Title:	Is prostate cancer different in black men? Answers from three natural history models
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| **Precis:** | We apply three models to study differences in prostate cancer natural history between black men and the general US population. We find black men have higher prevalence of preclinical disease at all ages and higher risk of metastasis, supporting further study into different screening policies for blacks. |

Abstract

Background: Black men in the US have substantially higher prostate cancer incidence rates than the general population. The extent to which the incidence disparity is due to prostate cancer being more prevalent, more aggressive, and/or more frequently diagnosed in black men is unknown.

Methods: We estimated three independently developed models of prostate cancer natural history in black men using an updated reconstruction of PSA screening, based on the National Health Interview Survey in 2005, and prostate cancer incidence from the Surveillance, Epidemiology, and End Results program in 1975–2000. Using the estimated models, we compared summary measures of prostate cancer natural history in black men and in the general population.

Results: The models projected that 29–45% (range across models) of black men develop preclinical prostate cancer in their lifetime, a risk that is (relatively) 24–54% higher than in the general population. Among men who have had preclinical disease onset, black men have a similar risk of diagnosis compared with the general population, but their risk of progression to metastatic disease by the time of diagnosis is 38–58% higher than in the general population.

Conclusions: Prostate cancer incidence patterns implicate substantially higher incidence of preclinical prostate cancer and a 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.

INTRODUCTION

Prostate cancer is the most frequent cancer diagnosis and the second leading cause of cancer death in US men. Black men in the US have significantly higher prostate cancer incidence and mortality than white men, but reasons for this disparity are unclear. Some studies[1] have suggested that differential access to care may partially explain the greater burden of disease in blacks, but others have concluded that differences in outcomes are more plausibly attributed to biologic differences.[2-4] Black race has been associated with higher prostate-specific antigen (PSA) levels at diagnosis[5-7] and a higher risk of recurrence following radical prostatectomy after controlling for other clinical and demographic characteristics.[8-10]

There is no question that the higher prostate cancer mortality in black men is at least partially due to their increased incidence of disease.[11] What is not known, however, is whether the higher observed incidence in black men arises from a higher risk of disease onset or faster progression to an aggressive or symptomatic state. In their multi-ethnic study of UK men, Metcalfe et al.[12] suggest that the latter is unlikely; however, they do not formally interrogate this hypothesis.

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, it may be of value to consider different screening policies for them. This issue was raised by Powell et al.,[13] who recommended aggressive screening of black men beginning at age 40 based on a narrowing of prostate cancer survival disparities observed following the adoption of PSA screening in the US.

We previously studied the natural history of prostate cancer in the general population via statistical and computer modeling of latent disease onset and progression to clinical and metastatic states.[14-16] 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.[17, 18]

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 our estimates for the general population (i.e., 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. We also provide natural history summaries, including lifetime risks of disease onset, post-onset progression, and detection, for black men compared with the population as a whole. Finally, we use our results to motivate consideration of differential screening policies among black men.

METHODS

In this section, we describe the data and three 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 population-based PSA screening utilization was not tracked in real time, we retrospectively reconstructed PSA screening patterns in the US separately for black and white men in a previous study.[19] 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 inter-screening intervals. We updated the resulting model of PSA screening patterns using responses to the NHIS in 2005, which moderately reduced the uptake of first PSA tests in the 1990s among the oldest age groups relative to our previous analysis.[19]

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 ages 50–84, years 1975–2000, SEER historic stages local-regional and distant, tumor grade well or moderately differentiated (low-grade) versus 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 imputed as the most frequent combination of 20 logistic regression imputations using the *mice* package in R.[20]

Three models of prostate cancer natural history

We estimated three models of prostate cancer natural history using PSA screening and prostate cancer incidence data separately for black men and for all races. The three models were previously used to study effects of PSA screening on incidence and mortality trends in the general US population.[21, 22]

Briefly, the 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 to metastatic spread and clinical presentation. The MISCAN model 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 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, a later stage at onset, a higher grade at onset, and faster progression are each associated 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 given in the Appendix.

