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Research Article

Reducing Prostate Cancer Racial Disparity: Evidence for Aggressive Early Prostate Cancer PSA Testing of African American Men

Isaac J. Powell^{1,2}, Fawn D. Vigneau^{1,2}, Cathryn H. Bock^{1,2}, Julie Ruterbusch^{1,2}, and Lance K. Heilbrun^{1,2}

Abstract

Background: There is continuing controversy about prostate cancer testing and the recent American Urological Association guidelines. We hypothesize that the reduction and elimination of racial survival disparity among African American men (AAM; high-risk group) compared with European American men (EAM; intermediate-risk group) during the PSA testing era compared with the pre-PSA era strongly supports the use of PSA testing in AAM.

Methods: We used Surveillance, Epidemiology, and End Results (SEER) data to investigate relative survival disparities between AAM and EAM. To evaluate pre-PSA testing era, we selected malignant first primary prostate cancer in AAM and EAM, all stages, diagnosed during 1973–1994. To evaluate relative survival disparities in the current PSA testing era, we selected malignant first primary local, regional, and distant stage prostate cancers diagnosed during 1998–2005 to calculate 5-year relative survival rates.

Results: Age-adjusted 5-year relative survival of prostate cancer diagnosed during 1973–1994 in the national SEER data revealed significantly shorter survival for AAM compared with EAM ($P < 0.0001$). The SEER-based survival analysis from 1995 to 2005 indicated no statistical difference in relative survival rates between AAM and EAM by year of diagnosis of local, regional, or distant stage prostate cancer.

Conclusion: We conclude that the elimination of prostate cancer racial disparity of local, regional, and metastatic prostate cancer relative survival in the current PSA testing era compared with pre-PSA era as an endpoint to test PSA efficacy as a marker for prostate cancer diagnosis is evidence for aggressive testing of AAM.

Impact: Evidence for screening AAM. *Cancer Epidemiol Biomarkers Prev*; 23(8); 1505–11. ©2014 AACR.

Introduction

African American men (AAM) have a greater risk of dying from prostate cancer than European American Men (EAM; ref. 1). The prostate cancer age-specific mortality rates are 2.4 times greater among AAM compared with EAM (1). AAM also have a higher incidence of prostate cancer than EAM [age adjusted rate: 220.0 (AAM) vs. 138.6 (EAM); refs. 1, 2]. The CDC Behavioral Risk Factor Surveillance Study from 2007 to 2009 reports similar rates of PSA testing among AAM and EAM of the age 40 years and above, and 81% and 88% of AAM and EAM, respectively, have insurance (3). Thus,

similar rates of testing appear to have had minimal effect on the substantial prostate cancer mortality disparity. We have reported evidence that strongly suggests that prostate tumors grow faster among AAM than EAM. Autopsy results demonstrated that prostate cancer starts at similar ages among AAM and EAM with similar stage and grade at diagnosis, but subsequent development of distant metastasis occurs at a disproportionate rate of approximately three AAM to one EAM (4). Therefore, we concluded that prostate cancer progresses faster among AAM than EAM. A study of outcomes after treatment from 1991 to 1996 for clinically localized prostate cancer reported more advanced disease and greater PSA recurrence among AAM compared with EAM of ages 40 to 69 years (5). This difference in disease severity and recurrence, in addition to disproportionate mortality among young AAM, provides strong evidence that AAM should be tested more aggressively and at earlier ages than EAM.

In May 2012, the United States Preventive Service Task Force recommended against PSA screening of healthy men (6). This recommendation was based primarily on

Authors' Affiliations: ¹Wayne State University; and ²Karmanos Cancer Institute, Detroit, Michigan

Corresponding Author: Isaac J. Powell, Wayne State University/Karmanos Cancer Inst., University Health Center, 7C, 4201 St. Antoine, Detroit, MI 48201. Phone: 313-577-5222; Fax: 313-577-5217; E-mail: ipowell@med.wayne.edu

