Original Article

Is Prostate Cancer Different in Black Men? Answers From 3 Natural History Models

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BACKGROUND: Black men in the United States have substantially higher prostate cancer incidence rates than the general population. The extent to which this incidence disparity is because prostate cancer is more prevalent, more aggressive, and/or more frequently diagnosed in black men is unknown. **METHODS:** The authors estimated 3 independently developed models of prostate cancer natural history in black men and in the general population using an updated reconstruction of prostate-specific antigen screening, based on the National Health Interview Survey in 2005 and on prostate cancer incidence data from the Surveillance, Epidemiology, and End Results program during 1975 through 2000. By using the estimated models, the natural history of prostate cancer was compared between black men and the general population. **RESULTS:** The models projected that from 30% to 43% (range across models) of black men develop preclinical prostate cancer by age 85 years, a risk that is (relatively) 28% to 56% higher than that in the general population. Among men who had preclinical disease onset, black men had a similar risk of diagnosis (range, 35%-49%) compared with the general population (32%-44%), but their risk of progression to metastatic disease by the time of diagnosis was from 44% to 75% higher than that in the general population. **CONCLUSIONS:** Prostate cancer incidence patterns implicate higher incidence of preclinical disease and higher risk of metastatic progression among black men. The findings suggest screening black men earlier than white men and support further research into the benefit-harm tradeoffs of more aggressive screening policies for black men. ***Cancer* 2017;123:2312-9**. *© 2017 American Cancer Society.*

KEYWORDS: cancer epidemiology, mass screening, natural history, prostate-specific antigen, prostatic neoplasms, racial disparities, statistical methods and models.

INTRODUCTION

Prostate cancer is the most frequent cancer diagnosis and the second leading cause of cancer death in US men. Prostate cancer incidence among black men in the United States is 60% higher and mortality is more than double the rate observed in white men.[1]

There is an extensive literature exploring likely drivers of the racial disparity in prostate cancer observed in the United States. Regarding mortality, a persistent question concerns the relative contributions of differential access to care versus biology. Some studies[2,3] have suggested that differential access to care may partially explain the greater burden of adverse outcomes among black men. Others have identified differences in germline and tumor genetics between black men and white men.[1,4-6] Black race has been identified as an independent prognostic factor for disease recurrence in multiple reports,[7,8] supporting a biologically more aggressive disease phenotype but also raising questions about disparities in surgery quality.[9] In general, black men are less likely to receive primary surgery,[10-12] but the extent to which this observation is related to demographics, access to care, or personal preference is unclear.

At least 1 major driver behind the higher rate of prostate cancer deaths among black men is their higher incidence of the disease. Taksler et al concluded that the majority (76%) of the disparity in prostate cancer mortality may be explained by higher prostate cancer incidence in black men.[13] The objective of the current study was to investigate and explain the higher observed incidence in black men. Whether this arises from a higher risk of disease onset or faster progression to an aggressive or symptomatic state is unclear. In their multiethnic study of UK men, Metcalfe et al[14] suggested that the latter is unlikely; however, they did not formally interrogate this hypothesis.

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Understanding whether and how natural history might be different in black men is important because, if black men have a higher susceptibility to prostate cancer and/or a greater tendency to develop aggressive disease, then it may be of value to consider different screening policies for them. This issue was first raised by Powell et al,[15] who observed more aggressive disease characteristics and more frequent recurrence among black men after radical prostatectomy and, again,[16] based on a narrowing of prostate cancer survival disparities observed after the adoption of prostate-specific antigen (PSA) screening in the United States.

We previously studied the natural history of prostate cancer in the general population through statistical and computer modeling of latent disease onset and progression to clinical and metastatic states.[17-19] By calibrating the models to observed population patterns of prostate cancer incidence before and after the advent of PSA screening, we estimated the risks of critical events in disease natural history and used these results to make inferences about potential impacts of different screening policies.[20,21]

In this article, we develop versions of our natural history models that pertain to black men and calibrate these using incidence trends in the Surveillance, Epidemiology, and End Results (SEER) program under updated PSA screening frequencies estimated specifically among the black population. We use the calibrated models to produce estimates of disease onset, progression, and diagnosis risks that pertain to the black population. We compare these risks with estimates for the general population (ie, all races) to determine the extent to which the increased incidence among black men is explained by higher risks of disease onset, progression, or diagnosis. Finally, we use our results to examine differential incidence of clinically relevant disease, motivating further research into differential screening policies among black men.

