Altered N-myc Downstream-Regulated Gene 1 Protein Expression in African-American Compared with Caucasian Prostate Cancer Patients

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ABSTRACT

Purpose: The protein encoded by N-myc downstream-regulated gene 1 (NDRG1) is a recently discovered protein whose transcription is induced by androgens and hypoxia. We hypothesized that NDRG1 expression patterns might reveal a biological basis for the disparity of clinical outcome of prostate cancer patients with different ethnic backgrounds.

Experimental Design: Patients who underwent radical prostatectomy between 1990 and 2000 at Veterans Administration Medical Center of New York were examined. We studied 223 cases, including 157 African Americans and 66 Caucasians (T2, n = 144; ≥T3, n = 79; Gleason <7, n = 122; ≥7, n = 101). Three patterns of NDRG1 expression were identified in prostate cancer: (a) intense, predominately membranous staining similar to benign prostatic epithelium; (b) intense, nuleocytoplasmic localization; and (c) low or undetectable expression. We then examined the correlations between patients’ clinicopathological parameters and different NDRG1 expression patterns.

Results: In this study of patients with equal access to care, African-American ethnic origin was an independent predictor of prostate-specific antigen recurrence (P < 0.05). We also observed a significant correlation between different patterns of NDRG1 expression and ethnic origin. Pattern 2 was less frequent in African Americans (21% versus 38%), whereas the reverse was observed for pattern 3 (60% in African Americans versus 44% in Caucasians; P = 0.03). This association remained significant after controlling for both grade and stage simultaneously (P = 0.02).

Conclusions: Our data suggest that different NDRG1 expression patterns reflect differences in the response of prostatic epithelium to hypoxia and androgens in African-American compared with Caucasian patients. Further studies are needed to determine the contribution of NDRG1 to the disparity in clinical outcome observed between the two groups.

INTRODUCTION

The reason for the disparity in prostate cancer risk, incidence, and clinical progression between African-American and Caucasian men is still controversial. A more biologically aggressive cancer has been proposed as one possible explanation for the younger age at presentation in African-American men compared with Caucasian men (1, 2). In addition, socioeconomic and environmental factors, such as diet, access to care, and screening, have been cited as factors contributing to the more clinically aggressive prostate cancer in African-American patients (3, 4). Nevertheless, limited attention has been focused on understanding the molecular basis of the response of the prostatic epithelium to stimuli as a possible factor in the discrepancy of prostate cancer clinical outcome among patients with different ethnic backgrounds.

N-myc downstream-regulated gene 1 (NDRG1; also known as Cap43) is a recently identified gene, the product of which is a 43-kDa protein that is induced under conditions of nickel exposure, hypoxia, androgens, and prolonged elevation of intracellular calcium (5, 6). The induction of NDRG1 expression by nickel and hypoxia is mediated by hypoxia-inducible factor-1 transcription factor (5), whereas the induction by calcium is mediated by activation protein-1 transcription factor (6). A role for deregulated NDRG1 expression in the pathogenesis of tumors is supported by several studies. In vitro, decreased NDRG1 transcription was noted in colon cancer cell lines compared with normal colon epithelium (7-9), as well as breast and prostate cell lines (10). These earlier publications indicated that the NDRG1 protein is down-regulated in tumor cells and up-regulated during growth arrest and differentiation of tumor cells. However, studies of different tumor types revealed a more complex picture. In MCF-7 breast cancer cells, growth inhibition was not associated with increased expression of NDRG1 (11). In addition, NDRG1 expression was found to be higher in mouse skin carcinomas and in hyperplastic skin epithelium than in normal mouse skin (12). Moreover, in brain and lung, NDRG1 protein expression was found only in tumor tissue, and not in normal tissue (13). In prostate LNCaP cells, NDRG1 is...
significantly induced after androgen treatment (14). These data suggest that NDRG1 might be linked to androgen-induced differentiation and signaling in the human prostate (15).

