

Prostate-Specific Antigen Testing of Older Men

H. Ballentine Carter, Patricia K. Landis, E. Jeffrey Metter, Lee A. Fleisher, Jay D. Pearson

Background: Elevated serum prostate-specific antigen (PSA) levels are predictive of a future diagnosis of prostate cancer. To test the hypothesis that older men with low PSA levels may require less intensive PSA testing because of a reduced prostate cancer detection rate, we evaluated the association between age, baseline PSA level, and prostate cancer detection. **Methods:** We conducted a prospective cohort study among participants in a study of aging who had serial PSA measurements taken from age 60 or 65 years until they either were diagnosed with prostate cancer (cancer case subjects) or reached the age of 75 years (subjects without prostate cancer). The time of cancer detection among cancer case subjects was defined as the measurement date on which a PSA level above 4.0 ng/mL was detected (i.e., PSA conversion). Cancer case subjects and subjects without prostate cancer were analyzed according to baseline PSA level and age. **Results:** All cancer case subjects in the 60-year-old cohort had baseline PSA levels above 0.5 ng/mL, and 14 of 15 cancer cases that would have been detected by a PSA conversion among the 65-year-old cohort were associated with baseline PSA levels of 1.1 ng/mL or more. If PSA testing were discontinued in men aged 65 years with PSA levels of 0.5 ng/mL or less, 100% (95% confidence interval [CI] = 78%–100%) of the cancers would still be detected by age 75 years; if PSA testing were discontinued in men aged 65 years who had PSA levels of 1.0 ng/mL or less, 94% (95% CI = 70%–100%) of the cancers would still be detected by age 75 years. **Conclusions:** These data suggest that a decrease in the intensity of screening among older men with low PSA values may not lead to an increase in undetected prostate cancer. [J Natl Cancer Inst 1999;91:1733–7]

Although controversial and not proven to decrease prostate cancer mortality, serum prostate-specific antigen (PSA) testing is now widely used for the early detection of prostate cancer.

Recommendations have been made for yearly PSA testing of men—beginning at age 50 years—who have more than a 10-year life expectancy (1). However, the majority of PSA testing that occurs in the population eventually proves to be unnecessary because most men who undergo repeated testing do not develop cancer, and most men with PSA elevations do not have cancer discovered at biopsy. Identification of those men who are unlikely to benefit from further PSA testing could markedly reduce health care costs and treatment-associated morbidity.

While no age has been established above which PSA testing is not recommended, there is general agreement that men with a less than 10-year life expectancy are unlikely to benefit from early detection because of the long natural history of untreated localized prostate cancer and competing causes of death (2). Thus, even healthy men from age 70 to 75 years are reaching an age where further PSA testing may not be beneficial in terms of lives saved. PSA values—even below the “normal” level—do predict a future diagnosis of prostate cancer, however (3). Recognizing the value of PSA measurements in the prediction of prostate cancer, we hypothesized that it may be possible to identify older men with very low PSA levels for whom further PSA testing could be reduced because of a low risk of a future prostate cancer diagnosis. The relationship between PSA level, age,

Affiliations of authors: H. B. Carter, P. K. Landis (Department of Urology), L. A. Fleisher (Department of Anesthesiology), The Johns Hopkins University School of Medicine, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, MD; E. J. Metter, Gerontology Research Center, National Institute on Aging, Baltimore; J. D. Pearson, Department of Urology, The Johns Hopkins University School of Medicine, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, and Department of Epidemiology, Merck Research Laboratories, Blue Bell, PA.

Correspondence to: H. Ballentine Carter, M.D., Department of Urology, 403 Marburg, The Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-2101 (e-mail: hcarter@jhmi.edu).

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and the probability of a prostate cancer diagnosis was evaluated to explore potential effects of the reduction of PSA testing in men who are unlikely to benefit from intensive screening.

SUBJECTS AND METHODS

Study Populations

Baltimore Longitudinal Study of Aging (BLSA). The BLSA is an ongoing, long-term, prospective study of aging conducted by the National Institute on Aging (Bethesda, MD); this study has been described previously (4). Since the inception of the BLSA in 1958, a total of 1570 men and 921 women have participated in the study for varying lengths of time. Participants in the study return for follow-up visits at approximately 2-year intervals. This study on aging has institutional approval, and all human subjects give written informed consent for the study prior to participation.

