Recommended Prostate-Specific Antigen Testing Intervals for the Detection of Curable Prostate Cancer

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Objective.—To evaluate prostate-specific antigen (PSA) testing intervals that maintain the detection of curable cancer and reduce unnecessary testing.

Design and Patients.—Historical prospective study of serial PSA measurements at 2- and 4-year intervals from frozen serum samples of 40 men who eventually developed prostate cancer and 272 men without prostate cancer who were participants in a prospective aging study (Gerontology Research Center of the National Institute on Aging, the Baltimore Longitudinal Study of Aging) and the case series of 389 consecutive men treated surgically for nonpalpable prostate cancer.

Main Outcome Measures.—Probability of a PSA conversion to 4.1 to 5.0 ng/mL and to greater than 5.0 ng/mL at 2 and 4 years and probability of detecting curable prostate cancer by age and PSA level.

Results.—When the pretreatment PSA level was less than or equal to 4.0 ng/mL, nonpalpable prostate cancers were highly likely (34/36, 94%) to be curable (organ-confined or capsular penetration with Gleason score <7 and negative margins), and the majority (25/36, 69%) were small cancers (confined tumor ≤ 0.5 cm^3 with no Gleason pattern 4 or 5). When the pretreatment PSA level was greater than 4.0 ng/mL and less than or equal to 5.0 ng/mL, cancers were highly likely to be curable (32/36, 89%), and a minority were small cancers (12/36, 33%). When the pretreatment PSA level was greater than 5.0 ng/mL, 96 (30%) of 317 cancers were noncurable. The PSA conversion (for cancer cases) to a level at which cure is less likely (>5.0 ng/mL) is rare (0%) after 2 or 4 years when the initial PSA is less than 2.0 ng/mL. PSA conversion to a range at which cancers are likely to be curable and less likely to be small (4.1-5.0 ng/mL) is rare after 2 years (0%-4%) when the baseline PSA level is less than 2.0 ng/mL but common when the baseline PSA level is between 2.1 and 3.0 ng/mL (27%) or 3.1 and 4.0 ng/mL (36%).

Conclusions.—These data suggest that for men with no cancer suspected on digital rectal examination, a PSA level of 4.0 to 5.0 ng/mL is an acceptable range for maintaining the detection of curable prostate cancer and a 2-year PSA testing interval is not likely to miss a curable prostate cancer when the initial PSA level is less than 2.0 ng/mL. Recognizing that 70% of a screened population between the ages of 50 years and 70 years have PSA levels less than 2.0 ng/mL, elimination of annual PSA testing for these men would result in large health care cost savings.

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THE USE of prostate-specific antigen (PSA) testing in asymptomatic men for detection of prostate cancer is controversial due to the lack of evidence from randomized trials demonstrating the efficacy of early detection and treatment.[1] Despite this controversy, PSA testing is being widely used in the United States for the early diagnosis of prostate cancer, and a recommendation for yearly PSA testing of men at greatest risk has been made.[2] Thus, even in the absence of evidence to support a policy recommendation for PSA screening, it is important to determine if unnecessary PSA tests can be reduced by testing lower-risk men on a less frequent basis.

The frequency of screening for any cancer is a trade-off between unnecessary testing and the downstream effects of false-positive tests as a result of frequent screening and the risk of missing curable cancer with less frequent testing. Thus, a reduction of testing necessarily requires evidence that the proposed testing interval will not result in a lost opportunity for cure of cancer. To identify those men who may not need yearly PSA testing, we evaluated PSA testing intervals that would maintain the detection of curable cancer while reducing the number of unnecessary tests.

METHODS

Study Groups

Baltimore Longitudinal Study of Aging (BLSA) Database.—The BLSA is an ongoing, long-term prospective study of aging conducted by the National Institute on Aging, Bethesda, Md, which has been described previously.[3] Since the inception of the BLSA in 1958, a total of 1527 men and 654 women have participated in the study for varying lengths of time. Participants in the study return for follow-up visits at approximate 2-year intervals.

Serum PSA levels have been measured on a total of 681 men aged 55 years and older either at the time of routine subject visits (since 1991) or using a frozen serum bank for retrospective samples. All PSA measurements were performed using a monoclonal immunoradiometric assay (Tandem-R, Hybritech Inc, San Diego, Calif). The stability of PSA in these frozen serum samples stored at -70°C has been previously described.[4] After excluding individuals whose medical history of prostate disease could not be verified, individuals with a prior history of prostate surgery, and individuals being treated with finasteride (Proscar, Merck, Whitehouse Station, NJ), 77 men with prostate cancer and 517 men with no evidence of prostate cancer remained in the study group.