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the PLCO (Prostate, Lung, Colon, and Ovarian) prospective randomized clinical trial, which reported no decrease in mortality rate in the screened arm and therefore no PSA screening benefit. This recommendation applied to men in the U.S. population that did not have symptoms that were highly suspicious for prostate cancer, regardless of age, race, or family history. Only 4% of the PLCO study population was AAM (7). The PLCO results, however, overstated the impact of screening on prostate cancer mortality due to a high contamination rate in the control arm. During the study, 52% of controls underwent opportunistic PSA testing. In addition, Pinsky and colleagues reported that 85% of controls had a PSA test before or during the study; only 15% of PLCO controls never had a PSA test (8). Furthermore, a 7-year median follow-up time was inadequate for estimating an impact of PSA screening on prostate cancer mortality, as the study was designed to report the mortality rate comparison after 13 years (7).

The 2013 American Urological Association (AUA) prostate cancer guidelines strongly recommended shared decision making for men of the age 55 to 69 years, at intermediate risk, who were considering PSA testing (9). The AUA panel did not recommend routine testing in men between ages 40 and 54 years at average risk. The panel further commented that "for men younger than the age of 55 years at higher risk (e.g., positive family history or African American race), decisions about prostate cancer screening should be individualized and discussed with their doctor." This statement was based on results from the updated European Randomized Study of testing for Prostate Cancer (ERSPC) that demonstrated a 31% reduction in mortality in the PSA testing arm at 9 years median follow-up (10). This trial included European men only, thus it did not directly apply to AAM. The AUA guideline was clearly inadequate and provided no clear direction or guideline for AAM (11). Thus, it is necessary to provide the most available scientific data to evaluate the benefit of PSA testing of AAM younger than 55 years of age.

Level 1 scientific evidence may not be achievable in this country because of the potential for a high PSA testing contamination rate, similar to that reported for PLCO, in any future clinical trial of PSA testing. Therefore, other scientific evidence with reasonable and achievable endpoints must be considered. We hypothesize that intensive education and aggressive and early PSA testing of AAM will result in the reduction and/or elimination of racial disparity in prostate cancer survival among AAM (a high-risk group) compared with EAM (an intermediate risk group). We will present data from the pre-PSA and current PSA era to demonstrate the reduction and elimination of prostate cancer racial disparity in relative survival that occurred after the introduction of PSA testing. Survival analyses are utilized to test the efficacy of therapies and therefore should be justified to test the utility of clinical markers between high- and intermediate-risk populations.

Materials and Methods

Study cohort

The cohort for our study analyses was the accumulated prostate cancer cases in the very large national Surveillance, Epidemiology, and End Results (SEER) registry. We used the national SEER registry data to investigate relative survival disparities by race in two successive time periods: the pre-PSA testing era and the current PSA testing era. We also used the national SEER registry data to investigate incidence and mortality disparities by race. The statistical methods used are described as follows for each of those three sets of analyses.

Relative survival disparities in the pre-PSA testing era. We selected malignant first primary prostate cancer in AAM and EAM diagnosed during 1973–1994. Cases of all stages were combined into one group because the national SEER registry data for 1973–1994 do not include prostate cancer stage. Age-adjusted 5-year relative survival rates and 95% confidence intervals (CI) were calculated for each race, by year of diagnosis. Z-scores were also generated by year of diagnosis and for the entire timeframe in SEER*Stat, comparing AAM and EAM. The Z-score for the entire timeframe was used to calculate an overall *P* value using GraphPad.

Relative survival disparities in the current PSA testing era. We selected malignant first primary local, regional, and distant stage prostate cancers diagnosed during 1998–2005 (with survival follow-up through December 31, 2010). Five-year relative survival rates, 95% CIs, and Z-scores were calculated by year of diagnosis and race for each stage, thus eliminating the need to adjust for stage. Z-scores were also calculated for the entire PSA testing era, comparing AAM and EAM within each stage. The overall *P* value was calculated and a graph prepared for each stage, comparing AAM and EAM across the entire PSA testing era. We also investigated survival disparities by treatment category in the PSA era. Within each stage, 5-year relative survival rates, 95% CIs, Z-scores, overall *P* values, and graphs by stage were calculated comparing AAM and EAM for cases that received radiation, for cases that received radical prostatectomy and for the combined group of cases that received either definitive prostate cancer treatment.

