Reducing the Harm of Prostate Cancer Screening: Repeated Prostate-Specific Antigen Testing

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Abstract

**Objective:** To determine if repeating a prostate-specific antigen (PSA) test in men with an elevated PSA level is associated with a decreased risk of prostate biopsy and cancer diagnosis.

**Patients and Methods:** A cohort of patients referred to the Ottawa Regional Prostate Cancer Assessment Clinic from April 1, 2008, through May 31, 2013, who had referral PSA levels between 4 and 10 ng/mL were included in the study. Univariate and multivariate associations between a normal result on repeated PSA testing and the risk of prostate biopsy, cancer diagnosis, and Gleason score of 7 or higher were examined.

**Results:** The study cohort included 1268 patients. Repeated PSA test results were normal in 315 patients (24.8%). Men with normal results on repeated PSA testing were younger (mean SD age, 61.5±8.2 years vs 65.2±8.2 years; P<.001) and had lower referral PSA levels (mean SD, 5.5±1.4 ng/mL vs 6.6±1.5 ng/mL; P<.001) than men with an abnormal repeated PSA result. In multivariate analysis, men with normal results on repeated PSA testing were less likely to undergo prostate biopsy (relative risk [RR], 0.42; 95% CI, 0.34-0.50) and were at lower risk for cancer diagnosis (RR, 0.22; 95% CI, 0.14-0.34) and Gleason score of 7 or higher (RR, 0.16; 95% CI, 0.08-0.34) compared with men who had an abnormal repeated PSA test result.

**Conclusion:** Routinely repeating a PSA test in patients with an elevated PSA level is independently associated with decreased risk of prostate biopsy and prostate cancer diagnosis. Men with an elevated PSA level should be given a repeated PSA test before proceeding to biopsy.
PSA is sensitive but not specific for detecting prostate cancer, especially when levels are moderately elevated between 4 and 10 ng/mL (to convert to μg/L, multiply by 1.0). Measures that render PSA testing more specific for prostate cancer and reduce overdiagnosis are needed. Several methods have been suggested to improve the discriminative performance of PSA testing including PSA velocity, free to total PSA ratio, age-specific PSA thresholds, and race-specific thresholds.

In 2008, a prostate cancer diagnostic center was established as a referral site to serve a region of over 1 million people in Canada. One of the purposes of this center was to centralize the diagnosis and evaluation of patients at risk for prostate cancer based on elevated PSA levels or abnormal prostate examination results. Since inception, all patients referred to the center were asked to undergo a repeated PSA test before assessment. The purpose of this study was to determine if routinely obtaining a repeated PSA test in men with an elevated screening PSA level is associated with a decreased risk of prostate biopsy and cancer diagnosis.

PATIENTS AND METHODS

Study Setting and Population
A historical cohort of men with an elevated PSA level (>4 ng/mL) referred to the Ottawa Regional Prostate Cancer Assessment Center (CAC) in Ottawa, Ontario, Canada, was reviewed. All patients seen at this clinic from April 1, 2008, through May 31, 2013, were eligible for inclusion. Clinicians in the region refer patients to the CAC for counseling and testing. Per protocol, all patients referred to the CAC are asked to undergo a repeated PSA test at the same laboratory where the referral PSA test was performed before consultation. The repeated PSA test result does not influence if or when the patient is evaluated in the CAC. Within the region, most prostate cancer screening is performed by primary care physicians, but these physicians rarely request a prostate biopsy without a urologist consultation. There is no protocol to select patients for prostate biopsy, and this decision is at the discretion of the patient and CAC physician.

Study Protocol
Patients were excluded from the study if the repeated PSA test was missing or performed more than 3 months after the referral PSA test, if they had a previous prostate biopsy or prostate cancer diagnosis, or if their consultation was more than 3 months after repeated PSA testing. Patients were also excluded if their referral PSA level was not between the predefined study PSA range of 4 to 10 ng/mL. Patient characteristics and outcomes were prospectively recorded. Patient age, DRE findings, and PSA values were documented. Results of DRE were classified as normal or abnormal; however, abnormal DRE results did not necessarily indicate a suspicion of malignant disease. Clinical stage information was not recorded. Transrectal ultrasound-guided prostate biopsies were performed in the CAC by highly experienced radiologists. Prostate biopsy pathologic results were transcribed from original pathology reports into the CAC database by trained data abstractors. All prostate biopsies for a given patient within 1 year of the initial consultation were included in analyses. Biopsies obtained more than 1 year after the initial consultation were excluded because they were deemed unlikely to be related to the repeated PSA result.

