HHS Public Access

Author manuscript

Eur Urol. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Eur Urol. 2017 May ; 71(5): 697–700. doi:10.1016/j.eururo.2016.07.026.

Prevalence and Prognostic Significance of PTEN Loss in African-American and European-American Men Undergoing Radical Prostatectomy

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Abstract

African-American (AA) men have a higher risk of lethal prostate cancer (PCa) compared to European-American (EA) men. However, the molecular basis of this difference, if any, remains unclear. In EA PCa, PTEN loss, but not *ERG* rearrangement, has been associated with poor

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Author contributions: Tamara L. Lotan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Almutairi, Tosoian, Lotan, Hicks, Humphreys, Han, Sundi, De Marzo.

Analysis and interpretation of data: Lotan, Tosoian, Trock.

Drafting of the manuscript: Lotan, Tosoian, Almutairi.

Critical revision of the manuscript for important intellectual content: Schaeffer, Ross, Trock, Sundi.

Statistical analysis: Tosoian, Trock.

Obtaining funding: Schaeffer, Lotan.

Administrative, technical, or material support: Hicks.

Supervision: None.

Other: None.

Financial disclosures: Tamara L. Lotan certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

outcomes in most studies. Although *ERG* rearrangement is less common in AA compared to EA PCa, the relative frequency of PTEN loss and the association of PTEN/ERG molecular subtypes with outcomes is unknown for AA PCa. We examined PTEN/ERG status by immunohistochemistry in self-identified AA patients undergoing radical prostatectomy at Johns Hopkins with tumor tissue available on tissue microarray (TMA; $n = 169$) and matched these cases by pathologic parameters to 169 EA patients from the same TMAs. The rate of PTEN loss was significantly lower in AA compared to EA PCa (18% vs 34%; $p = 0.001$), similar to the lower rate of ERG expression (25% vs 51%; $p < 0.001$). To examine the association of PTEN/ERG status with oncologic outcomes, we created an additional TMA of 87 AA tumors with Gleason score > 4 + 3 = 7. Among the total population of AA men with outcome data from all TMAs ($n = 222$), PTEN loss was associated with higher risk of biochemical recurrence (hazard ratio [HR] 2.25, 95% confidence interval [CI] 1.33–3.82) and metastasis (HR 3.90, 95% CI 1.46–10.4) in multivariable models.

Patient summary

PTEN and ERG alterations in prostate cancer are less likely in African- American than in European-American men. However, PTEN loss remains associated with poor prostate cancer outcomes among African-American men.

Keywords

Prostatic carcinoma; PTEN; ERG; Race; African-American; European-American; Immunohistochemistry; Radical prostatectomy; Biomarker

Diverse molecular subtypes of prostate cancer (PCa) may contribute to the wide range of clinical behaviors observed for the disease. Intriguingly, the prevalence of molecular subtypes may vary according to racial and ethnic background [1, 2]; however, it remains unclear whether this may account in part for racial disparities in disease outcome. Two of the most common genomic alterations in primary PCa have been studied predominantly in European-American (EA) men: rearrangements involving the *ERG* gene [3, 4], and genomic deletion of the *PTEN* tumor suppressor gene [4]. *ERG* rearrangements have been observed in approximately half of all PCas occurring in EA men, and are not associated with adverse outcomes in most studies [5]. By contrast, PTEN loss has a strong association with adverse outcomes in predominantly EA cohorts, in which genomic deletion of PTEN occurs in 20–50% of primary PCas [6]. Interestingly, PTEN loss is two to three times more common among *ERG*-rearranged tumors in EA cohorts and may modify the association between PTEN and lethal disease [6].

Although African-American (AA) men have the highest PCa incidence and mortality, the relative prevalence of molecular PCa subtypes in the AA population is only beginning to be elucidated. It is clear that *ERG* rearrangement is significantly less common in the AA population [7, 8]. However, the relative rate of PTEN loss in AA PCa has only been examined in a few small cohorts [8–10]. In addition, it is unknown whether *ERG* rearrangement and/or PTEN loss are prognostic in AA PCa since most large cohorts with clinical follow-up information studied to date are predominantly EA men.

Because PTEN loss is more prevalent among *ERG*-rearranged cases in EA PCa, and *ERG* rearrangement occurs less commonly in AA compared to EA PCa, we hypothesized that PTEN loss may be less frequent in AA PCa. We further hypothesized that these molecular alterations, when present in AA men, would have similar associations with cancer-specific outcomes to those observed in EA men. To test our hypotheses, we assessed tumor PTEN and ERG status among self-identified EA and AA men who underwent radical prostatectomy (RP) at our institution with long-term clinical follow-up.

