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Biopsy Follow-Up of Prostate-Specific Antigen Tests

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Abstract

Background—A prostate-specific antigen (PSA) level above 4 ng/mL has historically been recognized as an appropriate threshold to recommend biopsy; however the risk of high-grade disease observed among men with lower PSA levels in the Prostate Cancer Prevention Trial has led to calls to change the criteria for biopsy referral.

Purpose—To aid providers when discussing aggressiveness of biopsy by cataloging available community biopsy patterns and determine whether lower PSA thresholds are being used to recommend biopsy.

Methods—Laboratory and biopsy records were reviewed among 59,764 men in a large Washington State health plan between 1998 and 2007. Follow-up in the 12-month period after a test was categorized as biopsy, urology visit without biopsy, additional PSA testing with no urology visit, or no PSA-related follow-up. Data analysis occurred between 2010 and 2011.

Results—Twenty-eight percent of tests with PSA levels ≥4.0 ng/mL, 2.9% of tests with levels between 2.5 and 4.0 ng/mL, and 0.4% of tests with levels <2.5 ng/mL were followed with a biopsy within 12 months. Over 40% of elevated tests (≥4.0 ng/mL) were followed by a urologist visit without a biopsy, and over 30% of tests ≥4.0 did not have any PSA-related follow-up within 12 months. PSA velocity, defined as annualized rate of change in PSA level, was strongly associated with biopsy, especially when absolute PSA was <4.0 ng/mL. There appear to be no discernable temporal trends in biopsy thresholds or practice patterns based on PSA velocity.

Conclusions—Despite recent calls to more aggressively recommend biopsy at lower PSA thresholds, the practice in this large health plan has remained consistent over time.

Introduction

The prostate-specific antigen (PSA) test has been commonly used to screen for prostate cancer for the past 2 decades despite uncertainty about its risks and benefits. By 2000, over 45% of men aged >40 years in the U.S. had received at least one PSA test.[1]

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Because PSA is a continuous marker, there has been controversy about what threshold should be used to refer men for biopsy.[2,3] Initially, a cut-off of ≥4.0 ng/mL was considered serologically abnormal based on evidence that this level would achieve a positive predictive value of 25%.[4,5] However, even in the early years of PSA testing, there was controversy over this cutoff with calls to use age- and even race-specific thresholds, and suggestions that PSA velocity (the change in PSA over time) might be preferable rather than an absolute cut-off.[6,7] Findings from the Prostate Cancer Prevention Trial (PCPT), which biopsied 5,587 men in the placebo arm of the trial, identified many men with PSA levels <4.0 ng/mL who had cancer.[8] This finding has added to calls to lower cutoffs to 2.5 ng/mL or lower, and even abandon a specific cut-off altogether.[9,10]

The uncertainty about whether and when to biopsy has led to conflicting guidelines from national policy panels. Currently, the American Cancer Society recommends men opting for screening receive a biopsy at a threshold of 4.0 ng/mL. The U.S. Preventive Services Task Force stated in 2008[11] that there while there is insufficient evidence to make a recommendation about screening, a threshold of 4.0 ng/mL is suggested for patients preferring screening.. The National Comprehensive Cancer Network (NCCN)[12] recommends 2.5 ng/mL as a criterion for biopsy referral. The American Urology Association[13] recommends against using a specific threshold, but suggests individualized counseling about prostate cancer risk at various PSA levels so that men can decide to undergo biopsy based on their risk preferences.

A major reason for the lack of a consensus about an optimal PSA threshold to use is that the harm–benefit ratio associated with different thresholds is not clear, despite publication of results from recent screening trials. Two long-term randomized trials of PSA screening were published in 2009, with the European trial reporting a 20% reduction in prostate cancer–specific mortality (rate ratio = 0.80, 95% CI=0.65, 0.98) and the American trial reporting no mortality differences between the screening and control groups (rate ratio = 1.13, 95% CI=0.75, 1.13).[14,15] One of several differences between the trials was the PSA threshold used to refer men to biopsy, with the American trial recommending biopsy at a threshold of 4.0 ng/mL, while most centers in the European trial used a threshold of 3.0 ng/mL.