Repeated PSA values were classified as normal (<4 ng/mL) or abnormal (≥4 ng/mL).
The unadjusted and adjusted risk of undergoing a prostate biopsy (primary outcome) was determined in patients with a normal result on repeated PSA testing compared with patients with an abnormal repeated PSA result and expressed as relative risk (RR) with 95% CI. Adjusted associations controlled for patient age and DRE status because these factors were associated with risk of prostate biopsy in unadjusted analyses. In addition, unadjusted and adjusted associations between a normal repeated PSA test result and incidence of prostate cancer and Gleason score of 7 or higher were determined.

Sensitivity Analyses
Different PSA thresholds may be used by clinicians for determining normal and abnormal PSA status. To account for this variability, we performed preplanned sensitivity analyses using 2 additional PSA thresholds. First, we used a lower threshold of 2.5 ng/mL or higher as abnormal. Second, we used age-specific PSA thresholds (age 50-59 years, ≥3.5 ng/mL; age 60-69 years, ≥4.5 ng/mL; and age ≥70 years, ≥6.5 ng/mL).19 Also, because biopsy is the most common method of cancer diagnosis, we performed an additional sensitivity analysis by determining the association between repeated PSA test results and cancer diagnosis including only men who underwent biopsy. Statistical analyses were performed using SAS software (SAS Institute Inc). All tests were 2-sided. P<.05 was considered statistically significant.

RESULTS
Eleven attending physicians (9 urologists and 2 family physicians experienced in prostate cancer assessment) evaluated 2834 patients at the CAC from April 1, 2008, through May 31, 2013. Of these patients, 1268 met inclusion criteria (Figure).

Incidence of Normal Repeated PSA Results
Of the 1268 study patients, 315 (24.8%) had a normal result on repeated PSA testing (<4 ng/mL) (Table 1). Men with a normal repeated PSA level had a lower mean age (61.5±8.2 vs 65.2±8.2; P<.001) and a lower mean referral PSA level (5.5±1.4 vs 6.6±1.5; P<.001) than men with an abnormal repeated PSA result (≥4 ng/mL).

Association Between Repeated PSA Test Result and Use of Prostate Biopsy
Patients with a normal result on repeated PSA testing were less likely to undergo a prostate biopsy within 1 year of referral. Of the 315 patients who had normal repeated PSA test results, 89 (28.3%) underwent biopsy compared with 594 of the 953 patients (62.3%) who had abnormal repeated PSA levels (RR, 0.45; 95% CI, 0.38-0.54) (Table 2). Patient age and DRE result were also associated with use of biopsy (Table 2). The association between repeated PSA test result and biopsy use was adjusted for patient age and DRE result in multivariate analysis, and the association was maintained (RR, 0.42; 95% CI, 0.34-0.50).

Association Between Repeated PSA Test Result and Cancer Diagnosis
Patients with a normal result on repeated PSA testing were less likely to have a diagnosis of cancer compared with patients who had an abnormal repeated PSA result (26 of 315 [8.3%] vs 336 of 953 [35.3%]; RR, 0.23; 95% CI, 0.16-0.34). The association between a normal repeated PSA test result and Gleason score of 7 or higher at biopsy was similar (10 of 315 [3.2%] vs 185 of 953 [19.4%]; RR, 0.16; 95% CI, 0.09-0.30) (Table 2). These results were maintained when adjusting for patient age and DRE result in multivariate models.