In this study, we investigated NDRG1 expression patterns in a well-characterized cohort of prostate cancer patients who presented to Veteran Affairs Medical Center (VAMC), an equal-access facility. We hypothesized that investigating NDRG1 expression might reveal a biological basis for the disparity of clinical outcome of prostate cancer patients with different ethnic backgrounds.

MATERIALS AND METHODS

Patient Characteristics and Tissues. Patients were identified through review of the Department of Urology database at the VAMC/New York University School of Medicine. This prospective database enrolled patients with prostate cancer from 1990 to the present, documenting patient demographics, including ethnic origin, stage, and grade of the primary tumor. After Institutional Review Board approval and activation of the protocol, we retrospectively reviewed all relevant clinical information. Tumor grade, stage, pretreatment prostate-specific antigen (PSA) values, final pathological stage, PSA recurrence, and survival data were entered into a database. Representative H&E-stained tissue sections were examined by two attending pathologists (J. M. and R. W.) to evaluate the histopathological characteristics of each case. Of the 261 patients whose tumors were resected at the VAMC, representative tissue blocks of formalin-fixed, paraffin-embedded primary tumors were obtained from 223 patients. Patient selection was based solely on the availability of both adequate clinical follow-up and the availability of representative pathology specimens for immunohistochemical (IHC) analysis. Clinicopathological parameters included pretreatment PSA, pathological stage, and Gleason score. Cases were grouped as either low Gleason score (<7; n = 122) or as high Gleason score (≥7; n = 101). Cases were also grouped according to pathological stage into either early organ-confined tumors (pT2; n = 144) or advanced tumors extending beyond the prostatic capsule (pT ≥3; n = 79).

Assessment of Treatment Outcome. The response variable, time to PSA relapse, was defined as the time from radical prostatectomy to the time of the first detectable (non-zero) PSA measurement. To confirm PSA relapse, three consecutive increases in PSA were required; however, the time of relapse was defined as the time of the first detectable PSA measurement (16–18). Investigators performing IHC analysis and interpretation were blinded to the clinical data.

Immunohistochemistry. The specificity of NDRG1 antibody, which is specific for a 30-amino acid segment consisting of three 10-amino acid repeats in the COOH-terminal portion of the protein, has been demonstrated previously (11, 13). Immunohistochemistry was performed on all 223 cases. Tumor tissues were processed and embedded in paraffin wax. Sections (5 μm) were cut, deparaffinized by use of xylene, and stained with H&E for histopathological diagnosis. For IHC detection, slides were heated for 10 min in 1 M EDTA buffer in a microwave oven, and endogenous peroxide was blocked with methanol containing 0.35% H2O2 for 30 min. The rabbit polyclonal antibody against NDRG1 protein was incubated (1:1000 dilution) with the tissue sections and detected by routine avidin-biotin horseradish peroxidase complex and 3,3-diaminobenzidine as the chromagen. Negative controls were performed with nonimmune serum instead of primary antibodies. No staining was observed with pre-immune serum.

IHC Analysis. Because this is the first study examining NDRG1 expression in a large number of prostate cancer clinical specimens, we decided to comprehensively record the expression profile of each Gleason grade that was present in the tumor to accommodate tumor heterogeneity. The expression was recorded as subcellular localization (membranous, cytoplasmic, nuclear, or combination) as well as intensity of the signal (intense, 3+; moderate, +2; or low, +1/no expression). We first assigned a weight to each different grade area based on percentage of overall tumor that this represented: e.g., one case may have had 30% Gleason 3 with 0+ intensity and 70% Gleason 5 with 3+ intensity of cytoplasmic and nuclear staining. We also assessed the predominant expression pattern in the tumor, defined as the expression pattern seen in >70% of invasive tumor. Normal and benign hyperplastic glands consistently showed predominantly membranous localization of NDRG1 expression. This was considered an internal control pattern for all cases. We identified three different predominant expression patterns of the prostate tumor: pattern 1, intense staining (+3) predominantly in cell membrane similar to the pattern seen in benign prostatic glands; pattern 2, intense (+3) nucleocytoplasmic subcellular localization; and pattern 3, low (+1) or no detectable expression of NDRG1 protein in the tumor compared with the adjacent benign prostatic epithelium.