MATERIALS AND METHODS

In this section, we describe the data and 3 models that we use to examine evidence of differential prostate cancer natural history in black men. We also describe a test for differences in black natural history relative to the general population and quantify the models' goodness-of-fit after re-estimating key components of natural history.

PSA Screening and Prostate Cancer Incidence Data

Because the use of population-based PSA screening was not tracked in real time, we retrospectively reconstructed PSA screening patterns in the United States separately for black men and white men in a previous study.[22] Briefly, this reconstruction used responses to the National Health Interview Survey (NHIS) in 2000 to estimate the age at first PSA test and longitudinal claims data from the linked SEER-Medicare database to estimate the distribution of interscreening intervals. The current version of the PSA screening model updates the original version, incorporating responses to the 2005 NHIS as well as information on changes in disease-specific incidence after the advent of PSA (for a comparison of the original and updated PSA screening models, see the online supporting information).

We extracted prostate cancer incidence data from the SEER database before and after the introduction of PSA screening. Specifically, we extracted prostate cancer incidence for men ages 50 to 84 years from 1975 through 2000, SEER historic locoregional and distant states, tumor grade (well or moderately differentiated [low grade] vs poorly differentiated or undifferentiated [high grade]), and race categories ("black" or "all races"). Missing information on stage, grade, and race was assumed to be missing at random and was imputed as the most frequent combination of 20 logistic regression imputations using the *mice* package in R.[23]

Three Models of Prostate Cancer Natural History

We estimated 3 models of prostate cancer natural history using PSA screening and prostate cancer incidence data separately for black men and for all races. The 3 models were previously used to study the effects of PSA screening on incidence and mortality trends in the general US population.[24,25]

Briefly, the Fred Hutchinson Cancer Research Center (FHCRC) model is a microsimulation model that links individual PSA growth and cancer progression. In this model, higher and increasing PSA levels are associated with the presence of latent cancer, and shorter intervals are associated with metastatic spread and clinical presentation. The Microsimulation Screening Analysis (MISCAN) model (from Memorial Sloan-Kettering Cancer Center) is a microsimulation model that tracks progression through combinations of cancer stages and grades. In this model, advanced stages and higher grades are associated with potentially higher screening test sensitivity and shorter intervals to clinical presentation. The UMICH model (from the University of Michigan Comprehensive Cancer Center) is an integrated suite of analytic models that estimates transition probabilities from earlier to later stages and from lower to higher grades during the

preclinical detectable phase. In this model, later stage at onset, higher grade at onset, and faster progression are associated independently with shorter intervals to clinical presentation. In each model, screening potentially detects latent cancer at an earlier stage and/or grade. Key differences between models are the length of the preclinical detectable phase, how much early detection improves tumor characteristics, and how both natural history and screening effects depend on age. Detailed descriptions of the models are provided in the online supporting information.

A Framework to Explain Incidence Disparities

Sequential estimation

We first re-estimated natural history in all races using the SEER incidence and updated PSA screening data. Then, we substituted PSA screening patterns for black men and re-estimated natural history in black men after a systematic sequence of steps. Specifically, we re-estimated components of disease natural history, each containing a specific block of parameters. The blocks of parameters governed: 1) risk of disease onset and initial tumor features, 2) risks of progression to metastasis and/or high-grade disease, and 3) risk of clinical diagnosis. At each step, the re-estimation involved identifying values of the natural history parameters that allowed the models to most closely match SEER prostate cancer incidence in black men. All models proceeded in this sequential fashion until final versions of the models were obtained that re-estimated all natural history parameters for black men. To evaluate sensitivity to this sequence of re-estimated parameters, a model-selection exercise was used to examine alternative sequences.

