Published in final edited form as:

Eur Urol Focus. 2018 December ; 4(6): 818–824. doi:10.1016/j.euf.2017.02.016.

Predicting Prostate Cancer Progression as a Function of ETS-related Gene Status, Race, and Obesity in a Longitudinal Patient Cohort

Jennifer Cullen^{a,*}, Denise Young^a, Yongmei Chen^a, Michael Degon^{a,b}, James Farrell^{a,b}, Jason Sedarsky^{a,b}, Wagner Baptiste^{a,b}, Philip Rosen^{a,b}, Vladimir Tolstikov^c, Michael Kiebish^c, Jacob Kagan^d, Sudhir Srivastava^d, Huai-Ching Kuo^a, Joel T. Moncur^b, Inger L. Rosner^{a,b}, Niven Narain^c, Viatcheslav Akmaev^c, Gyorgy Petrovics^a, Albert Dobi^a, David G. McLeod^{a,b}, Shiv Srivastava^a, Isabell A. Sesterhenn^{a,e}

^aCenter for Prostate Disease Research, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

^bWalter Reed National Military Medical Center, Urology Service, Bethesda, MD, USA

^cBERG Health, Framingham, MA, USA

^dCancer Biomarkers Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA

^eJoint Pathology Center, Silver Spring, MD, USA

Abstract

Background—ETS-related gene (ERG) oncogenic activation is the most common genomic alteration in prostate cancer (CaP) although it occurs less frequently in African American (AA) versus Caucasian (CA) patients, and the potential role of ERG as a prognostic marker has not been confirmed.

Objective—This study was conducted to confirm strong racial variation in the prevalence of ERG oncoprotein expression and to examine ERG oncoprotein expression, race, and body mass

*Corresponding author. Center for Prostate Disease Research, Department of Surgery, Uniformed Services University of the Health Sciences, 1530 E. Jefferson Street, Rockville, MD 20852, USA. Tel. +1 (240) 453-8917. jcullen@cpdr.org (J. Cullen).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author contributions: Jennifer Cullen 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.

Study concept and design: Cullen, Dobi, Shiv Srivastava, Sesterhenn.

Acquisition of data: Young, Chen, Kuo, Degon, Farrell, Sedarsky, Baptiste, Rosen, Moncur, Sesterhenn.

Analysis and interpretation of data: Cullen, Chen, Young, Dobi, Petrovics, Shiv Srivastava.

Drafting of the manuscript: Cullen, Shiv Srivastava.

Critical revision of the manuscript for important intellectual content: Cullen, Shiv Srivastava, Sesterhenn.

Statistical analysis: Chen, Kuo.

Obtaining funding: McLeod, Shiv Srivastava.

Administrative, technical, or material support: Tolstikov, Kiebish, Narain, Akmaev.

Supervision: Kagan, Sudhir Srivastava.

Other: None.

index as independent and joint predictors of CaP biochemical recurrence (BCR) following radical prostatectomy (RP).

Design, setting, and participants—A retrospective cohort study of CA and AA CaP patients enrolled at Walter Reed National Military Medical Center, who donated clinically annotated, whole-mounted, prostatectomy specimens between 1994 and 2014 following RP, was conducted.

Outcome measurements and statistical analysis—Kaplan–Meier (KM) estimation curves and multivariable Cox proportional hazards models were used to examine time to BCR as a function of ERG status, patient race, and obesity.

Results and limitations—Among 930 eligible patients (36.1% AA and 63.9% CA), with 155 (16.7%) BCR events and a median follow-up time of 5.1 yr, ERG oncoprotein expression was significantly less prevalent in index tumors of AA versus CA patients (23.2% vs 49.3%; $p < 0.0001$). KM curves showed significantly poorer BCR-free survival for CA patients with ERG-negative index tumors but not for AA patients. Race-stratified multivariable analyses revealed a significant association between ERG-negative index tumors and poorer BCR-free survival among CA patients (hazards ratio = 1.67, confidence interval = 1.07, 2.61; $p = 0.024$). Less heterogeneity in ERG expression among AA patients may reduce the ability to show its association with BCR.

Conclusions—Striking racial variation in ERG oncoprotein expression was confirmed. A novel observation was the importance of index tumor ERG-negative status in predicting CaP progression for CA patients.

Patient summary—ETS-related gene (ERG) typing of tumors may be useful in prognosticating prostate cancer aggressiveness.

