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Relative Value of Race, Family History and Prostate Specific Antigen as Indications for Early Initiation of Prostate Cancer Screening

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Abstract

Purpose—Many guidelines suggest earlier screening for prostate cancer in men at high risk with risk defined in terms of race and family history. Recent evidence suggests that baseline prostate specific antigen is strongly predictive of the long-term risk of aggressive prostate cancer. We compared the usefulness of risk stratifying early screening by race, family history and prostate specific antigen at age 45 years.

Materials and Methods—Using estimates from the literature we calculated the proportion of men targeted for early screening using family history, black race or prostate specific antigen as the criterion for high risk. We calculated the proportion of prostate cancer deaths that would occur in those men by age 75 years.

Results—Screening based on family history involved 10% of men, accounting for 14% prostate cancer deaths. Using black race as a risk criterion involved 13% of men, accounting for 28% deaths. In contrast, 44% of prostate cancer deaths occurred in the 10% of men with the highest prostate specific antigen at age 45 years. In no sensitivity analysis for race and family history did the ratio of risk group size to number of prostate cancer deaths in that risk group approach that of prostate specific antigen.

Conclusions—Basing decisions for early screening on prostate specific antigen at age 45 years provided the best ratio between men screened and potential cancer deaths avoided. Given the lack of evidence that race or family history affects the relationship between prostate specific antigen and risk, prostate specific antigen based risk stratification would likely include any black men or men with a family history who are destined to experience aggressive disease. Differential screening based on risk should be informed by baseline prostate specific antigen.

Keywords

prostatic neoplasms; risk; age factors; African Americans; prostate specific antigen

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Data from ERSPC demonstrated that PSA screening decreases prostate cancer mortality in men who would not otherwise undergo screening.[1] The main ERSPC analyses were based on a core age group of men 55 to 69 years old. This has left guidelines groups with a conundrum as to screening recommendations for men outside this age range. There is a reasonable consensus that screening in men older than 70 years should be restricted on the grounds that ERSPC data demonstrate no benefit in this age group and reasons such as limited life expectancy suggest that screening would do more harm than good.

The situation in younger men remains more equivocal. Despite the lack of evidence from ERSPC due to a limited number of events in the younger age group there are several arguments for starting PSA screening earlier. In particular, although there is no reason to believe that mortality reductions increase after age 55 years (benefits would be similar), younger men have longer life expectancy and, therefore, are at decreased risk for overdiagnosis, suggesting that harms would be lower.

Recommendations for screening younger men vary among guideline groups. An approach has been to offer screening as an option starting at age 50 or 55 years with earlier screening restricted to men deemed to be at high risk. For instance, AUA recommends that in men younger than 55 years at higher risk, such as a positive family history or black race, decisions regarding prostate cancer screening should be individualized.[2] A similar approach was taken by NCCN Guidelines®, which recommend starting screening earlier in black men and in men with a first-degree relative diagnosed with prostate cancer.[3] ACS (American Cancer Society) also recommends that age at screening initiation should be based on race and family history.[4] Similar recommendations are found in national guidelines outside the United States, including those in Australasia[5] and the United Kingdom.[6]

If early screening should be restricted to men at higher risk, this raises 2 questions. 1) Do race and family history increase risk sufficiently to justify differential screening? 2) Might there might be other risk factors that lead to superior risk stratification? Specifically there is now excellent evidence that PSA before age 50 years is a strong predictor of subsequent aggressive prostate cancer.[7] For example, our group recently reported that almost half of prostate cancer deaths by age 75 years occur in men in the top 10% of PSA at ages 45 to 49 years.[8]

In the current study we derived and compared quantitative estimates of the risk of prostate cancer mortality based on race, family history and PSA to determine indications for early prostate cancer screening.

METHODS

Our initial intent was to systematically review studies predicting long-term prostate cancer mortality in terms of race, family history or PSA before age 50 years. However, our initial review of the literature revealed that the predictive ability of PSA was qualitatively greater than that of race and family history. Thus, we present best case scenarios for race and family history compared with PSA data. Instead of pooling estimates from studies and taking an

average, we assumed that the effect of race and family history on risk would be at the high end of the estimates that we obtained.

Our metric for comparing risk factors was the proportion of men defined as being at risk (the proportion with a positive family history) compared to the proportion of prostate cancer deaths in that risk group. The risk of prostate cancer mortality by baseline PSA before age 50 years was obtained from the Malmö cohort.[9,10] Briefly, this involved a representative group (74% participation rate) of 21,277 Swedish men who donated blood in 1974 to 1986 as part of a cardiovascular prevention study. Prostate cancer mortality was ascertained by case note review in 72% of cases. Because the PSA screening rate in Sweden has historically been low, the cohort provides a natural experiment for the association between PSA and prostate cancer mortality. To estimate the value of PSA before age 50 years we focused on 10,357 men 45 to 49 years old. The distribution of PSA in this cohort was similar to that in a cohort of American men 40 to 49 years old at a median of 0.68 (90th centile 1.60) vs 0.71 ng/ml (90th centile 1.48).[11] While many of studies show a strong association between baseline PSA and subsequent prostate cancer outcomes,[7] we focused on the Malmö cohort since it accrued the most number of men in the appropriate age range and provides a relatively precise estimate of the proportion of prostate cancer deaths by early PSA quantile.