Natural history summary measures

Given the final versions of the models for black men and for all races, we summarized natural history in terms of the risks of preclinical onset, clinical diagnosis, and metastatic clinical diagnosis; mean ages at these natural history events; and mean years between consecutive events. Because all models were calibrated using data up to age 85 years, the summary measures were truncated at this age.

Testing and quantifying contributions to incidence disparities

We used a likelihood ratio test to evaluate whether re-estimating components of disease natural history significantly improved the models' fits to the incidence data for black men. The likelihood used age at diagnosis as a survival time and was fit using a customized age-period approach.[19] To calculate likelihood ratio statistics, 2 likelihood functions were fit, 1 with and 1 without re-estimation of the component. Although we report the likelihood ratio test results, we anticipate that, given the large sample size in the SEER registry, all tests will be highly significant at a traditional threshold. Therefore, we also report the improvement in the goodness-of-fit achieved by re-estimating components of natural history, with goodness-of-fit expressed as the sum across years of the squared difference between annual model-projected and observed age-adjusted incidence rates.

RESULTS

Figure 1 illustrates the annual percentage of men ages 50 to 84 years who received at least 1 PSA test by race and age group over the period from 1988 through 2000 using responses from the 2005 NHIS. Relative to previous estimates using responses from the 2000 NHIS,[22] we observe that younger men received fewer tests; these differences were similar among black men and men of all races. The updated screening patterns indicate that, relative to the general population, modestly lower percentages of black men received at least 1 PSA test in all but the youngest ages throughout the 1990s. The greatest racial disparities in PSA testing were in the oldest ages.

Figure 2 illustrates the results from re-estimating natural history for all races. The figure shows age-adjusted prostate cancer incidence rates per 100,000 men ages 50 to 84 years reported in SEER by historic stage and corresponding model-projected incidence rates. Figure 2 also provides SEER incidence rates for black men and results from the sequential estimation of the models' natural history components. The sequential estimation indicates that allowing the risk of disease onset to be different for black men provided an immediate improvement in the models' fits to incidence in this population. Allowing the risk of progression to distant stage to be different produced higher distant stage incidence projections but similar locoregional stage incidence projections. Also, allowing the risk of clinical diagnosis to differ in black men provided modest improvements to the fit in some cases (eg, distant stage incidence in the FHCRC model). Results of the model-selection exercise described in the online supporting information demonstrate that this sequence for re-estimating parameter blocks reflects descending importance in the improvements in fits.

Improvements from re-estimating each block of natural history parameters were highly statistically significant from likelihood ratio tests (all $P < .0001$), and the final models' fits to stage-specific incidence were substantially improved by re-estimation of the natural history

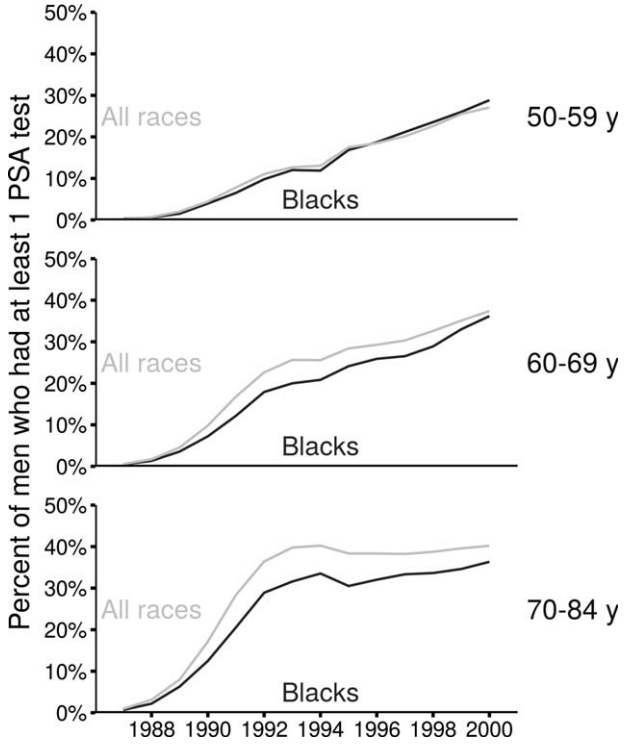

Figure 1. The annual percentage of men who receive at least 1 prostate-specific antigen (PSA) test is illustrated based on the updated reconstruction of PSA screening patterns in the United States.

components. The online supporting information indicates that sums of squared differences between observed and projected, age-adjusted incidence rates declined dramatically once disease onset was re-estimated, confirming the relative importance of disease onset risk in explaining incidence disparities. All models obtained the best fits (ie, the smallest errors) when all parameter blocks were re-estimated.