Following institutional review board approval, PTEN and ERG status was assessed by immunohistochemistry in three institutional tissue microarray (TMA) sets (Supplementary methods). TMA 1 was derived specifically to test the aforementioned hypotheses; grademated EA and AA subjects were selected among all men with available tissue and clinical follow-up who underwent RP from 1995 to 2005. TMA 2 included a nested case-control study comparing men with and without biochemical recurrence who underwent RP from 1993 to 2001. TMA 3 included consecutive RPs from 2000 to 2004 not included in the previous microarrays; subjects with Gleason score >6 were specifically selected, as in previous studies, owing to their higher risk of recurrence and metastasis, with the aim of evaluating the association of these genomic risk factors with the most clinically relevant cancers [10]. Because TMA 2 and 3 were not designed explicitly for comparison by race, and the RP population at our institution has been predominantly EA, all three TMAs cumulatively ultimately yielded 936 EA men with available PTEN/ERG status and clinical follow-up (Supplementary Table 1), compared to 169 AA men. To ensure genomic differences by race were not confounded by tumor grade or TMA design, AA men were matched by Gleason score and microarray to eligible EA men to yield 169 EA men for the study population. The index tumor from each case was sampled in triplicate or quadruplicate on each TMA and assessed using genetically validated immunohistochemistry assays [6] (Supplementary methods, Supplementary Fig. 1).

The matched AA and EA populations were not significantly different in terms of pathologic grade and stage at prostatectomy (Table 1). The median follow-up among those who did not experience biochemical recurrence (BCR) was 6 yr (interquartile range 2–11). The 5-yr incidence of BCR was 44% in AA men compared to 36% in EA men (Table 1), while metastatic disease was rare in both populations (7% in AA vs 8% in EA men at 5 yr; Supplementary Fig. 2). Consistent with our hypothesis, PTEN loss (18% in AA vs 34% in EA men; $p = 0.001$) and ERG expression (25% in AA vs 52% in EA men; $p < 0.001$) were significantly less prevalent in the AA population. Notably, PTEN loss was observed in 14 of 43 (33%) ERG-positive tumors, compared to 17 of 126 (14%) ERG-negative tumors, representing a more than twofold increase in PTEN loss when ERG expression was present, similar in both groups (Table 1).

We then evaluated the association between these alterations and clinical outcomes in the AA population. The primary outcome was BCR (prostate-specific antigen ≥0.2 ng/ml), and Cox proportional hazards models were used for time-to-event analysis. To increase the study power, we included an additional population of AA men who underwent RP from 2006 to 2010 with Gleason score ≥4 + 3 (Supplementary Table 2). Again, higher-grade cancers were selected to identify the association between these genomic alterations and clinically relevant

disease [10]. These men were not considered in the prevalence analysis owing to a lack of matched EA samples. In total, 87 such men were identified and included in a new TMA, of whom 53 had clinical follow-up, yielding 222 AA men with follow-up for analysis of outcomes.

The baseline characteristics of the combined AA cohort are listed in Supplementary Table 3. Some 89 men experienced BCR. There was no significant interaction between PTEN and ERG status ($p = 0.5$), and ERG status was not associated with BCR (HR 1.21, 95% CI 0.74–1.97; $p = 0.5$). In the multivariable model, PTEN loss was independently associated with higher risk of biochemical recurrence (HR 2.25, 95% CI 1.33–3.82; Table 2) in AA men, as were conventional clinicopathologic factors such as Gleason score and stage. Given the limited number of metastatic events ($n = 22$), a full multivariable analysis was not performed. In a limited model considering PTEN loss and high-grade cancer (Gleason score ≥8), however, PTEN loss was significantly associated with metastases in the AA population (HR 3.90, 95% CI 1.46–10.4; $p = 0.007$; Supplementary Table 4). Finally, the association between PTEN loss and BCR did not differ significantly by race when the original set of 338 matched EA and AA men (Table 1) was included in a multivariable model with the same variables as in Table 2 (interaction term for AA race and PTEN loss, HR 1.45, 95% CI 0.66–3.16; $p = 0.4$).

