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ORIGINAL ARTICLE

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.

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Serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE) have been used to screen men for prostate cancer for more than 20 years.[1] Prostate-specific antigen screening allows earlier detection of prostate cancer, and since PSA screening has been widely used in North America, there has been a dramatic decrease in the incidence of locally advanced prostate cancer, metastatic prostate cancer, and prostate cancer death.[2,3] However, PSA screening has also increased the detection of low-risk cancers that are unlikely to cause a patient harm.[4,5] Indeed, despite the benefits of PSA screening, the US Preventive Services Task Force, the Canadian Task Force on Preventive Health Care, and other guidelines have recommended against routine PSA testing.[6-9] This recommendation was primarily based on the observation that to prevent one prostate cancer death, many men would be exposed to unnecessary prostate biopsy and unnecessary treatment of clinically indolent disease.[10,11] Based on the European Randomised Study of Screening for Prostate Cancer, at 13 years of follow-up, 781 men need to undergo PSA screening and 27 cancers need to be detected to prevent 1 prostate cancer death.[7]

Prostate-specific antigen may be elevated because of prostate cancer or as a result of infection, physical activity, or sexual activity.[12] Variation in PSA concentrations can also be due to normal biological fluctuation or analytic (laboratory assay) differences.[13] As a result,

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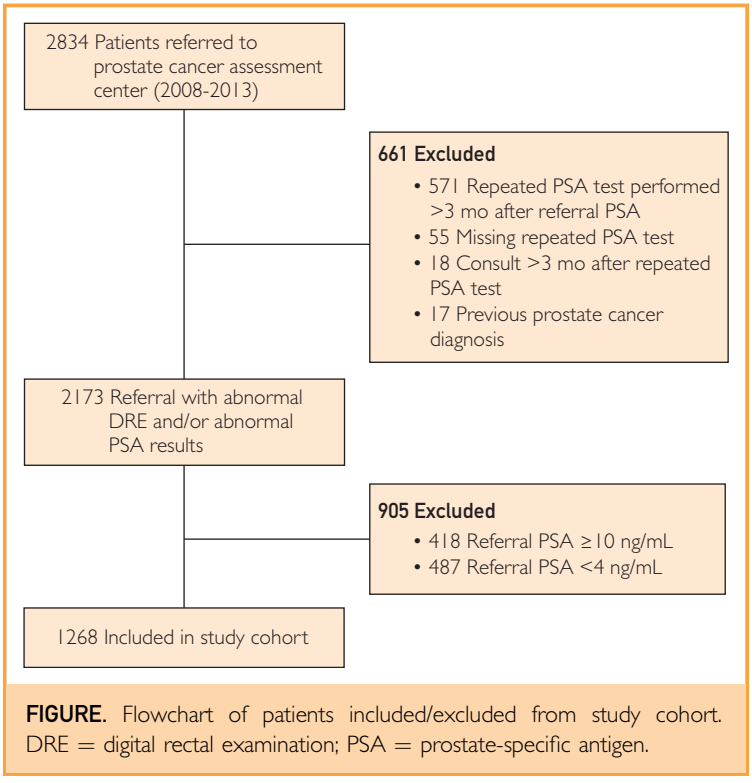

FIGURE. Flowchart of patients included/excluded from study cohort. DRE = digital rectal examination; PSA = prostate-specific antigen.

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).[14] 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.[15-18]

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).