Sensitivity Analyses
We analyzed these data using 2 additional preplanned PSA thresholds. Using a 2.5-ng/mL

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TABLE 1. Demographic Characteristics and Outcome in 1268 Study Patients, Stratified by Normal vs Abnormal Repeated PSA Test Resultsa,b,c

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (&lt;4 ng/mL)</th>
<th>Abnormal (≥4 ng/mL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>315 (24.8)</td>
<td>953 (75.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.5±8.2</td>
<td>65.2±8.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First PSA result (ng/mL)</td>
<td>5.5±1.4</td>
<td>6.6±1.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Repeated PSA result (ng/mL)</td>
<td>2.9±0.9</td>
<td>6.4±2.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abnormal DRE result</td>
<td>22/235 (9.4)</td>
<td>136/810 (16.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Biopsy</td>
<td>89 (28.3)</td>
<td>594 (62.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>26 (8.3)</td>
<td>336 (35.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gleason grade ≥7</td>
<td>10 (3.2)</td>
<td>185 (19.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

aDRE = digital rectal exam; NA = not applicable; PSA = prostate-specific antigen.
bData are presented as No. (percentage) or mean ± SD.
cSI conversion factor: To convert PSA values to μg/L, multiply by 1.0.

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TABLE 2. Univariate and Multivariate Associations Between Patient Age, Repeated PSA Result, and DRE Findings and Undergoing Prostate Biopsy, Cancer Diagnosis on Biopsy, and Gleason Score ≥7

<table>
<thead>
<tr>
<th>Variable</th>
<th>Biopsy, RR (95% CI)</th>
<th>Cancer diagnosis, RR (95% CI)</th>
<th>Gleason score ≥7, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate associations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (1-y increase)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.99 (0.98-1.00)</td>
<td>1.01 (0.99-1.02)</td>
</tr>
<tr>
<td>Repeated PSA result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.45 (0.38-0.54)</td>
<td>0.23 (0.16-0.34)</td>
<td>0.16 (0.09-0.30)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>DRE result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.51 (1.37-1.66)</td>
<td>2.04 (1.70-2.44)</td>
<td>3.44 (2.68-4.41)</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td><strong>Multivariate associations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (1-y increase)</td>
<td>0.97 (0.96-0.97)</td>
<td>0.99 (0.98-1.00)</td>
<td>1.00 (0.99-1.02)</td>
</tr>
<tr>
<td>Repeated PSA result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.42 (0.34-0.50)</td>
<td>0.22 (0.14-0.34)</td>
<td>0.16 (0.08-0.34)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>DRE result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.48 (1.34-1.63)</td>
<td>1.81 (1.52-2.14)</td>
<td>3.07 (2.41-3.92)</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

DRE = digital rectal examination; PSA = prostate-specific antigen; RR = relative risk.

PSA threshold (n=1516), 160 patients (11.0%) had normal results on repeated PSA testing, and a normal repeated PSA level was associated with a decreased risk of prostate biopsy (RR, 0.32; 95% CI, 0.23-0.45) and cancer diagnosis (RR, 0.19; 95% CI, 0.10-0.37) compared with an abnormal repeated PSA result. Using age-specific thresholds (n=1116), 333 patients (30.0%) had a normal repeated PSA test result, and a normal repeated PSA level was associated with a decreased risk of prostate biopsy (RR, 0.34; 95% CI, 0.25-0.46), cancer diagnosis (RR, 0.34; 95% CI, 0.25-0.45), and Gleason score of 7 or higher (RR, 0.28; 95% CI, 0.18-0.44) compared with an abnormal repeated PSA level. These results were maintained when adjusting for patient age and DRE result in multivariate models.

Associations between repeated PSA test results and cancer diagnosis were also determined among only men who underwent a prostate biopsy. In this subgroup analysis, patients with a normal repeated PSA level (26 of 89 [29.2%]) were less likely to have a diagnosis of cancer compared with patients who had an abnormal repeated PSA result (336 of 594 [56.6%]) (RR, 0.52; 95% CI, 0.37-0.72). The association between a normal repeated PSA test result and Gleason grade 7 or higher at biopsy was similar (RR, 0.70; 95% CI, 0.41-1.14). These results were maintained when adjusting for patient age and DRE result in multivariate models.

**DISCUSSION**

The US Preventive Services Task Force,6 the Canadian Task Force on Preventive Health Care,9 and other guidelines have recommended against routine PSA testing. One of the major reasons for this recommendation was the harm associated with unnecessary prostate biopsies initiated by false-positive PSA test results. Our data indicate that routinely repeating a PSA test in patients referred with a moderately elevated PSA concentration (<10 ng/mL) prevents many prostate biopsies and is associated with lower risk of prostate cancer diagnosis. In our study, 315 of the 1268 patients (24.8%) had a normal PSA level on repeated testing, and this result lowered their risk of undergoing prostate biopsy by 60%. In addition, men who had a normal result on repeated PSA testing were approximately 80% less likely to have a diagnosis of prostate cancer and Gleason score of 7 or higher.

