Editorial

A Risk Prediction Tool for Melanoma?

David C. Whiteman and Adèle C. Green
Queensland Institute of Medical Research, Brisbane, Queensland, Australia

By any definition, the measure of successful translation of knowledge gained through epidemiologic research must be the impact of such activity on improving human health. This journal has set itself the well-considered goal of disseminating high-quality research findings from diverse fields of scientific inquiry linked by a thread that runs from biology to prevention. But how might this knowledge be best used and are there practical ways in which it can contribute to cancer control?

Successful translation of knowledge to practice is achievable. This is well demonstrated in other disciplines of preventive medicine and so we can turn to them to see examples of how our own field could evolve in the years ahead. Cardiovascular researchers have long known that blood pressure, lipids, diabetes, family history, and smoking all have demonstrable effects on determining a person’s risk of suffering disease. By combining primary data from observational studies and trials, cardiovascular epidemiologists have been able to develop charts that convey the absolute risks of suffering from heart disease within a given time frame. Various algorithms have been produced, including the Sheffield table (1,2), New Zealand tables (3), and the Joint British chart (4), and these have proven to be popular and effective tools that have revolutionized the approach to predicting and communicating risk as a first step in the primary prevention of heart disease. Considerable evidence is accumulating that these tools can be correctly applied and interpreted by physicians and nurses (5) and that they are used to reliably improve decision making by patients and their carers.

Can this approach be adapted to cancer prevention? We believe it can, although formidable challenges present themselves. Unquestionably, the causal pathways to cancer are complex and, for the most part, remain poorly defined. Moreover, because most cancers are rare and have long latent periods, robust prospective data with which to calculate absolute risks of cancer for population subgroups are largely absent. In stark contrast to the cardiovascular paradigm, informative cancer prevention trials are relatively few in number so that even if people at moderate to high risks for cancer can be identified, there is often little in the way of evidence-based advice that can be offered to reduce their future risk (6).

Nevertheless, we believe the process should be undertaken even if the only immediate benefit will be to highlight those things that we do not know. For some cancers, substantial progress has already been made. Risk prediction models have been developed for breast cancer that aim to estimate a woman’s absolute risk of disease given information about her current age, age at first birth, family history of breast cancer, and her personal history of previous breast biopsies (7, 8). Such models have been shown to be well calibrated at the population level in that they reliably predict how many women in each population subgroup will develop breast cancer (9). However, for individual women, the models seem to have limited discriminatory accuracy and correctly identify only a modest proportion of women who go on to develop breast cancer.

In our own field of interest, cutaneous melanoma, considerable progress has been made in quantifying the relative risks of disease associated with a broad range of environmental, phenotypic, and genetic factors. During the 1980s and early 1990s, several groups used data derived from independent case-control studies to develop algorithms intended to identify patients at high risk of melanoma (10-13). Since that time, further progress has been scant and no formal validation of the instruments has been conducted. This has left practitioners with little but guesswork to advise patients about their likelihood of developing melanoma. To gain an impression of how a practical, predictive tool might be constructed, and how it might look, we have developed a prototype that we hope will serve as an impetus to make primary prevention of melanoma a reality for health care professionals.

We propose consideration of a tool similar to the New Zealand risk factor chart for cardiovascular disease (14) that provides a visual image of the absolute risk of melanoma for an individual according to their profile of risk factors (Fig. 1). We have stratified levels of risk using factors that are widely accepted as independent determinants of absolute risk of melanoma, namely, current age, place of residence, number of melanocytic nevi, and skin type. Lastly, in recognition of the rapidly moving field of genetic epidemiology and the expectation that the genetic susceptibility data so derived may offer additional information for risk counseling, we have included a putative marker of melanoma risk, the status of the melanocortin-1 receptor (MC1R) gene.

The two most important determinants of a White person’s absolute risk of melanoma are their country of residence and current age. Cancer registry data clearly show the enormous differences in melanoma incidence experienced by White populations living in Australia (39 × 10⁻⁵ for males and 30 × 10⁻⁵ for females), United States (17 × 10⁻⁵ for males and 12 × 10⁻⁵ for females), and United Kingdom (8 × 10⁻⁵ for males and 9 × 10⁻⁵ for females). Significant differences in melanoma incidence are apparent across the geographically dispersed populations of Australia and the United States, with highest rates observed among people living at lower latitudes. Moreover, this geographic component of a person’s melanoma risk seems to be largely due to ambient sun exposure experienced in the first decades of life (15) and this may need to be incorporated into any refinements of the table. Age-specific risks of melanoma are also well defined from population data, increasing by ~50% to 75% with each decade of age for both sexes.