Keywords

Prostate cancer; Biochemical recurrence; ERG fusion; Race; Obesity

1. Introduction

Cancer of the prostate (CaP) is the most commonly diagnosed nonskin malignancy and the second leading cause of cancer-related deaths in American men [1]. Oncogenic activation of ETS-related gene (*ERG*) due to gene fusion events represents one of the most common genomic alterations in CaP with a varying frequency among different ancestral groups [2–8]. Caucasian (CA) CaP patients exhibit the highest prevalence of ERG oncogene fusions, followed by Hispanics, African Americans (AAs), and Asians. Numerous studies have addressed both the biomarker and the therapeutic utility of ERG-based biological stratification of CaP [9]. The ERG status of prostate tumors has been shown to affect therapeutic response to hormonal axis targeted therapies and other treatments [10–12]. Thus, defining whether a CaP patient harbors ERG-positive versus ERG-negative tumor foci is clinically relevant.

Although many studies have addressed the prognostic value of ERG alterations in predicting CaP progression, data are conflicting [13–18], possibly due to the heterogeneity in ERG alterations across multiple tumor foci within a single patient, as well as racial variation in presence of ERG alterations or ERG associations with other prognostic markers [19]. A

recent study by Ahearn et al [20] examining the Health Professionals Follow-up Study and Physicians Health Study found an association between *PTEN* deletion and development of lethal CaP, but only among those who were ERG negative. Biological modulators of ERG have also been examined to help explain inconsistency in the association between ERG and CaP outcomes, including patient age, hormonal factors, body mass index (BMI), tumor microenvironment, and therapeutic adaptation [4,21,22]. A growing body of evidence supports a role of patient exposure to androgen deprivation therapy and a more aggressive CaP phenotype [23]. BMI has also been implicated in the relationship between ERG and CaP outcomes. For instance, Pettersson et al [21] described a significant association of *TMPRSS2-ERG* positivity among obese patients in predicting lethal CaP, while Egbers et al [24] showed a reciprocal relationship between obesity and *TMPRSS2-ERG*-positive cancers.

The primary aim of this study was to determine whether the presence or absence of ERG oncoprotein in index CaP tumors is predictive of disease progression, as indicated by biochemical recurrence (BCR). A secondary study aim was to explore the independent and joint roles of race and obesity on the relationship between ERG status and BCR.

2. Patients and methods

2.1. Study design and population

In this retrospective cohort study, patients who consented to enrolment in the Center for Prostate Disease Research (CPDR) biospecimen databank and multicenter national clinical database were of interest for inclusion in the study. These databases have been approved by the Institutional Review Boards at the Walter Reed National Military Medical Center (WRNMMC) and the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Maryland. All subjects provided written informed consent. Eligible study subjects included those who provided dual consent to the WRNMMC biospecimen data repository as well as the multicenter national clinical database, and who underwent radical prostatectomy (RP) between 1994 and 2014, and donated whole mount prostatectomy specimens at time of RP. At CPDR, the biospecimen data are linked to extensive patient demographic, clinical, pathologic, treatment, and cancer outcome information [25].

2.2. Demographic, clinical, and pathologic variables

Patients characteristics of interest included age at RP (years), self-reported race (AA and CA), BMI (in kg/m²), prostate-specific antigen (PSA) level (ng/ml) at the time of CaP diagnosis, pathologic Gleason sum (6, 3 + 4, 4 + 3, and 8–10), pathologic T stage (pT2 and pT3–4), and surgical margin status (positive and negative). BMI was dichotomized per Centers for Disease Control and Prevention categories of “obese” (BMI ≥ 30 kg/m²) versus “nonobese” (BMI < 30 kg/m²). Patient follow-up time was calculated as days elapsed between RP date and the last known medical visit or the end of study period (ie, December 31, 2014). These data are collected as part of routine data abstraction activities of the CPDR multicenter national database.

2.3. Immunohistochemistry analysis of ERG

Representative whole-mount 4- μ m cross sections from each prostatectomy specimen were processed, according to the methods described previously [26,27]. The index tumor, which was the largest tumor with the highest grade, was identified, along with all other tumor foci in each specimen. Each focus was then classified as ERG positive (any number of tumor cells staining positive) or negative (all tumor cells staining negative) using the 9FY antibody. In the event of two or more tumor foci colliding, tumor ERG status was labeled as positive, if any ERG staining was noted. All specimen sectioning, staining, grading, and interpretation were performed by a single pathologist (I.S.).