To examine the probability of PSA increases of different sizes at 2- and 4-year intervals, we identified all men who had 1 or more pairs of PSA measurements taken between 1½ and 2½ years apart. This led to the final study groups of 40 cancer cases (median age at

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diagnosis, 73 years; range, 54-87 years) and 272 men with no evidence of prostate cancer (median age at most recent BLSA visit, 69 years; range, 55-95 years). The clinical stage (TNM) among the cancer cases was T1 in 9 subjects, T2 in 7, T3 in 3, M1 in 1, and unknown in 20 subjects. The Gleason score was 6 or less for 17 of the cancer cases, 7 or more for 11 cases, and unknown for 12 cases. Among the 272 men without prostate cancer, 36 had a simple prostatectomy for benign prostatic hyperplasia and had no cancer in the final pathology specimen, 56 had 1 or more negative prostate biopsies, 156 had no suspicion of cancer by digital rectal examination (DRE) performed by 1 examiner (H.B.C.), and none had a PSA level above the age-specific range.[5]

Nonpalpable Tumors (Surgical Database).—The probability of detecting curable prostate cancer at a given pretreatment serum PSA level was determined from 389 men with nonpalpable prostate cancer who underwent radical prostatectomy at Johns Hopkins Hospital between 1989 and 1994. These 389 cases were selected from 398 men with nonpalpable cancer who had step-section analysis of prostate specimens; 157 consecutive cases treated surgically between 1989 and 1992 that were the subject of a previous report,[6] and 232 of 241 consecutive cases treated surgically between 1994 and 1996. Nine of these men were excluded because they did not have a PSA measurement at least 4 weeks after DRE and prostate biopsy and complete step-section analysis of prostate specimens for determination of tumor volume.

The mean and median ages for the 389 men with nonpalpable cancer treated surgically was 58.7 years and 60 years (range, 41-70 years), respectively. Serum PSA levels for the 389 men who underwent surgical treatment were determined from fresh serum samples drawn at the time of initial consultation. The mean and median pretreatment PSA levels were 9.85 ng/mL and 7.5 ng/mL (range, 0.5-114 ng/mL), respectively.

Radical Prostatectomy Specimens

After resection, prostate specimens were coated with india ink, completely embedded, and processed as previously described.[7] Tumors were graded using the Gleason system. Capsular penetration was defined as tumor extending out of the prostate into periprostatic soft tissue, and subclassified as focal and established (nonfocal).[7] Capsular margins of resection were designated as negative or positive, as previously described.[8] Seminal vesicle invasion was diagnosed when a tumor penetrated the muscular coat of the seminal vesicles. Tumor volume was calculated using a computer-assisted image analysis system, as previously described.[9]

Pathologic Classification of Nonpalpable Tumors

Prostate cancers were classified pathologically on a continuum (categories A to D), from smaller tumors (categories A and B) that may pose little threat to the life of some individuals (potentially unimportant) to larger and more extensive tumors (categories C and D) that may be life threatening.[6] Category A tumors were smaller than 0.2 cm^3, organ-confined without seminal vesicle or lymph node involvement, and without the presence of Gleason pattern 4 or 5. Category B tumors were between 0.2 and 0.5 cm^3, organ-confined without seminal vesicle or lymph node involvement, and without the presence of Gleason pattern 4 or 5. Category C tumors were confined, 0.5 cm^3 or larger, or with capsular penetration of low grade (Gleason score <7) with negative margins and no involvement of the seminal vesicles and lymph nodes. Category D tumors had capsular penetration of high grade (Gleason score ≥ 7) or established (nonfocal) capsular penetration with positive margins or involvement of seminal vesicles or lymph nodes.

Tumors classified as categories A to C were considered potentially curable since more than 75% of men with tumors in these categories will be progression free at 10 years using a detectable PSA level as the indicator of progression.[10] Category D tumors were considered potentially noncurable since less than 50% of men with tumors in this category will be progression free at 10 years.