Statistical Analyses. The F and χ2 tests were used to explore associations between the NDRG1 expression patterns 1, 2, and 3 and the clinicopathological parameters age, race, baseline PSA, Gleason score, and tumor stage. The Wilcoxon rank-sum test was used to assess the association between race and age. The χ2 test was used to assess the association between race and the categorical clinicopathological variables. The logistic model was used to determine whether the association of race with NDRG1 persisted after controlling for Gleason score and tumor stage. The Cox proportional hazards model was used to assess the relationship between the NDRG1 expression patterns and time free of disease recurrence, controlling for baseline PSA, Gleason score, tumor stage, and race. Recurrence-free survival was calculated from date of treatment to date of PSA relapse or last follow-up date, whichever was earliest; patients who died without PSA relapse were censored at the date of death. The association of NDRG1 patterns with PSA recurrence was explored by use of dummy variables as well as ordered categorical variables. All P values were two sided and significant as P < 0.05. All statistical analyses were done using SAS Release 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

We successfully retrieved 223 of 261 (85.4%) registered cases in the database of the Department of Urology at the VAMC. The remaining 38 cases lacked clinical information (n = 20) or did not have enough tissue for IHC analyses (n = 18). The median age at the time of surgery was 68 years (range, 50–85 years). The median follow-up was 4.7 years. Twenty-one
patients were excluded from the time to PSA recurrence analysis because their PSA did not decrease to the nonmeasurable level indicative of adequate resection of the prostate (n = 13), or because they did not have three consecutive PSA assays with increasing levels (n = 8). Sixty-five of the remaining 202 (32%) patients had PSA recurrence during the follow-up period.

The data comparing baseline characteristics of African-American and Caucasian patients, summarized in Table 1, clearly demonstrated the worse clinicopathological profile of prostate cancer in African-American men. In this study, African-American patients presented at a younger age (P < 0.03), with higher pretreatment PSA (P = 0.03), stage (P = 0.05), and Gleason score (P = 0.02) compared with Caucasian patients with equal access to care. The association with pretreatment PSA was assessed in 196 cases. The remaining 27 patients were not included because PSA testing did not become available on a routine basis at the VAMC until 1991, after the test was approved by the United States Food and Drug Administration.

Recent publications reporting on NDRG1 expression in pathological specimens took into account the intensity of staining and described the data as either increased or decreased relative to the normal tissue counterpart (7, 8, 13). We recorded the intensity of the signal and its subcellular localization. NDRG1 exhibited three different expression patterns. In the benign prostatic gland, NDRG1 protein expression appears to be restricted to the luminal epithelial cells. Hyperplastic prostatic glands show predominantly membranous staining of NDRG1 expression (Fig. 1, A and B). Nonepithelial cells, e.g., stroma, muscle, and invading lymphocytes, were negative for NDRG1 expression. No correlation was observed between different patterns of NDRG1 expression and grade (P = 0.54), stage (P = 0.35), or pretreatment PSA (P = 0.18); however, a significant correlation was observed between NDRG1 and ethnic origin of the patients. In our study of the correlation between NDRG1 expression and grade, we used our detailed record of each Gleason grade within a tumor specimen to explore any possible association with the worst grade, the most prevalent, or the most invasive part of the tumor. Our analysis revealed no association with these variables (data not shown). Pattern 1 (Fig. 1, C and D), which is the pattern observed in normal prostatic epithelium and prostatic hyperplasia, showed similar frequencies in African Americans and Caucasians (19% versus 18%). Pattern 2 (Fig. 1, E and F) was less frequent in African Americans than in Caucasians (21% versus 38%); however, the reverse was observed for pattern 3 (Fig. 1, G and H; 60% in African Americans versus 44% in Caucasians). This difference was statistically significant (P = 0.03; Table 2) and remained significant after controlling for both grade and stage simultaneously (P = 0.02).

