

Can We Quantify Melanoma Risk Based on a Specific Gene Mutation?

Recent data suggest a lower relative risk for melanoma associated with CDKN2A gene mutation.

By Jonathan Wolfe, MD

With improved understanding of genetics and the successful mapping of the human genome, researchers have now focused attention on identifying gene mutations that contribute to the development of various human diseases. At a minimum, pinpointing causative and contributory genetic mutations may permit the early identification of at-risk individuals in order to ensure appropriate monitoring and interventional therapy, if available. At best, gene repair technologies could alter the course of a disease and may even prevent its development.

In dermatology, one area of investigation has been the role of CDKN2A germ-line mutations in the development of cutaneous melanoma. While previous studies have found variable rates of risk associated with these germline mutations, a recent study suggests that the relative risk may be lower than generally believed.¹

Findings About Germline Mutations

CDKN2A germline mutations have been found in cutaneous melanoma patients who have a family history of the disease,^{1,2,3} as well as in some patients with sporadic melanoma.^{3,4} Estimates suggest that about 20 percent of individuals who develop melanoma and have a family history of the disease have a CDKN2A germline mutation.¹ One study found that 15 percent of patients (five of 33 patients) with multiple

primary melanomas but no known family history of melanoma had CDKN2A germline mutations. Researchers found identical mutations in family members of three of those five individuals.³

Another study identified CDKN2A germline mutations in 11 percent of 80 patients with two or more primary cutaneous melanomas.⁴ Seven of these individuals had a family history of melanoma, while two did not. Compared to individuals without CDKN2A germline mutations, patients with genetic mutations had a significantly lower median age at diagnosis of first melanoma and significantly higher num-

bers of primary melanomas.

Absolute average lifetime risk for developing melanoma due to CDKN2A germline mutations has been estimated at 67 percent, but relative risk associated with these mutations had not been firmly established.¹ Using a cohort of 3,613 melanoma patients from nine geographic regions in Australia, Canada, Italy, and the US, Berwick, et al attempted to quantify relative risk.¹ They devised a novel study design that established non-traditional "cases" (individuals with multiple primary melanoma, n=1,189) and "controls" (single primary melanoma, n=2,424). The team notes that, "under

New In Your Practice

A New Agenda. Genta Incorporated recently announced that French Health Products Safety Agency has granted authorization to open the company's phase 3 trial of Genasense (oblimersen sodium) injection in patients with advanced melanoma. The AGENDA trial is a randomized, double-blind, placebo-controlled study in which patients will receive either Genasense plus dacarbazine (DTIC) or DTIC alone. AGENDA will accrue approximately 100 sites worldwide, including North America, Europe, and Australia. Accrual is expected to complete in the fourth quarter of 2008.

In the Pipeline. Centocor's experimental treatment CNTO 1275 (ustekinumab) was shown to be safe and highly effective in a late-stage trial. Data were unveiled at last month's World Congress of Dermatology in Buenos Aires. More than two-thirds of patients with moderate-to-severe psoriasis achieved at least a 75 percent reduction in symptoms after 12 weeks of treatment. About 42 percent of patients taking lower doses and 51 percent of patients taking high doses of the drug reported a 90 percent reduction in symptoms after 12 weeks. Moreover, a significant number of patients who received another dose of ustekinumab at 16 weeks maintained symptom control for an additional three months, according to the company. • Results from a Phase II study extension evaluating the efficacy of Abbott's anti-IL-12/23 antibody, ABT-874, showed that a majority of patients who initially responded to treatment maintained a high level of response following discontinuation of therapy. In the study, also presented at the WCD, patients who achieved PASI 75 at 12 weeks stopped receiving the drug. At 24 weeks, more than two thirds of these patients maintained at least 50 percent improvement.

CDKN2A and NMSC

In addition to the clear association between CDKN2A mutations and risk for development of cutaneous melanoma, research also suggests that the gene could be associated with non-melanoma skin cancer.⁷ Studies demonstrate squamous cell carcinoma is associated with mutations in the p53 gene and suggest that non-expression of the CDKN2A gene may play a role. Mutations in p53 may be induced by UV-radiation, but findings suggest that silencing of the CDKN2A is not UV-dependent.⁷ Further study may elucidate the link between UV exposure, p53 mutation, CDKN2A expression, and development of NMSC.

TAN Act Succeeds

The Tanning Accountability and Notification Act or TAN Act, featured in this column last November, is now law. Enacted as part of the Food and Drug Administration Amendments Act of 2007, the legislation requires the FDA to re-examine warning labels on indoor tanning devices to ensure that wording and location are sufficiently effective to warn consumers about the risks of UV radiation, the AADA reports. The act gives the FDA one year to conduct consumer testing to assess comprehension of label warnings and report back to Congress about results and actions that will be implemented to reduce risks associated with UV tanning devices.

certain assumptions, this design gives the same relative risks as a classic case-control study using participants with a single primary cancer and unaffected controls.” Assumptions in this study were that the two or more primary melanomas of “case” patients are independent tumors and not metastases, that there is no survival bias associated with mutation status, and that the relative risk established for the population under investigation can be extrapolated to the general public.