Statistical Analysis

The unit of observation for the PSA conversion analysis was pairs of PSA tests that were collected 1½ to 2½ years apart or 3½ to 4½ years apart. Pairs of PSA measurements were analyzed depending on the PSA level at the initial visit and on whether the subsequent PSA test had increased to 4.1 to 5.0 ng/mL or exceeded 5.0 ng/mL. The crude proportion of pairs of PSA measurements that increased to these levels was compared statistically by means of χ^2 tests. A power analysis[11] indicated that the χ^2 analysis was capable of detecting small to moderate effect sizes (effect size index >0.125) with a power of more than 0.80 at an α level of .05 for the test when the initial PSA level was less than 2.0 ng/mL and had a power of more than 0.80 to detect moderate effect sizes (effect size index ≥ 0.3) when the initial PSA level was 2.0 to 2.9 ng/mL or 3.0 to 3.9 ng/mL (effect size index ≥ 0.4).

Logistic regression analyses were used to model the relationship of age and initial PSA level to the probability of a PSA conversion and the relationship of age and PSA level at time of prostatectomy to pathologic stage. Restricted cubic splines[12] were used to assess for nonlinear relationships with the predictor variables. Examination of the residuals indicated an adequate fit for the final models. Power analysis showed that the logistic regression analysis had a power greater than 0.80 with an α level of .05 to detect a relative risk of 2.0 or greater for PSA conversion to 4.1 to 5.0 ng/mL or a relative risk of 2.5 or greater for a PSA conversion to greater than 5.0 ng/mL. Power analysis showed that the logistic regression analysis had a power greater than 0.95 with an α level of .05 to detect a relative risk of 1.5 or greater for curable tumors.

The logistic regression analyses were performed using S-Plus for Windows, and all other analyses were performed using SAS. Two-tailed tests with an α level of .05 were used for all statistical tests.

RESULTS

Nonpalpable Cancers (Surgical Database)

Among 36 men with nonpalpable prostate cancers who had pretreatment PSA levels of 4.0 ng/mL or less, 34 (94%) had curable cancers (organ-confined or capsular penetration with Gleason score <7 and negative margins), and 25 (69%) were small cancers (confined tumor ≤ 0.5 cm^3 with no Gleason pattern 4 or 5) (Table 1). When the pretreatment PSA level was greater than 4.0 ng/mL but less than 5.0 ng/mL (n=36), 32 (89%) had curable cancers and 12 (33%) were small cancers. When the pretreatment PSA level was greater than 5.0 ng/mL, 96 (30%) of 317 cancers were noncurable. Logistic regression analysis demonstrated that the probability of noncurable cancer increased with PSA level and that the probability of noncurable cancer was higher in men aged 65 years compared with men aged 45 to 55 years at PSA levels less than 8.0 ng/mL ($P<.001$).

BLSA Database

The probability of a PSA conversion after 2 years (Table 2) to above 4.0 ng/mL was statistically significantly different (Mantel-Haenszel and χ^2 tests) between the cancer and noncancer groups when the baseline PSA level was 2.1 to 3.0 ng/mL ($P=.01$), but not when the baseline PSA level was 0.0 to 1.0

ng/mL (P=.71), 1.1 to 2.0 ng/mL (P=.09), or 3.1 to 4.0 ng/mL (P=.06). The probability of a PSA conversion to 4.1 to 5.0 ng/mL was only 4% at 2 years for cancer cases when the baseline PSA level was 1.1 to 2.0 ng/mL. The probability of a PSA conversion to 4.1 to 5.0 ng/mL and to greater than 5.0 ng/mL at 2 years (for cancer cases) was 27% and 0%, respectively, at baseline PSA levels of 2.1 to 3.0 ng/mL; and 36% and 32%, respectively, at baseline PSA levels of 3.1 to 4.0 ng/mL.

Table 1.—Pathologic Classification of 389 Men With Nonpalpable Prostate Cancer Treated Surgically

Pathologic Categories by PSA Level*	Patients, No. (%)
Pretreatment PSA <2.5 ng/mL	
A	14 (74)
B	2 (10)
C	3 (16)
D	0 (0)
Pretreatment PSA ≥2.5 to ≤4.0 ng/mL	
A	4 (24)
B	5 (29)
C	6 (35)
D	2 (12)
Pretreatment PSA >4.0 to ≤5.0 ng/mL	
A	7 (19)
B	5 (14)
C	20 (56)
D	4 (11)
Pretreatment PSA >5.0 to ≤6.0 ng/mL	
A	8 (16)
B	5 (10)
C	26 (53)
D	10 (21)
Pretreatment PSA >6.0 to ≤10.0 ng/mL	
A	23 (16)
B	16 (11)
C	79 (53)
D	30 (20)
Pretreatment PSA >10.0 ng/mL	
A	9 (8)
B	9 (8)
C	46 (38)
D	56 (46)

