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Editorial

Uveal Melanoma: Beyond a Baptism

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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 inabout 12% of unselected patients with UM [2]. The increased cancer predisposition is not limited to UM and isa 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 [3,7]. 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 [8-11].

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 suggeststhat 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 ocular 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% Cl, 0.67-3.5) and 1.7 (95% Cl, 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.

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REFERENCES

1. Singh AD, Shields CL, De Potter P, Shields JA, Trock B, Cater J, et al. Familial uveal melanoma. Clinical observations on 56 patients. Arch Ophthalmol. 1996; 114: 392-399.
2. Abdel-Rahman MH, Pilarski R, Ezzat S, Sexton J, Davidorf FH. Cancer family history characterization in an unselected cohort of 121 patients with uveal melanoma. Fam Cancer. 2010; 9: 431-438.
3. Lischko AM, Seddon JM, Gragoudas ES, Egan KM, Glynn RJ. Evaluation of prior primary malignancy as a determinant of uveal melanoma. A case-control study. Ophthalmology. 1989; 96: 1716-1721.
4. Holly EA, Aston DA, Ahn DK, Kristiansen JJ, Char DH. No excess prior cancer in patients with uveal melanoma. Ophthalmology. 1991; 98: 608-611.
5. Kindy-Degnan N, Char DH, Kroll SM. Coincident systemic malignant disease in uveal melanoma patients. Can J Ophthalmol. 1989; 24: 204-206.
6. Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, et al. Second primary cancers after enrollment in the COMS trials for treatment of choroidal melanoma: COMS Report No. 25. Arch Ophthalmol. 2005; 123: 601-4.
7. Bergman L, Nilsson B, Ragnarsson-Olding B, Seregard S. Uveal melanoma: a study on incidence of additional cancers in the Swedish population. Invest Ophthalmol Vis Sci. 2006; 47: 72-77.
8. Abdel-Rahman MH, Pilarski R, Cebulla CM, Massengill JB, Christopher BN, Boru G, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. J Med Genet. 2011; 48: 856-859.
9. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, Cox NJ, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43:1022-5.
10. Wiesner T, Obenauf AC, Murali R, Fried I, Griewank KG, Ulz P, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. 2011; 43: 1018-1021.
11. Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, Dubois-d'Enghien C, et al. Germline BAP1 Mutations Predispose to Renal Cell Carcinomas. Am J Hum Genet. 2013; 92: 974-80.
12. Aoude LG, Vajdic CM, Kricker A, Armstrong B, Hayward NK. Prevalence of germline BAP1 mutation in a population-based sample of uveal melanoma cases. Pigment Cell Melanoma Res. 2013; 26: 278-279.
13. Njauw CN, Kim I, Piris A, Gabree M, Taylor M, Lane AM, et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. PLoS One. 2012; 7: e35295.
14. Scott RJ, Vajdic CM, Armstrong BK, Ainsworth CJ, Meldrum CJ, Aitken JF, et al. BRCA2 mutations in a population-based series of patients with ocular melanoma. Int J Cancer. 2002; 102: 188-191.
15. Sinilnikova OM, Egan KM, Quinn JL, Boutrand L, Lenoir GM, Stoppa-Lyonnet D, et al. Germline brca2 sequence variants in patients with ocular melanoma. Int J Cancer. 1999; 82: 325-328.
16. Kannengiesser C, Avril MF, Spatz A, Laud K, Lenoir GM, Bressac-de-Paillerets B. CDKN2A as a uveal and cutaneous melanoma susceptibility gene. Genes Chromosomes Cancer. 2003; 38: 265-268.
17. Hearle N, Damato BE, Humphreys J, Wixey J, Green H, Stone J, et al. Contribution of germline mutations in BRCA2, P16(INK4A), P14(ARF) and P15 to uveal melanoma. Invest Ophthalmol Vis Sci. 2003; 44: 458-462.
18. Abdel-Rahman MH, Pilarski R, Massengill JB, Christopher BN, Noss R, Davidorf FH. Melanoma candidate genes CDKN2A/p16/INK4A, p14ARF, and CDK4 sequencing in patients with uveal melanoma with relative high-risk for hereditary cancer predisposition. Melanoma Res. 2011; 21: 175-179.
19. Bataille V, Pinney E, Hungerford JL, Cuzick J, Bishop DT, Newton JA. Five cases of coexistent primary ocular and cutaneous melanoma. Arch Dermatol. 1993; 129: 198-201.
20. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association of cutaneous and iris nevi with uveal melanoma: a meta-analysis. Ophthalmology. 2009; 116: 536-543.

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