



# Ethnicity Based Analysis of Prostatectomy Specimens and PSA Outcomes: Results from the NCI Cooperative Prostate Cancer Tissue Resource

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## ABSTRACT

The NCI-funded Cooperative Prostate Cancer Tissue Resource (<http://www.prostatetissues.org>) contains over 3318 prostate cancer cases, including 2895 prostatectomy specimens from 12 hospitals representing four separate academic institutions. In each case the pathologic specimens were reviewed by a panel of academic pathologists using defined criteria as established by the AFIP Prostate Fascicle (third series) and the Gleason grading web site at Johns Hopkins University (<http://162.129.103.34/prostate/>). The dataset includes people of the following defined ethnicity/race; 2030 Caucasians, 624 African-Americans, 58 Hispanic, 28 Asians/pacific islanders. The mean patient age is 62.7 years (range 35 to 85 years). An analysis of both pathologic, clinical, and outcomes parameters with respect to ethnicity have been performed. There was no significant difference identified between individual ethnicity and overall family history of prostate cancer, prostate weight, extraprostatic extension of tumor, Gleason score, order of Gleason score 7 tumors (i.e. 3+4 vs. 4+3), pathologic stage, or vital status. African Americans were slightly, more likely to have positive surgical margins at prostatectomy. PSA recurrence data was calculated on 1276 patients with a mean follow-up period of 40 months. In this dataset African-Americans were more likely than Caucasians to have PSA recurrence, but there was no significant correlation between the elevated post-surgical PSA values and the presence of positive surgical margins. People identifying themselves as Hispanic were not more likely than Caucasians to have post-prostatectomy elevated PSA or PSA recurrence. Thus despite similar overall pathologic and clinical characteristics, African-American men are more likely to have elevated PSA values post-prostatectomy. These samples are a component of the NCI-funded Cooperative Prostate Cancer Tissue Resource, and thus will become available for tissue based prostate cancer studies through such technologies as tissue microarrays for the discovery of biomarkers that may identify these ethnicity-based differences.

## INTRODUCTION

Prostate cancer is the most common tumor in American men, and comprises approximately 220,900 new cancer diagnoses and 28,900 cancer related deaths each year. The majority of men treated in the United States undergo radical prostatectomy for treatment of the disease. For prostate confined disease it is estimated that the potential for cure ranges between 80 and 96%. Evidence of prostatic adenocarcinoma is associated with elevated levels of prostate specific antigen (PSA) which used to lead to diagnostic biopsies for evidence of tumor. PSA levels decrease to undetectable levels in patients when entire prostate gland and tumor have been removed. This PSA nadir can be subsequently followed and evidence of rising PSA values (PSA recurrence) occurs in approximately 15-19% of patients and relates to recurrent prostate cancer. The relative rates of increase of the PSA values has been associated with either local tumor recurrence, or growth of metastatic disease. The presence of PSA recurrence often leads to the use of secondary treatment modalities including radiation, hormonal and chemotherapy. While of some benefit, the presence of disseminated disease reflects a poor prognosis, and currently there is no effective treatment for hormone refractory disease. The ability to predict which patients will undergo PSA recurrence would allow for the identification and focused examination and treatment of these high risk patients. Towards this end The Cooperative Prostate Cancer Tissue Resource (CPCTR) has been established to develop a repository of prostate tissues with detailed annotated clinical, demographic and outcomes data for use in the examination potential biomarkers for prostate cancer diagnosis and treatment. Here we present the current status of the CPCTR database, including an analysis of the retrospective prostate specimens currently banked by the CPCTR and their associated clinical data.

## METHODS

### Data collection sites

Cooperative Cancer Tissue Resource was established by the National Cancer Institute as a source for prostate cancer tissues for biomarker validation studies. This resource consists of four academic institutions (George Washington University Medical Center, Washington, DC, Medical College of Wisconsin, Milwaukee, WI, New York University, New York, NY, and the University of Pittsburgh, PA) and their associated hospitals (Howard University Medical Center, Fairfax INOVA Hospital, Fairfax, VA, Milwaukee VAMC, Community Memorial Hospital, Monomonee Falls, WI, Tisch Hospital, New York, NY, Bellevue Hospital, New York, NY, NYC VAMC, and the Pittsburgh VAMC). Thus this resource represents a broad range of American males undergoing prostate cancer surgery.