There is little evidence in the community about biopsy thresholds used in practice or patient adherence with biopsy recommendations.[16] Variation in follow-up of elevated tests has been documented in follow-up recommendations for elevated PSA levels, but most data have been from large screening or prevention trials and not from community practice. The Prostate Lung Colon and Ovarian (PLCO) screening trial notified providers of a suspicious result if the trial identified a PSA level ≥4.0 ng/mL. In examining compliance with this protocol, Pinsky et al. observed that 56% of subjects received a biopsy within 2 years if the elevated test was the first test the patient had in the trial, and 44% underwent a biopsy if the test was a subsequent screening test.

A study of Veterans in the Pacific Northwest identified that 33% of patients with a PSA test ≥4.0 ng/mL underwent biopsy within 2 years.[17] There are likely many factors influencing the type of follow-up patients receive, including provider practices, patient preferences, prior test results and patient clinical histories, financial and access barriers, and system logistic practices that may impede or facilitate coordination with specialty providers.[18]

The purpose of this study is to determine whether biopsy practices following a PSA test have changed over time, using a database from a large cohort of men with detailed PSA testing history information, including PSA laboratory values. As a second objective, available longitudinal PSA values were examined to determine if PSA velocity is associated with follow-up biopsy when PSA velocity exceeds one of the thresholds established in the

literature.[6] Because demographic, clinical, and socioeconomic factors may affect PSA levels as well as follow-up practices, adjustments were made for these factors to the extent possible.

Methods

Study Population. Men were enrolled in Group Health, a health plan that serves approximately 400,000 enrollees in Washington State and Northern Idaho through 26 Group Health owned and operated clinics.[19] All PSA tests conducted in Group Health laboratories between 1997 and 2008 among members who were continuously enrolled during this period were included. Tests occurring in close proximity were combined into single testing episodes in order to avoid counting follow-up tests as initiating events.[20]

Starting in 1998, the first test for each subject that was at least 11 months after any prior tests in 1997 was identified. Going forward, tests at least 11 months after a prior test started a new testing episode. The first test in each episode was defined as the index test, and the date of this test was used to construct each follow-up interval. Diagnostic tests were not excluded, as there is no recommendation that a different PSA level should be used to refer to biopsy for diagnostic tests compared to screening tests.

Tests were excluded when the subject had a diagnosis of prostate cancer on or prior to the PSA test date. Prostate cancer date of diagnosis was identified by the cancer registry and/or date of any visit with an ICD-9 code for prostate cancer. After meeting these criteria, tests were further excluded for the following reasons: (1) subject was aged <35 years or >85 years at the time of test; (2) the subject dis-enrolled or died within 12 months following the PSA test date; and (3) index test was missing PSA value or other covariate information. All data were collected in 2010 and analyzed between 2010 and 2011.

Covariates were linked with each index test. Year of test was grouped in three periods to facilitate data presentation; individual calendar years were explored in sensitivity analyses. For the primary analysis, PSA levels were categorized into three groups, <2.5 ng/mL, 2.5–3.9 ng/mL, and ≥4.0 ng/mL. In secondary analyses linear regression was used to establish PSA velocity defined as the average slope over time for each index test where at least one prior test was available.[21] Patients were grouped into four categories based on both PSA level (<4.0 ng/mL or ≥4.0 ng/mL) and velocity (<0.75 ng/mL/year and ≥0.75 ng/mL/year).[6] Additional groupings of PSA including 4–6.9 ng/mL, 7.0–9.9 ng/mL and ≥10 ng/mL, as well as continuous measures of PSA were explored in sensitivity analyses.

