The American Urological Association's Prostate Cancer Screening Guideline: Which Cancers Will Be Missed in Average-risk Men Aged 40 to 54 Years?

Thomas E. Moody, MD, Curtis L. Spraitzar, Elizabeth Eisenhart, Scott Tully, Jr.
Urology Centers of Alabama, Homewood, AL

To determine the impact of the American Urological Association's (AUA) guideline for early detection of prostate cancer that recommends against routine screening in men aged 40 to 54 years at average risk (eg, white men without a family history of prostate cancer), we undertook a study of 973 men who previously underwent a prostate biopsy at Urology Centers of Alabama (UCA) over the 5-year period from 2010 to 2014. We retrospectively reviewed the results of the prostate biopsies performed by urologists at UCA—and, where applicable, the final surgical pathology results and compared the results by race and family history. In white men with a family history of prostate cancer, 47% had cancer and 30% had Gleason score (GS) $\geq$ 7 disease. In white men without a family history of prostate cancer, 32% had cancer and 23% had GS $\geq$ 7 disease. By comparison, in African American men with a family history of prostate cancer, 56% had cancer and 42% had GS $\geq$ 7 disease. In African American men without a family history, 42% had cancer and 29% had GS $\geq$ 7 disease. In our study, 144 of 456 (32%) of the group of average-risk men had cancer and 105 of 456 (23%) had GS $\geq$ 7 cancer. Had the AUA guidelines been followed, these cancers would have been missed or the diagnoses delayed.

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KEY WORDS

Prostate cancer • AUA screening guideline • Prostate-specific antigen • Average-risk men

The value of prostate-specific antigen (PSA) testing for the early detection of prostate cancer remains a subject of robust debate in the medical and popular literature. Following the recommendation of the US Preventive Services Task Force against prostate cancer screening in 2012, the American Urological Association (AUA) issued a new clinical guideline for the early detection of prostate cancer in 2013.[1] The AUA recommended that average-risk men (eg, white men without a family history of prostate cancer) aged 40 to 54 years should not have routine screening for prostate cancer.

To determine the impact of the AUA's recommendation, important in its potential influence on practitioners and patients alike, we undertook a study of 973 men aged 40 to 54 years who had undergone a prostate biopsy at Urology Centers of Alabama (UCA; Homewood, AL) over the 5-year period between 2010 through 2014. Although previous studies have assessed PSA screening in cohorts of younger men in various age groups or in other countries,[2,3] as far as we can determine, this is the first multiyear study that specifically addresses the impact of the new AUA guideline from the perspective of average-risk men in this age group screened at a large urologic practice in the United States.

Material and Methods

We retrospectively reviewed the results of prostate biopsies performed by urologists at UCA—and, where applicable, the final surgical pathology results—in white and African American men, aged 40 to 54 years, over the 5-year period between 2010 and 2014. The criteria for prostate biopsy varied somewhat among UCA urologists; however, in general, they included an abnormal digital rectal examination regardless of PSA level, age-adjusted PSA levels with 2.5 ng/mL used as the cut-off for men in their 40s (and adjusted up according to the patient's age), family history, and overall health. In lieu of a formal ethics committee, the principles of the Helsinki declaration were followed.

We compared the results by race and family history. We further stratified the results by PSA at the time of biopsy. For patients undergoing a radical prostatectomy (RP), we noted the highest Gleason score (GS) at the time of final pathology and whether there was an upgrade in GS from the biopsy to the final surgical pathology report. We utilized a Pearson's χ^2 test and Fisher's exact test to determine whether race or family history made a statistically significant difference in the prostate biopsy or final pathology results, using JMP software (SAS Institute, Inc., Cary, NC) for analysis. Additionally, we utilized the *t*-test to compare PSA means across all stratifications.