Table 1 summarizes natural history measures among black men and for men of all races up to age 85 years estimated by the 3 final models. In the general population, the risk of developing preclinical disease is 24% to 29% (range across models). In black men, however, these risks rise to 30% to 43%, reflecting risks that are (relatively) 28% to 56% higher than those in the general population. According to the models, the risks of clinical diagnosis in black men are (relatively) 33% to 70% higher than the general population; the corresponding observed risk in SEER before the advent of PSA screening was 53% higher in black men than in white men (range, 42%-62% higher) over the period from 1975 to 1986. Among men who have had disease onset, the risk of clinical diagnosis is comparable for blacks (35%-49% across models) and all races (32%-44% across models), and this translates into sojourn times from disease onset to diagnosis that are very similar for black men and for the general population within each model. However, among men with preclinical disease, the models estimate a 44% to 75% higher risk of metastasis before diagnosis among black men, reflecting greater risk of progression in this population.

DISCUSSION

The observation that prostate cancer diagnosis is more common and more lethal among black men than among white men has never been fully explained. Our study uses 3 models,[17-19] which previously were calibrated to US population incidence trends, to learn about features of underlying disease onset and progression that are unaffected by differential practice patterns around prostate cancer screening and diagnosis. The model results consistently demonstrated that the risk of onset of a preclinical prostate cancer explains a large majority of the observed incidence disparities. Furthermore, in addition to the risk of onset, the risk of progression to metastatic disease before clinical diagnosis was higher among black men, but their risk of clinical diagnosis after disease onset was similar to that in the general population. The models cannot identify whether these apparent differences in disease natural history are driven by biology, behavioral, or environmental factors, but they are of value in generating hypotheses about underlying mechanisms and their implications for screening policies.

On the basis of these results, we conclude that black men have more preclinical and progressive prostate cancer than men in the general population. They are more likely to develop prostate cancer at a younger age, and they are more likely to progress to a metastatic state and/or higher grade before clinical diagnosis. Their higher risk of progression agrees with a previous study based on autopsy and surgical pathology data[26], which concluded that black men had an earlier transformation to clinically significant cancer than white men. That study indicated similar age-specific prevalence of prostate cancer among autopsies conducted in black and white men from the Detroit metropolitan area between 1992 and 2001. The study also reported evidence of more aggressive disease in radical prostatectomy specimens from black men, consistent with their markedly higher incidence of metastatic disease at diagnosis. These findings led the authors to conclude that the risk of prostate cancer initiation did not differ by race, but the risk of disease progression was higher among black men. However, similar latent prevalence and greater metastatic clinical incidence of disease among black men in