*PSA indicates prostate-specific antigen. A indicates an organ-confined tumor smaller than 0.2 cm^3 without seminal vesicle or lymph node involvement and without the presence of Gleason pattern 4 or 5. B indicates an organ-confined tumor between 0.2 and 0.5 cm^3 without seminal vesicle or lymph node involvement and without the presence of Gleason pattern 4 or 5. C indicates confined tumors 0.5 cm^3 or larger or a tumor with capsular penetration of low grade (Gleason score <7) with negative margins and no involvement of the seminal vesicles and lymph nodes. D indicates a tumor with capsular penetration of high grade (Gleason score ≥7) or established (nonfocal) capsular penetration with positive margins or involvement of seminal vesicles or lymph nodes. Category D is considered noncurable.

The probability of a PSA conversion after 4 years (Table 3) to above 4.0 ng/mL was statistically significantly different (Mantel-Haenszel and χ^2 tests) between the cancer and noncancer cases when the baseline PSA level was 1.1 to 2.0 ng/mL (P=.001) or 2.1 to 3.0 ng/mL (P=.005); but there was no statistically significant difference between the groups when the baseline PSA level was 0.0 to 1.0 ng/mL (P=.74) or 3.1 to 4.0 ng/mL (P=.15). When the baseline PSA level was 1.1 to 2.0 ng/mL, the probability of a PSA conversion (for cancer cases) to 4.1 to 5.0 ng/mL and to greater than 5.0 ng/mL was 30% and 0%, respectively. The probability of a PSA conversion to 4.1 to 5.0 ng/mL among cancer cases was 18% at a baseline PSA level of 2.1 to 3.0 ng/mL and 33% with a baseline PSA level of 3.1 to 4.0 ng/mL.

PSA Testing Guidelines

Logistic regression analysis revealed that the probability of a PSA conversion among cancer cases after 4 years increased with higher initial PSA levels (P<.02). While age was a statistically significant factor related to the probability of a PSA conversion to 4.1 to 5.0 ng/mL (P=.04), age was not a statistically significant factor for PSA conversion to 2.1 to 3.0 ng/mL (P=.08), to 3.1 to 4.0 ng/mL (P=.17), or to greater than 5.0 ng/mL (P=.93). When the initial PSA level is less than 2.0 ng/mL, a PSA conversion to greater than 5.0 ng/mL even at 4 years is a rare event. However, the risk of a PSA conversion increases as baseline PSA level rises above 2.0 ng/mL. Guidelines for appropriate PSA testing intervals are shown in the Figure based on the probability of a PSA conversion by initial PSA level and the surgical data suggesting that a PSA level of 4.1 to 5.0 ng/mL is an acceptable range for maintaining the detection of potentially curable cancer.

COMMENT

PSA testing increases the lead time for prostate cancer diagnosis[13] and results in increased detection of organ-confined cancers.[14] However, it is currently unknown whether PSA screening will reduce prostate cancer mortality. Regardless, PSA testing is being used routinely today for the early detection of prostate cancer, and annual testing is the common approach.[2] We previously demonstrated that changes in PSA, on average, occur slowly at lower PSA levels even among men who are destined to develop prostate cancer later in life.[4] Thus, annual testing may be unnecessary for those men with lower baseline PSA values; and PSA testing intervals exceeding 1 year may be consistent with early detection of curable cancers.

We have demonstrated for the first time in a longitudinal study the probability of PSA conversions among men who were destined for later development of prostate cancer and men without prostate cancer. Men who later developed prostate cancer were more likely to experience a PSA conversion than men without prostate cancer at a given baseline PSA level, and this probability was directly related to the initial serum PSA value. We did not observe a relationship between PSA conversions and age in cancer cases.