Incidence and mortality disparities in the current PSA testing era. We performed three sets of analyses. First, we calculated age-specific incidence rates of distant prostate cancer in AAM and EAM for ages 40 to 79 years (40–49, 50–59, 60–69, 70–79) from 1995–2010. Rate ratios and *P* values were calculated comparing AAM with EAM within each age stratum. Second, we generated age-specific prostate cancer mortality rates (no stage restrictions) by race (AAM and EAM) with rate ratios, 95% CIs, and *P* values for U.S. deaths from 1995–2010. These data were stratified by 5-year age of death categories (40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74). Within each age group, the rate ratio and *P* value were used to evaluate whether AAM had higher risk of prostate

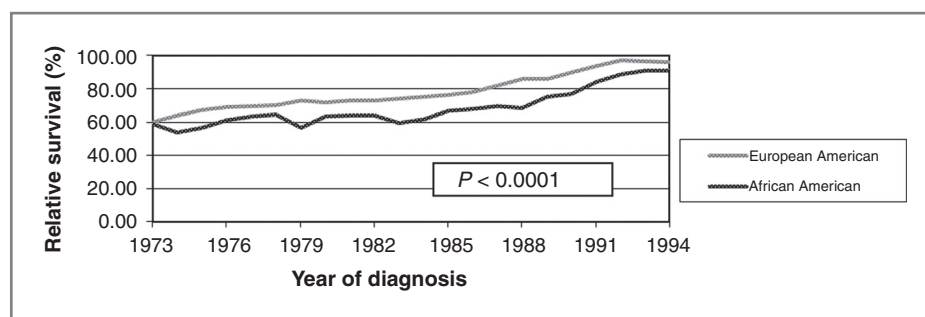


Figure 1. Age-adjusted 5-year relative survival of malignant first primary prostate cancer (all stages) in AAM and EAM by race, SEER-18, year of diagnosis 1973–1994 (survival time through 2010). Source: SEER Program (www.seer.cancer.gov) Seer*Stat Database: Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (1973–2010 varying)—Linked To County Attributes—Total U.S., 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.

cancer mortality than their EAM counterparts. Third, we evaluated Gleason score (2–6 vs. 7–10) in men diagnosed with prostate cancer in the most recent part (2004–2010) of the PSA era, who underwent radical prostatectomy. The racial distribution of patients was determined by 10-year age intervals for ages 40–69 years (40–49, 50–59, 60–69). Within each age group, the proportions of men with Gleason score 7–10 were compared by race using the χ^2 test, without continuity correction.

Results

The SEER dataset for the pre-PSA era survival analysis included $N = 212,719$ cases (AAM = 23,782 and EAM = 188,937) diagnosed in 1973–1994. Age-adjusted 5-year relative survival of first primary prostate cancer (all stages) in AAM and EAM males by race, in SEER cases diagnosed during 1973–1994 revealed statistically significantly shorter survival for AAM compared with EAM ($P < 0.0001$, Fig. 1) during the pre-PSA era.

The SEER dataset for survival analysis in the PSA era included $N = 309,793$ prostate cancer cases (AAM = 44,934 and EAM = 264,859), (local stage: AAM = 36,688, and EAM = 219,765; regional: AAM = 5,390 and EAM = 33,994; distant: AAM = 2,856 and EAM = 11,100) diagnosed from 1998 to 2005. Within each stage, there was no significant difference in survival rates between AAM and EAM for either local ($P = 1.0$), regional ($P = 0.1490$), or distant stage ($P = 0.8399$) prostate cancer for the PSA era. Analysis of treatment by each stage also revealed no significant racial disparities. For cases that received surgery, there were no significant differences in the PSA era (local: $P = 1.0$, regional: $P = 1.0$, distant: $P = 0.1416$). Likewise, for cases that received radiation therapy, there were no significant differences by race in the PSA era (local: $P = 1.0$, regional: $P = 0.2236$, distant: $P = 0.1004$). And, likewise, for the combined dataset of cases that received either radiation therapy or surgery, there were no significant differences by race in the PSA era (local: $P = 1.0$, regional: $P = 0.2059$, distant: $P = 0.0903$).