The prevalence of a family history positive for prostate cancer was directly estimated in several studies as well as the relative risk of mortality associated with a family history. Where D represents prostate cancer death, FH represents family history and RR represents relative risk, the absolute risk in patients with a family history is shown by the equation, $P(D|FH^+) = P(D)/[P(FH^+) + P(FH^-)/RR]$ and the proportion of all prostate cancer deaths in men with a family history is shown by the equation, $P(D|FH^+) \times P(FH^+)/P(D)$.

To calculate these statistics using race as a risk factor we obtained the proportion of men who are black from United States Census data.[12] The proportion of prostate cancer deaths in this risk group was obtained from SEER (Surveillance, Epidemiology and End Results) data, which are compiled from cancer registries covering about 28% of the American population.[13] There is evidence that the increased risk in black men is age dependent such that the difference in risk is greater in younger than in older men. Moreover, black men have greater other cause mortality with aging. As sensitivity analysis, we tried increasing the relative risk associated with race and the incidence of black race to see how this would influence our estimates.

RESULTS

PSA Before Age 50 Years

In the Malmö study 44% of prostate cancer deaths (95% CI 34–53) by age 75 years occurred in men in the top 10% of PSA at ages 45 to 49 years, equivalent to PSA 1.60 ng/ml or greater.[8]

Family History

The estimated incidence of a first-degree relative with a prostate cancer history was 5% in a 2006 population based study using NHIS (National Health Interview Survey) data[14] and 7%

in a 2001 population based study of more than 1,000 Connecticut residents[15] plus data on 150,000 participants in the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial.[16] Estimates of the increase in mortality risk associated with a family history included 1.5 overall, 2 if the relative was diagnosed before age 65 years[17] and 2.75 for an affected brother.[18,19]

Using a 1.5 relative risk of mortality we estimated the proportion of prostate cancer deaths in men with a family history, assuming a 5% or 10% prevalence of a positive family history. If 5% of men had such a family history, they would represent about 7.3% of all prostate cancer deaths and if 10% of men had such a family history, they would represent approximately 14.3% (see table). As an extreme scenario, we assumed that all men with a family history were at 3 times the risk of prostate cancer death compared to men with no family history, a greater increase in risk than that reported for the rare man with a brother diagnosed with prostate cancer. At a 5% prevalence these men represented 14% of prostate cancer deaths. Assuming the most extreme scenario with a relative risk of 3 and a prevalence of 10% men with a family history represented only 25% of prostate cancer deaths.

Since PSA screening has increased the number of diagnoses, the association between family history and mortality has become weaker, strengthening our conclusion that family history does not provide strong risk stratification.

Race

The 2010 United States Census reported that 12.6% of the American population identifies as black.[12] The age adjusted incidence of prostate cancer in black American men between 2006 and 2010 was 228.5/100,000 compared to 144.9/100,000 white American men. Age adjusted prostate cancer mortality in black men during that period was more than double that in white men (50.9/100,000 vs 21.2/100,000). Hispanic, American Indian and Asian men had even lower rates of prostate cancer diagnosis and death than white men. The total prostate cancer mortality for all races between 2006 and 2010 was 23/100,000 men.[20]

Where D represents death and AA represents black race, prostate cancer mortality in all other races combined was calculated using the equation, $P(D) = [12.6\% \times P(D|AA)] + (87.4\% \times P[D|nonAA])$. Age adjusted prostate cancer mortality in black men in the 5 years to 2010 was 50.9/100,000 compared to 19/100,000 in all other races combined. Thus, for every 100,000 American men there are 6.4 prostate cancer deaths in black men and 16.6 prostate cancer deaths in nonblack men so that death in black men represents 28% of all prostate cancer deaths.

As sensitivity analysis, we assumed that the relative risk of early prostate cancer death was close to 3, ie 69/100,000 men, rather than 2 and that younger black men would comprise 15% of the younger male population compared to 12.6% overall. The proportion of early death in black men would then be 39%. We tried various scenarios to obtain risk stratification similar to that of PSA for which the proportion of deaths is more than fourfold the proportion of the population at risk. Only when we assumed that black men were at

eightfold higher risk for early prostate cancer death and no increase in nonprostate cancer mortality did race approach PSA in terms of risk stratification.

