EVIDENCE FOR A CELL CYCLE PROLIFERATION FIELD EFFECT IN PROSTATE CANCER

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BACKGROUND

Gleason grading provides a strong predictor of prostate cancer risk, but due to sampling issues, diagnostic biopsies often misclassify patients. A classifier that is less affected by sampling error could improve risk assessment in prostate cancer biopsies. Several studies have yielded evidence for a "field effect" in prostate cancer, wherein molecular changes in benign prostate tissue reflect those in nearby prostate cancer.[1-3] Such efforts have sought to increase sensitivity of prostate needle biopsies in detecting cancer.[4] We sought to determine whether a classifier that predicts prostate cancer lethality might also demonstrate a "field effect." High expression of cell cycle proliferation genes (CCP) has been correlated with high risk of disease-specific mortality in prostate cancer patients.[5-7] Here we address the potential utility of a CCP assay in overcoming sampling error.

METHODS

Thirty-five radical prostatectomy specimens (2001-2011) with localized unilateral prostate cancers were selected. Patients with prior hormone therapy were excluded. Specimens were reviewed by a genitourinary pathologist (DMB) and assigned Gleason score (2005 ISUP criteria), stage, and margin status. Unstained formalin-fixed, paraffin-embedded (FFPE) sections (5 microns) were macrodissected under the direction of the pathologist to yield 1) Tumor; 2) Benign Adjacent (3 mm away from the tumor); 3) Benign near (10 mm away from the tumor); and 4) Benign contralateral (more than 20mm away from tumor) (Figure 1). CCP scores were generated as in previous studies.

RESULTS

1) There was a strong pair-wise correlation between tumor and benign regions of the prostate (Table 2). The correlations between regions were not significantly different from one another.
2) The correlation improved when we compared the CCP score from the average of tumor and benign adjacent to the average of benign near and contralateral (Pearson correlation coefficient = 0.77).
3) We observed a small shift toward lower CCP scores for each sampled region as we moved away from the tumor (Figure 2). Using a univariate linear mixed model, we found that the CCP score decreased 0.08 units {95% CI: (0.01, 0.13), p-value 0.020} for each step away from the tumor.
4) There was evidence that the field effect was dependent on Gleason grade (Figure 3). Here, we saw a negative correlation between CCP score and Gleason grade which might have resulted from selecting only small unilateral tumors for inclusion in this study.

TABLE 1.
Patient characteristics and summary measurements.

CHARACTERISTIC	N	SUMMARY MEASURE
CCP Score: mean ± SD		
Field = Tumor	35	-0.05 ± 0.77
Field = 3mm	33	-0.28 ± 0.67
Field = 10mm	34	-0.26 ± 0.62
Field = Remote	35	-0.31 ± 0.79
Gleason Score: (%)		
< 7	17	48.6
7	13	37.1
> 7	5	14.3
Tumor Volume: (%)		
Minimal	9	26.5
Moderate	23	67.6
Extensive	2	5.9
Pathologic Tumor Stage: (%)		
T2	28	80
T3a	7	20
Baseline PSA: mean ± SD	35	5.55 ± 2.55
Margins: (%)		
Positive	3	8.6
Negative	32	91.4

TABLE 2.
Pair-wise correlations between different sampled regions.

PAIRED FIELDS	N	PEARSON CORRELATION (95% CONFIDENCE INTERVAL)	p-VALUE FOR TEST OF ASSOCIATION
(Tumor, 3 mm)	33	0.54 (0.23, 0.74)	0.0013
(Tumor, 10mm)	34	0.46 (0.15, 0.69)	0.0061
(Tumor, Remote)	35	0.67 (0.44, 0.82)	8.9×10^{-6}
(3mm, 10mm)	33	0.73 (0.51, 0.86)	1.8×10^{-6}
(3mm, Remote)	33	0.61 (0.33, 0.79)	0.00017
(10mm, Remote)	34	0.69 (0.46, 0.84)	5.6×10^{-6}

FIGURE 1.
Regions sampled within prostate gland.

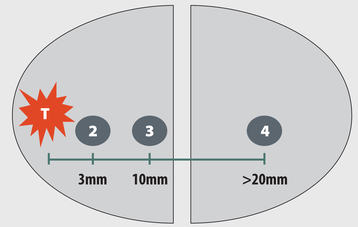


FIGURE 2.
Box plot of CCP score distribution across sampled regions.

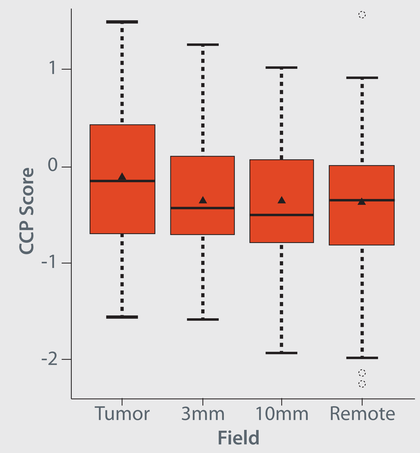
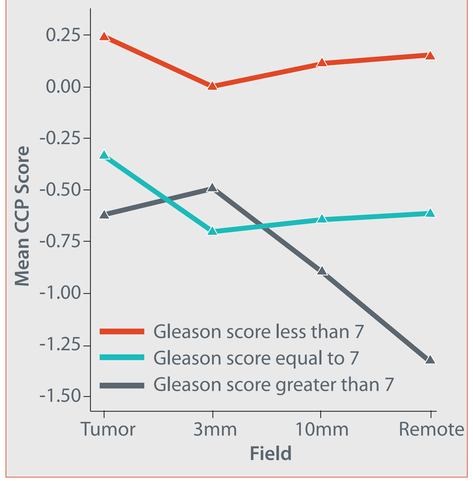


FIGURE 3.
Mean CCP score of sampled regions separated by Gleason score.



CONCLUSIONS

We found a striking correlation between cell cycle proliferation gene expression in prostate cancer tissue and in benign tissue in other regions of the same prostate. Additional studies could address whether increased proliferation in benign cellular compartments increases risk of developing a highly proliferative and deadly prostate cancer, or if highly proliferative prostate cancers more effectively elicit proliferative responses from benign cells within the prostate.

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Presented at EAU - March 18, 2013