protective influence of melanin outweighs its deleterious effects. (2) More heavily pigmented choroids may, in fact, represent an effect resulting from chronic exposure to higher levels of UV exposure. However, they suggest that this is less likely given the lack of iris hyperpigmentation in response to UV exposure. (3) This observation may simply reflect the higher probability of chance development of a uveal melanoma as the result of more choroidal melanocytes available to undergo malignant transformation. This final theory is undermined by the comparatively low incidence of uveal melanoma in more darkly complected races.

It is well documented that UV irradiation can result in DNA damage. However, the mutagenic role played by UV exposure has become more nuanced in light of the possible protective roles it may play. In addition to its mutagenic effects, UV exposure is critical for cutaneous vitamin D3 production. Vitamin D3 is subsequently acted upon by the liver and kidney to produce 1, 25 dihydroxyvitamin D3. This, in turn, has been shown to play a beneficial role in preventing tumorigenesis by reducing cell growth, angiogenesis, and tumor invasion, as well as encouraging cell differentiation and apoptosis.[50,51] Notably, vitamin D has been demonstrated to be beneficial in various cancers, including colon, prostate, and breast cancers.[52–54]

Yu et al. have further explored the potentially multi-faceted role of UV exposure in uveal melanoma by investigating the relationship between latitude and ocular melanoma.[55] They utilized the SEER database to analyze 2,142 non-Hispanic White patients and the incidence of ocular melanoma in light-exposed tissues (eyelids, conjunctiva) and light-protected (uveal tract) tissues, as it relates to geographic latitude as a substitute for environmental UV exposure. Unsurprisingly, tumors in light-exposed tissues occurred with increased frequency as latitude decreased (and UV exposure increased). In contrast, uveal melanoma tumors in light-protected tissues of the uveal tract were more frequent with increasing latitude (and decreasing sun exposure). They hypothesize that these findings suggest a double-edge role for UV exposure in ocular melanoma: UV exposure appears to be deleterious with respect to tumors in tissues on which it is directly incident and to be protective with respect to tumors in light-protected tissues. Yu and colleagues suggest that the indirect, protective role of UV exposure may reflect the protective effects of vitamin D.[55] However, we suggest that the apparent relationship between increased latitude and increased risk of uveal melanoma may be confounded by the greater presence of ethnicities at higher risk in these higher latitudes (see previous section on “Race”).

Occupational Exposures

The study of environmental exposures related to uveal melanoma is limited by the relative rarity of the disease, which inhibits the ability to conduct cohort studies investigating the impact of a specific exposure on the incidence of melanoma. Accordingly, most of the literature related to exposures and uveal melanoma is comprised of case-control studies, which are appropriate to study diseases with low prevalences. Case-control studies have highlighted the possible relationship between uveal melanoma and occupational exposures such as those experienced by workers in occupations ranging from arc welders to cooks to administrators, with arc welders having the strongest association.[44,56,57]

OTHER CONDITIONS

Though most cases of uveal melanomas are sporadic, the increased incidence of this rare disease in select families provides strong evidence for a familial form of uveal melanoma. Silcock described the first case of familial uveal melanoma in 1892. Since his initial description of a mother and her two affected daughters, later work by Jay et al. identified a total of eight affected individuals across four generations.[58,59] Singh and colleagues further characterized the familial form of uveal melanoma through their analysis of the family

histories of 4,500 uveal melanoma patients at a single referral hospital. They found that as many as 56 patients had a family history positive for uveal melanoma, leading to the estimate that familial uveal melanoma accounts for 0.6% of uveal melanoma cases.[58] Of these 56 patients, 63% had a first-degree relative who had been diagnosed with uveal melanoma. Generally, familial involvement was limited to a total of two or three affected family members. Notably, amongst patients with a positive family history of uveal melanoma, there was a four-fold increased risk of additional primary malignancy as compared to the general public. The most common additional primary malignancies were breast, prostate, cutaneous melanoma, and cervical cancers. Observations such as these suggested not only a familial susceptibility to uveal melanoma but also heritable increased risk of other cancers.[60]