The ordering provider for each test was characterized as either a primary care provider, urologist, or other specialist. Comorbidity scores using the pharmacy-based RxRisk method were calculated annually for each enrollee and linked to each test.[22] Census block median family income level from the 2000 U.S. Census based on enrollees' address served as a proxy for SES. All study methods were approved the Group Health Cooperative human subjects review committee.

Outcomes

Each index test was grouped into 1 of 4 mutually exclusive categories. The first level of follow-up was receipt of a biopsy within 12 months of the test date. The next level was attendance at a urology appointment within 12 months but no biopsy. Then all available PSA tests were queried to identify whether a subsequent test had been completed within 12 months of the index test. Patients who did not receive any of these 3 types of follow-up were categorized as not having any PSA-related follow-up.

Statistical Analysis

Unadjusted temporal trends for each of the follow-up outcomes were assessed using descriptive statistics. A log-binomial model was used for multivariate analysis. This model, rather than logistic regression, was used to facilitate inference about relative risk ratios rather than ORs, as the primary outcome – biopsy – was common.[23,24] Tests were clustered on patient to account for men who had multiple tests during the study period. An interaction between calendar year group and PSA level was explored to determine whether the threshold for biopsy changed over time.

To capture the absolute effect of each covariate on biopsy frequency given a positive PSA test, the predicted probability of biopsy was calculated setting PSA to be above 4.0 ng/mL for all subjects and setting all other covariates equal to the overall population mean. CIs for the predicted biopsy probabilities were obtained through bootstrap methods of 1,000 replications.

A second log-binomial model was fit to the subset of men in which PSA velocity could be calculated, using the same covariates and clustering structure as described above. Absolute PSA and PSA velocity were categorized into four groups (Table 4). Again, changes over time were explored by fitting an interaction between calendar year and PSA velocity category. The expected probability of biopsy for each of the four PSA and velocity categories was estimated setting all covariates to their overall population mean values.

Results

A total of 189,823 PSA tests were performed at Group Health between 1997 and 2008. The analysis cohort, which excluded short-term repeat tests within 11 months of a prior test, included 59,738 subjects and 121,591 index tests. Tests for patients aged >85 years or <35 years (n=2338) and tests for subjects who did not have 12 months of follow-up (n=900) were excluded. Tests with missing or indeterminate PSA levels (n=803), missing comorbidity data (n=554) and missing census tract family income information (n=312) were also excluded. The final sample included 111,369 index tests among 54,831 subjects. The tests were ordered by 1089 unique providers (18 urologists), with 208 providers ordering at least 100 tests. The mean number of index tests per subject was 2.03 (median = 2.0) with 27,329 men (49.8%) having a single test in the current sample, 12,681 having two index tests (23.1%), and 14,821 having three or more tests (27.0%).

The characteristics of the analysis cohort are described in Table 1. The majority of PSA tests were ordered by primary care providers (85.2%) and were <2.5 ng/mL (78.3%). While 11.7% of tests were suspicious, most (7.0%) were between 4.0 and 6.9 ng/mL, with 2.2% between 7 and 9.9 ng/mL, and 2.5% at 10 ng/mL or above. Unadjusted trends in receipt of biopsy, frequency of urology visit and additional PSA testing within 12 months are shown in Table 2. Overall, 28.0% of tests with a PSA value ≥4.0 ng/mL led to a biopsy within 12 months, and 38.6% of tests ≥4.0 ng/mL were followed-up by a urologist within 12 months but did not result in a biopsy. The frequency of biopsy among men with tests with mild to moderately elevated PSA levels (2.5–3.9 ng/mL) was 2.9% across years, and fewer than 0.4% of tests with a PSA level <2.5 ng/mL led to a biopsy within 12 months.