### Pathologic evaluation

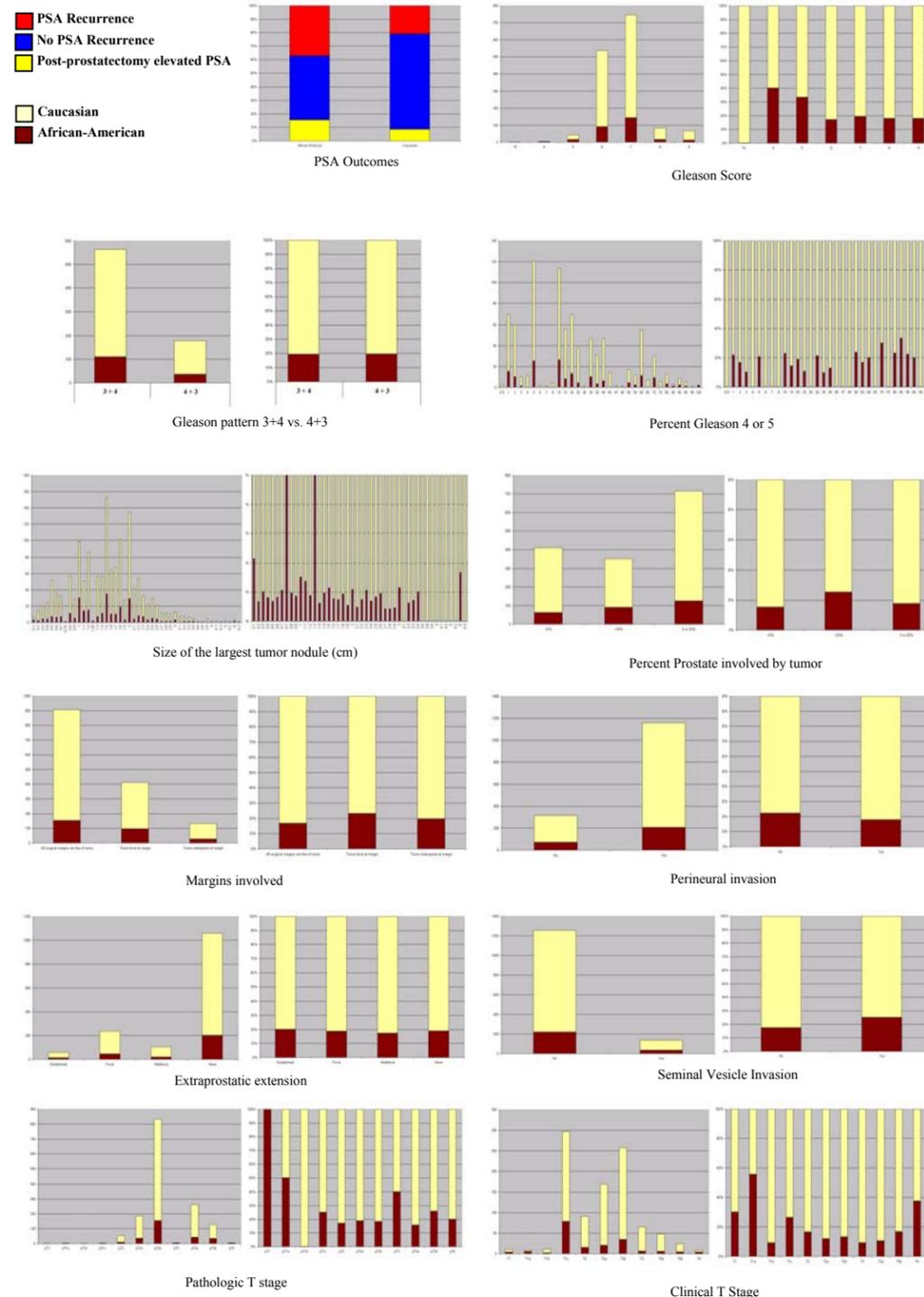
At each institution all the radical prostatectomy specimens from 1990 to 1995 were identified, and all pathologic material reviewed under standardized criteria using the Armed Forces Institute of Pathology Fascicle, Third Series, and the Johns Hopkins grading website (<http://162.129.103.34/prostate/>). In each of these cases review was done by academic pathologists including urologic pathology sub specialists. From these cases the associated archived paraffin embedded tissues were obtained for the CPCTR repository. In addition, prospective prostatectomy cases have been accrued over the last 2-5 years at the participating institutions.

### Clinical Data Collection

IRB approval was obtained for all data and specimen collection. Clinical data was abstracted from the medical records, clinic patient charts, and cancer registries, and included demographic, clinical staging, and PSA recurrence data. Quality assurance testing is performed on 10% of the entire database on an annualized basis through random review of patient data and re-review of the pathologic specimens. Additional quality assurance includes multi-site review of cases from each contributing site.

