LETTERS TO THE EDITOR

New cardiovascular risk determinants do exist and are clinically useful

I read with interest the article by Smulders et al., in which the authors noted that the key to understanding a statistically significant relationship between independent risk predictions, but no improvement in risk classifications, lies with the statistical methodology used for the assessment. But, it seems to me that the final criteria for defining biomarkers for clinical use must be from information obtained from well-designed prospective outcome studies that show clinical management can be altered on the basis of test results leading to improved outcomes, in an economically reasonable way. The statistical tests used to evaluate studies performed prior to outcome studies (preliminary studies) help in pointing towards which biomarkers might show sufficient diagnostic discrimination to be tested in what may be large expensive prospective studies that define clinical outcome.

In their article, Smulders et al. discussed a number of statistical techniques that may be used in preliminary studies to assess biomarkers for outcome studies. These include c-statistic, risk ratio/odds ratio (RR/OR), and reclassification. It has been demonstrated that RR/OR is more sensitive for identifying biomarkers than c-statistic. For inflammatory markers tested, so far there is a problem in that the RR/OR falls into a range of c-statistics between 0.6 and 0.5, denoting very poor diagnostic discrimination. With such weak associations, the between-study variance is large, giving rise to RR/ORs that vary between 1.0 and 4.4, so that the true RR/OR cannot be known. One way to determine whether such studies may be clinically useful is to calculate revised positive predictive values (those based on the actual incidence). Because the incidence of disease in the population is low and the relationship is weak, in the best case the predictive value is usually about 1%. That is to say for every 100 positive results (above a cut off) 99 are false positives. The same problem affects reclassification also. Thus, it has been shown in such cases that reclassification may cause many more persons without the condition to be reclassified into the high-risk group than persons with the condition, giving rise to worse performance. Moreover, because of the variability associated with weak relationships, reclassification of persons at intermediate risk for coronary disease to high risk varies substantially from study to study just as the RR/OR does. For example, in one study, reclassification of persons at intermediate risk for coronary disease to high risk on the basis of C-reactive protein was limited to 2.7%, whereas another study showed a reclassification of 12% for those at intermediate risk.

As Wang discussed in the accompanying article, recent clinical studies underscore just how well traditional biomarkers (that are true risk factors whose modification directly reduces risk) perform with regard to the prediction of future cardiovascular risk. In my view, the problem with new biomarkers, tested so far, is that the weak relationships make the challenge great in terms of design and cost for prospective outcome studies that are apt to fail.

References

Stanley S. Levinson
Department of Pathology and Laboratory Medicine
University of Louisville and Laboratory Service
VAMC
800 Zorn Avenue
Louisville
KY 40206
USA

Department of Veterans Affairs Medical Center
800 Zorn Avenue
Louisville
KY 40206
USA
Tel: +1 502 287 5565
Fax: +1 502 287 6265
Email: levinson@louisville.edu
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