We did not observe a statistically significant association between specific patterns of NDRG1 expression and disease recurrence after surgery in this cohort. However, in multivariate analysis, tumor stage, grade, patients’ ethnic background, and pretreatment PSA were the significant predictors of treatment outcome in this cohort (Table 3).

### DISCUSSION

We investigated NDRG1 expression in a well-characterized cohort of prostate cancer patients presenting to the VAMC in New York to control for access to care as a possible confounding variable in a patient’s disease outcome. Our data revealed that African-American patients present with a significantly worse clinicopathological profile than Caucasian patients and that ethnic origin is an independent factor in their disease recurrence after surgical treatment. In addition, our data demonstrate that the vast majority of cases had distinct NDRG1 expression in the invasive part of the tumor. Our analysis revealed no association with these variables (data not shown). Pattern 1 (Fig. 1, C and D), which is the pattern observed in normal prostatic epithelium and prostatic hyperplasia, showed similar frequencies in African Americans and Caucasians (19% versus 18%). Pattern 2 (Fig. 1, E and F) was less frequent in African Americans than in Caucasians (21% versus 38%); however, the reverse was observed for pattern 3 (Fig. 1, G and H; 60% in African Americans versus 44% in Caucasians). This difference was statistically significant (P = 0.03; Table 2) and remained significant after controlling for both grade and stage simultaneously (P = 0.02).

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### Table 1  Comparison between characteristics of African-American and Caucasian patients

<table>
<thead>
<tr>
<th></th>
<th>African Americans</th>
<th>Caucasians</th>
<th>Total (n)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Stage</td>
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<td></td>
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</tr>
<tr>
<td>2</td>
<td>95</td>
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<td>49</td>
</tr>
<tr>
<td>3, 4</td>
<td>62</td>
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<td>17</td>
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<tr>
<td>P = 0.05*</td>
<td>157</td>
<td>100.0</td>
<td>66</td>
</tr>
<tr>
<td>Gleason</td>
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<td></td>
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<tr>
<td>&lt;7</td>
<td>78</td>
<td>49.7</td>
<td>44</td>
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<td>≥7</td>
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<tr>
<td>P = 0.02*</td>
<td>157</td>
<td>100.0</td>
<td>66</td>
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<tr>
<td>Baseline PSA (ng/mL)</td>
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<td></td>
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<tr>
<td>&lt;4</td>
<td>7</td>
<td>5.0</td>
<td>7</td>
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<tr>
<td>4–10</td>
<td>63</td>
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<td>30</td>
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<tr>
<td>&gt;10</td>
<td>71</td>
<td>50.3</td>
<td>18</td>
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<tr>
<td>P = 0.03*</td>
<td>141</td>
<td>100.0</td>
<td>55</td>
</tr>
<tr>
<td>Median (range) age (years)</td>
<td>65 (51–78)</td>
<td></td>
<td>71 (50–85)</td>
</tr>
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</table>

*chi^2 test.

PSA, prostate-specific antigen.

Wilcoxon test.

E: 0.01; 
F: 0.02; 
G: 0.03; 
H: 0.05.
ters) have been controversial. Our clinical data are in concordance with large surgical study series that demonstrated poorer survival (progression-free survival or otherwise) among African-American men, particularly for pathologically localized prostate cancer (19–22). However, other surgical series and radiation oncologists have reported no difference in outcome (23, 24). Nevertheless, our study of a relatively large cohort of patients has gone beyond the clinical comparison to examine the