2.4. Dependent study outcome

A BCR event was defined in the following manner: a post-RP PSA level of ≤ 0.2 ng/ml followed by a successive, confirmatory PSA level of ≤ 0.2 , or the initiation of salvage radiation or hormonal therapy after a rising PSA level of ≥ 0.1 . Any PSA values drawn within 8 wk after RP were not considered due to known fluctuations, proximal to RP date. Patients who had salvage therapy *without* a rising PSA level of ≥ 0.1 were classified as a non-BCR event and censored at the date of the initiation of salvage therapy. Patients who had an initial PSA level of ≤ 0.2 ng/ml, but no confirmatory PSA ≤ 0.2 and no initiation of salvage therapy, were classified as a non-BCR event and censored at the last known date of PSA < 0.2 ng/ml. Patients who were lost to follow-up or who died without any evidence of BCR were censored as nonevents at date of last known medical visit or date of death, respectively.

2.5. Statistical analysis

Descriptive statistics were examined for the overall patient cohort as well as stratified for race and ERG status. Chi-square testing was used to compare categorical distributions of demographic and clinic-pathologic characteristics across race and ERG index tumor status (positive vs negative), while Student *t* test was performed to compare continuously and normally distributed patient features across race and ERG status. The primary study outcome was modeled as time to event end point using Kaplan-Meier estimation curves as well as univariable and multivariable Cox proportional hazards analysis, with ERG status (positive vs negative) as the key independent study predictor. The assumption of proportional hazards was verified by tests of correlations with time and examination of residual plots. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Hazards ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. All *p* values were computed using two-sided statistical tests (summary type I error/alpha error = 0.05).

3. Results

The study cohort consisted of 930 CaP patients who consented to donate whole-mount prostatectomy specimens at the time of surgery and who self-reported as either AA (36.1%) or CA (63.9%). Other racial groups were too small in number to be meaningfully evaluated. Comprehensive patient data including demographic, clinical, pathologic, treatment, and outcome information (Table 1) were obtained for all patients. The median patient age at the

time of RP was 59.5 yr (range = 35–77 yr) and the median PSA at diagnosis was 5.0 ng/ml (range = 0.20–64.0 ng/ml). Positive surgical margins were observed in 16% of RP patients. Almost one-quarter of the cohort was obese (≥ 30 kg/m²). A total of 155 (16.7%) BCR events were observed over a median patient follow-up time of 5.2 yr (range = 0–21 yr).

Multiple tumor foci in representative whole-mount prostate sections were evaluated, per patient, for the presence or absence of the ERG oncoprotein (a surrogate for a patient's ERG fusion status) by immunostaining using a well-characterized, highly specific anti-ERG monoclonal antibody, 9FY [26]. As expected, the distribution of ERG positivity was strikingly different across races (Table 1). The tumor focus that was of the largest and/or poorest grade was defined as the “index” tumor. ERG positivity in the index tumor was much lower in AA patients as compared with that in CA patients (23.2% vs 49.3%; $p < 0.0001$). Similarly, when multiple foci were considered (index plus nonindex) per patient, ERG positivity remained markedly lower in AA patients (*data not shown*). Multifocal staining was performed on 564 (60.6%) patients in the cohort. The distribution of ERG positivity for index tumors and satellite lesions are as follows: 20.9% +/+, 15.3% +/-, 22.3% -/+, and 41.5% -/-. The AA patients were also observed to have slightly younger age at RP ($p = 0.024$), a higher PSA at diagnosis ($p = 0.0002$), and a greater BMI ($p < 0.0001$).

Patient characteristics were then compared across ERG statuses (Table 2). The noteworthy differences in patient characteristics for those with ERG-positive index tumors included slightly younger age at RP ($p = 0.0037$), a lower median PSA at CaP diagnosis ($p < 0.0001$), a slightly lower prevalence of obesity ($p = 0.0123$), and a more favorable pathologic Gleason sum ($p = 0.0007$).