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 re-estimated natural history in black men following a systematic sequence of steps. First, we substituted PSA screening patterns for black men. Then we re-estimated components of disease natural history, each containing a specific block of parameters. The blocks of parameters governed (a) risk of disease onset and initial tumor features, (b) risks of progression to metastasis and/or high-grade disease, and (c) 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.

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 lifetime risks of preclinical onset, post-onset progression, and clinical diagnosis; mean ages at these natural history events; and mean years between consecutive events.

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 uses age at diagnosis as a survival time and is fit via a customized age-period approach.[16] To calculate likelihood ratio statistics, two likelihood functions are fit, one with and one without re-estimation of the component. While 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 50–84 who received at least 1 PSA test by race and age group over the period 1988–2000 using responses from the NHIS in 2005. Relative to previous estimates using responses from the NHIS in 2000,[19] we find that younger men received more tests, particularly in the late 1990s, and older men received fewer tests; these differences were similar among black men and 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 shows the results of re-estimating natural history for all races. The figure shows age-adjusted prostate cancer incidence rates per 100,000 men ages 50–84 reported in SEER by historic stage and corresponding model-projected incidence rates. Figure 2 also shows SEER incidence rates for black men and results of the sequential estimation of the models' natural history components. The sequential estimation found 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 but similar local-regional stage incidence projections. And allowing the risk of progression to clinical diagnosis to differ provided modest improvements to the fit in some cases (e.g., distant-stage incidence in the FHCRC model).

Improvements from re-estimating each block of natural history parameters were highly statistically significant from likelihood ratio tests (all p-values < 0.0001), and the final models' fits to stage-specific incidence were substantially improved by re-estimation of the natural history components. Table 1 shows that sums of squared differences between observed and projected age-adjusted incidence rates declined dramatically once disease onset was re-estimated, confirming the importance of disease onset risk in explaining incidence disparities. All models obtained the best fits (i.e., smallest errors) when all parameter blocks were re-estimated, though the UMICH fit was similar after re-estimating diagnosis.

Table 2 summarizes natural history measures among black men and for all races estimated by the three final models. In the general population, the lifetime risk of developing preclinical disease is 23–29% (range across models). In black men, however, these risks rise to 29–45%, reflecting risks that are (relatively) 24–54% higher than the general population. According to the models, the risk of clinical diagnosis is 25–66% higher than the general population; the corresponding observed risk in SEER prior to the advent of PSA screening was 53% higher in black men than white men (range 42%–62% higher)

over the period 1975 to 1986. Among men who have had disease onset, the risk of clinical diagnosis is comparable for blacks (39–85% across models) and all races (36–86% across models), and this translates into sojourn times from disease onset to diagnosis that are very similar for black men and the general population. However, among men with preclinical disease, the models estimate a 38–58% higher risk of metastasis before diagnosis among black men, reflecting greater risk of progression in this population.

DISCUSSION

The observation that prostate cancer is more is more frequent and more lethal among black men than among white men has never been fully explained. Our study uses three models[14-16] previously calibrated to US population incidence trends. After updating the frequency of PSA testing and re-estimating these models for all races, we substituted PSA testing frequencies observed among black men into the models for all races and then systematically explored re-estimating individual components of disease natural history to fit disease incidence patterns in this population. The model results consistently showed that the risk of onset of a preclinical prostate cancer explains a large majority of the observed incidence disparities. Additional improvements achieved by re-estimating other natural history components produced moderate additional improvements in reproducing overall observed incidence among black men but yielded noticeable improvement in reproducing observed advanced-stage incidence. Estimation of natural history summaries based on the full race-specific models confirmed that, in addition to the risk of onset, the risk of progression to metastatic disease before clinical diagnosis was higher among black men, but the risk of progression to clinical diagnosis was not higher than in the general population.

Based on these results, we conclude that black men have more preclinical and progressive prostate cancer than 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[4] that concluded that black men had an earlier transformation to clinically significant cancer than white men. This study found 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 found 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 is in fact only possible if latent incidence is also higher in this subgroup. For, if latent incidence is similar among black men but progression is faster, this would actually lead to lower latent prevalence at autopsy. Therefore, we conclude that the prior study results are in fact consistent with our finding that the risks of latent incidence and progression are likely both higher among black men.