With respect to the use of PSA testing in the early detection of prostate cancer, the major investigative focus has been to determine the PSA cutoff level that will produce both high sensitivity (detection of the largest number of prostate cancers) and high specificity (exclusion of men without prostate cancer). However, the goal of PSA testing should be the detection of curable tumors that pose a threat to life expectancy or quality of life and not the detection of all cancers. The

Table 2.—Two-Year Prostate-Specific Antigen (PSA) Interval Analysis

	Initial PSA Level							
	0.0-1.0 ng/mL		1.1-2.0 ng/mL		2.1-3.0 ng/mL		3.1-4.0 ng/mL	
Observations	Noncancers	Cancers	Noncancers	Cancers	Noncancers	Cancers	Noncancers	Cancers
PSA pairs, No.	493	33	210	27	91	30	38	25
Median initial PSA level, ng/mL (range)	0.5 (0.1-1.0)	0.7 (0.1-1.0)	1.4 (1.1-2.0)	1.6 (1.1-2.0)	2.5 (2.1-3.0)	2.7 (2.1-3.0)	3.5 (3.1-4.0)	3.6 (3.1-4.0)
Median age at initial PSA test, y (range)	64 (44-89)	61 (47-75)	67 (49-90)	63 (46-79)	71 (53-95)	68 (53-78)	77 (62-91)	70 (59-86)
Median time before diagnosis* at initial PSA test, y (range)	4.0 (0.0-19.9)	13.6 (1.3-24)	2.1 (0.0-17.5)	7.9 (0.1-19.6)	2.0 (0.0-16.1)	3.7 (0.0-14.9)	2.0 (0.0-15.0)	3.9 (0.0-28.7)
Median interval between PSA tests, y (range)	2.0 (1.5-2.5)	1.7 (1.5-2.5)	2.0 (1.5-2.5)	2.0 (1.5-2.3)	2.0 (1.5-2.5)	2.0 (1.5-2.3)	2.0 (1.7-2.5)	2.0 (1.6-2.2)
Second PSA levels ≤2.0 ng/mL, No. (%)	485 (98)	31 (94)	146 (70)	13 (48)	19 (21)	2 (7)	1 (3)	0 (0)
Second PSA levels 2.1-3.0 ng/mL, No. (%)	5 (1)	2 (6)	53 (25)	11 (41)	39 (43)	11 (37)	6 (16)	3 (12)
Second PSA levels 3.1-4.0 ng/mL, No. (%)	1 (0.2)	0 (0)	10 (5)	2 (7)	25 (27)	9 (30)	16 (42)	5 (20)
Second PSA levels 4.1-5.0 ng/mL, No. (%)	0 (0)	0 (0)	0 (0)	1 (4)	7 (8)	8 (27)	11 (29)	9 (36)
Second PSA levels >5.0 ng/mL, No. (%)	2 (0.4)	0 (0)	1 (0.5)	0 (0)	1 (1)	0 (0)	4 (11)	8 (32)

*Time of diagnosis for noncancers is time of last PSA measurement.

Table 3.—Four-Year Prostate-Specific Antigen (PSA) Interval Analysis

Observations	Initial PSA Level							
	0.0-1.0 ng/mL		1.1-2.0 ng/mL		2.1-3.0 ng/mL		3.1-4.0 ng/mL	
	Noncancers	Cancers	Noncancers	Cancers	Noncancers	Cancers	Noncancers	Cancers
PSA pairs, No.	414	23	146	20	51	33	22	9
Median initial PSA level, ng/mL (range)	0.5 (0.1-1.0)	0.7 (0.3-1.0)	1.4 (1.1-2.0)	1.4 (1.1-2.0)	2.5 (2.1-3.0)	2.5 (2.1-3.0)	3.4 (3.1-4.0)	3.6 (3.1-3.8)
Median age at initial PSA test, y (range)	60 (40-84)	58 (47-74)	65 (47-86)	62 (40-72)	70 (52-87)	67 (49-77)	73 (60-89)	64 (58-76)
Median time before diagnosis* at initial PSA test, y (range)	2.7 (0.0-22.0)	7.5 (1.4-20.3)	2.0 (0.0-19.2)	6.1 (0.2-20.6)	2.0 (0.0-15.0)	2.2 (0.0-20.5)	2.0 (0.0-13.5)	3.8 (1.9-6.2)
Median interval between PSA tests, y (range)	4.0 (3.5-4.5)	3.9 (3.5-4.4)	4.0 (3.5-4.5)	4.0 (3.6-4.5)	4.0 (3.6-4.5)	4.0 (3.5-4.5)	4.0 (3.6-4.5)	4.1 (3.9-4.4)
Second PSA levels ≤2.0 ng/mL, No. (%)	397 (96)	18 (78)	88 (60)	4 (17)	6 (12)	1 (3)	0 (0)	0 (0)
Second PSA levels 2.1-3.0 ng/mL, No. (%)	12 (3)	5 (21)	42 (29)	6 (30)	16 (31)	5 (15)	5 (23)	1 (11)
Second PSA levels 3.1-4.0 ng/mL, No. (%)	3 (0.7)	0 (0)	11 (8)	4 (20)	18 (35)	10 (30)	5 (23)	1 (11)
Second PSA levels 4.1-5.0 ng/mL, No. (%)	0 (0)	0 (0)	3 (2)	6 (30)	6 (12)	6 (18)	8 (36)	3 (33)
Second PSA levels >5.0 ng/mL, No. (%)	2 (0.5)	0 (0)	2 (1)	0 (0)	5 (10)	11 (33)	4 (18)	4 (44)