The incidence analysis of distant stage cases in the PSA era included $N = 2,742$ AAM and $N = 9,804$ EAM cases from SEER diagnosed during 1995–2010. In each age group, AAM with distant disease had significantly higher prostate cancer incidence than EAM (Table 1). Analysis of local/regional disease cases combined yielded similar results (data not shown). Although PSA testing has apparently eliminated racial disparity in the ability to survive for at least 5 years following a prostate cancer diagnosis, there still appear to be disparities in the ratios of new prostate cancer diagnoses and deaths. AAM diagnosed with distant stage prostate cancer had a 3-fold increased risk of being diagnosed with a prostate cancer, compared with their same age cohort EAM counterpart (Table 1). AAM also had about a 3-fold increased risk of dying from prostate cancer, compared with EAM of the same age cohort (Table 2). This potentially indicates a difference in the biology of prostate cancers in AAM compared with EAM,

Table 1. Age-specific incidence rates of malignant distant stage prostate cancer in AAM and EAM, SEER-13, 1995–2010

Age at diagnosis	EAM rate	AAM rate	Rate ratio	Ratio P
40–49	0.70	2.49	3.55	<0.0001
50–59	5.45	16.91	3.10	<0.0001
60–69	19.78	57.76	2.92	<0.0001
70–79	43.16	104.52	2.42	<0.0001

NOTE: Rates are per 100,000 males.

Source: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Research Data, Nov 2012 Sub (1992–2010) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.

Table 2. Age-specific prostate cancer mortality rates and rate ratios in AAM and EAM, U.S., 1995–2010

Age at death	AAM		EAM		Rate ratio	95% CI	Ratio P
	Rate	95% CI	Rate	95% CI			
40–44 y	0.55	0.45–0.66	0.18	0.16–0.21	3.00	2.39–3.75	<0.0001
45–49 y	2.42	2.21–2.65	0.76	0.71–0.80	3.21	2.87–3.58	<0.0001
50–54 y	9.01	8.55–9.50	2.81	2.72–2.90	3.21	3.01–3.41	<0.0001
55–59 y	25.30	24.40–26.22	8.21	8.03–8.38	3.08	2.96–3.21	<0.0001
60–64 y	64.23	62.57–65.92	20.55	20.24–20.86	3.13	3.03–3.22	<0.0001
65–69 y	131.97	129.26–134.72	46.07	45.56–46.59	2.86	2.80–2.93	<0.0001
70–74 y	264.63	260.16–269.16	93.05	92.25–93.85	2.84	2.79–2.90	<0.0001

NOTE: Rates are per 100,000 males.

Source: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. (1969–2010) <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

with AAM having a more aggressive prostate cancer phenotype.

There is a mortality rate lead time of approximately 5 years among AAM compared with EAM (Table 2). The mortality rate for AAM ages 40 to 44 years is 0.5, similar to the mortality rate for EAM 5 years older (0.8 for ages 45–49 years). Likewise, the mortality rate for AAM ages 45 to 49 years is 2.4, close to the mortality rate of 2.8 for EAM 5 years older (ages 50–54 years). The mortality rates increase among older AAM as compared with EAM, and by the age of 50 to 54 years, the mortality rate among AAM (9.0) is higher than the rate among EAM approximately 5 years older (8.2). Early, more aggressive PSA testing and aggressive treatment will be necessary to eliminate this prostate cancer mortality racial disparity.

Discussion

SEER data demonstrate a lead time of approximately 5 years in age-specific prostate cancer mortality rate between ages 45 and 70 years among AAM compared with EAM as well as 2.4 times greater mortality rate (12, 13). Age-adjusted 5-year relative survival analysis of all prostate cancer cases diagnosed from 1973 to 1994 reveals a significantly shorter survival for AAM than for EAM ($P = 0.0001$), but no racial difference in survival is observed for prostate cancer cases with local, regional, or distant stage disease from 1998 to 2005 (14). Southwest Oncology Group (SWOG) trials S8894 (pre-PSA era) and S9346 (current PSA era) reported similar results for distant disease, shorter survival among AAM versus EAM in the pre-PSA era, but no racial difference in survival in the current PSA era. SWOG current PSA era study also revealed less extensive disease (15). Therefore, there is evidence that PSA testing significantly reduces or eliminates racial disparity in prostate cancer survival.

