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# Generalizability of Prostate-Specific Antigen (PSA) Screening Trials in a “Real World” Setting: A Nationwide Survey Analysis

Deepansh Dalela, Akshay Sood, Jacob Keeley, Craig Rogers, Mani Menon, and Firas Abdollah

## COMMENTARY

The Prostate, Lung, Colorectal and Ovarian cancer (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trials<sup>1,2</sup> have been widely used to inform policy decisions regarding prostate-specific antigen (PSA) screening in the US. However, the generalizability of any trial to its intended population is directly contingent on the study subjects being “representative” of the “universe” (ie, US men without symptoms or known diagnosis of prostate cancer [PCa]). In the context of PSA screening, its efficacy and effectiveness is predicated upon age, ethnicity, and family history of PCa (amongst other factors).

Using publicly-available data from CDC-NCHS National Health Institution Survey (NHIS) 2000-2018, men aged  $\geq 40$  years without prior history of PCa who underwent PSA testing in the 12 months preceding the survey as a part of “routine testing” were considered to have undergone PSA screening.<sup>3</sup> Results are weighted based on population-level data, and can be extrapolated to the noninstitutionalized US population. Age at PSA screening, self-reported ethnicity and family history of PCa (ie, PCa in father and/or brother, data available for NHIS 2000, 2005, 2010, and 2015) were compared with results reported in the PLCO and ERSPC trials, using Rao-Scott Chi-Square tests. Additionally, for NHIS 2000, 2005, and 2010, sensitivity analyses were done for age at first PSA testing (“How old were you when you had your FIRST PSA test?”).

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Overall, 14,941 (weighted  $n = 15,405,057$ ) men underwent annual PSA screening within the available years. The median (interquartile range) age for these men was 61 (53.3-69.0) years, compared to 60.3 in ERSPC. Interestingly, 43% of men were aged  $\leq 60$  in our cohort, vs 32% in PLCO [ $P < .001$ ; PLCO only reported the percentages in each age category; Fig. 1A]. Sensitivity analyses showed that the majority of men were aged  $< 60$  at their first PSA screening test (34% aged 40-49, 23.8% aged 50-54 and 13.5% aged 55-59).

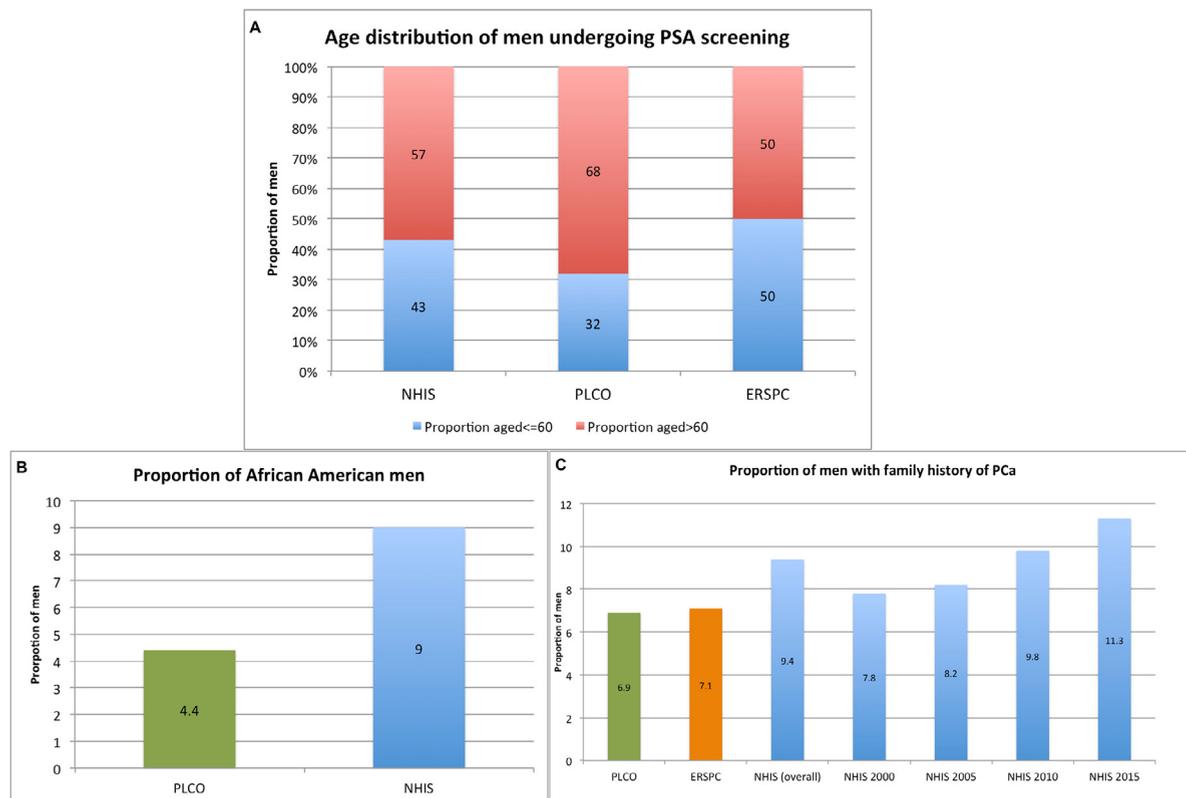
In terms of ethnicity, 1786 (weighted  $n = 1,393,977$ ; 9%) of screened men within NHIS were African-American, compared to 4.4% in PLCO ( $P < .001$ ; Fig. 1B). Over the study years, this proportion did not change significantly (9.3% in 2000, 9.8% in 2018,  $P = .8$ ). Lastly, 9.4% of screened men within NHIS had positive family history (increasing from 7.8% in 2000 to 11.3% in 2015 [ $P < .01$ ]; Fig. 1C). This was comparable to 7% and 6.8%-7.3% with family history of PCa in PLCO and ERSPC respectively.<sup>1,2,4,5</sup>