*Time of diagnosis for noncancers is time of last PSA measurement.

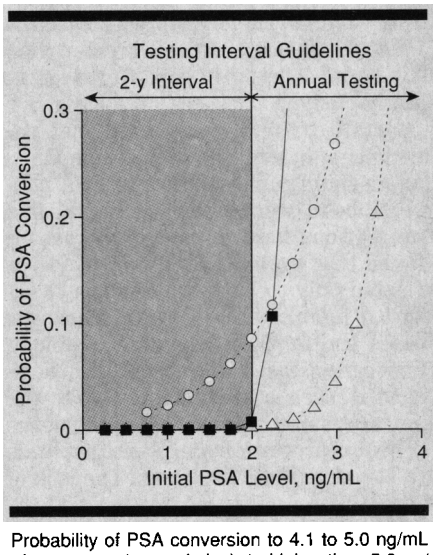
current lack of knowledge regarding predictors of tumor behavior prevents an accurate determination of which early cancers are likely to progress and what PSA cutoff is most likely to detect the important cancer. Recognizing these limitations, there is some rationale for classifying tumors that are smaller than 0.2 to 0.5 cm^3 as potentially unimportant,[6,15] especially among older men, and a strong rationale for using tumor grade as a predictor of aggressive behavior.[10]

In this case series, potentially curable cancer was almost always found at PSA levels less than 4.0 ng/mL (95% of cases) in men without suspicion of cancer on DRE, but it was found at the expense of detecting a high percentage (69%) of smaller, potentially unimportant tumors (Table 1). In comparison, when pretreatment PSA levels were between 4.0 and 5.0 ng/mL in the setting of a nonsuspicious DRE, the majority of men still had potentially curable cancers (89%) and the risk of detecting a smaller, potentially unimportant cancer was reduced (33%). These data suggest that a PSA level of 4.0 to 5.0 ng/mL represents a range at which the detection of potentially curable cancer is maintained and the detection of potentially unimportant cancers is reduced.

The 4-year PSA interval analysis for cancer cases revealed no PSA conversions to greater than 5.0 ng/mL when the initial PSA level was less than or equal to 2.0 ng/mL. The 2-year interval analysis for cancer cases revealed a low risk of a PSA conversion to 4.1 to 5.0 ng/mL (4%) when the baseline PSA level was less than or equal to 2.0 ng/mL; whereas PSA conversions to 4.1 to 5.0 ng/mL occurred in 27% and 36% of cancer cases when baseline PSA levels were 2.1 to 3.0 ng/mL and 3.1 to 4.0 ng/mL, respectively. Based on these data it would appear that annual PSA testing is not beneficial for most men with initial PSA levels less than 2.0 ng/mL if there is no suspicion of cancer on DRE. In contrast, annual testing may be an appropriate interval when the PSA level is above 2.0 ng/mL because of the higher risk of a PSA conversion to 4.1 to 5.0 ng/mL and to greater than 5.0 ng/mL.