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

We recognize that a consensus about general population screening is still lacking. The US Preventive Services Task Force[23] recommends against routine prostate cancer screening in men of average risk, while the American Cancer Society[24] recommends shared decision making around prostate cancer screening beginning at age 50 and the American Urological Association[25] provides similar guidance with a starting age of 55. However, black men are not average risk and the benefit-harm tradeoffs of screening are likely to be different for this population.[26]

While starting at an earlier age is unlikely to impact overdiagnosis, other more aggressive screening policies, e.g., shortening intervals between screens or lowering the PSA threshold for biopsy referral, could increase risks of overdiagnosis.[27] 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 pre-requisite for this important work. At this point, however, our findings do support starting screening at an earlier age in black men than in the general population. Powell et al.[13] also recommend aggressive early prostate cancer PSA testing of African American men. Our work adds to theirs by providing a formal, quantitative justification for an age 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. Since 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. While 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 includes 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, while 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 occurs rarely before age 40. Finally, the PSA screening rates used by all the 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 justify exploring different screening policies among white and black men. In pursuit of policies that will reduce disparities in disease outcomes, it may ultimately be necessary to intervene with greater intensity among population subgroups at highest risk.

Figure 1. Annual percentage of men receiving at least 1 PSA test based on the updated reconstruction of
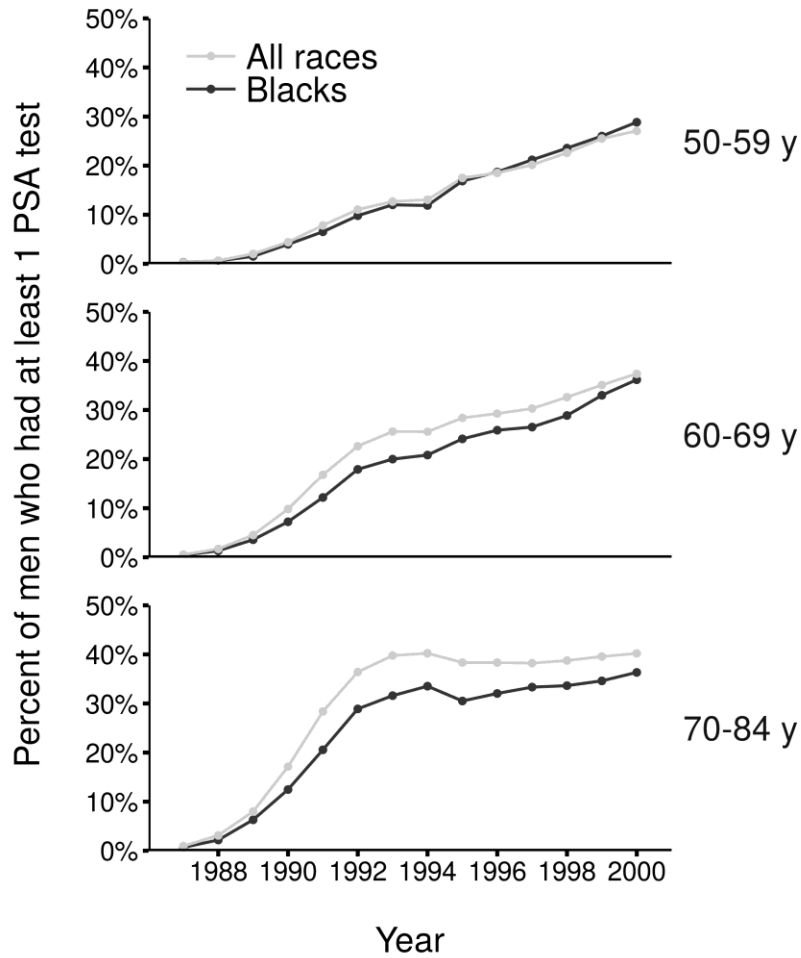
PSA screening patterns in the US.

