Background:

Gleason score
- Morphologic measure of loss of normal tissue structure
- One of strongest clinical predictors of prostate cancer survival

mRNA Signatures of Gleason score
- Distinct set of genes and pathways may affect the de-differentiation
- Understanding gene signatures of Gleason pattern may give insight into prostate cancer progression
- Prior studies identified mRNA signatures for Gleason pattern results across studies not validated, likely due to small sample sizes

Aim: To examine Gleason grade, defined histopathologically and by mRNA signature, to elucidate pathways of de-differentiation and testability of Gleason grade to discriminate lethal outcomes

Materials & Methods:

Patients
- 650 TURP samples from a Swedish Watchful Waiting Cohort (1977-1999)
- 950 prostatectomy samples from the US Physicians’ Health Study and Health Professionals Follow-up Study cohorts (1983-2004)

Gleason grading
- Original Gleason score data from medical records
- Standardized re-review Gleason score from histopathological review by study pathologists

Gene expression profiling
- Illumina DASL platform: ~6100 genes
- Available for 388 Swedish men and 116 US men from PHS

Statistical methods
- Calculated hazard ratios (95% CI) and c-statistics to examine prognostic ability of standardized Gleason grading to predict lethal prostate cancer
- Prediction Analysis in Microarrays to build mRNA signature of high and low grade prostate cancer in Swedish cohort → applied to PHS cohort
- Used Gene Set Enrichment to explore pathways distinguishing grade

Results:

Figure 2: Distribution of Gleason scores following original and re-reviewed Gleason scores

Figure 4: Identification of 157-gene signature of high vs. low grade prostate cancer through Prediction Analysis of Microarrays

Table 1 and Figure 3: Ability of a re-reviewed Gleason score to predict lethal prostate cancer. In standardized review, 4+3 vs. 3+4 added prognostic value

Conclusions:
- Ignoring predominance of Gleason pattern 4 in Gleason 7 cancers may conceal prognostic information.
- Standardized review of Gleason can improve prediction of prostate cancer survival.
- mRNA expression signature may enhance understanding of the de-differentiation process of prostate tumors
- Gene set enrichment analysis identified pathways involved in cell cycle, PI3K/AKT pathway, pyrimidine metabolism, and one-carbon folate metabolism.
- Signature may have clinical application for men with Gleason 7, improving classification of a high or low risk of dying from cancer

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