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Interaction of CDKN2A and Sun Exposure in the Etiology of Melanoma in the General Population

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TO THE EDITOR

A major goal in cancer prevention is to identify genetic and environmental risk factors and determine if they interact to increase risk. Melanoma is an excellent model because intermittent sun exposure is a well supported environmental risk factor for the development of melanoma and a genetic factor, CDKN2A, plays a major role in melanoma etiology. We have sequenced CDKN2A, the major familial melanoma gene, in 3,624 melanoma patients from nine centers in four countries (Berwick \textit{et al.}, 2006, Orlow \textit{et al.}, 2007), and we have...
identified the same patterns of sun exposure in risk for a second primary melanoma (Kricker et al., 2007) as are found for incident, first primary melanomas (Gandini et al., 2005). We therefore wanted to identify whether and how these two important risk factors – sun exposure and CDKN2A – might interact to increase melanoma risk.

We identified incident cases of melanoma from eight population-based registries in Australia (New South Wales and Tasmania), Italy (Piedmont area), Canada (British Columbia and Ontario), the United States (New Jersey, North Carolina, and Orange and San Diego Counties) and one hospital center in Michigan, which sees approximately 50% of the melanoma diagnosed in the state. The study design and details of the data collection have been previously published (Begg et al., 2006). Briefly, single primary melanoma (SPM) controls were people diagnosed with an incident first invasive primary melanoma within a defined accrual period of 6 months during the year 2000, and multiple primary melanoma (MPM) cases were people diagnosed with an incident second- or higher-order invasive or in situ melanoma during a 3.5 year period from January 1, 2000. Inclusion of in situ cases was designed to avoid exclusion of people who could have been diagnosed with an invasive subsequent primary if the in situ lesion had not been removed. Participants gave informed consent, donated 4–6 buccal swabs or blood for DNA extraction, and completed questionnaires detailing demographics, phenotypic characteristics, family history of cancer and lifetime sun exposure behavior. The study protocol was approved by the Institutional Review Board of each participating institution. All study procedures adhered to the Helsinki guidelines. Sequencing was conducted for exons 1α, 2 and 3 of the CDKN2A gene, which code for the p16 and or p14ARF proteins as previously described (Berwick et al., 2006; Orlow et al. 2007).

Functional CDKN2A mutations (Orlow et al. 2007) were identified in 30 of 2,469 individuals with single primary melanomas (1.3%) and in 35 of 1,207 individuals with multiple primary melanoma (2.9%) (Berwick et al., 2006). As we previously published, those with CDKN2A mutations are significantly younger than those with wildtype CDKN2A, more likely to have a family history of melanoma, more likely to have multiple melanomas and more nevi.

We used five measures of sun exposure previously reported by our group as important risk factors for second primary melanomas (Kricker et al., 2007): (1) Ambient erythemal UVR (UVE) exposure at age 10 – a measure of early life sun exposure supported by migrant studies where the effect of ambient sun exposure is greatest in those who migrated before 10–15 years of age, (2) average annual hours on sunny holidays, (3) average annual hours of beach and waterside exposure, (4) lifetime painful or blistering burns, and (5) lifetime painful or blistering burns to the site of the melanoma. The latter four measures reflect an intermittent pattern of sun exposure, usually indicated by recreational exposure, the major form of sun exposure that has been associated with the development of melanoma (Armstrong and Kricker 1993; Gandini et al., 2006). Odds ratios were calculated using logistic regression for unadjusted and adjusted stratified analyses, controlling for age, sex, study center, an age*sex interaction and ability to tan. Multiplicative interactions were assessed using cross product terms. All statistical analyses were undertaken using SAS Statistical Packages Version 9.2 (SAS, Inc, Cary, NC). All statistical tests were two-sided.
We observed no statistically significant multiplicative interactions between any measure of intermittent sun exposure and mutation of CDKN2A (Table 1). The stratified analyses show no statistically significant differences in effects of increasing sun exposure between mutation carriers and non-carriers, and the relative risk estimates are generally smaller than for the non-carriers.

These findings suggest that increasing sun exposure may add little to the increased risk of melanoma that is conferred by carriage of a CDKN2A mutation, and that those with a mutation are at high risk for the development of melanoma regardless of sun exposure. The adjusted relative risk of melanoma in carriers is 4.2 (95% CI 2.4, 7.7), as reported earlier in Berwick et al., 2006.

