Validation of Biomarkers for Active Surveillance of Prostate Cancer

May 20, 2013

ME Arnegard

Prostate cancer is the second leading cause of cancer-related deaths among men in the United States and the most commonly diagnosed non-cutaneous form of cancer in this population. Treatment of early-stage prostate cancer is controversial, particularly when tumors are detected via prostate-specific antigen (PSA) screening. Use of this biomarker has certainly increased prostate cancer detection. Yet, it has also led to the over-diagnosis of low-risk forms of this heterogeneous disease. In a large majority of cases, new diagnoses of prostate cancer are aggressively treated, though there is evidence that many of the diagnosed cancers are low risk and may never become clinically evident during a patient's lifetime even if he is never treated (Wilt et al., 2012).

In a recent study led by Dr. Daniel Lin, who is an associate member in the Public Health Sciences Division of the Fred Hutchinson Cancer Research Center and Professor of Urology at the University of Washington, a team of scientists performed a baseline analysis of new prostate cancer biomarkers, which may eventually allow oncologists to distinguish between lower- and higher-risk prostate cancers. Application of a panel of such biomarkers in an 'active surveillance' approach to monitoring localized prostate cancer non-invasively holds the promise of reducing the costs of overtreatment, including reduced quality of life, while improving the detection of those cancers warranting aggressive treatment. Contributors to the study include Drs. Lisa Newcomb, Elissa Brown and Peter Nelson of the Hutchinson Center, as well as several other medical researchers in the Canary Prostate Active Surveillance Study (PASS) consortium.

Radiation therapy and surgery, including radical prostatectomy, are the main immediate curative treatment options for prostate cancer. While life-saving in select patients, these treatments come with significant potential side effects, such as the possibility of urinary incontinence, erectile dysfunction, bowel dysfunction and attendant risks of surgery. Led by Dr. Lin, the Canary PASS consortium aims to test and confirm new prostate cancer biomarkers that can be collected with low invasiveness (e.g., from urine or blood samples) and which might help identify low-risk patients and avoid overtreatment. This multicenter prospective study opened for enrollment late in 2008, accepting men with previously diagnosed, but untreated, early-stage prostate cancer who have elected active surveillance as their preferred course of action (Newcomb et al., 2010). Clinical data
such as cancer progression and multiple biomarker levels are being followed in these men for at least five years.

The consortium’s most recently published paper presents promising baseline data, collected from 387 men at the time of enrollment, for two biomarkers that appear to be associated with aggressive prostate cancer: PCA3 and the TMPRSS2:ERG fusion. Prostate carcinomas overexpress PCA3, a prostate-specific noncoding RNA (Whitman et al., 2008). In contrast, TMPRSS2:ERG is the product of a fusion between TMPRSS2, a gene regulated by androgens, and the ERG oncogene (Tomlins et al., 2005). In aggressive forms of prostate cancer TMPRSS2:ERG seems to be the most prevalent of the many genomic alterations involving the ETS oncogene family.

Lin et al. tested for a statistical association between each of these biomarkers and prostate cancer grade, measured by the Gleason score (i.e., based on microscopic appearance), or cancer volume, measured by the percentage of prostate biopsy cores containing cancer. The researchers found that both PCA3 and TMPRSS2:ERG scores were positively correlated with cancer volume and Gleason score (see figure), which are better predictors of post-surgical outcome than serum PSA level. Additional analyses suggested that PCA3 may outperform TMPRSS2:ERG in predicting aggressive prostate cancer. In a final analysis, however, the authors found that levels of PSA, PCA3 and TMPRSS2:ERG, together, were not statistically superior to PSA alone in predicting high-grade cancers, though this three-biomarker panel did exhibit a trend towards significantly enhanced predictive ability.

PCA3 and TMPRSS2:ERG have not yet been approved by the FDA for prostate cancer monitoring. Though the baseline findings of Lin et al. are encouraging for these candidate biomarkers, additional work is clearly needed to further define their utility in detecting aggressive disease during active surveillance. Indeed, the PASS consortium plans to extend enrollment to at least 1,000 men and to continue adding to their centralized biorepository of tissue samples and data for several more years (Newcomb et al., 2010). The biomarkers that are developed from this extensive research may eventually help appropriate populations of men safely delay prostate cancer treatment while under active surveillance, while concurrently identifying men who may benefit from immediate treatment.


Scores at study enrollment for the PCA3 biomarker (yellow) and the TMPRSS2:ERG biomarker (blue) increased significantly with each incremental increase in prostate cancer grade, measured by at least 10-core biopsies around the time of study entry. Each colored box contains half of all observations, with the horizontal line segment (i.e., the median) dividing upper and lower quartiles. Vertical whiskers show the non-outlier range of observations, while outliers are shown as individual points outside this range. Disease grade, an indicator of pathological severity, was categorized based on the Gleason score (as indicated along the x-axis for both plots). Biomarker scores are given as natural logarithms (y-axes).

*Adapted from the manuscript*