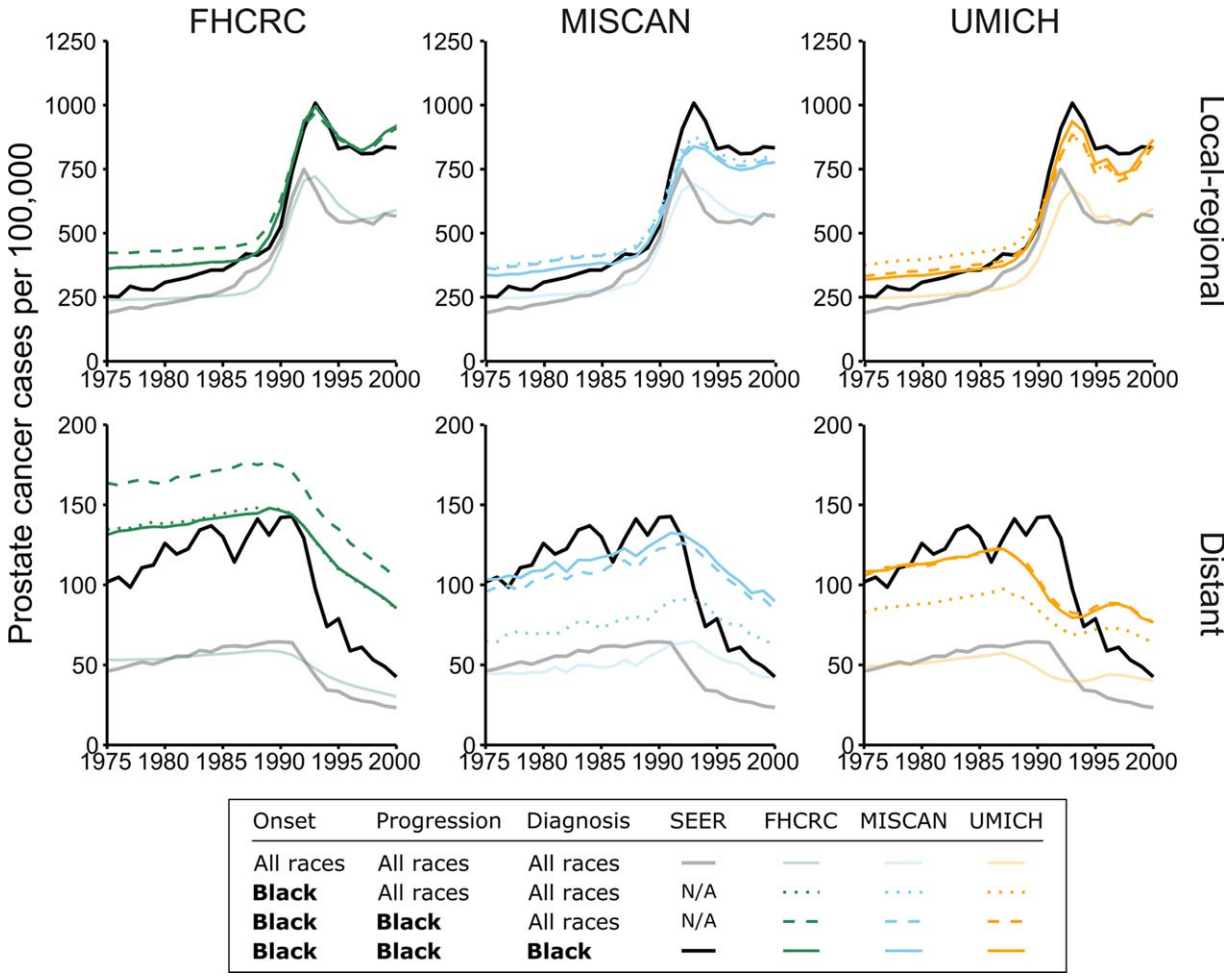

Figure 2. Age-adjusted prostate cancer incidence rates per 100,000 men ages 50 to 84 years are illustrated for black men (black line) and for all races (gray line) along with corresponding projections by 3 models (colored lines). Model projections are based on the models estimated for all races combined with prostate-specific antigen screening among black men and sequentially re-estimating components of natural history to allow differential risk of onset of preclinical cancer ("onset"), risk of progression to metastasis and/or higher grade disease ("progression"), and risk of clinical diagnosis ("diagnosis"). FHCRC indicates the Fred Hutchinson Cancer Research Center model; MISCAN, Microsimulation Screening Analysis (Erasmus University Medical Center model); N/A, not applicable; SEER, the National Cancer Institute Surveillance, Epidemiology, and End Results program; UMICH, the University of Michigan model.

fact is only possible if latent incidence is also higher in this subgroup. Because, if latent incidence is similar among black men but progression is faster, then this actually would lead to lower latent prevalence at autopsy. Therefore, we conclude that the prior study results are indeed consistent with our finding that the risks of both latent incidence and progression are likely higher among black men.

Our findings motivate considering more intensive screening, eg, beginning earlier and/or screening more frequently, among black men than among the general US population. To illustrate this, Figure 3 illustrates the cumulative incidence of "relevant disease," ie, disease fated to present before other-cause death. At all ages, the cumulative incidence is higher for black men than for men of all races. At ages 46 to 52 years (range across models), the cumulative incidence among black men reaches the value estimated at age 55 years among all races. Thus, if it is agreed that prostate cancer screening is worthwhile, and if starting at age 55 years is determined for the general population, then our results suggest starting from 3 to 9 years earlier for black men.