Previous efforts to document a gene-environment interaction among CDKN2A carriers have reported similar findings. Consistent with the present results, Goldstein et al. (1998) did not find that sun exposure (measured as sunburns) was a significant risk factor for melanoma among families with CDKN2A mutations. Recently, Cust et al. (2011) reported that CDKN2A carriers appeared to have the same cumulative risk of melanoma regardless of ambient sun exposure thus suggesting that our observation of risk of second primary melanoma may be generalizable to all primary melanoma. Most studies of CDKN2A have focused on smaller populations (e.g., Nielson et al., 2010) or on familial studies (such as Goldstein et al., 1998; Bishop et al., 2002; Cust et al., 2011); GEM is the largest population-based series to sequence CDKN2A among individuals diagnosed with melanoma. Clearly, since the prevalence of CDKN2A mutations is very low, the ability to analyze the interaction between CDKN2A and solar exposure in the general population is necessarily limited, and inferences from such analyses are uncertain.

In summary, our study provides no evidence to suggest that the influences of CDKN2A mutational status and sun exposure on melanoma risk are related. In addition, we found little evidence that sun exposure increases the risk of melanoma in carriers, although our sample sizes are too small for a definitive conclusion on this issue. In the absence of further evidence people with CDKN2A mutations should receive at least the same sun protection advice as other people with similar phenotypic risk factors.

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Abbreviations

| Abbreviation | Description                      |
|--------------|----------------------------------|
| OR           | odds ratio                       |
| CI           | Confidence Interval              |
| UVR          | ultraviolet radiation            |
| UVE          | erythemal ultraviolet radiation  |
| KJ/m²        | kilojoules per square meter      |
| MPM          | multiple primary melanoma        |
| SPM          | single primary melanoma          |

References

1. Begg CB, Hummer AJ, Mujumdar U, et al. A design for cancer case-control studies using only incident cases: experience with the GEM study of melanoma. Int J Epidemiol. 2006; 35:756–64. [PubMed: 16556646]
2. Begg CB, Orlow I, Hummer AJ, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. J Natl Cancer Inst. 2005; 97:1507–15. [PubMed: 16234564]
3. Berwick M, Orlow I, Hummer AJ, et al. The prevalence of CDKN2A germ-line mutations and relative risk for cutaneous malignant melanoma: an international population-based study. Cancer Epidemiol Biomarkers Prev. 2006; 15:1520–5. [PubMed: 16896043]
4. Cust AE, Harlnad M, Makalic E, et al. Melanoma risk for CDKN2A mutation carriers who are relatives of population-based case carriers in Australia and the UK. J Med Genet. 2011; 48:266–72. [PubMed: 21325014]
5. Bishop DT, Demenais F, Goldstein AM, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. J Natl Cancer Inst. 2002; 94:894–903. [PubMed: 12072543]
6. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005; 41:45–60. [PubMed: 15617990]
7. Goldstein AM, Falk RT, Fraser MC, et al. Sun-related risk factors for melanoma-prone families with CDKN2A mutations. J Natl Cancer Inst. 1998; 90:709–711. [PubMed: 9586669]
8. Kricker A, Armstrong BK, Goumas C, et al. Ambient UV, personal sun exposure and risk of multiple primary melanomas. Cancer Causes Control. 2007; 18:295–304. [PubMed: 17206532]
9. Nielsen K, Harbst K, Måsbäck A. Swedish CDKN2A mutation carriers do not present the atypical mole syndrome phenotype. Melanoma Res. 2010; 20:266–72. [PubMed: 20526219]
10. Orlow I, Begg CB, Cotignola J, et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. J Invest Dermatol. 2007; 127:1234–43. [PubMed: 17218939]
Table 1

Analyses of the associations of multiple primary melanoma (MPM) with sun exposure measures stratified by CDKN2A mutational status.