Univariable Cox proportional hazards models were used to examine each covariate of interest in association with time to BCR (Table 3). In these unadjusted analyses, significant predictors of greater odds of BCR included increasing patient age at RP (per incremental year: HR = 1.03, CI = 1.01–1.05, $p = 0.01$), higher diagnostic PSA (per incremental ng/ml: HR = 1.04, CI = 1.03–1.06, $p < 0.0001$), higher BMI (per incremental kg/m²: HR = 1.05, CI = 1.01–1.09, $p = 0.04$), AA race (HR = 1.38, CI = 1.00–1.89, $p = 0.048$), negative index tumor ERG status (HR = 1.51, CI = 1.07–2.12, $p = 0.0178$), higher pathologic T stage (HR_{T3–4vsT2} = CI =, $p < 0.0001$), highest pathologic Gleason sum versus lowest, only (HR_{4+3,8–10vs6} = 5.22, CI = 3.79–7.18, $p < 0.0001$), and positive surgical margin status (HR = 4.81, CI = 3.49–6.62, $p < 0.0001$).

Given the striking difference in ERG index tumor positivity across race, unadjusted Kaplan–Meier estimation curves were produced to predict BCR as a function of ERG, separately for CA and AA patients (Fig. 1 and 2). A clear and statistically significant association was observed for ERG negativity with greater odds of BCR for CA patients (HR = 1.69, CI = 1.10–2.60, log-rank $p = 0.02$), but no such association was observed for AA patients (HR = 1.01, CI = 0.57–1.80, log-rank $p = 0.97$).

Given these disparate findings between ERG status and study outcome across races, multivariable models were examined as race stratified (Table 4). In both race-specific models, higher PSA at diagnosis, poorer pathologic T stage, and pathologic Gleason 4 + 3

and 8–10 diseases were all predictive of greater odds of BCR. Neither age at RP nor BMI was predictive of study outcome across races. Two key differences were noted in study associations across racial groups: positive surgical margin status was predictive of greater odds of BCR for AA patients ($p = 0.004$) but not for CA patients ($p = 0.22$), while ERG-negative index tumor status was an important predictor of BCR ($HR = 1.67$, $p = 0.0243$) for CA patients only.

Statistical interaction was examined between ERG status and obesity on BCR-free survival for CA patients; both those who had an ERG-negative index tumor and those who were obese had the poorest outcome, as compared with those who had an ERG-positive index tumor and who were nonobese, but this association did not achieve statistical significance ($p = 0.0765$) (*data not shown*).

4. Discussion

This study examined a racially diverse, longitudinal cohort of military health-care beneficiaries. This setting reduces disparity in socioeconomic status, health-care access, and lifestyle factors that potentially influence CaP progression. Consistent with previous studies, the proportion of patients with ERG oncoprotein expression was significantly lower in case of AA patients whether comparing the index tumor or all tumor foci.

The strong association between negative index tumor ERG status and poorer BCR-free survival was observed only in CA patients. While a significant association was also observed between ERG-negative index tumor status and metastatic progression, very few patients developed metastasis ($n = 40$; median follow-up time = 5 yr); therefore, these data are not included in this report. Both positive and negative correlations between ERG status and CaP outcomes have been reported in literature, likely due to cohort selection, as exemplified in this study, showing a potential interaction of age, race, obesity, tumor molecular subtype (ERG-positive or ERG-negative status), and other as-yet-unknown potential biological factors [28]. Interactions of ERG and obesity are also not clear due to apparent discrepancies between two studies [21,24]. The current study further highlights less understood biological factors in prognostication of prostate tumors, stratified by ERG status. A recent study showing an association of *PTEN* deletion and *ERG*-negative status with lethal CaP of CA men lends support for this report highlighting interactions of *ERG* with clinical and molecular features [20].

Although not statistically significant, a trend was observed toward poorer CaP outcomes among CA patients who both had negative index ERG tumors and were obese, as compared with those with ERG-positive index tumors who were nonobese. The underlying mechanisms of attenuating effects of ERG on prostate tumor progression under conditions of patient obesity are not known and warrant future evaluation. This study further underscores that the specific characteristics of the patient cohort may be important when evaluating prognostic significance of ERG on CaP progression. The absence of an association between ERG expression and CaP outcome among the AA patients may be due to the significantly lower frequency of ERG expression in AA patients, resulting in less heterogeneity in ERG expression.

Among limitations of the current study was the reliance on patient self-report to assign race/ethnicity. Although race/ethnicity information inferred from ancestry-associated single-nucleotide polymorphism data is considered to be more accurate, neither approach is definitive [29]. A second limitation is the limited generalizability of the CPDR cohort to other US longitudinal cohorts, as well as RP patients in other nations. The CPDR cohort is unique in its racial diversity, equal access health-care setting, and military health-care beneficiary population. This study also had a limited median follow-up time of 5.2 yr, preventing examination of important longer-term study end points such as metastasis and CaP-specific mortality.