Results

During the study period, the urologists at UCA performed 973 prostate biopsies (Table 1). During the study period, 608 white men underwent prostate biopsy. Of these, 152 (25%) had a family history of prostate cancer and 456 (75%) did not. The median PSA for white men at the time of biopsy was 4.43 ng/mL. For white men with a family history of prostate cancer, the median PSA was 4.30 ng/mL, whereas the median PSA for those without a family history of prostate cancer was 4.46 ng/mL. In white men, there were 216 positive prostate biopsy results. The positive biopsy rate in white men was 36% (216/608). For those white men with a family history of prostate cancer, the positive biopsy rate was 47% (72/152), whereas for those without a family history, the positive biopsy rate was 32% (144/456). Of the 216 patients with positive biopsy results in the group of white patients, 100 (46%) had GS $\leq$ 6, whereas 116 (54%) had GS $\geq$ 7. In white men with a family history who had a positive biopsy, 50% had GS $\geq$ 7. Conversely, in white men without a family history, 56% had GS $\geq$ 7.

In white men with a family history who underwent RP, nine were upgraded from GS 6 at biopsy to GS $\geq$ 7 on final pathology. Accordingly, 45 of 152 (30%) of white men with a family history had GS $\geq$ 7 prostate cancer on either biopsy or final pathology results (for those white men with a family history who tested positive

TABLE 1

Summary of Prostate Biopsy Results

Race	Family History	Negative Biopsy Results n	Negative Biopsy Results % of Row	Negative Biopsy Results Median PSA (ng/mL)	Positive Biopsy Results n	Positive Biopsy Results % of Row	Positive Biopsy Results Median PSA (ng/mL)	All Biopsies n	All Biopsies Median PSA (ng/mL)
White	Yes	80	52.63	4.00	72	47.37	4.59	152	4.30
	No	312	68.42	4.30	144	31.58	4.80	456	4.46
White (total)		392	64.47	4.20	216	35.53	4.78	608	4.43
African American	Yes	39	44.32	4.90	49	55.68	5.31	88	5.00
	No	161	58.12	4.40	116	41.88	5.00	277	4.60
African American (total)		200	54.79	4.50	165	45.21	5.05	365	4.70
Grand Total		592	60.84	4.30	381	39.16	4.90	973	4.50

PSA, prostate-specific antigen.

on biopsy, this translates to 63%). In white men without a family history who underwent RP, 25 were upgraded from GS 6 to GS ≥ 7 on final pathology. Accordingly, 105 of 456 (23%) of white men without a family history had GS ≥ 7 prostate cancer on either biopsy or final pathology results (for those white men without a family history who tested positive on biopsy, this translates to 73%).

By comparison, 365 prostate biopsies were performed on African American men; 88 of 365 (24%) of these men had a family history of prostate cancer, whereas 277 (76%) did not. The median PSA for African American men at the time of biopsy was 4.70 ng/mL. In African American men with a family history of prostate cancer, the median PSA was 5.00 ng/mL, whereas the median PSA of African American men without a family history of prostate cancer was 4.60 ng/mL.

In African American men there were 165 positive biopsy results. The positive biopsy result rate in African American men was 45% (165/365). For those African American men with a family history of prostate cancer, the positive biopsy rate was 56%, whereas for those without a family history, the positive biopsy rate was 42%. Of the 165 positive biopsy results in the African American group, 76 (46%) had GS ≤ 6, whereas 89 (54%) had GS ≥ 7 (Table 2).

In African American men with a family history of prostate cancer who had a positive biopsy, 55% had GS ≥ 7. Conversely, in African American men without a family history who had a positive biopsy, 53% had GS ≥ 7. In African American men who underwent RP with a family history, 10 were upgraded from GS 6 at biopsy to ≥ GS 7 on final pathology (Table 3). Accordingly, 37 of 88 (42%) of African American men with a family history had GS ≥ 7 prostate cancer on either the biopsy or final pathology results (for those African American men with a family history who tested positive after at biopsy, this translates to 76%). In African American men without a family history who underwent RP, 18 were upgraded from GS 6 to GS ≥ 7 on final pathology. Accordingly, 80 of 277 (29%) of African American men without a family history had GS ≥ 7 prostate cancer on either biopsy or final pathology results (for those African American men without a family history who tested positive at biopsy, this translates to 69%).