In unadjusted analyses, biopsies were slightly more common in the earliest years of the study compared to later years among tests ≥4.0 ng/mL (29.7%) and <2.5 ng/mL (0.9%) but there was no difference in biopsy rates over time for men with mild to moderate PSA levels (2.5–3.9 ng/mL) (data not shown). In adjusted analysis, the relative risk of biopsy was 13% higher for the early period 1998–2001 (RR 1.13, 95% CI=1.06, 1.20) compared to 2002–2004 (Table 3). The interaction with PSA category and calendar year was not significant

(Wald p=0.206), indicating that there did not appear to be a change over time in the threshold used for biopsy referral.

Older age was associated with a lower biopsy rate. Approximately 11% of the PSA tests were conducted among men aged ≥75 years; however, these men were less likely to undergo biopsy if the test was elevated (RR 0.42, 95% CI=0.38, 0.46) compared to men aged 55–64 years. Tests ordered by urologists (13%) more likely to result in biopsy compared to those ordered in primary care (RR 1.13, 95% CI=1.05, 1.21). Men living in neighborhoods with higher income levels were more likely to undergo biopsy compared to those living in lower-income areas.

Comorbidity score was not associated with biopsy frequency. Results were similar in sensitivity analyses which excluded tests ordered by urologists. For example, 28.2% of tests ≥4.0 ng/mL ordered by primary care providers led to a biopsy within 12 months. In analyses excluding second or later PSA tests focusing only on the 54,831 initial tests, slightly more men (34.9%) with a value ≥4.0 ng/mL received a biopsy in 12 months. All trends in adjusted analyses were similar compared to the primary analyses.

The PSA velocity was strongly associated with biopsy among the subset of tests where prior test information allowed for the calculation of PSA velocity (Table 4). PSA velocity was available for 65,372 index tests (58.7%). Among men with PSA tests ≥4.0 ng/mL, those with a rapidly rising velocity were more likely to undergo biopsy, compared to slow-growing velocity, 36.9% vs 21.7% respectively (p<0.001). There was no interaction between calendar year and PSA velocity (Wald test p=0.099), suggesting that the association between velocity and biopsy frequency has been consistent across calendar years in this sample. The associations of the covariates with biopsy frequencies by PSA velocity were consistent with the main analysis and are not presented. The Wald test for the model including interaction terms between ordering provider and PSA velocity leading to biopsy was not significant (p<0.275), suggesting that there was not a distinct pattern in how urologists used velocity compared to other providers in referring tests for a biopsy.

Discussion

While there has been considerable debate[8,25] about lowering the threshold for referring men to biopsy in recent years, within this integrated delivery system, no change was detected toward more-aggressive biopsy referral practices over time within the current study cohort. In fact, an opposite pattern was observed with biopsy practices becoming more conservative over the study period, possibly reflecting growing awareness of the problems of overdiagnosis and overtreatment.[11,26] PSA velocity was strongly associated with receipt of biopsy.

PSA velocity has been promoted for many years as having predictive value,[6] although several recent large studies and evidence from screening trials have demonstrated that in practice, velocity adds little value.[27,28,29] This is not surprising given that PSA is a continuous marker and whether providers formally calculate velocity or not, a rapid rise may be likely to trigger action. It is notable that velocity had a similar effect on biopsy patterns across all ordering providers.

This study highlights a generally low biopsy rate for suspicious PSA values, which has been observed in other population-based studies. In an early study from 1993, 46% of men with PSA levels over 4.0 ng/mL went on to receive a biopsy within 1 year.[30] The PLCO screening trial observed that biopsy rates declined over time,[31] although it is unclear whether this was a true trend or whether patients were less inclined to receive a biopsy for a later elevated test after having several prior normal tests. At the initial screening test in

PLCO, 2718 men (7.1%) were identified with a PSA value ≥4 ng/mL with 40.2% undergoing biopsy within 12 months. At the final screening visit, 2676 men (7.5%) were identified with a PSA value ≥4 ng/mL, with 30.1% receiving a biopsy.[32]

In a recent study of over 13,000 Veterans with PSA ≥ 4.0 ng/mL, 33% went on to receive a biopsy within 2 years, with biopsy rates declining over time.[17] Reasons for these trends are unclear, but they could be related to growing conservatism following increased experience with variable PSA values, awareness of the problems of overdiagnosis and overtreatment, and a difference between the risk profiles of patients who presented earlier versus later for PSA testing.