The current study provided a robust sample size for each racial group considered. Moreover, ERG status was examined in both index tumors and other foci in the prostate gland at RP. Regardless of foci type (index vs nonindex), the results were highly consistent. A detailed examination of unique tumor foci phenotype is warranted in follow-up studies. Another key strength of the analysis was consideration of two pathologic grading systems, pre- and postmodification of the International Society of Urological Pathology (ISUP) guidelines in 2006 [30,31]. Study associations were unchanged when considering the two grading systems, so findings are presented for the most recent ISUP system.

5. Conclusions

Overall, this study offers a comprehensive examination of ERG in the context of multifocal disease addressing racial variation in an equal-access military health-care system. A novel and provocative finding of this study is the strong association between ERG-negative index tumor status and more aggressive CaP in CA men. These data suggest that there may be a prognostic value of index tumor ERG status, possibly in combination with obesity status, in predicting CaP progression (BCR) after RP.

The current findings warrant independent validation of combined prognostic utility of race, ERG status, and obesity in predicting biological aggressiveness of CaP. These data may be incorporated into current nomograms predicting CaP progression after prostatectomy. This report has generated a new hypothesis suggesting a potential role of ERG in modulating the metabolic pathways. The signatures of serum lipids, proteins, and metabolites may reflect the combined biological influence of ERG, race, and obesity, and deserve attention. In preliminary ongoing work, a subset of this study patient cohort is undergoing evaluation for serum proteome-, lipidome-, and metabolome-derived signatures that might shed light on underlying biological mechanisms of poor prognosis associated with ERG and obesity status in CA patients.

Acknowledgments

Financial disclosures: Jennifer Cullen 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.

Funding/Support and role of the sponsor: This research was supported in part by the National Cancer Institute grant (R01CA162383) to S. Srivastava; by the Early Detection Research Network, National Cancer Institute (ACN12011-001-0) to Gyorgy Petrovics, Albert Dobi, Isabell A. Sesterhenn, David G. McLeod, and S. Srivastava;

and by USUHS-CPDR fund (HU0001-10-2-0002) to David G. McLeod. The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US government.

References

1. American Cancer Society. Cancer facts & figures. Atlanta, GA: American Cancer Society; 2016.
2. Farrell J, Young D, Chen Y, et al. Predominance of ERG-negative high-grade prostate cancers in African American men. *Mol Clin Oncol*. 2014; 2:982–6. [PubMed: 25279185]
3. Hu Y, Dobi A, Sreenath T, et al. Delineation of TMPRSS2-ERG splice variants in prostate cancer. *Clin Cancer Res*. 2008; 14:4719–25. [PubMed: 18676740]
4. Khani F, Mosquera JM, Park K, et al. Evidence for molecular differences in prostate cancer between African American and Caucasian men. *Clin Cancer Res*. 2014; 20:4925–34. [PubMed: 25056375]
5. Petrovics G, Liu A, Shaheduzzaman S, et al. Frequent overexpression of ETS-related gene-1 (ERG1) in prostate cancer transcriptome. *Oncogene*. 2005; 24:3847–52. [PubMed: 15750627]
6. Rosen P, Pfister D, Young D, et al. Differences in frequency of ERG oncoprotein expression between index tumors of Caucasian and African American patients with prostate cancer. *Urology*. 2012; 80:749–53. [PubMed: 22950997]
7. Tomlins SA, Laxman B, Varambally S, et al. Role of the *TMPPRSS2-ERG* gene fusion in prostate cancer. *Neoplasia*. 2008; 10:177–88. [PubMed: 18283340]
8. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science*. 2005; 310:644–8. [PubMed: 16254181]
9. Barbieri CE, Rubin MA. Genomic rearrangements in prostate cancer. *Curr Opin Urol*. 2015; 25:71–6. [PubMed: 25393273]
10. Attard G, de Bono JS, Logothetis CJ, et al. Improvements in radiographic progression-free survival stratified by *ERG* gene status in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. *Clin Cancer Res*. 2015; 21:1621–7. [PubMed: 25593303]
11. Galletti G, Matov A, Beltran H, et al. ERG induces taxane resistance in castration-resistant prostate cancer. *Nat Commun*. 2014; 5:5548. [PubMed: 25420520]
12. Han S, Brenner JC, Sabolch A, et al. Targeted radiosensitization of ETS fusion-positive prostate cancer through PARP1 inhibition. *Neoplasia*. 2013; 15:1207–17. [PubMed: 24204199]
13. Font-Tello A, Juanpere N, de Muga S, et al. Association of ERG and TMPRSS2-ERG with grade, stage, and prognosis of prostate cancer is dependent on their expression levels. *Prostate*. 2015; 75:1216–26. [PubMed: 25939480]
14. Hermans KG, Boormans JL, Gasi D, et al. Overexpression of prostate-specific TMPRSS2(exon 0)–ERG fusion transcripts corresponds with favorable prognosis of prostate cancer. *Clin Cancer Res*. 2009; 15:6398–403. [PubMed: 19825963]
15. Kim SH, Kim SH, Joung JY, et al. Overexpression of ERG and wild-type PTEN are associated with favorable clinical prognosis and low biochemical recurrence in prostate cancer. *PLoS One*. 2015; 10:e0122498. [PubMed: 25897494]
16. Perner S, Svensson MA, Hossain RR, et al. ERG rearrangement metastasis patterns in locally advanced prostate cancer. *Urology*. 2010; 75:762–7. [PubMed: 20018353]
17. Rubicz R, Zhao S, April C, et al. Expression of cell cycle-regulated genes and prostate cancer prognosis in a population-based cohort. *Prostate*. 2015; 75:1354–62. [PubMed: 25990700]
18. Yamoah K, Johnson MH, Choeurng V, et al. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. *J Clin Oncol*. 2015; 33:2789–96. [PubMed: 26195723]
19. Box A, Alshalalfa M, Hegazy SA, Donnelly B, Bismar TA. High alpha-methylacyl-CoA racemase (AMACR) is associated with ERG expression and with adverse clinical outcome in patients with localized prostate cancer. *Tumour Biol*. 2016; 37:12287–99. [PubMed: 27271990]
20. Ahearn TU, Pettersson A, Ebot EM, et al. A prospective investigation of PTEN loss and ERG expression in lethal prostate cancer. *J Natl Cancer Inst*. 2015; 108:djv346. [PubMed: 26615022]
21. Pettersson A, Lis RT, Meisner A, et al. Modification of the association between obesity and lethal prostate cancer by TMPRSS2:ERG. *J Natl Cancer Inst*. 2013; 105:1881–90. [PubMed: 24292212]