Serum PSA levels have been measured on a total of 963 men, either at the time of routine subject visits (since 1991) or by use of a frozen serum bank for retrospective samples (prior to 1991). All PSA measurements were performed by use of a monoclonal immunoradiometric assay (Tandem-R; Hybritech, Inc., San Diego, CA). The stability of PSA in these frozen serum samples stored at -70°C has been previously described (5). Four hundred eighty-two of 963 participants had PSA follow-up until age 75 years or until the diagnosis of prostate cancer. Two hundred twenty-seven of 482 men had a baseline PSA level less than 4.0 ng/mL within 5 years of age 60 years (60 ± 5 years) or of age 65 years. The age 60- and 65-year cohorts were not mutually exclusive.

After the exclusion of individuals whose medical history could not be verified, individuals with a history of prostate surgery, and individuals being treated with finasteride (Proscar; Merck, Whitehouse Station, NJ), 47 men with prostate cancer (mean age at diagnosis, 74.6 years; range, 63–90 years) and 154 men with no evidence of prostate cancer (noncancers) (median age at most recent BLSA visit, 77.1 years; range, 62–94 years) remained in the study group. The mean age of all prostate cancer subjects in the BLSA population (75.0 years) was similar to the mean age of the final study group. The race distribution of the prostate cancer subjects in the study group (95.7% Caucasian and 4.3% African-American) was similar to all BLSA subjects with prostate cancer (93.4% Caucasian, 5.9% African-American, and 0.7% Chinese). The clinical stage (tumor–node–metastasis) (6) among the cancer cases was T1 in 10 subjects, T2 in nine, T3 in three, M+ in three, and unknown in 22. The Gleason score (combined Gleason grade) (7) was 6 or less for 22 of the cancer cases, 7 or more for 13

cases, and unknown for 12 cases. Presumably, these subjects would have been diagnosed at earlier stages with PSA testing because PSA increases the lead time for diagnosis by half a decade (3). Of these men, 40 cancer case subjects and 85 men without prostate cancer had PSA follow-up (median, five tests) from age 60 years until age 75 years or cancer diagnosis, and 36 cancer case subjects and 101 men without prostate cancer had PSA follow-up (median, four tests) from age 65 years until age 75 years or cancer diagnosis (Table 1). These subjects constituted the final study group. Among the men diagnosed with prostate cancer after age 75 years, 10 participants died, but none were documented to have died of prostate cancer. The median interval from the last cancer-free PSA to diagnosis was 0.9 years (range, 0–12.4 years).

Medicare claims data. We evaluated Medicare claims data for PSA testing to assess the potential cost savings of eliminating unnecessary testing. A 5% nationally random sample of the aged Medicare population for 1995 and 1996 was used to identify a cohort of patients who underwent PSA testing. All Medicare beneficiaries aged 65 years and older living in any of the 50 states or in the District of Columbia, and with both part A and part B coverage, were eligible for analysis. Prior to selection of the random sample, men who had a pre-existing condition of prostate or urethral cancer based on the presence of the International Classification of Diseases, 9th Revision, clinical modifiers code (8) were excluded from the analysis to ensure that Medicare claims for PSA monitoring of prostate cancer were not included. From this population, the Medicare program creates a research dataset by randomly selecting 5% of the population based on the final two digits of the person's Social Security number; the final four digits of the Social Security number are assigned randomly. Patients who were enrolled in health maintenance organization plans were not included.

The entire database included 1.2 million individuals, 62% female and 84% Caucasian. PSA testing was identified by the presence of the appropriate current procedural terminology, 4th revision code, in the part B data.

Study Design

We examined the PSA outcomes of men in the BLSA cohort during follow-up until age 75 years as a function of age (60 or 65 years) and baseline PSA level (0–0.5, 0.6–1.0, 1.1–1.5, 1.6–2.0, 2.1–2.5, 2.6–3.0, and >3.0 ng/mL). The age of 75 years was chosen as a stop-point for this analysis because the early diagnosis and treatment of prostate cancer in a population beyond age 75 years (men with a <10 -year life expectancy) are unlikely to extend life (2). The baseline PSA level was defined as the PSA level measured closest to the age of 60 or 65 years (see study populations).

