

Telomere dysfunction in prostatic carcinogenesis.

Tumor Biology and Human Genetics

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[\[Abstract\]](#)

Background: Telomeres are composed of tandemly repeated DNA sequences (TTAGGG) and specific binding proteins located at the ends of eukaryotic chromosomes. They stabilize chromosomal ends; telomere shortening is an important mechanism of genomic instability and can lead to end-to-end chromosomal fusion, rearrangements and cell death. Here we evaluate the hypothesis that telomere shortening contributes to the development of prostate cancer (CaP).

Methods: We used telomeric, centromeric and chromosome specific peptide-nucleic acid probes with z-stacked quantitative fluorescence in-situ hybridisation analysis to initially analyse 15 radical prostatectomy specimens and then subsequently sextant core biopsies from 80 men obtained in 1998-2001 containing high-grade prostate intraepithelial neoplasia (HPIN) only. The biopsy cohort outcome is blinded to prevent experimental bias and has a minimum follow-up of 2 years with 41 men diagnosed subsequently with CaP and 39 men without CaP on rebiopsy. Regions of interest were identifying with an overlying haematoxylin and eosin slide. **Results:** We found a significant decrease in telomere length in both HPIN and CaP in comparison to normal prostatic epithelium accompanied by elevated rates of aneusomy. Telomere erosion in HPIN was more common in regions of the prostate-containing CaP. We now have analyzed ~4000 cells of matching HPIN and surrounding stroma. Preliminary analysis demonstrated that the median telomere length in HPIN is approximately 27% of the surrounding stroma with upper and lower quartiles being 16% and 38% respectively. Logistic regression analysis is in progress to determine whether the length of the shortest telomeres or the average telomeric length in a sample predicts for subsequent diagnosis of CaP. Secondary analyses are examining the effect of telomere length on the interval to the diagnosis of CaP, the effect of age on telomere length and the eventual Gleason score.

Conclusions: Analysis of telomere length holds great promise for developing improved prognostic markers in prostatic carcinogenesis. This is a first of its kind study in the field.