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Letters to the Editor

Correspondence re: B-L. Adam *et al.*, Serum Protein Fingerprinting Coupled with a Pattern-matching Algorithm Distinguishes Prostate Cancer from Benign Prostate Hyperplasia and Healthy Men. Cancer Res., *62:* 3609–3614, 2002

Letter

In an interesting article, Adam *et al.* (1) recently described the use proteomics on serum samples whereby they distinguished prostate cancer patients from healthy controls. They reported that the sensitivity and specificity of the proteomics test was 83% and 97%, respectively, and stated that they obtained a positive predictive value of 96% for the study population. This is irrelevant information, because the predictive value depends not only on the sensitivity and specificity (validity) but also on the prevalence of disease in the study population. Any positive predictive value can be obtained by changing the prevalence of disease in a population, regardless of the validity of a test (2). The case-control ratio of their study was roughly one control per case, i.e. a prevalence of 50%, a ratio that is not attained even in high-risk populations. Had the authors chosen to have 10 controls per case, the positive predictive value would have decreased from 96% to 75%, although the validity of the test would have remained the same.

The authors also state that a positive predictive value of 91% would be obtained in a "general population," a value that is based on an estimate of a population prevalence of 30% for prostate cancer. This is an overestimated prevalence of clinically relevant prostate cancer; prevalence of that magnitude has only been observed for microfocal prostate cancer in autopsy series or in men selected for elevated levels of serum PSA.[1]

Therefore, if such a high detection rate could be obtained in a general population, it would entail a large proportion of over diagnosis. In previous prostate screening studies using PSA, about 1–4% of unselected, middle-aged men in general populations have been found to have prostate cancer (3). Assuming a prevalence of 2%, the application of proteomics test with the cited validity would result in a positive predictive value of 36%. In comparison, the corresponding value for PSA testing has been ~30% when applied to a population with the same prevalence (4). It should also be recognized that the cases in the study by Adam *et al.* (1) were clinically detected cases, and data from comparisons between clinical cases and healthy controls cannot be extrapolated to a screening program in which preclinically cases will be detected.

However, this criticism does not belittle the findings of Adam *et al.* (1). The application of proteomics in screening for cancer is novel and promising, and it may improve early prostate cancer detection, perhaps most likely in combination with PSA testing, which has a rather low specificity. If the cited validity of proteomics could be preserved when applied to serum samples from men selected for intermediately elevated levels of PSA (e.g., range, 3–10 ng/ml, a range in which one of four men has cancer on subsequent prostate biopsies), a positive predictive value of 90% would be obtained. This would translate into a large reduction in the number of negative prostatic biopsies without decreasing sensitivity for prostate cancer detection too much. Studies on prediagnostically collected samples from large, nonselected cohorts are needed to evaluate the potential role of proteomics in early prostate cancer detection.

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Reply

We thank Stattin and Hakama (1) for their careful and critical reading of our report, and appreciate the opportunity to respond. The statistical objections regarding how we calculated the positive predictive value of the SELDI profiling approach are relevant and accepted. Since the objective of our study was entirely a proof-of-principle study using preselected patient and control samples, we agree that calculating the positive predictive value using this study population was inappropriate. However, it was not our intent to determine whether this diagnostic approach has potential to detect only the clinically important cancers using this study population. As Stattin and Hakama (1) correctly state in their final paragraph, a large population of nonselected preclinical cohorts will be required to appropriately address the potential clinical utility of this proteomic approach. We agree, and such studies are in progress.

Indeed, a discussion of preclinical and clinical cases of prostate cancer with regard to ultimate biologic relevance is always clouded. Amongst the vast pool (30% prevalence) of preclinical cancers, a pool in which all of the cancers at some time reside, are both those destined to indolent or aggressive behavior. The likelihood that a proteomic pattern with very high sensitivity and specificity will accurately detect

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[1] The abbreviation used is: PSA, prostate-specific antigen.

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a large percentage of preclinical tumors is great. The corollary envisioned is that variations in proteomic signature pattern will specifically identify those cancers with lethal potential and direct therapy more rationally.

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See "Insert A"

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