To our knowledge, this is the first study to examine the impact of prompt repeated PSA testing in an unselected cohort of patients being screened for prostate cancer. It is also the first to report patient outcomes such as prostate biopsy and prostate cancer diagnosis. The substantial proportion of our patients with a normal repeated PSA test result is consistent with findings in other studies. One study examined blood samples from 972 men in a colon cancer randomized trial and found that approximately 50% of patients with moderately elevated PSA levels had a normal subsequent PSA test result.20 Furthermore, in 65% of those patients, the PSA levels remained normal 1 year later. In a cohort study of 101 patients with lower urinary tract symptoms and an elevated PSA level, 35% had a normal level on repeated PSA testing, and of those, the PSA level remained normal in 82% at 2 years of follow-up.21

In a related study, the usefulness of repeating a PSA test that yielded an abnormal result was questioned.22 The authors reviewed the Northern Ireland Cancer Registry (n=7052; mean age, approximately 70 years) between 1994 and 2003. They found that 38% of patients with a PSA level between 4 and 10 ng/mL had another PSA test result that was less than 4 ng/mL during...
the 10-year study period. Among this subset of 2664 men, 321 (12%) had a prostate biopsy, 74 (3%) had a diagnosis of cancer, and only 21 (<1%) had a Gleason score of 7 or higher. The authors concluded that a normalized PSA level did not rule out prostate cancer and therefore may falsely reassure patients and physicians. Although the Ireland study did not specifically address the impact of an immediate repeated PSA test, our interpretation of the data differs from theirs. We believe that their study actually supports the prognostic value of a normal result on repeated PSA testing, given the relatively low number of high-grade cancers observed in their cohort with a median follow-up of almost 6 years. In the placebo arm of a prostate cancer prevention trial, 27% of men with a PSA level between 3.3 and 4.0 ng/mL had cancer diagnosed on per-protocol end of study biopsy. Given this information, it is expected that a normal repeated PSA result does not rule out the presence of prostate cancer or the subsequent development of prostate cancer. However, it seems that repeating a PSA test will avoid or delay many prostate biopsies in patients whose PSA level may have been transiently elevated.

A large proportion of men in North America report having a PSA test performed. The American Urological Association PSA best practice statement (2009 update) and the European Association of Urology guidelines on prostate cancer (2013 update) recommend that management decisions, such as proceeding to prostate biopsy, should not be made on the basis of a single elevated PSA level. However, studies of primary care physicians revealed that only 16% to 56% of patients underwent a repeated PSA test after an abnormal result. These findings indicate that if repeating a PSA test when initial results are abnormal becomes standard practice, a substantial proportion of the population may benefit.

Our study has several potential limitations. First, our study primarily examined patients whose referral PSA level was between 4 and 10 ng/mL. Sensitivity analyses using a PSA threshold of 2.5 ng/mL and age-specific thresholds yielded consistent results, but we cannot comment on patients whose referral PSA level is below these thresholds or above 10 ng/mL. Also, the classification of an abnormal DRE result in our study did not necessarily imply that the physician was concerned that the patient had a prostate tumor, so the influence of a concerning DRE result remains inadequately characterized. Furthermore, race and family history of prostate cancer were not consistently documented; therefore, we were unable to adequately assess the impact of repeated PSA testing on high-risk subgroups. We also do not know the prevalence of prostate cancer in patients who did not undergo biopsy. Finally, follow-up of patients beyond 1 year would be helpful to determine the proportion of patients who avoid prostate biopsy in their lifetime.

CONCLUSION
A significant proportion of patients with an elevated serum PSA concentration will have a normal PSA concentration when retested. We observed that a normal result on repeated PSA testing was associated with a lower risk of undergoing biopsy, cancer diagnosis, and Gleason score of 7 or higher within 1 year of referral. These findings indicate that routine repeated PSA testing influences patient management and should be adopted by physicians who make decisions regarding prostate biopsy.

Abbreviations and Acronyms: CAC = Ottawa Regional Prostate Cancer Assessment Center; DRE = digital rectal examination; PSA = prostate-specific antigen; RR = relative risk

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REFERENCES