We recognize that a consensus about general population screening is still lacking. The US Preventive Services Task Force[27] recommends against routine prostate cancer screening in men of average risk, whereas the American

TABLE 1. Summary Measures for Natural History Events Occurring Within a Man's Lifetime, up to Age 85 Years, Projected by the 3 Models

Measure	FHCRC			MISCAN			UMICH		
	Black Men	All Races	Ratio[a]	Black Men	All Races	Ratio[a]	Black Men	All Races	Ratio[a]
Risk of onset, %	43	28	1.56	30	24	1.28	37	29	1.29
Risk of clinical diagnosis, %	15	9	1.70	13	10	1.33	18	13	1.44
Risk of metastatic clinical diagnosis, %	4	2	2.53	4	2	1.84	4	2	2.26
Risk of clinical diagnosis given onset, %	35	32	1.09	45	43	1.04	49	44	1.12
Risk of metastatic clinical diagnosis given onset, %	9	6	1.63	13	9	1.44	12	7	1.75
Mean age at onset, y	57	59	0.97	64	67	0.96	65	66	0.99
Mean age at clinical diagnosis, y	71	72	0.99	70	72	0.98	75	76	0.98
Mean age at metastatic clinical diagnosis, y	70	72	0.98	71	73	0.98	74	74	0.99
Mean time from onset to clinical diagnosis, y	18	18	1.02	10	10	0.98	17	18	0.92
Mean time from onset to metastatic clinical diagnosis, y	16	15	1.03	12	13	0.94	16	21	0.79
Risk of PSA or clinical diagnosis, %[b]	16	10	1.65	20	16	1.23	20	14	1.45
Risk of PSA or clinical diagnosis given onset, %[b]	38	36	1.06	66	68	0.97	53	47	1.12
Mean age at PSA or clinical diagnosis, y[b]	70	71	0.99	69	71	0.98	73	74	0.98
Mean time from PSA to clinical diagnosis, y[b]	7	7	1.03	8	9	0.95	7	7	0.96

Abbreviations: FHCRC, Fred Hutchinson Cancer Research Center model; MISCAN, Microsimulation Screening Analysis (Erasmus University Medical Center model); PSA, prostate-specific antigen; UMICH, the University of Michigan model.

[a] Ratios are for black men relative to all races and are calculated using 4 significant digits for all measures.

[b] These measures are in the presence of modeled PSA screening patterns during 1987 through 2000 and are included for reference.