### Data used for analysis and statistical evaluation

Through June 2002 the CPCTR has collected identified 3318 prostate cancer cases, including 2895 prostatectomies. There are 939 cases with both the prostatectomy specimen and an associated diagnostic biopsies prior to surgery. 624 African-Americans and 2030 Caucasians are identified in the resource. PSA nadir values were calculated based on residual elevated PSA values and took into account the serum PSA half-life. For PSA nadir the PSA values needed to drop below 0.4 ng/dl at a timepoint greater than 59 days (if the initial PSA was less than 50 ng/dl – 2406 cases) or a timepoint greater than 89 days (if the initial PSA was greater than 50 ng/dl – 61 cases). For PSA recurrence serum PSA values needed to increase above 0.6 ng/dl (single value) or have a value between 0.4 – 0.6 ng/dl and demonstrate a continued rise in the subsequent PSA values. In the latter situation the PSA recurrence data was calculated based on the initial elevated PSA value above 0.4 ng/dl. 1766 cases had associated PSA follow-up data status post prostatectomy. PSA outcomes were evaluated on all cases with follow-up PSA values and 1276 demonstrated interpretable outcomes. Loss of cases included no post-surgical PSA values (1653 cases) or no initial PSA values (851 cases). 193 African-American and 863 Caucasian cases were identified with associated calculated PSA outcomes data. Statistical analysis was performed using Chi-squared probability analysis and corrected for multiple tests using the Bonferroni method.



## FIGURES

Graphs represent the analyzed data in the Co-Operative Prostate Cancer Tissue Resource. Paired graphs demonstrate the data as either the total count of samples in the evaluated subgroup, or as the the percent of the evaluated subgroup. The bar code is presented as Caucasian (tan), and African-American (Brown), Post-prostatectomy elevated PSA (yellow), PSA nadir without recurrence (blue) or PSA nadir with PSA recurrence (red). Significant studies are shown in table 1.

	African-American vs. Caucasian
Post-prostatectomy elevated PSA	N.S.
PSA recurrence	0.00000003
Gleason Score	N.S.
Gleason score 6 vs. 7	N.S.
Gleason pattern 3+4 vs. 4+3	N.S.
Percent of Gland involved buy tumor	
cutoff 5%	N.S.
cutoff 25%	N.S.
Extraprostatic extension	
none vs focal	N.S.
focal vs. established	N.S.
focal vs multifocal or established	N.S.
Margins	
Positive vs. negative	N.S.
focal vs. established	N.S.
negative vs. focal	N.S.
Perineural invasion	N.S.
Seminal Vesicle Invasion	N.S.
Pathologic Stage	
pT2a vs. pT2b	N.S.
pT3a vs. pT3b	N.S.
pT2 vs pT3	N.S.
Clinical Stage	
cT2a vs. cT2b	N.S.
cT3a vs. cT3b	N.S.
cT2 vs cT3	N.S.
Vital Status (Death)	< 0.0000005

### Extraprostatic extension definitions:

Focal = 1 site less than 0.8 mm.  
Established = at least one site greater than 0.8 mm.  
Multifocal = more than one site involved.

### Margin positivity definitions:

Focal = 1 site less than 2 mm.  
Established = multiple sites or at least one site greater than 2 mm.

## RESULTS & DISCUSSION

Of the 3318 prostate cancer cases present in the NCI-funded Cooperative Prostate Cancer Tissue Resource (<http://www.prostatetissues.org>) 2030 Caucasians, 624 African-Americans, 58 Hispanic, 28 Asians/pacific islanders were identified. These cases were evaluated for associations between ethnicity and various standard pathologic parameters present within the database. There was no significant difference identified between Caucasians and either African-Americans or Hispanics for family history of prostate cancer, prostate weight, Gleason score, order of Gleason score 7 tumors (i.e. Gleason pattern 3+4 vs. 4+3), tumor size, extraprostatic extension of tumor, seminal vesicle invasion, pathologic stage, or clinical stage. PSA recurrence data was calculated on 1276 patients with a mean follow-up period of 40 months. In this dataset African-Americans were more likely than Caucasians to have PSA recurrence, but there was no significant correlation with the presence of elevated post-surgical PSA values. In addition, African-Americans were more likely to have died, based on vital status records, although there was correlation with death when only patients with documented PSA recurrence were examined. Thus despite similar overall pathologic and clinical characteristics, African-American men are more likely to have elevated PSA values post-prostatectomy and have died. This study demonstrates the limitations of traditional pathologic parameters in the identification of the causes for the increased risk of death from prostate cancer in African-Americans, and emphasizes the need to identify other indicators of their worse prognosis. The tissue specimens associated with these patients are available for validation research studies of candidate biomarkers to identify these differences at a molecular level through technologies such as tissue microarrays.