However, the most important finding in this analysis is the continued prostate cancer racial disparity in the diagnosis of distant disease (16), and the 2.4 times greater

prostate cancer mortality rate of AAM compared with EAM (12, 13). Even though the mortality rates for AAM and EAM have decreased during the PSA era, significant prostate cancer racial disparity persists. Because PSA testing has apparently contributed to the reduction and elimination in relative survival and age-adjusted 5-year survival differences, more aggressive community education and PSA testing need to be implemented beginning at the age of 40 years among AAM. SEER data demonstrate that AAM ages 40 to 49 years are more likely to have a higher Gleason score compared with EAM² ($P < 0.0001$, Table 3), and the mortality rate is 2.8 to 3.2 times greater in AAM compared with EAM ages 40 to 49 years (Table 2; ref. 13).

Table 3. Gleason score for malignant prostate cancer cases who underwent radical prostatectomy, SEER-18, 2004–2010

Age at diagnosis, y	Gleason score	EAM	AAM	P
40–49	2–6	52.4%	45.4%	<0.0001
	7–10	47.6%	54.6%	
50–59	2–6	44.8%	37.6%	<0.0001
	7–10	55.2%	62.4%	
60–69	2–6	37.4%	32.4%	<0.0001
	7–10	62.6%	67.6%	

Source: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (1973–2010 varying) - Linked To County Attributes - Total U.S., 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.

In addition, we previously reported that high-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer started as early as ages 20 to 30 years, without any difference in prevalence or Gleason grade between AAM and EAM, but at the age of 40 to 49 years, the high-grade PIN incidence was greater among AAM compared with EAM, 46% versus 29%, respectively, and that difference persisted with increasing age (4). It has been reported that high-grade PIN is associated with aggressive prostate cancer (17). The proportion of men treated for prostate cancer at ages 40 to 49 years with Gleason score 7–10 at diagnosis is significantly higher among AAM compared with EAM ($P < 0.0001$, Table 3). To prevent a 3:1 disproportionate mortality rate in the decade of 50 to 59 years, diagnosis in the decade of 40 to 49 years is required. Therefore, to eliminate or significantly reduce the mortality rate disparity, we recommend that PSA testing for AAM begin at the age of 40 years.

It has been suggested that if the biology represented by the grade of the disease is more aggressive among AAM then it may not be possible to eliminate prostate cancer mortality rate racial disparity. We recently reported that prostate cancer is growing faster among AAM versus EAM as stated above and we also reported that genes associated with more advanced prostate cancer are more highly expressed among AAM compared with EAM and may explain our clinical findings. We examined RNA expression of genes associated with prostate cancer in tumors of men who underwent radical prostatectomy to identify upregulated genes and associated functional gene networks and signaling pathways that may contribute to prostate cancer progression. For example, inflammatory cytokines IL6, IL8, and IL1B show significantly higher expression levels in AAM compared with EAM (18). These functional cytokines have been reportedly associated with advanced prostate cancer. There was also increased expression of fatty acid synthase (FASN) in prostate cancer specimens from AAM versus EAM in our study. FASN germline polymorphisms were reported to be significantly associated with risk of lethal prostate cancer (19). These factors and other biologic/genetic mechanisms likely explain the racial disparity in tumor aggressiveness.

Specifically, even though we present evidence of AAM having several genetic and biologic factors associated with aggressive prostate cancer in comparison with EAM, intervention with early PSA testing and aggressive therapy before transformation to aggressive and advanced phenotypic expression has drastically reduced/eliminated survival disparity and may eventually nullify prostate cancer racial mortality disparity.