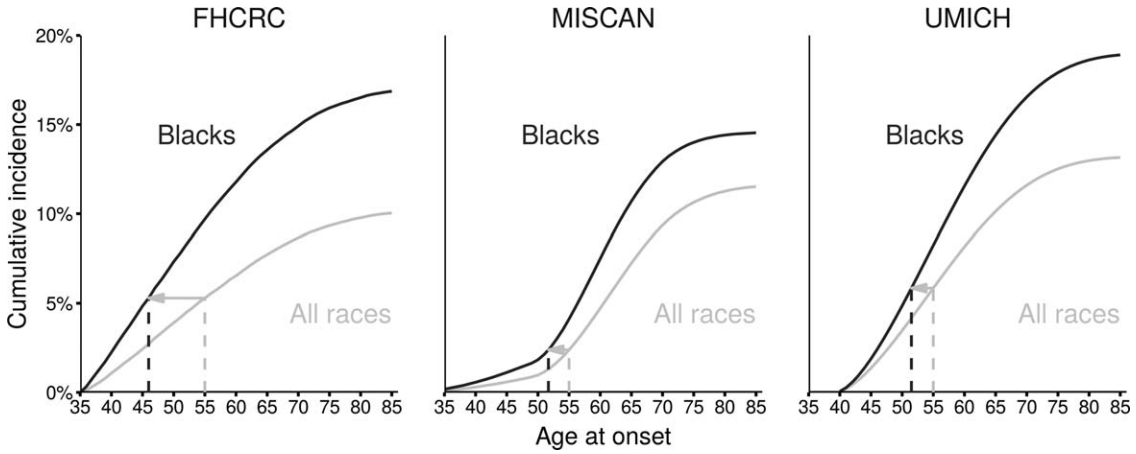

Figure 3. The cumulative incidence of the onset of preclinical prostate cancer that would be clinically diagnosed in black men and in men of all races projected by the models is illustrated. Line segments indicate the ages at which black men have incidence corresponding to levels estimated at age 55 years in all races. FHCRC indicates Fred Hutchinson Cancer Research Center model; MISCAN, Microsimulation Screening Analysis (Erasmus University Medical Center model); UMICH, the University of Michigan model.

Cancer Society[28] recommends shared decision making around prostate cancer screening beginning at age 50 years, and the American Urological Association[29] provides similar guidance with a starting age of 55 years. However, black men are not at average risk, and the benefit-harm tradeoffs of screening are likely to be different for this population.[30]

Although starting screening at an earlier age is unlikely to impact overdiagnosis, other more aggressive screening policies, eg, shortening intervals between screens or lowering the PSA threshold for biopsy referral, could increase risks of overdiagnosis.[31] A comprehensive policy-development process addressing whether and how best to screen black men will have to carefully weigh benefit-harm tradeoffs of candidate policies. Understanding race-specific natural history will be a critical prerequisite for this important work. At this point, however, our findings support considering screening beginning at an earlier age in black men than in the general population. Powell et al[16] also recommend aggressive,

early prostate cancer PSA testing of African American men. Our work adds to theirs by illustrating 1 quantitative justification for an age at which to initiate screening in black men.

In practice, the policy-development process will require going beyond examining incidence patterns to projecting mortality in the presence and absence of screening. Because screening benefit is contingent on access to efficacious therapies, benefits of screening in different race groups may be affected by any disparities in access to treatment and any racial differences in treatment efficacy. Future work will extend the models used in this article to project the downstream outcomes of different screening policies in black men under race-specific treatment distributions and efficacies.

Limitations of this study relate primarily to modeling assumptions and data limitations. Although the use of multiple models provides some sense of robustness to the specific assumptions made, all models assume that disease is progressive. Thus, none of the models explicitly include an indolent subpopulation, although each allows heterogeneity of disease progression, with some cases progressing rapidly and others slowly. The FHCRC model allows the likelihood of developing high-grade disease to vary with age but does not model grade progression; the other models allow both grade and stage progression. Other differences across models are also driven by differences in the conceptualization of onset and how the risk of onset depends on age. In the FHCRC model, onset refers to the latent incidence of disease that would be detectable by biopsy, which can occur as early as age 35 years; whereas, in the MISCAN and UMICH models, onset refers to the latent incidence of disease that can be detected based on elevated PSA and diagnostic workup, and this rarely occurs before age 40 years. Finally, the PSA screening rates used by all models are based on a retrospective reconstruction rather than a prospective tracking of prostate cancer screening dissemination in the US population.

In conclusion, this study represents the first examination of how prostate cancer natural history must differ in black men to account for racial variation in patterns of disease incidence before and after the advent of PSA screening. We use observed patterns of disease incidence and screening to learn about key events in the latent process of disease by race. Our results provide quantitative information about the prostate cancer natural history that may support prior suggestions to explore different screening policies among white men and black men.[13,15]

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Alex Tsodikov: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and funding acquisition. **Roman Gulati:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Tiago M. de Carvalho:** Methodology, software, validation, formal analysis, investigation, and writing–review and editing. **Eveline A. M. Heijnsdijk:** Methodology, software, validation, formal analysis, writing–review and editing, and supervision. **Rachel A. Hunter-Merrill:** Software, validation, investigation, data curation, and writing–review and editing. **Angela B. Mariotto:** Methodology and writing–review and editing. **Harry J. de Koning:** methodology, resources, supervision, and funding acquisition. **Ruth Etzioni:** Conceptualization, methodology, validation, formal analysis, resources, writing–original draft, writing–review and editing, supervision, project administration, and funding acquisition.

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