These data indicate that alterations in both PTEN and ERG in PCa are significantly less likely among AA compared to EA men. However, the association between PTEN loss and higher risk of BCR does not differ significantly by race and remains similar among AA men to what has been reported for predominantly EA cohorts [6]. In addition, we did not see evidence that ERG expression is associated with risk of PCa BCR among AA men, also similar to what has been observed in EA cohorts [5]. The lower prevalence of PTEN loss among AA tumors at radical prostatectomy suggests that other molecular alterations or factors are likely to account for racial disparities in PCa outcomes. Future work should examine whether alternative (non– PTEN-mediated) mechanisms activate PI3K signaling in AA cancers, such as mutations in PI3K pathway components. Alternatively, it is possible that altered prevalence of other molecular subtypes, such as SPINK1 expression and/or *TP53* and *SPOP* mutation, may contribute to differences in outcome between AA and EA patients.

The main study limitation is that the population is from a single tertiary-care institution and may not represent the general population. However, it is unlikely that this would affect the population in a race-specific manner. If validated in additional populations, these data suggest the intriguing hypothesis that the prevalence, but not the underlying biology, of the most common PCa molecular subtypes differs by racial background. Future work will aim to elucidate whether other molecular alterations contribute to disparities in PCa outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

***Funding/Support and role of the sponsor*:** This research was funded in part by an award from the Prostate Cancer Foundation, a CDMRP Transformative Impact Award (W81XWH- 12-PCRP-TIA), and NIH Cancer Center Support Grant 5P30CA006973-52. The sponsors played a role in data collection.

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Table 1

Clinicopathologic characteristics and PTEN/ERG status for the matched African-American (AA) and European-American (EA) cohort

Variable	AA (*n* = 169)	EA (*n* = 169)	*p* value
Median age, yr (IQR)	58 (53–62)	61 (56–65)	<0.001
Median year of surgery (IQR)	2001 (1998–2002)	2001 (1998–2002)	0.98
Median PSA, ng/ml (IQR)	8.3 (5.8–13.1)	6.0 (4.7–8.3)	<0.001
Clinical stage, *n* (%)			
T1c	120 (71)	103 (61)	0.14
T2a	32 (19)	41 (24)	
≥T2b	17 (10)	25 (15)	
Biopsy grade group, *n* (%)			
1 (GS 6)	91 (54)	92 (54)	0.99
2 (GS 3 + 4)	41 (24)	37 (22)	
3 (GS 4 + 3)	23 (14)	25 (15)	
4 (GS 8)	11 (6.5)	12 (7.1)	
5 (GS 9–10)	3 (1.8)	3 (1.8)	
RP grade group, *n* (%)			
1 (GS 6)	43 (25)	43 (25)	0.99
2 (GS 3 + 4)	63 (37)	63 (37)	
3 (GS 4 + 3)	31 (18)	31 (18)	
4 (GS 8)	23 (14)	23 (14)	
5 (GS 9–10)	9 (5)	9 (5.3)	
Pathologic stage, *n* (%)			
T2N0	72 (43)	76 (45)	0.7
T3aN0	67 (40)	59 (35)	
T3bN0	18 (11)	17 (10)	
N1	12 (7)	17 (10)	
Tissue microarray, *n* (%)			
1	110 (65)	110 (65)	0.99
2	36 (21)	36 (21)	
3	23 (14)	23 (14)	
Biochemical recurrence (*n*)	68	67	
5-yr biochemical recurrence (%)	44	36	
Metastasis (*n*)	19	20	
5-yr metastasis (%)	7	8	
PCa death (*n*)	10	8	
5-yr PCa death (%)	1	1	
PTEN loss, *n* (%)	31 (18)	57 (34)	0.001
ERG expression, *n* (%)	43 (25)	87 (52)	<0.001

IQR = interquartile range; PSA = prostate-specific antigen; GS = Gleason score; RP = radical prostatectomy; PCa = prostate cancer.

Table 2

Multivariable Cox proportional hazard models assessing association of clinicopathologic parameters and PTEN/ERG status with biochemical recurrence in the combined African-American prostate cancer cohort (n = 222)

Variable	Multivariable HR (95% CI)	p value
Prostate-specific antigen	1.01 (0.99–1.04)	0.4
RP grade group		
1 (GS 6)	1.00 (reference)	
2 (GS 3 + 4)	2.16 (0.90–5.23)	0.086
3 (GS 4 + 3)	5.02 (1.92–13.1)	0.001
4 (GS 8)	5.45 (2.03–14.6)	0.001
5 (GS 9–10)	4.03 (1.39–11.9)	0.011
Pathologic stage		
T2N0	1.00 (reference)	
T3aN0	1.89 (1.03–3.57)	0.041
T3bN0	3.14 (1.56–6.30)	0.001
N1	6.64 (2.92–15.1)	<0.001
PTEN loss	2.25 (1.33–3.82)	0.003

HR = hazard ratio; CI = confidence interval; RP = radical prostatectomy; GS = Gleason score.