Using the χ^2 test, we found an association between a positive family history and a positive prostate biopsy result when race is of no consideration ($P < .0001$). The χ^2 test also revealed a significant association between African American race and a positive prostate biopsy result ($P = .0017$). Among African American men, there is a significant association between a positive family history for prostate cancer and a positive biopsy result ($P = .0236$). A similar association between family history and positive biopsy result was found in white men ($P = .0005$).

The χ^2 and Fisher's exact test revealed that, among white men in this study group, there is a trend toward an association between family history and having a GS ≥ 7 prostate cancer, although this

TABLE 2

Positive Prostate Biopsies Grouped by Gleason Score 6 and Gleason Score ≥ 7

		Gleason 6			Gleason ≥ 7			All Positive Biopsy Results	
Race	Family History	n	% of Row	Median PSA (ng/mL)	n	% of Row	Median PSA (ng/mL)	n	Median PSA (ng/mL)
White	Yes	36	50.00	3.99	36	50.00	5.84	72	4.59
	No	64	44.44	4.78	80	55.56	4.95	144	4.80
White (total)		100	46.30	4.31	116	53.70	5.25	216	4.78
African American	Yes	22	44.90	4.55	27	55.10	5.96	49	5.31
	No	54	46.55	4.26	62	53.45	5.70	116	5.00
African American (total)		76	46.06	4.36	89	53.94	5.90	165	5.05
Grand Total		176	46.19	4.32	205	53.81	5.40	381	4.90

PSA, prostate-specific antigen.

TABLE 3

Gleason Score ≥ 7 Prostate Cancers Found on Biopsy or on Final Pathology After Radical Prostatectomy

Race	Family History	Gleason ≥ 7 on Biopsy	Gleason Upgrades From 6 on Biopsy to ≥ 7 on Final Pathology	Gleason ≥ 7 Cancers on Biopsy or Final Pathology	Men With Positive Biopsy Result (n)	Men With Positive Biopsy Result Having Gleason ≥ 7 Cancers (%)	Total Men Biopsied (N)	All Men Biopsied Having Gleason ≥ 7 Cancers (%)
White	Yes	36	9	45	72	62.50	152	29.61
	No	80	25	105	144	72.92	456	23.03
White (total)		116	34	150	216	69.44	608	24.67
African American	Yes	27	10	37	49	75.51	88	42.05
	No	62	18	80	116	68.97	277	28.88
African American (total)		89	28	117	165	70.91	365	32.05
Grand Total		205	62	267	381	70.08	973	27.44

TABLE 4

Contingency Table for White Men: Family History Versus Gleason Score ≥ 7 Prostate Cancer

	Men Without Gleason ≥ 7 Cancers on Biopsy or Final Pathology				Men With Gleason ≥ 7 Cancers on Biopsy or Final Pathology				Total Men With or Without Gleason ≥7 Cancers	
Family History	N	% of Row	% of Column	% of Total	N	% of Row	% of Column	% of Total	N	% of Grand Total
Yes	27	37.50	40.91	12.50	45	62.50	30.00	20.83	72	33.33
No	39	27.08	59.09	18.06	105	72.92	70.00	48.61	144	66.67
Grand Total	66			30.56	150			69.44	216	

trend did not reach statistical significance ($P = .1172$ and $P = .1209$, respectively; Table 4).