22. Wang J, Cai Y, Shao LJ, et al. Activation of NF- κ B by TMPRSS2/ERG fusion isoforms through Toll-like receptor-4. *Cancer Res.* 2011; 71:1325–33. [PubMed: 21169414]
23. Volante M, Tota D, Giorcelli J, et al. Androgen deprivation modulates gene expression profile along prostate cancer progression. *Hum Pathol.* 2016; 21:30119–8.
24. Egbers L, Luedeke M, Rinckleb A, et al. Obesity and prostate cancer risk according to tumor *TMPPRSS2:ERG* gene fusion status. *Am J Epidemiol.* 2015; 181:706–13. [PubMed: 25852077]
25. Brassell SA, Dobi A, Petrovics G, Srivastava S, McLeod D. The Center for Prostate Disease Research (CPDR): a multidisciplinary approach to translational research. *Urol Oncol.* 2009; 27:562–9. [PubMed: 19720304]
26. Furusato B, Tan SH, Young D, et al. ERG oncoprotein expression in prostate cancer: clonal progression of ERG-positive tumor cells and potential for ERG-based stratification. *Prostate Cancer Prostatic Dis.* 2010; 13:228–37. [PubMed: 20585344]
27. Rosen P, Sesterhenn IA, Brassell SA, McLeod DG, Srivastava S, Dobi A. Clinical potential of the ERG oncoprotein in prostate cancer. *Nat Rev Urol.* 2012; 9:131–7. [PubMed: 22331093]
28. Szasz AM, Majoros A, Rosen P, et al. Prognostic potential of ERG (ETS-related gene) expression in prostatic adenocarcinoma. *Int Urol Nephrol.* 2013; 45:727–33. [PubMed: 23686669]
29. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet.* 2006; 38:904–9. [PubMed: 16862161]
30. Egevad L, Mazzucchelli R, Montironi R. Implications of the International Society of Urological Pathology modified Gleason grading system. *Arch Pathol Lab Med.* 2012; 136:426–34. [PubMed: 22458905]
31. Montironi R, Cheng L, Lopez-Beltran A, et al. Original Gleason system versus 2005 ISUP modified Gleason system: the importance of indicating which system is used in the patient's pathology and clinical reports. *Eur Urol.* 2010; 58:369–73. [PubMed: 20478652]

Fig. 1.