DISCUSSION

We used estimates from the literature to determine the level of risk stratification for prostate cancer mortality by race, family history and baseline PSA before age 50 years. Even the worst case scenario for PSA based on the lower bound of the 95% CI provided far better risk stratification than the most optimistic and, indeed, somewhat unrealistic estimates for race and family history. Therefore, we conclude that if early screening for prostate cancer is to be restricted to a small number of men at higher risk, as recommended by AUA, ACS and many other groups, the criteria for high risk should be based on PSA rather than on race or family history.

As an example strategy, instead of screening black men and men with a family history starting at age 45 years and in other men at age 55 years, an alternative strategy would be to perform a PSA test in all men at age 45 years with subsequent screening until age 55 years restricted to the 10% with PSA 1.6 ng/ml or greater. The current definition of high risk involves screening 20% to 25% of men who account for 35% to 40% of prostate cancer deaths. After an initial PSA test stratification by PSA would require additional screening before age 55 years only in the 10% of men who account for 44% of prostate cancer deaths. Stratifying screening based on a baseline PSA measurement around age 45 years would enable identification of patients at highest risk for earlier screening while decreasing unnecessary screening and the possibility of over-diagnosis and overtreatment in men at low risk.

Using baseline PSA to identify risk raises 2 major concerns. 1) The first concern is that PSA testing is associated with harms in terms of overdiagnosis and overtreatment, and extending PSA testing to younger men might increase those harms. However, there are reasons to believe that the risk of over-diagnosis and overtreatment is markedly decreased in younger men based on straightforward consideration of lead time and life expectancy. Briefly, at age 45 years most men are expected to live 30 years or more and few screen detected prostate cancers remain clinically occult during the course of many decades. We used a conservative estimate for lead time (median 13 years) and 10% of men have a lead time of greater than 21 years.[21] Life expectancy in a 45-year-old man is 34 years with an 8.3% and 17.9% risk of death at 13 and 21 years, respectively.[22] This indicates an approximately 11.2% risk of death before clinical diagnosis in a 45-year-old man.

2) The second concern with using a PSA based risk stratification strategy to determine early screening is the possibility of excluding young black men at high risk or men with a positive family history from necessary screening. Researchers found higher PSA in black than in white men at all ages[23] and PSA sensitivity for cancer is higher in black men.[24] Using data from a longitudinal screening study of 26,111 men enrolled between 1991 and 2001 Mondo et al examined the importance of baseline PSA for predicting prostate cancer when stratified by race and family history.[25] Race and family history were only significant predictors of prostate cancer risk in men with PSAs above the age specific median. The group concluded

that prostate cancer was unlikely to develop in black men with a positive family history when baseline PSA was below the age specific median. Therefore, there is no evidence to suggest that men truly at high risk who are currently identified for early screening based on race or family history would be excluded when using an early screening strategy based on PSA at age 45 years.

A possible counterargument to our findings is the lack of evidence that early PSA screening decreases prostate cancer mortality. While ERSPC found that screening decreased prostate cancer mortality, the core group in this study included men 55 to 69 years old, few 50 to 54 years old and none younger than 50 years.[1] However, our point is not to argue directly for baseline PSA at age 45 years. Rather, if a recommendation is made to start screening early in men at high risk, a baseline PSA measurement at age 45 years would be a better method to identify men at high risk than family history or race. This strategy would allow for more intensive screening of men at high risk while decreasing screening and overdiagnosis in those at average risk.

CONCLUSIONS

Many current guidelines, including AUA guidelines, include differential prostate cancer screening based on risk with black men and those with a positive family history recommended to consider screening at an earlier age than the general population. We found that baseline PSA at ages 45 to 49 years provided risk stratification superior to that of race or family history with a smaller risk group representing a larger proportion of prostate cancer deaths. We found no evidence that black men or men with a positive family history are at importantly high risk for low PSA at age 45 years and for later development of cancer that would become incurable if subsequent screening were delayed. If, according to AUA, screening in men younger than 55 years should be restricted to those at higher risk, risk should then be determined by baseline PSA.

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Abbreviations and Acronyms

AUA	American Urological Association
ERSPC	European Randomized Trial of Screening for Prostate Cancer
PSA	prostate specific antigen

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Table

Proportion of prostate cancer deaths in men defined as at high risk by family history, race or PSA in middle age

Risk Factor (scenario)	Assumption	% High Risk/% Death	Risk Group Size/No. Risk Group Deaths
PSA	–	10/44	4.4
PSA (worst case)	Taking lower bound of 95% CI	10/34	3.4
Family history	–	10/14	1.4
Family history (best case)	Relative risk of 3 vs 1.5 for typical estimate	5/13.6	2.7
Black	–	12.6/28	2.2
Black (best case)	Relative risk of 3 for early prostate Ca death instead of 2 for all prostate Ca deaths	15/39	2.6