Although we report median PSAs in our data tables, we utilized mean PSAs as the most appropriate measure for our statistical comparison of PSA values between groups. The mean PSA for African American men was higher than that for white men, but was not statistically significant. The mean PSAs for both races with a positive biopsy result were higher than those with a negative biopsy result, but did not reach statistical significance. In African American men, there was a significant difference in the mean PSA between those with and without GS ≥ 7 cancers ($P < .0001$). African American men with GS ≥ 7 prostate cancer measured a significantly higher mean (mean = 7.66) than their counterparts with GS ≤ 6 disease (mean = 4.47). In white men, there was a significant difference in the mean PSA between those with and without GS ≥ 7 cancers ($P < .0191$). White men with GS ≥ 7 prostate cancer measured a significantly higher mean (mean = 7.01) than their counterparts with GS ≤ 6 disease (mean = 4.80; $P = .0191$).

Comment

In 2013, the AUA guideline for early detection of prostate cancer recommended against routine screening in men of average risk between ages 40 and 54 years.[1] The panel acknowledged a paucity of evidence to demonstrate a survival benefit from screening, because the two large randomized trials (The Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial and the core group of the European Randomized Study of Screening for Prostate Cancer) did not include men under age 55. Other studies did show a small survival benefit from screening in this age group; however, the panel concluded that the harms of screening outweighed the benefits. They further recognized that the "absence of evidence does not constitute evidence of absence." We asked the urologists at UCA whether they had changed their prostate cancer screening practices to exclude men of average risk in the 40- to 54-year age group based on the revised AUA guideline. Their uniform answer was "no" because the revised guideline, in their view, was not consistent with their medical experience.

In 2013, the AUA guideline for early detection of prostate cancer recommended against routine screening in men of average risk between ages 40 and 54 years.

In a previous review of 1 year of data from UCA's urologic practice, the results of which were presented at the meeting of the Southeastern Section of the AUA in 2014, we found that, had the AUA guideline for prostate cancer screening been followed, many cancers would have been missed in the 40- to 54-year age group of men considered at average risk.[2] The 5-year data presented here confirm that finding. As expected, race and family

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history are important predictors of prostate cancer. However, the status of white race and the lack of a family history of prostate cancer do not preclude men aged 40 to 54 years from having the disease.

Carlsson and colleagues[3] concluded that men before age 55 did develop significant cancers and that the initiation of screening in a man's early 50s significantly and substantially reduced prostate cancer mortality by two-thirds. In a review of the Surveillance, Epidemiology, and End Results Program (SEER) data between 2004 and 2011, Winters and colleagues[4] found that 9% of men diagnosed with high-risk prostate cancer (GS 8-10) were under age 55. They concluded that a failure to screen this age group may result in a missed opportunity for treatment with curative intent. Dantanarayana and associates[5] found no significant difference in the rates of high-risk prostate cancer between men younger than age 55 and men over age 55. Their findings did not support the AUA guideline changes for PSA testing.

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Moreover, Suardi and coworkers[6] found that, despite using stringent criteria for selection of active surveillance in patients with low-risk prostate cancer, 28% of those who ultimately had RP had GS 7 disease. This prompted the statement from Walsh[7] that it caused him concern to offer active surveillance to younger men, implying that younger men do get high-risk cancers.

Although the above studies did not segregate men at average risk for prostate cancer in the 40- to 54-year age group for analysis, they did confirm that men in this cohort do have significant prostate cancer. Our study confirms that these significant cancers are not isolated to the men of African American ethnicity or white men solely with a family history of prostate cancer. It is noteworthy that 56% of men in this age group of average risk who had positive biopsy results had GS $\geq$ 7 disease at biopsy, and 25 of these men with GS 6 on biopsy—and who underwent subsequent RP—were upgraded to GS $\geq$ 7 on the final pathology results. Therefore, of the men of average risk who had positive biopsy results, 73% had GS $\geq$ 7 cancer. It is noteworthy that, in white men with positive biopsy results, the percentage with GS $\geq$ 7 cancer was greater for those without a family history than it was for those with a family history (56% vs 50%).