The team looked only at “functional” mutations: 1.) those in the coding region that changed the amino acid sequence or 2.) those in the noncoding region but known to inhibit transcription of wild-type p16. Odds ratio estimates were made after adjusting for subjects’ age, sex, geographic region, and relevant phenotypic characteristics (mole count on back, hair color, eye color, freckles in childhood, and propensity to tan or burn). Estimated relative risk for primary melanoma associated with any CDKN2A germline mutation (adjusted for the factors just described) is 4.3. Different mutations appear to confer

different relative risks. Missense mutations affecting both p16INK4a and p14ARF and non-coding mutation at -34G>T were associated with the most significant increases in risk.

The team notes that their findings demonstrate a higher incidence (1.2 percent) of CDKN2A germline mutations in individuals with newly diagnosed melanoma than has been found in previous studies (0.2 percent). However, at 4.3, the relative risk of melanoma associated with CDKN2A germline mutations is lower than previously suggested.

An interesting finding from the study relates to phenotypic risk factors for melanoma. The current investigation found no strong associations between presence of CDKN2A mutations and any of the known phenotypic risk factors for melanoma, leading the team to conclude, “that CDKN2A mutations exert their effect on risk essentially independently of other known risk factors.”

A Future for Screening?

Evidence clearly indicates that CDKN2A germline mutations are asso-

ciated with increased risk for developing melanoma, though recent data suggest the relative risk may not be as significant as previously suggested.¹ Nonetheless, findings suggest potential applications for genetic screening of newly diagnosed melanoma patients with a family history of melanoma as well as screening of their family members in order to identify individuals at highest risk for developing multiple primary tumors. These patients could then undergo regular monitoring/examination and undertake appropriate strategies to minimize other melanoma risk factors (such as UV exposure).

Further study may uncover specific types of CDKN2A mutations associated with greatest risk for development of melanoma and could enhance the clinical utility of genetic screening results. Already, a more recent publication based on the same cohort discussed above identified 44 different variants in CDKN2A in patients with melanoma. The team noted that functional variants were rare but, “increased the risk of melanoma significantly.”⁶

1. Berwick M, Orlow I, Hummer AJ, Armstrong BK, Kricke A, Marrett LD, Millikan RC, Gruber SB, Anton-Culver H, Zanetti R, Gallagher RP, Dwyer T, Rebbeck TR, Kanetsky PA, Busam K, From L, Mujumdar U, Wilcox H, Begg CB; GEM Study Group. The prevalence of CDKN2A germline mutations and relative risk for cutaneous malignant melanoma: an international population-based study. *Cancer Epidemiol Biomarkers Prev.* 2006 Aug;15(8):1520-5.

2. Hogg D, Brill H, Liu L, Monzon J, Summers A, From L, Lassam NJ. Role of the cyclin-dependent kinase inhibitor CDKN2A in familial melanoma. *J Cutan Med Surg.* 1998 Jan;2(3):172-9

3. Monzon J, Liu L, Brill H, Goldstein AM, Tucker MA, From L, McLaughlin J, Hogg D, Lassam NJ. CDKN2A mutations in multiple primary melanomas. *N Engl J Med.* 1998 Mar 26;338(13):879

4. Hashemi J, Platz A, Ueno T, Stierner U, Ringborg U, Hansson J. CDKN2A germline mutations in individuals with multiple cutaneous melanomas. *Cancer Res.* 2000 Dec 15;60(24):6864-7.

5. Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, Champret A, Ghiarzo P, Gruis N, Hansson J, Harland M, Hayward N, Holland EA, Mann GJ, Mantelli M, Nancarrow D, Platz A, Tucker MA; Melanoma Genetics Consortium. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst.* 2002 Jun 19;94(12):894-9

6. Orlow I, Begg CB, Cotigola J, Roy P, Hummer AJ, Clas BA, Mujumdar U, Canchola R, Armstrong BK, Kricke A, Marrett LD, Millikan RC, Gruber SB, Anton-Culver H, Zanetti R, Gallagher RP, Dwyer T, Rebbeck TR, Kanetsky PA, Wilcox H, Busam K, From L, Berwick M; GEM Study Group. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J Invest Dermatol.* 2007 May;127(5):1234-43.

7. Pacifico A, Leone G. Role of p53 and CDKN2A Inactivation in Human Squamous Cell Carcinomas. *J Biomed Biotechnol.* 2007;2007(3):43