Table 1. Observed distribution of prostate-specific antigen (PSA) levels at ages 60 and 65 years in prostate cancer case subjects and subjects without prostate cancer*

Stratification by PSA and age		Prostate cancer case subjects							Subjects without prostate cancer with follow-up until age 75 y or death	
		Total No. of men	PSA conversion before diagnosis	No PSA conversion	PSA conversion after diagnosis	Prostate cancers diagnosed after age 75 y				Total
Diagnosed at age 75–79 y	Diagnosed at age 80–84 y					Diagnosed at age 85–89 y	Diagnosed at age ≥ 90 y			
Age 60 y	n = 125	n = 19	n = 5	n = 5	n = 4	n = 5	n = 1	n = 1	n = 85	n = 9
0–0.5	37	0	0	0	3	0	0	0	34	0
0.6–1.0	45	4	2	1	1	3	1	1	32	2
1.1–1.5	14	4	2	1	0	1	0	0	6	1
1.6–2.0	11	3	1	1	0	0	0	0	6	1
2.1–2.5	5	2	0	1	0	0	0	0	2	1
2.6–3.0	5	1	0	0	0	0	0	0	4	3
>3.0	8	5	0	1	0	1	0	0	1	1
Age 65 y	n = 137	n = 15	n = 6	n = 4	n = 4	n = 5	n = 1	n = 1	n = 101	n = 7
0–0.5	32	0	1	0	1	1	0	0	29	0
0.6–1.0	40	1	2	0	2	2	0	1	32	0
1.1–1.5	25	2	0	0	0	1	1	0	21	1
1.6–2.0	13	3	1	1	0	1	0	0	7	1
2.1–2.5	10	3	1	1	1	0	0	0	4	1
2.6–3.0	7	2	0	1	0	0	0	0	4	2
>3.0	10	4	1	1	0	0	0	0	4	2

*Numbers represent number of men with specified PSA level.

In this study, the date of prostate cancer detection was defined either as the actual date of diagnosis of prostate cancer or as the date of a PSA conversion to a level greater than or equal to 4.0 ng/mL in men who were later diagnosed with prostate cancer, whichever occurred first. Although other PSA criteria could have been used to define detection (rate of change in PSA, PSA cutoff of 2.5 ng/mL, etc.), a PSA level of 4.0 ng/mL is used more commonly to indicate a higher risk of cancer, and no other criteria have been shown to have greater validity (3).

Men who were diagnosed with prostate cancer before or after age 75 years and who had had a PSA conversion to greater than or equal to 4.0 ng/mL before age 75 years were considered to have had the cancer detected at the time of PSA conversion and to benefit from PSA testing because testing may have detected the cancer at a time when cure was more likely. In contrast, unnecessary PSA testing was presumed to have occurred in those men who were diagnosed with prostate cancer when there was no PSA conversion to greater than or equal to 4.0 ng/mL before diagnosis, the conversion occurred after the diagnosis of cancer (cases for which PSA would not have suggested the presence of cancer), or men in whom no diagnosis of prostate cancer was made before age 75 years.

Statistical Analysis

The crude percentage of cancer case subjects and subjects without prostate cancer with a PSA conversion to greater than 4.0 ng/mL was observed for men with a PSA follow-up from age 60 to 75 years and from age 65 to 75 years. Robust estimates of the percentages and 95% confidence intervals (CIs) were obtained from 1000 bootstrap samples on the basis of the original cohort. The medians of the 1000 bootstrap percentages and 1000 bootstrap exact binomial 95% CIs are less vulnerable to the potential influence of outliers in this small sample.

We evaluated PSA testing in the Medicare database by calculating the number of PSA tests per enrollee and the percentage of males who received a PSA test by age.