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In our study, we divided our positive biopsy results by GS. It is widely accepted that GS $\geq$ 7 carries a higher risk than GS $\leq$ 6; GS $\geq$ 7 disease has been defined by Epstein and associates[8] as a significant cancer. Additionally, GS $\geq$ 7 disease is an exclusionary criterion for many active surveillance protocols.[9-11] Notwithstanding, we are not suggesting that GS 6 prostate cancers should be discounted as insignificant. Our study does not assess other factors that might help gauge the seriousness of a GS 6 prostate cancer, such as the number of positive cores in the prostate biopsy or the percentage or location of cancer found in the prostatectomy specimen. Also, we note that, although 271 out of 381 of men with positive biopsy results (71%) underwent RP (270 robotic, 1 perineal), there was no ability to assess for GS upgrades in those men who did not elect surgery as a treatment option. Finally, one can question whether a GS 6 cancer in a 40-year-old man is equal to a GS 6 cancer in a 70-year-old man, given the longer period of time the disease may progress in a younger, otherwise healthy man.

Since the advent of the PSA era, there has been a 45% reduction in disease-specific mortality from prostate cancer.[12] Our study is too short to comment on survival implications. However, we expect some decrease in disease-specific mortality, as seen in the PSA era, for this group of average-risk men aged 40 to 54 years. If this group were not screened, we would expect a cohort of men presenting in the future with more advanced disease, possibly having lost the option for early detection and treatment with curative intent.

Limitations of our study include its retrospective nature at a single practice involving multiple urologists whose biopsy criteria and technique are very similar but not identical. Further, many of the patients in this study came from one geographic area (Alabama). Although data from public sources show that the incidence for prostate cancer in white men in Alabama is not statistically different from the nation as a whole, the data do not allow a comparison regarding risk stratification between Alabama and the rest of the nation (ie, those aged 40 to 54 years with and without a history of prostate cancer). Nor do the data allow a comparison regarding the severity of the disease at diagnosis.

Conclusions

The potential harms of screening and treatment of prostate cancer are acknowledged, but progress is being made to address and mitigate those concerns. We don't expect the prostate cancer screening process to be flawless; however, the opportunity for early detection and treatment should not be discouraged for this group of average-risk men (white men without a family history), aged 40 to 54 years. In this study, 144 of 456 (32%) of this group had cancer and 105 of 456 (23%) of this group had GS ≥7 cancers on either biopsy or final pathology. Therefore, almost 25% of men in this category who underwent a prostate biopsy had GS ≥ 7 cancers. Had the AUA guideline been employed for these men, these cancers would have been missed or the diagnosis delayed, possibly losing the opportunity for early diagnosis and treatment with curative intent. We recognize that there are certain limitations to this study, but if these findings are confirmed by other investigators, we recommend amendments and updates to the AUA guideline consistent with these findings. ■

The authors report no real or apparent conflicts of interest.

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MAIN POINTS

- The value of prostate-specific antigen (PSA) testing for the early detection of prostate cancer remains a subject of robust debate in the medical and popular literature. In 2013, the American Urological Association (AUA) issued a new clinical guideline for the early detection of prostate cancer: they recommended that average-risk men (eg, white men without a family history of prostate cancer) aged 40 to 54 years should not have routine screening.
- In a previous review of 1 year of data from the Urology Centers of Alabama urologic practice, we found that, had the AUA guideline for prostate cancer screening been followed, many cancers would have been missed in men aged 40 to 54 years considered at average risk. The 5-year data presented here confirm that finding.
- Race and family history are important predictors of prostate cancer; however, the status of white race and the lack of a family history of prostate cancer do not preclude men in this age group from having the disease.
- Since the advent of the PSA era, there has been a 45% reduction in disease-specific mortality from prostate cancer. We expect some decrease in disease-specific mortality for this age group of average-risk men. If this group were not screened, we would expect a cohort of men presenting in the future with more advanced disease, possibly having lost the option for early detection and treatment with curative intent.