Evaluating Cell Cycle Gene Expression for Prostate Cancer Prognosis

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Prostate cancer is the second leading cause of cancer-related death among American men. Substantial biological heterogeneity, however, makes it clinically challenging to predict tumor aggressiveness and determine the appropriate course of treatment. Prognosis is currently estimated using measures of tumor stage, diagnostic prostate-specific antigen (PSA) level, and Gleason score (a quantitative measure of tissue architecture based on microscopic analysis). Additional prognostic biomarkers could help to provide more accurate predictions of individual outcomes, and stratify patients for more precise care regimens. The expression levels of cell cycle-regulated genes are commonly dysregulated in various cancer types, and have been associated with cancer aggressiveness and poor patient outcomes.

Several commercial tests have been developed to evaluate gene expression in relation to prostate cancer progression. These panels, however, were developed based on selected patient groups and the clinical utility of these tests has been questioned. To see if cell cycle-regulated gene dysregulation might provide additional prognostic information for prostate cancer in a population-based cohort, Drs. Rohina Rubicz and Janet Stanford and colleagues in the Public Health Sciences Division evaluated a panel of 30 cell cycle-regulated genes for differential expression in prostate cancer tumors. As recently reported in *The Prostate*, mean expression in these genes was associated with a twofold higher risk of lethal prostate cancer.

The expression levels of cell cycle-regulated genes increase or decrease according to the timing and duration of the cell cycle. These genes are important for normal growth and development, as they are involved in various processes necessary for cell duplication. As such, these genes may be more highly expressed in actively dividing cells, such as within a tumor, with transcript levels reflecting the growth rate of the tumor. Previous studies have used expression profiles of cell cycle-regulated genes to measure tumor aggressiveness and help inform prognostic groups in breast cancer and lymphoma, suggesting that a similar approach might be useful for classifying patients at risk for prostate cancer recurrence and death.

The authors evaluated existing data and tumor samples from nearly 400 men diagnosed with prostate cancer in King County, Washington, who had undergone a radical prostatectomy. Genome-

wide gene expression profiling was performed on archived tumor tissue blocks from these patients, providing mRNA transcript levels for each individual. The mean expression levels for a panel of 30 candidate cell cycle-regulated genes were then evaluated for an association with prostate cancer recurrence or lethality, over an average 12.3 years of follow-up.

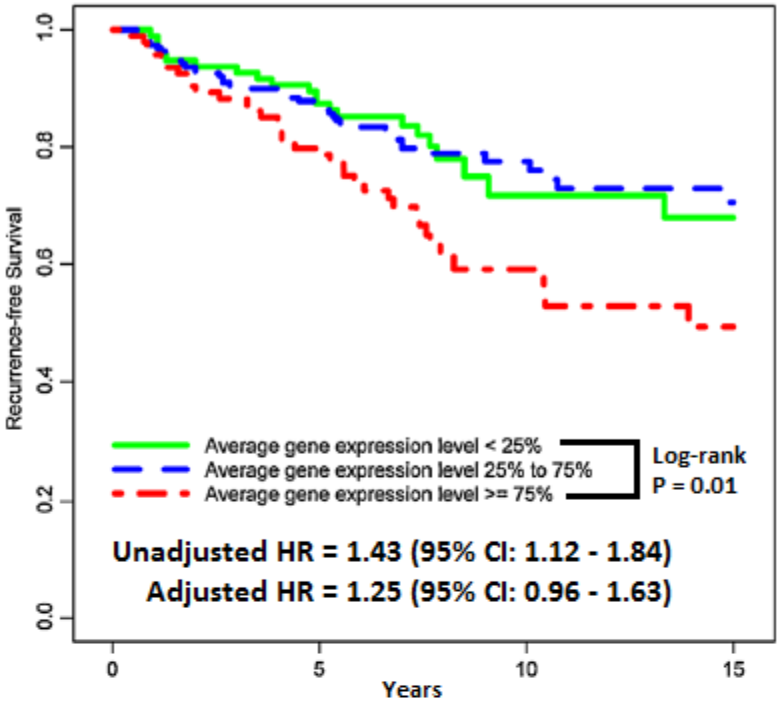
The mean expression level of this gene panel was found to vary by prognostic group, with the lowest expression for the group of cases that did not recur, higher expression for the recurrence group, and highest expression for the group that progressed to metastatic or lethal prostate cancer. These levels were then evaluated for an association with recurrence and lethality. "The average expression level of these genes was associated with time to prostate cancer recurrence for patients with the highest expression levels," said lead author Dr. Rubicz (see figure). "Similar results were observed when the analysis was limited to patients who progressed to lethal prostate cancer." In addition, 10 of these genes individually demonstrated statistically significant differences in expression between the groups, highlighting potential targets for future investigation.