In attempting to identify those men that may not need yearly PSA testing, we have taken into consideration the probability of a PSA conversion given the initial PSA level and the PSA range at which the detection of curable cancer remains high. We have recommended, as a guideline, a 2-year sampling interval for men with PSA levels below 2.0 ng/mL and an annual sampling interval for men with PSA levels of 2.0 ng/mL and above. This conservative approach takes into consideration the individual physiologic variability between consecutive PSA measurements that may be as high as 20% to 30%.[16,17] This substantial variability could lead to false low PSA readings that could delay repeat PSA testing and delay prostate biopsy. Thus, a more conservative approach would attempt to reduce the possibility of missing a PSA conversion to above 5.0 ng/mL—a level at which detection of curable cancer becomes less likely. Although there is an extremely low probability of PSA conversion when the baseline PSA is 0.0 to 1.0 ng/mL, we feel that further studies will be necessary before a recommendation can be made for testing intervals that exceed 2 years among individuals with very low PSA levels.

Interpretation of the significance of a given serum PSA level requires consideration of risk factors such as age, family history, and race and also factors such as patient health and level of risk aversion which affect the potential downstream benefits and disadvantages of therapeutic options. Thus, a decision regarding the timing of repeat PSA testing should also take these factors into consideration. An annual PSA testing interval, even when the baseline PSA level is less than 2.0 ng/mL, may be appropriate for men at higher risk of prostate cancer development in whom PSA thresholds below 4.0 ng/mL would raise suspicion of cancer. In contrast, a 4-year PSA testing interval when the baseline PSA level is less than 2.0 ng/mL may be adequate for an older individual with comorbidities who has less to gain from a prostate cancer diagnosis and in whom a PSA threshold above 4.0 ng/mL might be used to signal a higher risk of cancer. Tables 2 and 3 provide the clinician with information regarding the chance of a PSA conversion to various PSA levels (depending on the initial PSA level) that can be used to make recommendations for appropriate PSA testing intervals for the individual patient.



Probability of PSA conversion to 4.1 to 5.0 ng/mL after 2 years (open circles), to higher than 5.0 ng/mL after 2 years (open triangles) and 4 years (solid squares). A 2-year testing interval appears to be appropriate when the initial PSA level is less than 2.0 ng/mL because there is a negligible risk of conversion to 5.0 ng/mL even after 4 years. The testing interval guidelines may be adjusted depending on individual patient risk factors for development of prostate cancer or based on factors that affect the potential benefits and disadvantages of therapy.

In the current study, we were unable to evaluate PSA testing intervals of 1 year and 3 years, which could have affected the results. Given the individual biologic variability between PSA measurements, more frequent PSA testing intervals could have resulted in the detection of PSA conversions that were not detected in this study. Smith et al[18] found that after 4 years of PSA screening at 6-month intervals, 4% of the men screened had PSA conversions to greater than 4.0 ng/mL when the baseline PSA level was less than 2.5 ng/mL; whereas 48% had PSA conversions to greater than 4.0 ng/mL when the baseline PSA level was 2.6 to 4.0 ng/mL. These data include both men with and without prostate cancer and are similar to our 4-year interval analysis for men with baseline PSA values less than and greater than 2.0 ng/mL, despite the differences in study design.

Smith et al[18] also reported that patient age, in addition to baseline PSA, was a significant predictor of PSA conversions to greater than 4.0 ng/mL in a proportional hazards model; whereas we found that age was a significant factor related only to PSA conversions to 4.1 to 5.0 ng/mL after 4 years in cancer cases and for PSA conversions among non–cancer cases. The age effect in non–cancer cases is presumably due to the age-associated increase in the prevalence of benign prostatic hyperplasia that leads to elevations of PSA levels. The lack of an age effect in cancer cases may reflect the fact that PSA conversion is closely related to cancer progression and that tumors arise at different ages in different patients. Thus, the current study represents a unique longitudinal evaluation of the natural history of PSA changes among men with prostate cancers that were detected without PSA screening later in the natural history of the disease.

Several limitations of the current study deserve discussion. First, the use of frozen serum samples to determine serum PSA levels could have affected the results. However, the stability of total PSA in frozen serum samples at −70°C has been shown in the BLSA population and in other studies.[4,19] Second, we evaluated PSA conversions among men who were diagnosed in the pre-PSA testing era (BLSA participants) and may have had tumors with greater biologic potential compared to men diagnosed with use of PSA testing (T1c surgical series). Thus, we may have overestimated the PSA conversion rates by using the BLSA cancer cases since these were tumors that were destined to progress and were diagnosed without the use of PSA testing. In comparison, cancers detected using PSA testing could have slower PSA conversion rates, which favors the safety of lowering the frequency of PSA testing in men with no suspicion of cancer on rectal examination. Third, the present study used a referral population to evaluate the pathologic characteristics of nonpalpable prostate cancers, and a referral population may not be comparable to screened populations. However, comparisons of the pathologic features of nonpalpable screened cancers[20] and nonpalpable referral cancers[6] demonstrate minimal differences. Therefore, we believe that these data are representative of the findings in a screened population.