Fig. 1 Photomicrographs of NDRG1 expressed in benign and malignant prostate, as analyzed by immunohistochemistry. A, low-power magnification (×10) of benign hyperplastic prostatic gland demonstrating predominantly membranous localization of NDRG1. B, high-power magnification (×40) of a single hyperplastic prostatic gland showing predominantly membranous staining with NDRG1 antibody. C, low-power magnification (×4) of prostatic adenocarcinoma, Gleason grade 8 (left), with membranous staining similar to internal positive control benign prostatic glands (right). D, high-power magnification (×40) of a Gleason 4 prostatic adenocarcinoma showing predominantly membranous staining with NDRG1 antibody similar to the pattern seen in benign glands (NDRG1 pattern 1). E, low-power magnification (×4) of prostatic adenocarcinoma, Gleason score 9, showing nuclear and cytoplasmic subcellular localization for NDRG-1. Note the lack of expression in the stromal tissues in between the invasive tumor cells. F, high-power magnification (×40) of poorly differentiated prostatic adenocarcinoma seen in E, showing shift of subcellular localization to nucleus and cytoplasm (NDRG1 pattern 2). G, low-power magnification (×10) of prostatic adenocarcinoma Gleason grade 6 (center and to left) with loss of detectable NDRG1 expression in the presence of internal positive control benign prostatic glands showing predominantly membranous staining. H, high-power magnification (×40) of prostate cancer Gleason 4 with undetectable NDRG1 expression (NDRG1 pattern 3) in the presence of positive control benign prostatic glands (left) retaining the membranous NDRG1 expression.
molecular determinates that may underlie the differences in disease outcome within a system providing equal access to care.

We decided to study NDRG1 expression in this cohort of patients for several reasons. First, NDRG1 is abundantly expressed in hormone-sensitive LNCaP cells, and its transcription is stimulated 14-fold after androgen treatment. These data suggest that NDRG1 expression is linked with androgen-induced differentiation in the human prostate (14). We postulated that NDRG1 expression might represent a molecular signature of altered androgen signaling in African-American men, who are known to have more active androgen receptor transactivation (25, 26). Second, our group has previously shown that the induction of the hypoxia-inducible transcription factor-1, which mediates the induction of genes required by cells to survive hypoxia, including NDRG1 transcription, was the highest in the most aggressive PC-3M prostate cancer cell lines (15). Third, we have previously demonstrated that nickel exposure induces hypoxic signaling pathways and NDRG1 expression (5). In this regard, nickel exposure is of interest because it is a known carcinogen (27), and several epidemiological studies have suggested an association between nickel exposure and prostate cancer risk (28, 29).

Limited numbers of human prostate cancer tissues were studied previously for differences in NDRG1 expression relative to normal prostatic epithelium (9, 10, 13, 30). Three studies demonstrated decreased and/or no expression of NDRG1 protein in the tumor compared with normal prostate epithelium, which suggests that the loss of the protein is related to transformation (9, 10, 30). Another study reported increased NDRG1 protein expression in tumor compared with normal tissue (13). The dichotomy of results reflects the limitation of the small sample sizes in these studies. This limitation was adequately addressed in our analysis of a large cohort of patients (n = 223), which revealed that both patterns do exist in prostate cancer human tissues.

In general, the overriding observation in the whole cohort of patients was that the NDRG1 expression seen in benign prostatic glands was very clearly different from the pattern seen in the vast majority of cases (80%), which showed either a shift of NDRG1 subcellular localization (pattern 2) or significant decreases to the point of virtually no detectable expression (pattern 1). These altered patterns of expression were consistently observed in the presence of the internal control of predominantly membranous localization of NDRG1 expression seen in benign glands (see Fig. 1, G and H). In addition, altered patterns of NDRG1 expression were observed in all 18 retrieved metastatic cases. Nevertheless, the limited number of available metastatic cases and the lack of adequate clinical information for most of them precluded us from drawing firm conclusions regarding the clinical relevance of altered NDRG1 expression in the metastatic setting (data not shown).