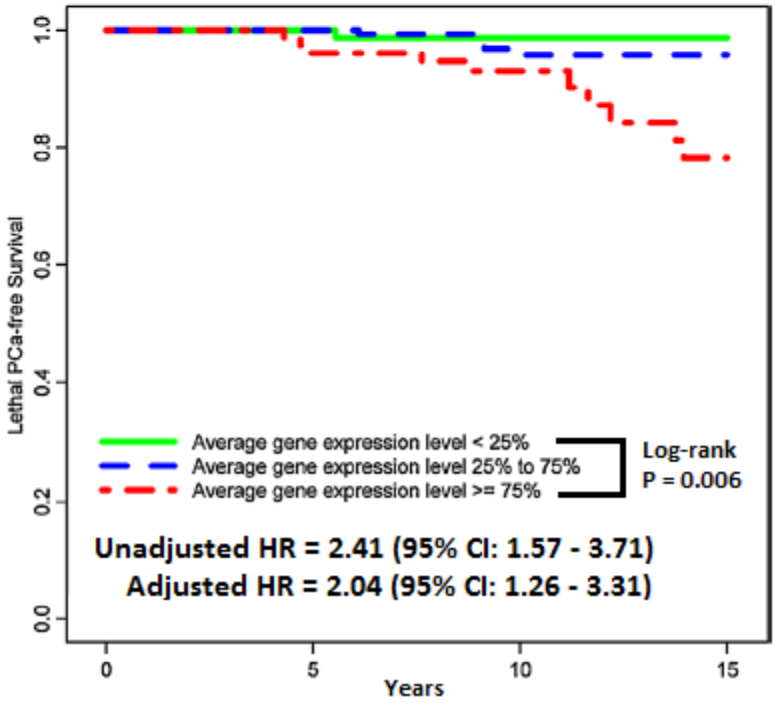
These results suggest that gene expression of some or all of these genes may potentially be useful as a prognostic biomarker for prostate cancer. "However, in our cohort the mRNA levels for this panel of genes did not substantially improve upon Gleason sum as a prognostic marker for overall prostate cancer recurrence," said Dr. Rubicz. Thus while higher mean gene expression was associated with a twofold increase in risk of lethal prostate cancer in this study, further work is needed before this finding might be useful for informing clinical practice. "The next step for this project will be to expand the analysis to include transcriptome-wide DASL array (Illumina, Inc.) data to identify top-ranked differentially expressed genes that may be clinically useful for stratifying patients into prognostic subgroups."

Other Fred Hutch investigators contributing to this project were Drs. Shanshan Zhao, Jonathan Wright, Suzanne Kolb, Daniel Lin, and Peter Nelson.

Citation:

Rubicz R, Zhao S, April C, Wright JL, Kolb S, Coleman I, Lin DW, Nelson PS, Ostrander EA, Feng Z, Fan JB, Stanford JL. 2015. Expression of cell cycle-regulated genes and prostate cancer prognosis in a population-based cohort. *Prostate*. doi: 10.1002/pros.23016.





Kaplan-Meier plot of time to prostate cancer recurrence (top) or death (bottom), according to the percentile distribution of the mean expression levels of 30 cell cycle-regulated genes. Hazard ratio (HR) and 95% confidence interval (95% CI) associated with a change from the 25th to the 75th percentile of mean expression level distribution. The adjusted HR adjusts for age at diagnosis, Gleason score, diagnostic prostate specific antigen level, and pathologic tumor stage.

Image provided by Dr. Rohina Rubicz