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

Emily A. Vertosick, Bing Ying Poon and Andrew J. Vickers*,†

Health Outcomes Research Group, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York

Abbreviations and Acronyms

AUA = American Urological Association

ERSPC = European Randomized Trial of Screening for Prostate Cancer

PSA = prostate specific antigen

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* Correspondence and requests for reprints: Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 East 63rd St., 2nd floor, New York, New York 10021 (telephone: 646-735-8142; FAX: 646-735-0011; e-mail: vickersa@mskcc.org).

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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% of prostate cancer deaths. Using black race as a risk criterion involved 13% of men, accounting for 28% of 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.

Key Words: prostatic neoplasms, risk, age factors, African Americans, prostate specific antigen

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

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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 over diagnosis, suggesting that harms would be lower.

Recommendations for screening younger men vary among guideline groups. One 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 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 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 positive family history of 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]