This study was conducted within an integrated healthcare system and may not be reflective of community patterns nationally. The population of providers does include a broad range of providers including 18 urologists and more than 1000 non-urology providers. Between 1992 and 1999 Group Health did not recommend PSA screening for asymptomatic men of any age, although PSA was a covered benefit.[33–35] In 1999 the guideline was changed to state that “a shared decision making process between provider and patient is recommended in counseling asymptomatic men regarding screening for prostate screening.” Following this change, PSA use in Group Health became similar to national patterns: 40% of men in Group Health in 2004 received a PSA test in the past 2 years;[36] and 2006 Behavioral Risk Factor Survey reported that 42% of men aged 40 years received a PSA test in the past 2 years.[37]

The guidelines have consistently highlighted that values greater than 4.0 should be considered positive with a recommendation for a urology consultation above that level.[5] Throughout the study period, PSA guidelines were provided in print and electronically to all Group Health providers including both urologists and primary care providers. In 2004, the guideline was updated to read: “Some experts have recommended a lower cutoff level because the use of a lower value may result in higher rates of detection; however, the value of increased detection rates and harms of using lower levels are unknown.” The guideline was updated in 2010 to reflect age recommendations of the USPSTF;[11] however, the guideline did not encourage a lower PSA threshold.

An additional limitation of this study is that other reasons for referral to urology are not easily accessed through administrative data such as suspicious digital rectal exam results, nor can screening tests be distinguished from diagnostic or symptomatic tests. Thus although there is no recommendation to use a more aggressive PSA threshold for diagnostic tests, this study cannot directly examine the influence of other symptoms on biopsy patterns. In Group Health it is likely that the majority of tests performed by urologists were diagnostic or related to other genitourinary conditions as men do not see urologists for routine primary care services. Thus the 13% increased biopsy rate for tests ordered by urologists may be due to presence of other symptoms.

This study highlights the importance of acknowledging that aggressiveness of biopsy is an important component of the PSA screening discussion, as even small changes in the PSA threshold can substantially alter the potential harms and benefits of screening.[38] However, there is limited evidence to aid providers in having this discussion with patients. This database reflects one of the largest existing repositories of population-based PSA lab values, as well as outcomes, and provides valuable insight into trends in biopsy practices given specific PSA test results over the past decade.

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Table 1

Characteristics of 111,369 PSA tests among 54,831 enrollees

	Count	%
PSA value, ng/mL		
0–2.4	87,185	78.3
2.5–3.9	11,249	10.1
≥4.0	12,935	11.6
Enrollee age at test (years)		
35 – 44	3,235	2.9
45 – 54	26,844	24.1
55 – 64	40,042	36.0
65 – 74	29,137	26.2
75 – 84	12,111	10.9
Ordering provider		
Primary care	94,828	85.2
Urologist	7,809	7.0
Other	8,732	7.8
Year of test		
1998 – 2001	37,615	33.8
2002 – 2004	35,096	31.5
2005 – 2007	38,658	34.7
RxRisk comorbidity score		
0–1000 (low comorbidity)	15,939	14.3
1001–2000	31,828	28.6
2001–3000	22,844	20.5
3001–4000	15,670	14.1
4001–5000	8,037	7.2
≥5001 (high comorbidity)	17,051	15.3
Family income (based on enrollee's census tract in year test was ordered), $		
<50,000	23,370	21.0
50,000–99,000	59,509	53.4
100,000–149,000	22,182	19.9
≥150,000	6,308	5.7

