Improved Biomarkers for Prostate Cancer: A Definite Need

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Prostate-specific antigen (PSA) screening for prostate cancer is now widespread in the United States among men of all ages (1). Although prostate cancer mortality has fallen in the United States since the onset of widespread screening, a relationship between screening and the decline in mortality has not been proven.

There is general agreement among clinicians that the PSA test has the highest predictive value for prostate cancer, that PSA screening can detect early-stage cancers possibly 10 years earlier than without the PSA test, and that most cancers detected by PSA screening appear clinically important when their pathologic characteristics are used as a surrogate for biologic potential. However, all experts agree that PSA has limited specificity (i.e.,
the ability to correctly identify men without cancer) because benign disease, including prostatic enlargement and inflammation, can increase PSA levels.

This lack of specificity when using PSA to screen for cancer uncovers some cancers that would not have been detected during the life of the patient in the absence of PSA screening—i.e., overdiagnosis—among men for whom the biopsy is done for a benign increase in PSA level. Computer simulations suggest that the overdiagnosis rate with PSA screening may be as high as 30% or more in a screened population over age 55 (2,3). Furthermore, PSA is not an ideal marker of aggressive cancer when the grade of disease is used as a surrogate marker for aggressiveness, because high-grade cancers actually produce less PSA than low-grade cancers when the levels are corrected for the cancer volume (4). Thus, we need not only more specific prostate cancer markers but also better markers of biologically relevant disease.

One such potential marker is α-methylacyl-CoA racemase (AMACR), an enzyme that is involved in peroxisomal β-oxidation of dietary branched-chain fatty acids. Recent studies have shown that, compared with expression in normal or benign prostate epithelium, AMACR is consistently overexpressed in prostate cancer epithelium, making it a specific marker for cancer cells within the prostate gland (5–7). Furthermore, overexpression of AMACR may increase the risk of prostate cancer because its expression is increased in premalignant lesions (prostatic intraepithelial neoplasia) (5–7). In addition, epidemiologic, genetic, and laboratory studies point to the importance of AMACR in prostate cancer. Indeed, there is an association between higher dietary intake of the main sources (e.g., beef) of branched-chain fatty acids and prostate cancer risk (8); genome-wide scans for linkage in hereditary prostate cancer families suggest that the chromosomal region for AMACR (5p13) is the location of a prostate cancer susceptibility gene (9,10), and AMACR gene sequence variants (polymorphisms) cosegregate with cancer of the prostate in families with hereditary prostate cancer (11). Also, experimentally induced loss of AMACR expression slows the growth of some prostate cancer cell lines (12). Thus, because AMACR has recently been shown to be detectable in the urine of men with prostate cancer after prostatic biopsy (13), AMACR may be a valuable biomarker for prostate cancer.

In this issue of the Journal, Sreekumar et al. (14) screened sera from men with biopsy-proven prostate cancer and men without known prostate cancer for a humoral immune response to AMACR, because it has not been possible to consistently detect AMACR in the circulation. Using protein microarrays, they found that AMACR immunoreactivity was significantly higher in the sera from cancer case subjects than from control subjects; this finding was not seen for other proteins on the microarray. Interestingly, all men showed evidence of a humoral response to PSA, regardless of cancer status.

The authors validated the specificity of the AMACR immune response by using quantitative immunoblot analysis and an enzyme-linked immunosorbent assay, with the results of both approaches suggesting the presence of high-affinity antibodies to AMACR in the sera of prostate cancer case subjects. In addition, the immune response against AMACR (when used to discriminate between cancer patients and control subjects) had a statistically significantly greater sensitivity and specificity than that of the PSA test.

In their paper, Sreekumar et al. (14) say little about the control group of subjects (those thought not to harbor prostate cancer) and how prostate cancer was excluded from them. Although these patients presumably also underwent prostate biopsies, it is well known that a prostate biopsy can have a false-negative rate approaching 30% depending upon the technique used, so the possibility of missed cancer in the control group must be considered when evaluating their data. Additionally, most of the cancers were PSA-detected tumors, and the biologic relevance of the tumors is not known. The authors found no relationship between the AMACR immune response and accepted surrogate markers of tumor biology [Table 2 in (14)]. Furthermore, as the authors mention, AMACR is also found in nonprostate normal tissues and other malignant tissues—a finding that will have to be addressed in future studies before an AMACR immune response can be considered a clinical biomarker of prostate cancer.

The value of the present study may be the proof of principle that screening for an immune response to cancerspecific antigens by using protein microarrays could lead to improved markers of disease. This approach may help provide clinicians of the future with panels of biomarkers (15) that will more specifically identify men who have the biologically relevant prostate cancers that need aggressive treatment.

REFERENCES