In summary, we have presented evidence that men with baseline PSA levels less than 2.0 ng/mL are unlikely after even 4 years to reach a PSA level that would be inconsistent with cure of cancer. Furthermore, even if the initial "true" PSA level was 2.0 to 3.0 ng/mL and the initial serum measurement was less than 2.0 ng/mL, it is unlikely that noncurable cancer (PSA conversion to >5.0 ng/mL) would be detected 2 years later. Thus, it would appear safe to alter the current recommendations regarding PSA testing. For men between the ages of 50 years and 70 years who have no suspicion of prostate cancer on DRE, and in whom a PSA threshold of 4.0 ng/mL would be considered abnormal, a 2-year PSA testing interval is appropriate when the baseline PSA level is less than 2.0 ng/mL. When the baseline PSA level is 2.0 ng/mL and higher, an annual PSA testing interval is appropriate. This approach would result in substantial cost savings for the health care system.

References

1. US Preventive Services Task Force. Screening for prostate cancer. In: *Guide to Clinical Preventive Services*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1996:119-134.
2. Mettlin C, Jones G, Averette H, Gusberg SB, Murphy GP. Defining and updating the American Cancer Society guidelines for the cancer-related checkup: prostate and endometrial cancers. *CA Cancer J Clin*. 1993;43:42-46.
3. Shock NW, Greulich RC, Andres R, et al. *Normal Human Aging: The Baltimore Longitudinal Study of Aging*. Washington, DC: US Government Printing Office; November 1984. NIH publication 84-2450.
4. Carter HB, Pearson JD, Metter JE, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA*. 1992;267:2215-2220.
5. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. *JAMA*. 1993;270:860-864.
6. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA*. 1994;271:368-374.
7. Epstein JI, Carmichael M, Pizov G, Walsh PC. Influence of capsular penetration on progression following radical prostatectomy: a study of 196 cases with long-term follow-up. *J Urol*. 1993;150:135-141.
8. Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression following radical retropubic prostatectomy. *Cancer*. 1993;71:3582-3593.
9. Partin AW, Epstein JI, Cho KR, Gittelsohn MA, Walsh PC. Morphometric measurement of tumor volume and percent of gland involvement as predictors of pathological stage in clinical stage B prostate cancer. *J Urol*. 1989;141:341-345.
10. Epstein JI, Partin AW, Sauvageot J, Walsh PC. Prediction of progression following radical prostatectomy: a multivariate analysis of 721 men with long-term follow-up. *Am J Surg Pathol*. 1996;20:286-292.
11. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
12. Stone CJ, Koo CY. Additive splines in statistics. In: *Proceedings of the Statistical Computing Section of the American Statistical Association*. Washington, DC: 1985:45-48.
13. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA*. 1995;273:289-294.
14. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen–based screening. *JAMA*. 1993;270:948-954.
15. Stamey TA, Freiha FS, McNeal JE, Redwine EA, Wittemore AS, Schmid H-P. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer*. 1993;71:933-938.
16. Carter HB, Pearson JD, Waclawiw Z, et al. Prostate-specific antigen variability in men without prostate cancer: effect of sampling interval in prostate-specific antigen velocity. *Urology*. 1995;45:591-596.
17. Prestigiacomo AF, Stamey TA. Physiological variation of serum prostate specific antigen in the 4.0 to 10.0 ng/mL range in male volunteers. *J Urol*. 1996;155:1977-1980.
18. Smith DS, Catalona WJ, Herschman JD. Longitudinal screening for prostate cancer with prostate-specific antigen. *JAMA*. 1996;276:1309-1315.
19. Jacobsen SJ, Klee GG, Lilja H, Wright GL, Oesterling JE. Stability of serum prostate-specific antigen determination across laboratory, assay, and storage time. *Urology*. 1995;45:447-453.
20. Humphrey PA, Keetch DW, Smith DS, Shepherd DL, Catalona WJ. Prospective characterization of pathological features of prostatic carcinomas detected via serum prostate specific antigen based screening. *J Urol*. 1996;155:816-820.