Kaplan–Meier estimation curve of time to BCR as a function of index tumor ERG status (negative vs positive) for CA patients ($n = 594$). For CA patients, the log-rank p value ($p = 0.0160$) indicates that there is a statistically significant relationship between ERG status and BCR. In such patients, an index tumor that is ERG negative (ie, not expressing the ERG oncoprotein) is predictive of greater odds of having a BCR event over time. BCR = biochemical recurrence; CA = Caucasian ERG = ETS-related gene.

Fig. 2.

Kaplan–Meier estimation curve of time to BCR as a function of index tumor ERG status (negative vs positive) for AA patients ($n = 336$). For AA patients, the log-rank p value ($p = 0.9686$) indicates that there no relationship between ERG status and BCR over time. AA = African American; BCR = biochemical recurrence; ERG = ETS-related gene.

Table 1Distribution of demographic, clinical, and pathologic variables stratified for race ($n = 930$)

	Overall	Caucasian	African American	<i>p</i> value
<i>N</i> (%)	930	594 (63.9)	336 (36.1)	
Age at RP (yr)				
Median	59.5	60	58.8	0.0244
Range	35.3–76.8	35.3–76.8	40.3–76.1	
Diagnostic PSA (ng/ml)				
Median	5.0	4.7	5.4	0.0002
Range	0.2–64.0	0.2–64.0	0.5–43.0	
BMI ³ (kg/m ²)				
Median	27.2	26.8	27.9	<0.0001
Range	14.6–42.0	14.6–40.2	16.3–42.0	
<30	707 (76.0)	478 (80.5)	229 (65.2)	
30	223 (24.0)	116 (19.5)	107 (31.8)	<0.0001
1st quartile (<25)		157 (26.4)	72 (21.4)	
2nd quartile (25–27.2)		169 (28.4)	64 (19.0)	
3rd quartile (27.2–29.8)		145 (24.4)	88 (26.2)	
4th quartile (≥ 29.8)		123 (20.7)	112 (33.3)	<0.0001
Index tumor ERG status				
Negative	559 (60.1)	301 (50.7)	258 (76.8)	
Positive	371 (39.9)	293 (49.3)	78 (23.2)	<0.0001
Pathologic T stage, <i>N</i> (%)				
pT2	661 (71.1)	412 (69.4)	249 (74.1)	
pT3–4	269 (28.9)	182 (30.6)	87 (25.9)	0.13
Pathologic Gleason sum, <i>N</i> (%)				
6	503 (54.1)	332 (55.9)	171 (50.9)	
3 + 4	279 (30.0)	176 (29.6)	103 (30.6)	
4 + 3, 8–10	148 (15.9)	86 (14.5)	62 (18.4)	0.20
Surgical margin status, <i>N</i> (%)				
Negative	783 (84.2)	501 (84.3)	282 (83.9)	
Positive	147 (15.8)	93 (15.7)	54 (16.1)	0.87
Follow-up time after RP (yr)				
Median (range)	5.2	5.1	5.6	0.20
Range	0.1–20.8	0.1–20.8	0.1–19.1	
BCR ^a	155 (16.7)	88 (14.8)	67 (19.9)	–

RP = radical prostatectomy; PSA = prostate-specific antigen; BMI = body mass index; ERG = ETS-related gene; BCR = biochemical recurrence.

^aBCR is measured as time to event; therefore, *p* values, from formal statistical tests of comparison, are not presented here.

Table 2Distribution of demographic, clinical, and pathologic variables stratified for index tumor ERG status ($n = 930$)

	ERG–	ERG+	<i>p</i> value
<i>N</i> (%)	559 (60.1)	371 (39.9)	
Age at RP (yr)			
Median	60	58.3	0.004
Range	35.3–76.8	37.1–76.1	
Diagnostic PSA (ng/ml)			
Median	5.2	4.6	<0.0001
Range	0.2–45.5	0.5–64.0	
BMI (kg/m ²)			
Median	27.3	27	0.12
Range	17.9–42.0	14.6–40.2	
<30	409 (73.2)	298 (80.3)	
30	150 (26.8)	73 (19.7)	0.01
Pathologic T stage, <i>N</i> (%)			
pT2	403 (72.1)	258 (69.5)	
pT3–4	156 (27.9)	113 (30.5)	0.41
Pathologic Gleason sum, <i>N</i> (%)			
6	275 (49.2)	228 (61.5)	
3 + 4	181 (32.4)	98 (26.4)	
4 + 3, 8–10	103 (18.4)	45 (12.1)	0.001
Surgical margin status, <i>N</i> (%)			
Negative	468 (83.7)	315 (84.9)	
Positive	91 (16.3)	56 (15.1)	0.63
Follow-up time after RP (yr)			
Median (range)	5.2	5.3	0.72
Range	0.1–19.1	0.1–20.8	
BCR ^a	107 (19.1)	48 (12.9)	–