The updated follow-up of the ERSPC study and the Goteborg report clearly show benefit of PSA testing based on a 31% and 44% reduction in prostate cancer mortality rate, respectively (10, 20). However, the issue of "harm" from PSA testing is aggressively debated, specifically with regard to posttreatment erectile dysfunction and urinary incontinence. Both of these com-

plications of therapy can be successfully treated, and some men with erectile dysfunction are not bothered by this loss. But the harm of not being tested for prostate cancer and appropriately treated in a timely fashion has been essentially ignored, especially in a high-risk population. The harm is delayed diagnosis of aggressive prostate cancer, the serious morbidity of metastatic disease, and ultimately prostate cancer death. The issue of overdiagnosis and overtreatment are very controversial. There is no clear definition of either. Prostate cancer is a genetic and biologic disease that is very heterogeneous and dynamic, not static (4, 18). Until the genetics and biology are understood, we cannot clearly define overdiagnosis and overtreatment. In the interim, the introduction of active surveillance has reduced overtreatment of low-risk disease; however, one must use caution in including young AAM in surveillance. It has been reported that AAM are 3-fold more likely than EAM to have disease progression (21, 22). In addition, the harms of diagnostic testing and treatment should be uncoupled. The PLCO trial reported that the percentage of complications associated with PSA blood draw and prostate biopsy was less than 1% (7).

Piper and colleagues report, "Men dying of prostate cancer incur significant costs in the last year of life. On the basis of recent epidemiologic data, the cost of death due to prostate cancer in the United States is over three quarters of a billion dollars a year," and the cost of prostate cancer death and care before death was greater than the cost of treatment of local disease (23). The cost of treatment for metastatic prostate cancer has increased drastically. The cost of recently FDA-approved biologically targeted therapy for metastatic disease is approximately \$8,000.00 per month, and the cost is significantly higher for an immunotherapeutic agent. Because AAM have a 2.4 times greater mortality rate and risk of metastatic disease than EAM, it would be prudent to eliminate this disparity and save these prostate cancer health care system dollars. In addition, in the year before prostate cancer death, there may be comorbidities requiring multiple hospitalizations, which include pathologic fractures, lumbar nerve compression, anemia, gross hematuria, and urinary clot retention and retention from bladder obstruction, and uremia.

The cost/benefit ratio strongly favors early and aggressive PSA testing, early diagnosis, and appropriate treatment of AAM given the improved survival and disparity reduction. Therefore, we strongly recommend aggressive prostate cancer education and testing at age the age of 40 years in the African American community to avoid increased prostate cancer health care cost, comorbidities, premature prostate cancer death, and most importantly to continue the reduction and elimination of racial outcome disparity. This recommendation should be included and highlighted in all prostate cancer testing guidelines.

Our study has several limitations. First, to facilitate the comparison of the racial differences during the pre-PSA era and the current PSA era, we had to choose a cutoff

year, which was 1995. Our results might differ somewhat from the use of a different dichotomy. Second, the limitations of the national SEER registry data about prostate cancer staging (for 1973–1994) precluded our doing either stage-stratified or stage-adjusted analyses of 5-year relative survival rates during the pre-PSA era. Third, other limitations in the SEER stage data meant that for the current PSA era, we could only analyze 5-year relative survival rates beginning in 1998 (not 1995).

Our study also has several strengths. First, by utilizing SEER data, our results are based on very large sample sizes that are specified throughout the Results section. Second, by using the national SEER data, our results should be generalizable to the entire U.S. population. Third, the identification of an approximate 5-year lead time in mortality among prostate cancer cases compared with European American prostate cancer cases is a compelling observation about the racial disparity we have investigated.

Conclusion

We reported the reduction and elimination of prostate cancer racial disparity of relative survival of local, regional, and distant disease in the current PSA testing era. Therefore, we conclude that prostate cancer racial disparity reduction is a reasonable endpoint to establish the benefit of PSA testing. However, the prostate cancer mortality rate is now 2.4 times greater among AAM

compared with EAM. Therefore, we recommend robust education and PSA testing as well as digital rectal examination to begin at the age of 40 years for AAM and that this recommendation should be included in all prostate cancer guidelines.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: I.J. Powell, C. Bock, L.K. Heilbrun

Development of methodology: I.J. Powell, C. Bock

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Ruterbusch

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F.D. Vigneau, C. Bock, J. Ruterbusch, L.K. Heilbrun

Writing, review, and/or revision of the manuscript: I.J. Powell, F.D. Vigneau, C. Bock, L.K. Heilbrun

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F.D. Vigneau

Study supervision: I.J. Powell

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