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Predicting Risk for the Appearance of Melanoma

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The incidence rate of cutaneous melanoma is rapidly increasing and because the disease frequently manifests itself in young people, the economic, social, and morbidity costs are high. The etiologic factors contributing to this phenomenon are complex and include hereditary and familial contributions, a complex relationship with sunlight and other ultraviolet-light exposure (such as sunlamps), and more recently, a reconsideration of the role of metal and other substances that bind melanin.¹ Identifying individuals at high risk of a malignancy is an important overall goal of cancer control. Although these individuals are limited to only a small subset of the population, the potential patients at risk should be easily identifiable in most cases, with an appropriate surveillance program instituted and a plan for intervention developed. At the other extreme is the use of age as the major consideration for enhanced surveillance, as patient age at about 50 years is a major threshold for an increase in many cancers. For the most part, surveillance programs for breast, colon, and prostate cancers begin at this age,³ notwithstanding arguments for starting earlier.

The overall recommendations for surveillance of cutaneous melanoma represent a different type of challenge, as the etiologic factors contributing to this disease are complex. A familial contribution is present in many cases, but is poorly understood, and the patterns of incidence are sex- and age-dependent. However, factors that may seem to be correlated with risk may or may not be important in assessing the risk for progression to frank malignancy. The model by Fears et al² in this issue of the *Journal of Clinical Oncology* suggests that the many risk factors that are commonly assessed can be collapsed into two broader categories: host interaction with sunlight and the number of melanocytes (ie, moles) present at a particular time point in the participant's life.

The current predictor is based on the model by Gail et al,⁴ which is used widely to calculate the risk of breast cancer. Such models are derived from two types of data. The relative risks associated with specific possible predictors are estimated from case-control study results, as is in this report about melanoma.² However, because case-control studies describe only relative risk, absolute risk must be calculated by combining those results with rates in a group obtained from population-based studies, such as the Surveillance, Epidemiology, and End Results program (SEER).

The risk estimates that such models provide can be used for two related, but different, purposes. For a research purpose, to help design clinical trials, the "risk of . . . cancer in various subgroups"⁶ can be assessed by such models in order to select groups with higher risks, resulting in trials that are more efficiently powered, using

smaller numbers of participants. The use of models for this purpose has been clearly demonstrated.

For a clinical purpose, to discriminate among individual persons, those "who will develop . . . cancer from those who will not,"⁵ risk estimates can be "important for decisions made at the individual level for clinical decision making and screening."⁶ The problem, though, is that risk estimates, even if accurate, may not necessarily be useful in clinical decision making. Utility depends on the degree of absolute risk indicated by a model and whether that degree is high or low enough to support a specific clinical decision. An underlying problem is that the absolute risk of cancer is generally so low that a higher risk indicated by a model may still be low in absolute terms. As noted by Rockhill et al, "the probability that a person with a certain risk factor profile will develop even a relatively common cancer. . . [is] low because the lifetime risk of developing common cancers [is] low. . . . Therefore, most individuals will remain cancer-free over a considerable period of time; most cancers will arise among individuals from the population with close to an average individual risk."⁶ The situation, further discussed by Rockhill et al⁷ and by Gail and Costantino,⁵ is inherent to many risk models of cancer. As noted by Fears et al, for the melanoma model, even for high-risk "patient 6" who has an estimated relative risk of 24.2, the 5-year absolute risk of developing melanoma may be less than 1%.² That degree of risk, though numerically low, would also seem to be high enough to justify the authors' suggestion that such individuals undergo complete skin examination, counseling, or surveillance.²

This model raises two important issues for clinicians and researchers to consider. First, what absolute risk in any individual should trigger increased surveillance or further assessment? The recent development of sophisticated noninvasive technology such as diffuse optical spectroscopy that is nevertheless simply applied may make the options more attractive in the future by providing an alternative to biopsy, but the technology needs to be validated before that can occur.⁸ Second, in the currently assessed population, many thousands of at-risk individuals will need to be entered onto a study to assure sufficient power to attain a difference in a reasonable time period in a chemoprevention trial.⁷ As emphasized by these investigators, their model is not meant to identify current melanoma cases and is not meant to be used in patients with a prior melanoma or nonmelanoma skin cancer or in patients with a first-degree relative with melanoma. These latter two groups, however, are likely to be good candidates for chemoprevention trials and to require considerably fewer candidates to attain sufficient

power for a valid result. We would encourage these and other investigators to develop risk predictors for this group of patients as well. Overall, this article represents an important and seminal contribution to the field of cancer control,² similar to the contributions by Gail et al for breast cancer prediction.⁴

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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