ERG = ETS-related gene; RP = radical prostatectomy; PSA = prostate-specific antigen; BMI = body mass index; BCR = biochemical recurrence.

^aBCR is measured as time to event; therefore, *p* values, from formal statistical tests of comparison, are not presented here.

Table 3

Univariable Cox proportional hazards regression models predicting time to BCR per independent variable

Variable	BCR events N (%)	HR	95% CI	p value
Age at RP (yr, continuous)		1.03	1.01–1.05	0.01
Diagnostic PSA (ng/ml, continuous)		1.04	1.03–1.06	<0.0001
BMI (kg/m ² , continuous)		1.05	1.01–1.09	0.02
Obesity (yes vs no)				
<30	108 (15.3)	1.00		
≥30	47 (21.1)	1.42	1.01–2.01	0.04
Race				
Caucasian	88 (14.8)	1.00		
African American	67 (19.9)	1.38	1.00–1.89	0.048
Index tumor ERG status				
Positive	48 (12.9)	1.00		
Negative	107 (19.1)	1.51	1.07–2.12	0.018
Multifocal tumor ERG (<i>n</i> = 640) ^a				
Index tumor+/other tumor+		1.00		
Index tumor+/other tumor–		0.89	0.50–1.56	0.68
Index tumor–/other tumor+		1.10	0.74–1.64	0.62
Index tumor–/other tumor–		1.03	0.71–1.48	0.89
Pathologic T stage				
pT2	47 (7.1)	1.00		
pT3–4	108 (40.2)	7.26	5.15–10.24	<0.0001
Pathologic Gleason sum				
6	38 (7.6)	1.00		
3 + 4	51 (18.3)	1.14	0.82–1.60	0.43
4 + 3, 8–10	66 (44.6)	5.22	3.79–7.18	<0.0001
Surgical margin status				
Negative	90 (11.5)	1.00		
Positive	65 (44.2)	4.81	3.49–6.62	<0.0001

BCR = biochemical recurrence; HR = hazards ratio; CI = confidence interval; RP = radical prostatectomy; PSA = prostate-specific antigen; BMI = body mass index; ERG = ETS-related gene.

^a A total of 640 (68.8%) patients in the study cohort had multifocal disease and were stained for ERG status in more than one tumor focus.

Table 4
Race-stratified multivariable Cox proportional hazards analyses for time to biochemical recurrence

Variable	Caucasian (<i>n</i> = 594)			African American (<i>n</i> = 336)		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age at RP (yr, continuous)	1.01	0.98–1.04	0.53	0.998	0.966–1.031	0.89
Diagnostic PSA (ng/ml, continuous)	1.04	1.01–1.07	0.01	1.043	1.012–1.075	0.01
Pathologic T stage (pT3–4 vs pT2)	4.43	2.54–7.74	<0.0001	3.675	1.920–7.033	<0.0001
Pathologic Gleason sum						
3 + 4 vs 6	1.51	0.82–2.78	0.19	1.547	0.826–2.899	0.17
4 + 3, 8–10 vs 6	6.91	3.9–12.3	<0.0001	2.747	1.413–5.349	0.002
Surgical margin status (positive vs negative)	1.36	0.83–2.2	0.22	2.508	1.351–4.656	0.004
BMI, kg/m ² (30 vs <30)	1.61	0.99–2.61	0.05	1.186	0.701–2.006	0.52
Index tumor ERG status (negative vs positive ^a)	1.67	1.07–2.61	0.02	0.768	0.419–1.408	0.39

HR = hazards ratio; CI = confidence interval; RP = radical prostatectomy; PSA = prostate-specific antigen; BMI = body mass index; ERG = ETS-related gene.

^aERG negative index tumor status was compared with the referent category of ERG-positive status, since expectation was for greater odds of poor outcome for those who were ERG negative, based on unadjusted findings.