| Mutational Status | Exposure | SPM N=2469 | MPM n=1207 | OR$_{\text{crude}}$ (95% CI) | * OR$_{\text{adjusted}}$ (95% CI) | p$^1$ | p$^2$ |
|-------------------|----------|------------|------------|-------------------------------|---------------------------------|------|------|
| UVE at age 10 (KJ/m$^2$) |          |            |            |                               |                                 |      |      |
| No mutation       |          |            |            |                               |                                 |      |      |
| 303–912           | 1230     | 463        | 1.00       | 1.00                          |                                 |      |      |
| 913–2084          | 1042     | 643        | 1.64 (1.42, 1.89) | 1.26 (0.95, 1.67) |                                 |      |      |
| missing            | 167      | 66         |            |                               |                                 |      |      |
| With mutation     |          |            |            |                               |                                 |      |      |
| 303–912           | 17       | 15         | 1.00       | 1.0                           |                                 |      |      |
| 913–2084          | 12       | 20         | 1.89 (0.69, 5.12) | 1.18 (0.39, 3.54) | 0.92 (0.83) |      |      |
| missing            | 1        | 0          |            |                               |                                 |      |      |
| Sunny Holiday – Average Hours per Year |          |            |            |                               |                                 |      |      |
| No mutation       |          |            |            |                               |                                 |      |      |
| 0–19              | 1013     | 406        | 1.00       | 1.00                          |                                 |      |      |
| 20–678            | 969      | 454        | 1.17 (0.99, 1.37) | 1.33 (1.11, 1.59) |                                 |      |      |
| missing            | 457      | 312        |            |                               |                                 |      |      |
| With mutation     |          |            |            |                               |                                 |      |      |
| 0–19              | 12       | 11         | 1.00       | 1.00                          |                                 |      |      |
| 20–678            | 14       | 16         | 1.25 (0.42, 3.69) | 0.92 (0.28, 2.99) | 0.55 (0.24) |      |      |
| missing            | 4        | 8          |            |                               |                                 |      |      |
| Beach and Waterside Activities – Average Hours per Year |          |            |            |                               |                                 |      |      |
| No mutation       |          |            |            |                               |                                 |      |      |
| 0–24              | 1203     | 570        | 1.00       | 1.00                          |                                 |      |      |
| 25–1857           | 1164     | 575        | 1.04 (0.91, 1.20) | 1.20 (1.02, 1.41) |                                 |      |      |
| Missing            | 72       | 27         |            |                               |                                 |      |      |
| With mutation     |          |            |            |                               |                                 |      |      |
| 0–24              | 7        | 10         | 1.00       | 1.00                          |                                 |      |      |
| 25–1857           | 23       | 25         | 0.76 (0.25, 2.33) | 0.87 (0.26, 2.85) | 0.59 (0.41) |      |      |
| Missing            | 0        | 0          |            |                               |                                 |      |      |
| Lifetime Painful or Blistering Sunburns |          |            |            |                               |                                 |      |      |
| No mutation       |          |            |            |                               |                                 |      |      |
| 0–10              | 1362     | 613        | 1.00       | 1.0                           |                                 |      |      |
| 11–700            | 1023     | 533        | 1.16 (1.01, 1.33) | 1.33 (1.13, 1.56) |                                 |      |      |
| missing            | 54       | 26         |            |                               |                                 |      |      |
| With mutation     |          |            |            |                               |                                 |      |      |
| 0–10              | 18       | 21         | 1.00       | 1.00                          |                                 |      |      |
| 11–700            | 12       | 14         | 1.00 (0.37, 2.71) | 0.99 (0.33, 2.91) | 0.59 (0.25) |      |      |
| missing            | 0        | 0          |            |                               |                                 |      |      |
## Mutational Status

| Lifetime Painful or Blistering Burns to the Site of the Melanoma | OR\textsubscript{crude} (95% CI) | OR\textsubscript{adjusted} (95% CI) | \(p\) | \(p^2\) |
|---|---|---|---|---|
| **No mutation** | | | | |
| None | 1310 | 522 | 1.00 | 1.00 |
| Any | 945 | 544 | 1.45 (1.25, 1.67) | 1.49 (1.27, 1.77) |
| missing | 184 | 106 | | |
| **With mutation** | | | | |
| None | 13 | 22 | 1.00 | 1.00 |
| Any | 11 | 13 | 0.69 (0.25, 1.94) | 0.57 (0.19, 1.74) |
| missing | 6 | 0 | | |

*Analyses are adjusted for age, sex, age-sex interaction, center and ability to tan.

1 Multiplicative interaction using categories of sun exposure.

2 Multiplicative interaction using continuous values of sun exposure.