Cancer Prevention Research

Risk Factor Models and Personalized Health: Opportunities and Challenges for Asymptomatic Individuals

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See related article by J.A. Usher-Smith et al., p. 13

Risk prediction for disease in asymptomatic individuals and its appropriate utilization translated through lifestyle modifications, therapeutically oriented prevention, and screening, and early detection has resulted in widespread improvements in population health, particularly for cardiovascular disease outcomes. The challenge in the last decade or two has been to extend this approach to cancer, both at the population and individual levels. How should we move forward in developing risk models that can provide high-level guidance for improvements in population health and to the individual? In what can only be described as a *tour de force*, Usher-Smith and colleagues have provided a systematic review of risk prediction models for colorectal cancer in asymptomatic individuals and, in doing so, set a new bar for cancer prevention and control approaches to the broad problem of defining the best way to assess a risk for colorectal cancer in asymptomatic individuals, and perhaps providing a strong basis for a similar assessment in other common cancers as well.

After a careful review and vetting of the available literature, a detailed analysis of 87 nongenetic variables was assessed in each model. In addition, the possible role of SNPs and genes in each model was assessed, and the predictive ability of the different risk models and their potential applicability and practical use for population-based stratification were discussed using the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines, the most advanced state-of-the-art approach according to the epidemiologists and statisticians involved in the peer review of this seminal article. Nevertheless, even with this degree of effort, randomized trials in large cohorts will be needed to sort out the value of any particular risk model. However, epidemiologists, public health advocates, preventionists, biomarker aficionados, and others dedicated to reducing mortality from cancer should read this seminal and sentinel article by our English and Australian colleagues from cover to cover. It is an important document. Now to the "fun" stuff—at least to an editorialist!

There is a great deal of discussion in the public health and cancer-preventive medicine communities about the meaning and usage of risk models. The patient populations being assessed by these groups are frequently quite different, and it is critical, as done in the current report, to clarify which group of individuals is being studied. Although the value of SNPs and other genetic markers in asymptomatic persons shows promise in their evaluations, studies to date involved small cohorts and potentially the problem of false positives and overdiagnosis. The challenges in obtaining genetic information about asymptomatic individuals outside an epidemiologic or clinical trial are substantial, and the generalizability and usefulness of information will need to be validated. Surprisingly, family history of cancer did not seem to play a role in their assessment. However, despite the mantra that family history is important in assessing risk, we and others have raised the issue that family history as a process needs to be validated as a risk factor (1, 2). There is much opportunity for interested investigators to explore this arena, which should be considerably easier with the availability of electronic records and widespread interest of the general population in their genealogy. But maybe not, as obtaining accurate information in the primary care or oncology setting can be quite challenging.

On the other hand, a recent analysis proposed by one of the world leaders in the field of colorectal cancer biology and genetics has proposed that genetic risk is largely random or as some have put it, "bad luck" (3). Not surprisingly, the backlash to this viewpoint has been enormous, with many pointing out (and I agree) that personal nongenetic risk factors exist that influence the outcome (4). In that regard, an important conclusion from the current study is that no improvement in prediction performance occurs with an increasing number of variables added to models and that models with SNPs perform no better than simpler models with more readily available variables—even with only a limited number of variables (three to four) suitable for clinical practice implementation. This observation potentially has enormous importance for moving forward with risk stratification for prevention intervention for screening for colorectal cancer. I also suspect as well, maybe for screening and early detection for a broad range of cancers. It would behoove our epidemiologic and statistical colleagues to take on evaluating risk models for breast, prostate, lung, and perhaps even less common cancers.

Now, onto an even broader issue. Beyond these population-related issues, what implications do risk prediction models have for individuals and society as a whole?

First, a simple one: the presence of a Mendelian hereditary disease, such as familial adenoma polyposis or Lynch Syndrome, overrides the importance of personal risk factors, although the effect of smoking always needs to be considered and there may well be a role for therapeutic prevention in this setting (5). Although the article is focused on assessing risk profiles in asymptomatic people, utilizing the same general principles in assessing the usefulness of nongenetic factors in people with hereditary diseases, those at risk for secondary cancers, such as immuno-compromised individuals, organ transplant patients, and cancer survivors, should apply.

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Second, a critical practical issue is the usage of various terms, such as Personalized Medicine, Precision Medicine, Precision Prevention, and others, each with its adherents and publicists. The major concern and conundrum, though, are that we see such usage trends as Precision Medicine or Precision Prevention, which are largely genetically or genomically oriented, replacing or relegating nongenetic risk factors to a distant secondary role, and marginalizing the broader terminology of Personalized Medicine. Certainly, measurement of genomic features of cancers has become increasingly important, but identification of actionable targets has been limited, and it remains to be seen whether the clinical and economic value will result in common usage in the treatment setting. However, in the prevention setting, we need to be more nuanced and inclusionary, particularly in this era of patient-oriented outcomes. I would be surprised indeed if, in the setting of asymptomatic individuals, genomic approaches alone lead to much useful generalizable information. But since hope springs eternal, perhaps a composite of low-risk SNPs or a rare new Mendelian genetic abnormality will be discovered.

Third, I offer the term Personalized Health, which, by its very wording, engages the patient in the process of decision making. With the increasing participation of patients in their own health care and shared decision making (6), what could be more important than providing validated risk factor guidelines? Our society is being overwhelmed with the marketing of functional foods, herbal entities, and "natural" supplements, almost all without oversight or regulatory assessment of benefit or harm, although the FDA has begun to deal with the issue (7). The negative and adverse outcomes *vis a vis* randomized trials with β-carotene as a candidate for lung cancer prevention in smokers (8) and with α-tocopherol in individuals at high risk for prostate cancer based on PSA measurements (9) indicate that a cautionary approach to assessing risk for both populations and individuals needs to continue in a proactive manner. And finally, the development of validated risk factor profiles should lead to more utilization of screening and early detection targeted to those at the highest risk, educational uptake by the population at large, and the comparative effectiveness of population-based colorectal cancer (CRC) screening, including cost and harm from colonoscopy. The identification of high risk in asymptomatic individuals also should enhance the adoption of effective chemoprevention agents as the risk-benefit ratio using different modeling systems is validated. The work performed and reported in this issue significantly expands the playing field for readers of *Cancer Prevention Research* and provides an important platform for developing the entire field of cancer prevention in and of itself and to challenging the screening and early detection experts how best to incorporate preventive risk-benefit models into their paradigms, whether it be for colorectal, breast, prostate, lung, or other cancers. Much work ahead!

Disclosure of Potential Conflicts of Interest

F.L. Meyskens is co-founder of Cancer Prevention Pharmaceuticals.

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