RESULTS

Table 1 shows the observed outcomes of PSA testing in the cohorts of men with PSA follow-up beginning at age 60 years and age 65 years and stratified by initial PSA level. Among 125 men who had a PSA follow-up from age 60 years, 40 men were eventually diagnosed with prostate cancer. Among these 40 cancer case subjects, 19 would have potentially benefited from PSA testing over the next 15 years (to age 75 years) by a PSA conversion and by early diagnosis of cancer. The remaining 21 cancer case subjects would have been unlikely to benefit from PSA testing, either because there was no PSA conversion prior to diagnosis (n = 5), since the conversion occurred after diagnosis (n = 5) or because the cancer was diagnosed after age 75 years (n = 11). All cancer case subjects diagnosed in the 15 years after age 60 years had baseline PSA levels of more than 0.5 ng/mL, and all subjects without prostate cancer with a PSA conversion between 60 and 75 years of age had baseline PSA levels of more than 0.5 ng/mL.

Among 137 men who had PSA follow-up from age 65 years, 36 men were eventually diagnosed with prostate cancer. Among these 36 cancer case subjects, 15 would have potentially benefited from PSA testing over the next 10 years (to age 75 years) by a PSA conversion and an early diagnosis of cancer. The remaining 21 cancer case subjects would have been unlikely to benefit from PSA testing, either because there was no PSA conversion prior to diagnosis (n = 6), since the conversion occurred after diagnosis (n = 4), or because the cancer was diagnosed after age 75 years (n = 11). All cancer case subjects who would have potentially benefited from PSA testing diagnosed in the 10 years after age 65 years had baseline PSA levels of more than 0.5 ng/mL, and all subjects without prostate cancer who had a PSA conversion between the ages of 65 and 75 years had baseline PSA levels of more than 0.5 ng/mL.

Table 2 shows the outcome in terms of cancer detection and reduction in unnecessary PSA testing if men with low PSA levels were no longer tested. For example, if PSA testing were discontinued at age 65 years in men with PSA levels of less than 1.0 ng/mL, 94% (95% CI = 70%–100%) of prostate cancers would still be detected over the next 10 years and there would be a more than 50% reduction in the number of men tested unnecessarily in this cohort of men.

Review of the Medicare claims data for 1995 and 1996 demonstrates that, in both years, 29% of the Medicare population had at least one PSA test, with an average of 1.3 tests per enrollee tested. Fig. 1 shows the percentage of male Medicare enrollees receiving a PSA test in 1996 by age. More than 20% of the Medicare population is still being tested at age 85 years.

DISCUSSION

The benefit of PSA testing in terms of prostate cancer mortality reduction has not been proven. However, PSA testing is widespread as a method for the early detection of prostate cancer, the second most common cause of male cancer deaths in the United States (9). Appropriate guidelines for PSA testing that would reduce unnecessary testing and maintain the rate of detection of prostate cancer have not been defined. Appropriate guidelines determine the burden of screening in the population in terms of unnecessary tests, false-positive tests, and the downstream effects of false-positive testing and are thus an important aspect of a successful screening program.

It has been shown that serum PSA level is a predictor of a future diagnosis of prostate cancer, even when levels are below "normal" (3). With the use of a single serum sample collected 10 years before disease ascertainment, Gann et al. (3) demonstrated a twofold increased risk of a prostate cancer diagnosis in men with PSA levels of 1.01–1.50 ng/mL and a fivefold increased

Table 2. Observed and robust estimates (bootstrap median, bootstrap 95% confidence intervals [CIs]) of the outcomes of prostate-specific antigen (PSA) testing based on age and PSA level

