Ophthalmologists focus on a very specialized region of the body; however, our years of general medical training are useful for patients, especially those with uveal melanoma. While hereditary uveal melanoma (UM) is very rare (<1% of uveal melanomas) [1], patients with a high frequency of personal and/or family history of cancer are found in about 12% of unselected patients with UM [2]. The increased cancer predisposition is not limited to UM and is a diverse cancer phenotype. It is interesting that concurrent second primary cancers have been reported in 8-13% of patients with UM [3-6]. Furthermore, some studies have detected a small increased risk of additional primary malignancies in UM patients [7]. In the Collaborative Ocular Melanoma Study, the 10 year cumulative rate of second primary cancer was 14.9% (95% CI: 12.9-17.1%), while the estimated 10-year rate for similar patients was only 9% [6]. Interestingly, the COMS excluded patients who had prior malignancy; thus, the increased rate of second primary cancer is striking since the exclusion criteria likely created a bias against patients with elevated cancer predisposition. These studies suggest that a subset of patients with UM is at an increased risk of cancer. Why do some UM patients have the propensity to develop multiple cancers? Is this the effect of inheritance of one dominant gene or a combination of multiple genes? Is there any genetic/environmental interaction? The answers to these questions are unknown at this time.

Recently, we and others have identified a novel cancer syndrome due to germline mutation in the BAP1 gene, which increases the patient’s risk for several cancers including uveal melanoma, cutaneous melanoma, renal cell carcinoma, mesothelioma, lung adenocarcinoma, breast carcinoma and several other internal malignancies [7-11].

However, BAP1 mutation is not the whole story when it comes to hereditary cancer risk and UM. For example, we found that only 1/53 such families in our study had a disease-associated germline mutation [8]. Similarly, Aoude et al. [12] and Njauw et al. [13] showed that the frequency of germline BAP1 mutation is rare. Overall, the literature suggests that approximately 3% of uveal melanoma-associated hereditary cancer predisposition syndromes are caused by germline BAP1 mutation. Germline mutations in BRCA2 have been reported in several UM patients with personal or family history of breast cancer [14,15]. Also, germline mutation in CDKN2A has been identified in a single family with UM and cutaneous melanomas [16]. However, larger studies have indicated that the frequency of germline mutation in these genes is less than 1% in UM patients with evidence of hereditary cancer predisposition [17,18]. We are currently working to identify other genes and mechanisms which are responsible for this hereditary cancer risk. Importantly, identification of cancer predisposition syndromes would not have been possible without asking a thorough personal and family cancer history, which includes grandparents, aunts/uncles, and cousins.

Although UM and cutaneous melanoma are biologically different, they appear to be associated in hereditary cancer predisposition. Importantly, the most common cancer associated with UM in our study of unselected UM patients was cutaneous melanoma (relative risk: 2.97, 95% CI: 1.00-6.94) [2]. Others have demonstrated the association of UM with cutaneous melanoma and other pigmented lesions. For example, Bataille et al. reported a series of patients with uveal melanoma (3 choroidal, 1 conjunctival, 1 primary acquired melanosis), in 5 patients out of a cohort of 207 patients [19]. Bergman et al. found an increased odds ratio, 1.75 (95% CI 0.78-3.89), for UM patients developing cutaneous melanoma. Similarly, the case-control study by Lischko et al. identified that prior skin malignancy (melanoma and basal or squamous cell types) tended to increase the estimated risk for developing UM in both non-related and sibling case comparisons (relative risk, 1.5 (95% CI 0.67-3.5) and 1.7 (95% CI 0.93-2.9), respectively). Furthermore, in a meta-analysis, Weis and colleagues found an association between UM and iris nevi, cutaneous common and atypical nevi [20]. Thus, there appears to be a significant association between UM and cutaneous melanoma and possibly other skin cancers. To address this risk we now include dermatology referral in our practice pattern for most patients with UM, particularly for any who have pigmented skin lesions.

In summary, UM is a disease with a genetic basis and an association with other cancers in a subset of patients. Germline mutation in BAP1 is responsible for only a minority of UM with hereditary cancer predisposition; the remaining genes/mechanisms are being explored. Since cutaneous melanoma is the cancer most associated with UM, dermatology referral may be considered in the management of these patients.

ACKNOWLEDGMENTS

We thank the Patti Blow fund and the Ohio Lions Eye Research Foundation. Research reported in this publication was supported by the National Eye Institute of the National Institutes of Health under Award Number K08EY022672. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Cite this article: Cebulla CM, Davidorof FH, Abdel-Rahman MH (2013) Uveal Melanoma: Beyond a Baptism. JSM Ophthalmol 1: 1009.
REFERENCES


Cite this article