PSA, prostate-specific antigen

Table 2

Type of follow-up received within 12 months of an index PSA test (unadjusted), %

PSA value, ng/mL	All years	1998–2001	2002–2004	2005–2007
Biopsy				
0–2.4	0.4	0.9	0.4	0.4
2.5–3.9	2.9	3.0	3.1	2.6
≥4.0	28.0	29.7	26.4	27.1
Urology visit without biopsy				
0–2.4	12.5	13.7	11.9	11.9
2.5–3.9	21.2	22.6	19.9	20.8
≥4.0	38.6	37.0	39.3	40.2
Follow-up PSA without biopsy or urology visit				
0–2.4	3.8	3.4	3.9	4.1
2.5–3.9	5.1	4.6	5.0	5.8
≥4.0	3.0	2.6	3.8	2.7
No observed PSA-related follow-up				
0–2.4	83.2	82.3	83.8	83.6
2.5–3.9	70.8	69.8	71.9	70.9
≥4.0	30.5	30.8	30.6	30.0

PSA, prostate-specific antigen

Table 3

Multivariable model: Factors associated with biopsy within 12 months of index PSA test

	Relative risk ratio	*p*-value	Predicted probability of biopsy (PSA ≥4 ng/mL), % (95% CI)	
Age at test (years)				
35–44	0.67	0.096	24.6	(12.8, 36.6)
45–54	1.02	0.531	36.6	32.8, 40.0
55 – 64	ref	—	36.1	34.2 38.0
65 – 74	0.73	<0.001	26.5	25.0 28.0
75 – 84	0.42	<0.001	15.1	13.8 16.5
Ordering provider				
Primary care	ref	—	29.8	28.6 31.0
Urologist	1.13	0.001	35.5	33.1 37.9
Other	0.93	0.170	28.3	25.5 31.0
Year of test				
1998 – 2001	1.13	<0.001	33.0	31.5 34.5
2002 – 2004	ref	—	29.0	27.4 30.6
2005 – 2007	0.98	0.572	28.3	26.7 29.9
RxRisk comorbidity score				
0 – 1000	ref	—	25.6	21.7 29.6
1001 – 2000	1.18	0.054	30.3	28.4 32.3
2001 – 3000	1.24	0.017	32.2	30.1 34.3
3001 – 4000	1.21	0.039	31.0	28.8 33.3
4001 – 5000	1.21	0.052	31.1	28.1 34.2
≥ 5001	1.16	0.110	29.8	27.6 32.0
Family income (based on enrollee's census tract in year test was ordered), $				
<50,000	0.91	0.012	27.1	25.3 28.9
50,000–99,000	ref	—	30.0	28.7 31.4
100,000–149,000	1.07	0.048	32.2	30.2 34.1
≥150,000	1.14	0.012	34.6	31.1 38.1

PSA, prostate-specific antigen

Table 4

Frequency of biopsy within 12 months of index PSA test by PSA level and velocity

PSA/Velocity Threshold	Predicted Probability of Biopsy, % (95% CI)			
	All Years	1998–2001	2002–2004	2005–2007
PSA <4 and velocity <0.75	0.67 (0.60, 0.74)	0.72 (0.62, 0.82)	0.68 (0.58, 0.75)	0.68 (0.60, 0.75)
PSA <4 and velocity ≥0.75	5.6 (3.9, 7.3)	6.0 (3.9, 8.2)	5.6 (3.8, 7.6)	5.7 (3.8, 7.6)
PSA ≥4 and velocity <0.75	21.7 (19.9, 23.5)	23.2 (22.5, 24.0)	21.6 (19.0, 24.2)	21.9 (20.9, 22.9)
PSA ≥4 and velocity ≥0.75	36.9 (35.2, 38.6)	39.5 (36.2, 42.9)	36.7 (33.6, 39.7)	37.2 (35.3, 39.1)

Note: Velocity given in ng/mL/year

PSA, prostate-specific antigen