PSA level, ng/mL, by age cohort, below which PSA testing is discontinued	% of prostate cancers detected before age 75 y*		% reduction in No. of men tested unnecessarily†	
	Observed (%)	Bootstrap, median (95% CI)	Observed (%)	Bootstrap, median (95% CI)
Age 60 y				
≤0.5	19/19 (100)	100 (82–100)	37/106 (35)	35 (26–45)
≤1.0	15/19 (79)	80 (55–94)	78/106 (74)	74 (64–82)
≤1.5	11/19 (58)	58 (34–80)	88/106 (83)	83 (74–90)
≤2.0	8/19 (42)	41 (19–66)	96/106 (90)	90 (83–95)
≤2.5	6/19 (32)	31 (12–56)	99/106 (93)	93 (87–97)
≤3.0	5/19 (26)	25 (9–50)	103/106 (97)	97 (92–99)
Age 65 y				
≤0.5	15/15 (100)	100 (78–100)	32/122 (26)	26 (18–35)
≤1.0	14/15 (93)	94 (70–100)	71/122 (58)	58 (49–67)
≤1.5	12/15 (80)	80 (52–96)	94/122 (77)	77 (68–84)
≤2.0	9/15 (60)	60 (32–84)	104/122 (85)	85 (77–91)
≤2.5	6/15 (40)	39 (16–67)	111/122 (91)	91 (84–95)
≤3.0	4/15 (27)	27 (8–55)	116/122 (95)	95 (90–98)

*Prostate cancers detected before age 75 years were cases in which a PSA conversion to >4.0 ng/mL occurred before age 75 y.

†Men tested unnecessarily were those men who were diagnosed with prostate cancer when there was no PSA conversion to >4.0 ng/mL before diagnosis, men diagnosed with cancer after age 75 years if no PSA conversion occurred prior to age 75 years, or men without a prostate cancer diagnosis by age 75 years.

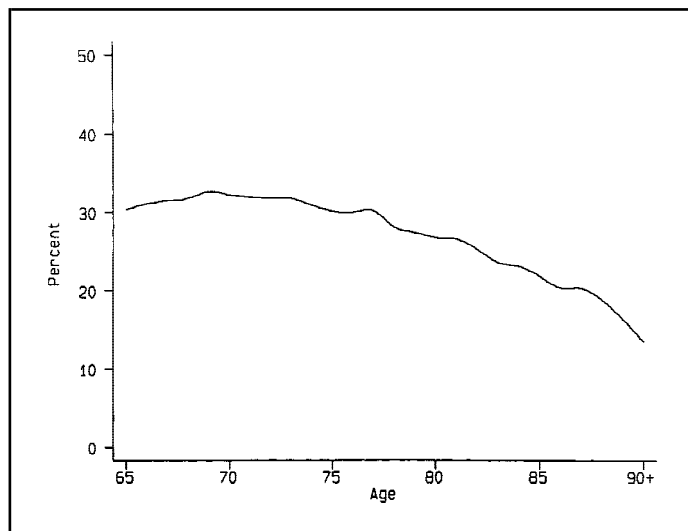


Fig. 1. Percentage of male Medicare enrollees receiving a prostate-specific antigen test in 1996 by age in years (based on Medicare part B claims data).

risk in men with PSA levels of 2.01–3.00 ng/mL compared with men with PSA levels of 1.0 ng/mL or less. Thus, baseline PSA levels reflect the future risk of a prostate cancer diagnosis. Given the predictive value of PSA, it would seem reasonable to use PSA measurements to identify older men at low risk for a future prostate cancer diagnosis who may not benefit from intensive screening.

To our knowledge, we have demonstrated for the first time in a longitudinal study of repeated PSA levels over 10–15 years the relationship between baseline PSA level and a future prostate cancer diagnosis. These data suggest that, by age 65 years, men with very low PSA levels (≤ 0.5 or ≤ 1.0 ng/mL) are not likely to be diagnosed with prostate cancer over the next decade and that prostate cancer detection would be affected little—if at all—if these men had less intensive PSA testing (Table 2). Since an early diagnosis of prostate cancer is not likely to extend life when made after age 75 years, the target population for PSA testing is below age 75 years. An estimated 26%–58% reduction in the number of men tested unnecessarily would occur (on the basis of this nonscreened population) if PSA testing were discontinued in men at age 65 years with very low PSA levels.

The use of low PSA levels to identify older men for less intensive screening would reduce the number of men undergoing PSA testing unnecessarily and would likely not affect cancer detection appreciably. However, the number of false-positive PSA tests in those men without cancer would also be unlikely to be affected, since men with low baseline PSA levels rarely have PSA conversions (>4.0 ng/mL) that would prompt further evaluation before age 75 years (Table 1). Thus, any cost savings of less intensive screening in an older population with low PSA levels would accrue from the avoidance of serial PSA tests over a decade or more and not from the avoidance of downstream costs of false-positive PSA tests.