We noted that US men undergoing PSA screening were significantly younger compared to those sampled in the PLCO study, with 43% (vs 32%) of men aged  $\leq 60$ , and  $\sim 70\%$  men aged  $\leq 60$  at their first PSA screening test. Interestingly, the median age of men undergoing PSA screening within NHIS was 61 years, similar to the ERSPC study. Our results could be skewed since PLCO and ERSPC enrolled men aged 55-74 and 50-74 respectively, while we included men aged  $\geq 40$ . This was intentional: the lower age limit for both PLCO/ERSPC studies was based on arbitrary cut-offs. Indeed, follow up of ERSPC trials revealed that number needed to diagnose with PCa to prevent 1 PCa-specific death drops by nearly 50% (from 37 to 18) with increasing follow-up, especially for men aged 50-54.<sup>6,7</sup> In a cohort of US men, Preston et al.<sup>9</sup> showed that mid-life PSA values  $> 90^{\text{th}}$  percentile for US men aged 40 through 60 were strongly associated with future risk of lethal PCa with  $> 70\%$  of lethal cases occurring in men with PSA above age-adjusted median,<sup>8</sup>

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**Figure 1.** Comparison of age distribution (aged  $\leq 60$  vs.  $>60$ ) [top, A], proportion of African American men as a percentage of all men [bottom left, B] and men with family history of prostate cancer as a percentage of all men [bottom right, C] undergoing prostate specific antigen (PSA) screening within the National Health Interview Survey (2000-2018), the Prostate, Lung, Colorectal and Ovarian cancer (PLCO) and European Randomized Study of Screening for Prostate Cancer (ERSPC) trials. A: ERSPC is an approximation from published data (based on median age of 61 years for men in the trial). B: ERSPC is not represented given the insignificant number of African American men in the study. C: The bar for ERSPC (7.1%) represents the average of Finnish (6.8%) and Swiss (7.3%) arms of the ERSPC trials. (Color version available online.)

and similar findings were later confirmed amongst African American men. Shoag et al. recently concluded using mathematical modelling that longer ( $\geq 25$ -year) follow up further optimizes the mortality benefit from PSA screening.<sup>10</sup> In recognition of these findings, the most recent NCCN and American Cancer Society guidelines recommend initiating PSA screening at age 45 (40 for African-American men)<sup>11</sup> and 50,<sup>12</sup> respectively. Therefore, we believe that including all eligible men above the age of 40 would provide a more representative assessment of PSA screening at a nationwide/community level.

Even more important are our findings that US men reporting PSA screening were more than twice as likely to be African-American ( $\sim 9\%$ ) compared to PLCO (4.4%). The ERSPC, on the other hand, did not directly report the proportion of black men,<sup>2</sup> although that number is probably even lower than the PLCO study. Racial/ethnic minorities have been historically under-represented in clinical trials, and Pinsky and colleagues reported similar logistical challenges with enrolling racial minority men in the PLCO study.<sup>13</sup> To the best of our knowledge, our results provide the first published evidence that this resulted in under-representation of African-American men in the PLCO when compared to a nationally representative sample of US

men. Further, the proportion of African-American men remained largely constant throughout the study period, from 9.3% in 2000 to 9.8% in 2018. While the higher proportion compared to PLCO could indicate healthcare providers in the community recognizing black race as an important risk factor for PCa,<sup>14</sup> the fact that it did not increase significantly to match the representation of African American men in the US (14.7%, US Census Bureau 2019<sup>15</sup>) also implies disparities in access to screening/preventive services. The low proportion of African-American men in PLCO is further concerning as modelling studies have shown earlier onset and more aggressive PCa in African American men with potential mortality benefit from PSA screening<sup>11,16</sup> leading some to suggest that separate PSA screening guidelines may be warranted for these men.<sup>17</sup>

Lastly, the proportion of PSA screened men with family history of PCa in NHIS (9.4%) was comparable with the PLCO (6.9%) and ERSPC trials (6.8%-7.3%). Interestingly, subgroup analyses from these trials indicate that men with family history of PCa may have 30%-60% higher likelihood of PCa,<sup>4,5</sup> and PSA screening may potentially provide mortality benefit.<sup>18</sup> In contrast to trends seen for African American representation, the number of men with family history of PCa increased

significantly in the more contemporary years (7.8% in NHIS 2000 to 11.3% in NHIS 2015). Multiple patient-level factors (such as family member's experience, partner's insistence,<sup>19</sup> or patient anxiety about cancer<sup>20</sup>) may have been the driving force behind this increase, although like for African-American men, the current study was not designed to analyze reasons for this trend.

Notable limitations of our study include retrospective analysis of survey data (subject to recall bias), lack of data regarding shared-decision making and oncologic outcomes of screening within NHIS. The PLCO/ERSPC studies enrolled men during the 1990s-early 2000s, however PSA screening was reliably ascertained within NHIS from 2000 onwards. Nonetheless, our work represents the first attempt highlighting that US men undergoing screening over last two decades were younger and more than twice as likely to be African American than those represented in PLCO/ERSPC trials, suggesting that these studies might not be generalizable to contemporary US men. These findings should be kept in mind when formulating population-based policies regarding PSA screening and discussion of its potential risks vs benefits for US men, especially those who are younger or African American.

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