

## A Piece of the Melanoma Puzzle

*Alisa M. Goldstein, Margaret A. Tucker*

Cutaneous malignant melanoma (CMM) is a complex disorder with genetic, environmental, and host factors contributing to its pathogenesis. CDKN2A is the major known high-risk melanoma susceptibility gene. MC1R also influences melanoma risk but is described as a low-risk susceptibility gene (1–3). Although much has been learned since CDKN2A was identified, much remains to be discovered. The article by Begg et al. (4) in this issue of the Journal provides another piece of the intricate puzzle.

Begg et al. (4) estimated the lifetime risk of melanoma among relatives of CDKN2A mutation carriers who were ascertained using a population-based study design. Proband was incident CMM case patients with either first (SPM) or subsequent melanoma (MPM). As has been observed recently, the response rate was much lower than hoped, with a participation rate of 53% ranging from greater than 75% for two small sites to 55%–58% in New South Wales and British Columbia (40% of the sample) and less than 50% in all four U.S. sites and Ontario (52% of the sample). The low response rate may have led to greater participation of subjects with a family history of melanoma as suggested by a 16% family history of melanoma compared with 8% from a previous meta-analysis (5). The authors evaluated 3550 probands for mutations in CDKN2A and identified 33 mutations in 65 patients (1.8%) (4). Melanoma histories in first-degree relatives of these probands were used to calculate the lifetime risk in CDKN2A mutation carriers using the kin-cohort method (6,7). Overall, the risk of melanoma in mutation carriers was 14% (95% confidence interval [CI] = 8% to 22%) by age 50 years and 28% (95% CI = 18% to 40%) by age 80 years. The risk varied depending on whether the proband had one or more melanomas with risks by age 80 years of 19% (95% CI = 7% to 37%) for SPM versus 35% (95% CI = 22% to 51%) for MPM. These results expand the spectrum of melanoma risks by extending findings to CMM patients without extensive familial aggregation but do not provide a lower bound because mutation carriers were identified by their melanoma status (8).

Previously, the largest evaluation of melanoma penetrance in CDKN2A mutation carriers came from a Melanoma Genetics Consortium study of 80 families with CDKN2A mutations and multiple case patients with CMM (average of five melanoma patients per family) (9). Bishop et al. (9) modeled penetrance for melanoma using a logistic regression model incorporating survival analysis. Overall, CDKN2A mutation penetrance was 0.30 (95% CI = 0.12 to 0.62) by age 50 years and 0.67 (95% CI = 0.31 to 0.96) by age 80 years. These estimates were considered upper bounds of penetrance because of the selection of families. Penetrance estimates differed according to the population incidence rate of melanoma: by age 50 years, 0.13 in Europe, 0.50 in the United States, and 0.32 in Australia; by age 80 years, 0.58 in Europe, 0.76 in the United States, and 0.91 in Australia. The results suggested that the same factors that affect population incidence of melanoma may also mediate CDKN2A penetrance (9).

Although Begg et al. (4) and Bishop et al. (9) used different study designs and analytic approaches for estimating melanoma risk/penetrance, the findings are complementary and consistent with what would be expected. As has been shown in several family-based studies of melanoma, genetic (e.g., MC1R), host (e.g., dysplastic and typical nevi), and environmental factors (e.g., sun exposure) increase the risk for melanoma in CDKN2A mutation carriers and may influence penetrance for melanoma (10–15). Given the importance of these other modifying factors for penetrance, it is expected that families with many cases of melanoma may share the CDKN2A mutation as well as the other factors (4,8,9). Melanoma risks derived from population-based or other non-family-based sources of data would be anticipated to be lower than the risks observed in multiple-case families. This phenomenon has been observed in the much larger body of literature on the risks of breast cancer in BRCA1/BRCA2 mutation carriers (4). Comparison of multiple-case melanoma families and population-based samples may provide a fertile pathway to help to identify the many factors contributing to the complementary penetrance/risk estimates observed in these studies (4,9).

It is not currently possible to accurately predict who may be carrying a CDKN2A mutation; however, two factors previously consistently associated with an increased frequency of CDKN2A mutations were observed by Begg et al (4)—MPM and the number of melanoma patients in a family (2,3,16). Overall, 3% of MPM patients compared with 1.3% of SPM patients had CDKN2A mutations. Begg et al. (4) found only 1 of 18 carrier probands with three or more reported relatives with melanoma. However, the frequency of mutations statistically significantly increased as the number of reported relatives with melanoma increased overall and in all subgroups reported (4). If the estimated mutation frequencies are representative for the U.S. population, testing all newly diagnosed melanoma patients in 2005 ( $n = 59\,580$ ; 98% SPM) (17) would yield only 779 carriers. Of these, 36% would have neither a family nor personal history of melanoma.

The results by Begg et al. (4) reinforce why it is premature to consider widespread genetic testing for CDKN2A. Mutations are rare events even among higher risk groups. Risk estimates are imprecise and most importantly, clinical care would not be altered (1,16). The highly variable penetrance among mutation carriers

---

*Affiliation of authors:* Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD.