Of the remaining predictive factors, the largest and most consistently observed relative risks have been for people with numerous melanocytic nevi on their skin. Estimates vary somewhat across studies, but it seems reasonable to conclude that people with large numbers of melanocytic nevi are at up to 10-fold increased risks of melanoma compared with people who have very few nevi (16-21). For ease of use, we have used numbers of nevi on the upper limbs as an indicator of total nevus burden. Skin type, measured as skin color or skin reaction upon exposure to the sun, has also been consistently observed as an independent risk factor for melanoma, conferring about a

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**Figure 1.** Hypothetical table of absolute risks for melanoma among Caucasians, combining information on environmental, phenotypic and genotypic causal factors [after Jackson (3)].

<table>
<thead>
<tr>
<th>Number of nevi (arms)</th>
<th>$MC1R$ variant negative</th>
<th>$MC1R$ variant positive</th>
<th>Number of nevi (arms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21+</td>
<td>Olive</td>
<td>Fair</td>
<td>21+</td>
</tr>
<tr>
<td>11-20</td>
<td>Northern Australia</td>
<td>Fair</td>
<td>11-20</td>
</tr>
<tr>
<td>6-10</td>
<td>Southern Australia</td>
<td>Fair</td>
<td>6-10</td>
</tr>
<tr>
<td>0-5</td>
<td>Southern USA</td>
<td>Fair</td>
<td>0-5</td>
</tr>
<tr>
<td>21+</td>
<td>Northern USA</td>
<td>Fair</td>
<td>21+</td>
</tr>
<tr>
<td>11-20</td>
<td>Europe</td>
<td>Fair</td>
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<td>UK</td>
<td></td>
<td>6-10</td>
</tr>
<tr>
<td>0-5</td>
<td></td>
<td></td>
<td>0-5</td>
</tr>
</tbody>
</table>

10 year risk of cutaneous melanoma

- **Very high**: > 10%
- **High**: 6-10%
- **Moderate**: 4-6%
- **Low**: 2-4%
- **Very low**: 1-1.5%
- **Lowest**: 0.5-1.0%
- **Lowest risk**: <0.5%
doubling of risk for people with fair skin compared with olive skin in Caucasians (22).

Finally, and perhaps most tentatively, we have included information about the status of the MC1R gene. This gene encodes a transmembrane receptor for the α-melanocyte–stimulating hormone and is of interest because it appears to regulate the activity of melanocytes, the target cells for melanoma. Whereas various patterns of MC1R have been strongly linked to fair skin, it seems that these variants may substantially increase the risk of melanoma when present in persons of olive skin color who might otherwise be considered to be at low risk (23). Such findings need to be validated in other populations, but if confirmed, suggest that risk prediction tools for melanoma may need to incorporate genotypic factors to properly account for population differences in susceptibility.

As with all clinical aids, our preliminary risk-prediction tool for melanoma does have important limitations. First, the absolute risks estimated for each combination of risk factors are based on relative risks derived from case-control studies. Most of the studies were small, and the magnitude of relative risks varied considerably, presumably due to limited statistical power and different measurements and exposure prevalence. Such variations can lead to quite large changes in risk estimates. Notwithstanding this imprecision, we are confident that our depicted rankings of melanoma risk are generally accurate. (Independent sensitivity analyses could usefully be undertaken before any such tools were considered for policy or practice decisions.) Second, the force of morbidity is dynamic, shaped by underlying patterns of disease that change with birth cohort, time period, and age, yet risk prediction tools treat the population as a static entity. To overcome this limitation, tools must be regularly monitored for performance and revised as new data come to light. Finally, there are other potentially important exposures that have not been incorporated into this chart (such as past history of sunburns, freckling density, or patterns of occupational and recreational sun exposure) that may have a bearing on predicting risk. Our decision to exclude these factors reflects the lack of consistency in the available data and a desire for parsimony in the predictive charts.

We view this as an initial step in translating knowledge gained from epidemiologic research regarding melanoma risk factors into applications of clinical relevance for primary prevention of melanoma. We encourage responses and comments both on the specific melanoma-related proposal and on similarities and differences with other cancers that might have impact on its generalization.

References


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