Figure 2. Age-adjusted prostate cancer incidence rates per 100,000 men ages 50–84 years for black men (black line) and all races (gray line) and corresponding projections by three models (colored lines). Model projections are based on the models estimated for all races combined with PSA screening in 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 ("Onset-Progression"), and risk of clinical diagnosis ("Onset- Progression -Diagnosis").
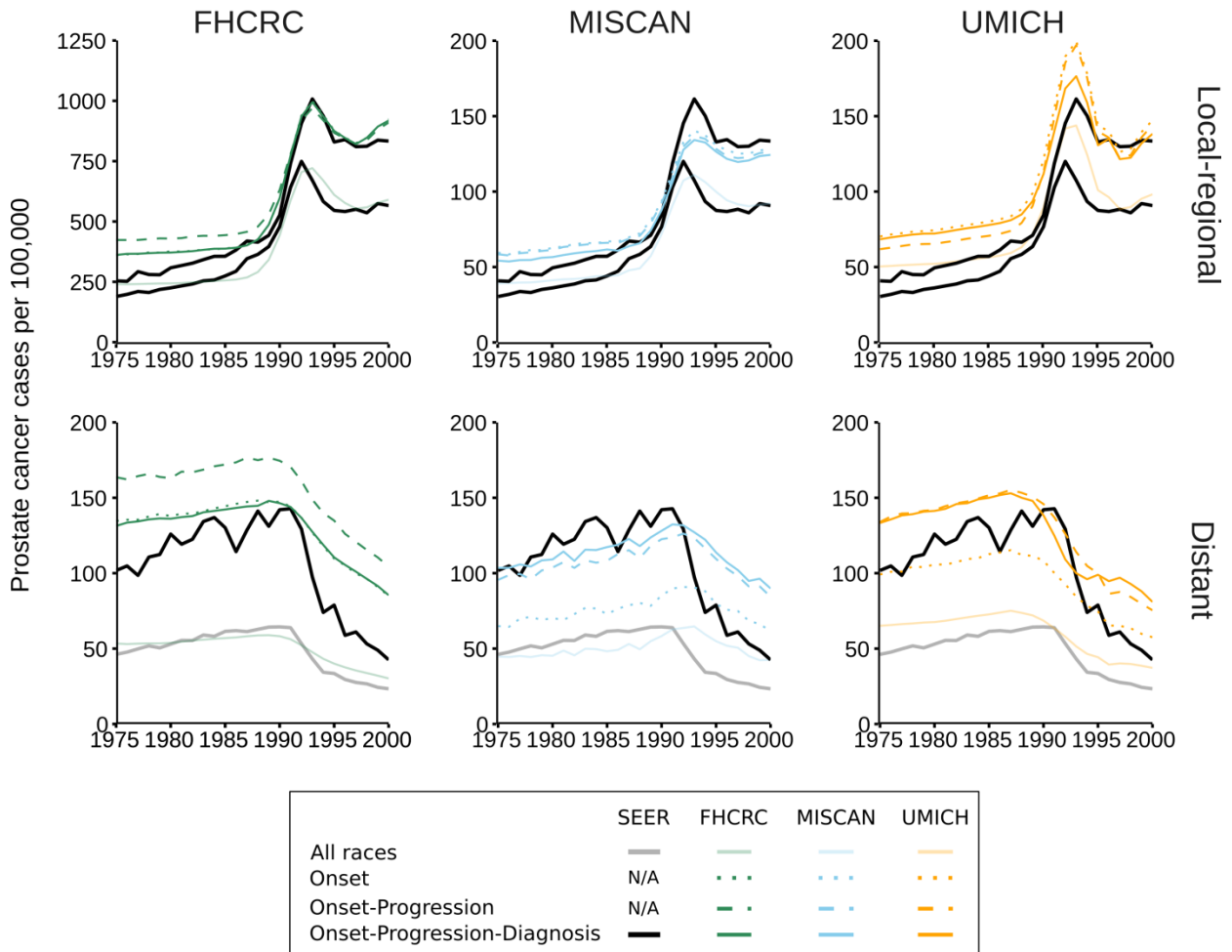
Figure 3. Cumulative incidence of onset of preclinical prostate cancer that would be clinically diagnosed in black men and all races projected by the models. Line segments show ages at which black men have incidence corresponding to levels estimated at age 55 in all races.
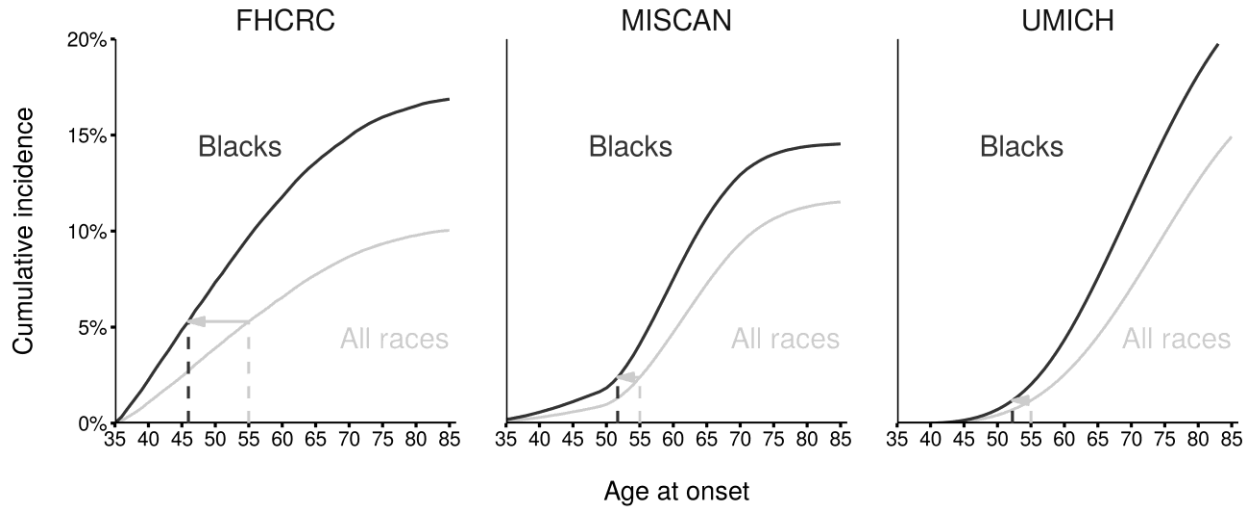
Table 1. Squared differences between age-adjusted prostate cancer incidence rates per 100,000 men ages 50–84 years for black men and corresponding model projections, summed across years 1975–2000. Model projections are based on the models estimated for all races combined with PSA screening in black men ("Black screening") 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 ("Onset-Progression"), and risk of clinical diagnosis ("Onset-Progression-Diagnosis").