*Correspondence to:* Alisa M. Goldstein, PhD, Genetic Epidemiology Branch/NCI/NIH/DHHS, Executive Plaza South, Rm. 7004, 6120 Executive Blvd. MSC 7236, Bethesda, MD 20892–7236 (e-mail: goldstea@exchange.nih.gov).

See “Note” following “References.”

DOI: 10.1093/jnci/dji359

© The Author 2005. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.

would not be advisable to use alone for counseling. Although CDKN2A mutation status is an important component of familial melanoma susceptibility, it is not the only risk factor that should be considered in counseling patients or their family members.

There is extensive research ongoing to identify other genetic factors for melanoma. The success of identifying other high-risk or low-risk susceptibility genes depends on many issues including the wide variation in melanoma risk and risk factors observed in multiple studies. The types, frequencies, and effect sizes of the genetic factors will determine how challenging they are to identify. To further our understanding of the complex etiology of melanoma, family-based, population-based, tumor-based, and molecular-based study designs and their corresponding analytic approaches will all be essential to continue to add pieces to the challenging puzzle that is melanoma.

## REFERENCES

- (1) Kefford R, Newton Bishop J, Tucker M, Bressac-de Paillerets B, Bianchi-Scarra G, Bergman W, et al., on behalf of the Melanoma Genetics Consortium. Genetic testing for melanoma. *Lancet Oncol* 2002;3:653–4.
- (2) Hayward NK. Genetics of melanoma predisposition. *Oncogene* 2003;22:3053–62.
- (3) Goldstein AM, Tucker MA. Familial melanoma and its management. In: Eeles RA, Easton DF, Ponder BAJ, Eng C, editors. *Genetic predisposition to cancer*, 2nd ed. London (U.K.): Arnold; 2004. p. 352–9.
- (4) Begg CB, Orlow I, Hummer AJ, Armstrong BK, Krickler A, Marrett LD, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst* 2005;97:1507–15.
- (5) Ford D, Bliss JM, Swerdlow AJ, Armstrong BK, Franceschi S, Green A, et al. Risk of cutaneous melanoma associated with a family history of the disease. The International Melanoma Analysis Group (IMAGE). *Int J Cancer* 1995;62:377–81.
- (6) Chatterjee N, Wacholder S. A marginal likelihood approach for estimating penetrance from kin-cohort designs. *Biometrics* 2001;57:245–52.
- (7) Wacholder S, Hartge P, Struewing JP, Pee D, McAdams M, Brody L, et al. The kin-cohort study for estimating penetrance. *Am J Epidemiol* 1998;148:623–30.
- (8) Begg CB. On the use of familial aggregation in population-based case probands for calculating penetrance. *J Natl Cancer Inst* 2002;94:1221–6.
- (9) Bishop DT, Demenais F, Goldstein AM, Bergman W, Newton Bishop J, Bressac-de Paillerets B, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* 2002;94:894–903.
- (10) Box NF, Duffy DL, Chen W, Stark M, Martin NG, Sturm RA, Hayward NK. MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. *Am J Hum Genet* 2001;69:765–73.
- (11) van der Velden PA, Sandkuijl LA, Bergman W, Pavel S, van Mourik L, Frants RR, et al. Melanocortin-1 receptor variant R151C modifies melanoma risk in Dutch families with melanoma. *Am J Hum Genet* 2001;69:774–9.
- (12) Chaudru V, Chompret A, Minière A, Laud K, Avril M-F, Bressac-de Paillerets B, et al. Joint effects of MC1R gene, naevus phenotypes and sun-related covariates on CDKN2A penetrance in French melanoma-prone families. *Proceedings of the First International Melanoma Research Congress, 2003 June 21–14; Philadelphia, (PA)*.
- (13) Chaudru V, Chompret A, Bressac-de Paillerets B, Spatz A, Avril MF, Demenais F. Influence of genes, nevi, and sun sensitivity on melanoma risk in a family sample unselected by family history and in melanoma-prone families. *J Natl Cancer Inst* 2004;96:785–95.
- (14) Goldstein AM, Falk RT, Fraser MC, Dracopoli NC, Sikorsky RS, Clark WH, et al. Sun-related risk factors for melanoma-prone families with CDKN2A mutations. *J Natl Cancer Inst* 1998;90:709–11.
- (15) Goldstein AM, Landi MT, Tsang S, Fraser MC, Munroe DJ, Tucker MA. Association of MC1R variants and risk of melanoma in melanoma-prone families with CDKN2A mutations. *Cancer Epidemiol Biomarkers Prev* 2005;14:2208–12.
- (16) Kefford RF, Newton Bishop JA, Bergman W, Tucker MA, on behalf of the Melanoma Genetics Consortium. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma. *J Clin Oncol* 1999;17:3245–51.
- (17) National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Surveillance, Epidemiology and End Results Program. SEER\*Stat Database: Populations—Total U.S. (1969–2002), 2005. Available at: <http://www.seer.cancer.gov>.

## NOTE

Supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.