In almost 20% of all cases and independent of a patient’s ethnic background, NDRG1 expression showed similar patterns in tumors compared with benign glands (pattern 1). This pattern probably reflects the basal level of NDRG1 expression, most likely attributable to physiological androgen stimulation. Localization to the membrane has been described previously in both normal prostate and colonic epithelium. In both cases, nonepithelial cells, e.g., stroma, muscle, and invading lymphocytes, were negative for NDRG1 expression (8). In line with this observation is the fact that all patients included in this study were surgical candidates with no history of treatment with androgen ablation before surgery and, therefore, were expected to have physiological testosterone levels.

In NDRG1 pattern 2 expression, the protein subcellular localization has been clearly shifted to the nucleus and the cytoplasm. We postulate that this observation might represent the response to hypoxia. The wide discrepancy between the half-lives of hypoxia-inducible factor-1α (15–30 min) and NDRG1 (24 h) considerably limited our ability to demonstrate the simultaneous expression of the two proteins at the tissue level (13). Nevertheless, we have previously demonstrated the dependence of NDRG1 expression on hypoxia-inducible factor-1α signaling in vitro (6).

The decreased expression of NDRG1 (pattern 3) has been described previously in various tumor cell lines (7–10). In addition, the introduction of the NDRG1 cDNA into human cancer cells reduced cell growth both in vitro and in nude mice (10). It is not clear why decreased NDRG1 expression was seen more frequently in African-American patients. This might be related to deregulated androgen signaling in African-American patients attributable to a difference in their polymorphic microsatellites; however, this is speculative and remains to be examined. Nevertheless, a recently published study showed significantly reduced NDRG1 expression in metastatic prostate cancer compared with primary tumor. In addition, in a spontaneous metastatic assay performed in a severe combined immunodeficient mouse model, NDRG1 almost completely inhibited lung colonization of highly metastatic prostate cancer cells (30). These results support our postulate that loss of NDRG1 might contribute at least in part to the disparity in outcome seen in African-American patients.

Our study has important distinctive features. First, this is the first study to examine NDRG1 expression in a large number of clinical specimens in any type of tumor. Second, the unique resources provided by the VAMC in New York allows the generation of a complete clinical database containing large numbers of African-American and Caucasian prostate cancer patients, which per-

### Table 2

Comparison between patterns of NDRG1 expression in African-American versus Caucasian patients with prostate cancer

<table>
<thead>
<tr>
<th>Patterns</th>
<th>Africans</th>
<th>Caucasians</th>
<th>Total (n)</th>
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<tr>
<td>1</td>
<td>19.11</td>
<td>18.18</td>
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<td>2</td>
<td>21.02</td>
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<tr>
<td>3</td>
<td>59.87</td>
<td>43.94</td>
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</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>223</td>
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*P = 0.026, χ² test.

### Table 3

Multivariate analysis of predictors of PSA relapse

<table>
<thead>
<tr>
<th>Variable</th>
<th>P (χ² test)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Baseline PSA</td>
<td>0.004</td>
<td>2.037</td>
<td>1.262–3.288</td>
</tr>
<tr>
<td>Tumor size</td>
<td>0.033</td>
<td>1.852</td>
<td>1.051–3.264</td>
</tr>
<tr>
<td>Gleason</td>
<td>0.005</td>
<td>2.382</td>
<td>1.330–4.266</td>
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<tr>
<td>Ethnicity</td>
<td>0.047</td>
<td>2.508</td>
<td>0.996–6.315</td>
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</table>

*PSA, prostate-specific antigen; CI, confidence interval.
mits us to control for equal access of care as a possible confounding factor in treatment outcome. Third, the high retrieval rate of tissues (85.4%) minimizes the chance of selection bias, which is usually a major issue in this type of retrospective analysis. These factors strongly support the credibility of the presented data.

In summary, our study supports the role of African-American ethnicity as an independent predictor of worse outcome in prostate cancer and reveals significantly different patterns of NDRG1 expression in African-American men compared with Caucasians. Further studies are under way to define the molecular mechanism(s) governing the altered patterns of NDRG1 protein expression and to better understand the clinical relevance of NDRG1.

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