Run	FHCRC	MISCAN	UMICH
Black screening	287160	271140	127130
Onset	41130	18340	136110
Onset-Progression	121280	23180	120650
Onset-Progression-Diagnosis	39250	18670	122780

Table 2. Natural history summary measures for black men (Blacks) and for all races (All) projected by the three models. Lifetime risks are given as percentages; mean ages and durations are given in years.

Measure	FHCRC		MISCAN		UMICH	
	Blacks	All	Blacks	All	Blacks	All
Lifetime risk of onset	45	29	31	25	29	23
Lifetime risk of clinical diagnosis	17	10	15	12	25	20
Lifetime risk of metastatic clinical diagnosis	5	2	4	3	5	3
Lifetime risk of clinical diagnosis given onset	39	36	48	47	85	86
Lifetime risk of metastatic clinical diagnosis given onset	10	6	14	10	17	12
Mean age at onset	58	60	65	68	67	70
Mean age at clinical diagnosis	73	74	72	74	74	77
Mean age at metastatic clinical diagnosis	73	75	73	76	73	75
Mean years from onset to clinical diagnosis	19	18	10	10	3	3
Mean years from onset to metastatic clinical diagnosis	16	16	12	13	6	8
Lifetime risk of PSA or clinical diagnosis*	18	11	20	17	26	20
Lifetime risk of PSA or clinical diagnosis given onset*	41	39	66	68	88	85
Mean age at PSA or clinical diagnosis*	72	73	70	72	72	75
Mean years from PSA to clinical diagnosis*	7	7	8	9	4	4

* These measures are in the presence of modeled PSA screening patterns in 1987–2000 and are included for reference.

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