To put the potential cost savings of less intensive PSA testing into perspective, we evaluated Medicare claims data. Our Medicare claims analysis suggests that the cost savings of less intensive screening in selected older men could be large because the percentage of men undergoing PSA testing is 29% in the Medicare population and is above 20%, even at age 85 years (Fig. 1). With an estimated 14.3 million male Medicare enrollees

in 1996 (10), four million men ($14.3 \times .29$) may have undergone PSA testing in the Medicare population in 1996. On the basis of our estimate of a 26%–58% reduction in the number of men undergoing PSA testing, if testing were discontinued in men with very low PSA levels (≤ 0.5 or ≤ 1.0 ng/mL), as many as 1–2 million men could forego further testing or be tested less frequently (e.g., every 5 years). Given the average of 1.3 tests per enrollee for these 1–2 million men and a Medicare reimbursement rate of \$26 per test, less intensive screening could result in a \$32 500 000–\$65 000 000 cost savings per year.

Several limitations of this study deserve discussion. First, the use of frozen sera to determine serum PSA levels could have affected the results. However, the stability of total PSA in frozen sera at -70°C is well recognized (11). In addition, we have not been able to demonstrate a statistically significant relationship between PSA level and sample storage time in the BLSA population (5). Therefore, we believe that measurements from the frozen samples represent accurate measurements of serial serum PSA levels in the subjects tested. Second, we assumed that prostate cancer in case subjects without a PSA conversion above 4.0 ng/mL would have remained undetected and that PSA testing was not beneficial in these men. This assumption could have overestimated the number of men who underwent PSA testing unnecessarily, since a diagnosis may have been made by other PSA criteria (PSA density, PSA velocity, and free PSA). Third, we also assumed that the discovery of prostate cancer at the time of a PSA conversion to 4.0 ng/mL would be beneficial because virtually all of these men have curable disease (12). This assumption forms the basis of current enthusiasm for PSA testing. However, lack of benefit, either because of detection of advanced (noncurable) disease or because of detection of disease not destined to progress, is possible for some of these men with cancer detected at PSA levels of 4.0 ng/mL. Thus, this assumption could have resulted in an underestimate of unnecessary testing in this study. Fourth, the distribution of PSA levels and cancers within our cohort may not reflect those of a screened population because of the eligibility requirements of our study. Since our study design excluded men who had had prior treatment for prostate disease, the proportion of men with lower PSA levels was somewhat greater than that in screened populations. This overrepresentation of lower PSA values at baseline could have lowered the number of subjects with PSA conversions, leading to an overestimation of the number of subjects tested without benefit. However, this possibility does not change the findings in our dataset, suggesting that less frequent screening may be rational for older men with low PSA values. Fifth, the small number of prostate cancers in our study resulted in wide CIs for outcome estimates by use of the bootstrap method. Therefore, it is not possible to identify a PSA cut point below which PSA testing should be discontinued. However, given our findings and the risk estimates of Gann et al. (3), it would appear that men older than age 65 years with very low PSA levels seldom benefit from further PSA testing. Finally, our calculated potential savings to the Medicare system may, in fact, underestimate “true” savings, since claims data may underestimate rates of PSA testing. At the current time, routine PSA screening of asymptomatic men is not reimbursed by Medicare, but it will be reimbursed beginning in the year 2000 as part of the Balanced Budget Act of 1997. This could increase the percentage of Medicare patients undergoing routine testing beginning in the year 2000. Therefore, the establishment of rational

approaches to routine PSA testing may lead to substantial cost savings.

In summary, we have shown that by age 65 years, men with very low PSA levels are at a low risk of a prostate cancer diagnosis over the next decade. These data suggest that, for men with lower PSA levels, less intensive screening could maintain the detection of the majority of prostate cancers up until age 75 years and markedly reduce the number of men undergoing unnecessary PSA testing. Less intensive screening among lower risk men at an older age could result in large cost savings. Prospective studies of larger cohorts will be required to clearly define the PSA level below which testing intensity can be relaxed to result in the cost-effective detection of important prostate cancers.

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NOTES

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