Recent discoveries now suggest that much of the familial susceptibility to uveal melanoma likely reflects the *BAP1* hereditary cancer predisposition syndrome. This syndrome is the result of germline mutations in the *BAP1* gene, a tumor suppressor gene found on chromosome 3. This syndrome has been linked to a predisposition to developing uveal melanoma in addition to cutaneous melanoma, malignant mesothelioma, renal cell carcinoma, and other malignancies.[61] *BAP1* hereditary cancer predisposition syndrome was first described in 2011 by Testa et al. in their investigation of two families with a high incidence of malignant mesothelioma and uveal melanoma.[62] *BAP1* (*BRCA1*-associated protein 1) encodes a nuclear deubiquitinase whose roles in cellular processes are numerous, ranging from cell differentiation to DNA repair, but whose exact role in carcinogenesis remains unclear.[61] Notably, *BAP1* mutations can be either germline mutations, resulting in the familial cancer predisposition, or sporadic in the uveal melanoma tumor cells alone. Either type of recessive *BAP1* mutation is unmasked by a loss of chromosome 3. *BAP1* mutations have been shown to relate to uveal melanoma metastatic potential and the classification of tumors as higher-risk, class 2 tumors.[63]

In addition to familial cancer susceptibility syndromes, which increase the risk of uveal melanoma, there are several ocular conditions associated with an increased incidence of uveal melanoma. For instance, ocular and oculodermal melanocytosis are rare conditions characterized by increased melanocytic pigmentation of the eye, orbital skin, or both, which is in turn associated with an increased risk of uveal melanoma. Oculodermal melanocytosis is estimated to affect approximately 0.04% of the general Caucasian population but is found in as many as 1.4% of patients with a diagnosis of uveal melanoma.[64,65] Additionally, Shields et al. conducted a retrospective chart review of 7,872 uveal melanoma patients and found that patients with a coexisting diagnosis of ocular or oculodermal melanocytosis were at twice the risk of metastasis relative to patients without ocular or oculodermal melanocytosis.[66]

Furthermore, interactions between genetically mediated host susceptibility and environmental exposures have been shown to increase the risk of development of uveal melanoma. Weis et al. conducted a meta-analysis evaluating the relationship between uveal melanoma and typical and atypical cutaneous nevi, as well as iris nevi. They suggest that nevi and freckles represent both host susceptibility and UV exposure, as both factors are necessary for the development of these pigmented lesions. Statistically significant collective

odds ratios were 2.82, 1.74, 1.22, and 1.53 for atypical cutaneous nevi, typical cutaneous nevi, cutaneous freckles, and iris nevi, respectively.[67]

Additionally, dysplastic nevus syndrome, also known as familial melanoma syndrome, increases individuals' risk of uveal melanoma.[68] Rodriguez-Sains explored the ocular manifestations of 257 individuals with dysplastic nevus syndrome and 264 controls. He found statistically significant increases in the number of iris (2.6-fold), conjunctival (7.5-fold) and choroidal (2.7-fold) nevi.[69] Van Hees and colleagues took a different approach and assessed the history of dermatologic manifestations present in 109 consecutive uveal melanoma patients and their families. Two uveal melanoma patients were found to also have cutaneous melanoma, and four patients were found to have first-degree relatives with cutaneous melanoma. Three of these four relatives had dysplastic nevus syndrome. Therefore as many as 2.8% of patients in this study had a known family history of dysplastic nevus syndrome.[70]

The relationship between xeroderma pigmentosum and uveal melanoma further suggests a relationship between host susceptibility and UV exposure. Xeroderma pigmentosum is a rare autosomal recessive condition resulting in defective DNA repair of UV-mediated pyrimidine dimers. This condition increases individuals' susceptibility to the carcinogenic effects of UV exposure. Though the development of uveal melanoma amongst patients with this rare disease is itself an infrequent event, it is estimated that patients with xeroderma pigmentosum are at as high as 23 times the risk of uveal melanoma as the general population. Such increased risk has been taken as support for a causal role of UV exposure in the pathogenesis of uveal melanoma, at least in this patient group.[71,72]

CONCLUSIONS

Recent compelling evidence suggests that not all uveal melanomas are themselves equivalent with respect to metastatic potential and patient survival. Furthermore, there are significant disparities in the incidence and outcomes of uveal melanoma based on patient characteristics such as age, gender, race, and exposure history. We have examined the literature relating to uveal melanoma to synthesize the evidence of disparities in the incidence and outcomes of uveal melanoma as they relate to patient characteristics.

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