ORIGINAL ARTICLE

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Can Percent Free Prostate-Specific Antigen Reduce the Need for Prostate Biopsy?

BACKGROUND. In a recent multicenter study, percent free prostate-specific antigen (PSA) enhanced the specificity of PSA testing in prostate cancer screening.

OBJECTIVE. To determine whether the percent free PSA could be as effective in reducing the need for biopsy in a managed care setting as in an academic setting.

SETTING. Kaiser Permanente Northwest Region (Portland, Oregon) and Kaiser Permanente Oakland/Berkeley (California).

DESIGN. Prospective blinded study conducted by using Hybritech Tandem PSA and Hybritech Tandem free PSA assays (Beckman Coulter, Inc., Fullerton, California).

PARTICIPANTS. 250 men (63 with prostate cancer and 187 with benign prostate conditions) who were older than 40 years of age, had a PSA level of 4.0 to 10.0 ng/mL, and had a histologically confirmed diagnosis.

MAIN OUTCOME MEASURES. Sensitivity and specificity of percent free PSA.

RESULTS. The median percent free PSA values for patients with cancer (free PSA, 13%) significantly differed from that for patients without cancer (free PSA, 17%) (P = 0.001). When a free PSA cutoff of 25% was used, the sensitivity was 97% (95% CI, 92% to 100%) and the specificity was 13% (CI, 8% to 18%). These results were not significantly different from those obtained in the multicenter study (95% sensitivity, 20% specificity for a free PSA cutoff of 25%).

CONCLUSION. The results obtained in a managed care organization were similar to those obtained at large university medical centers and show that the percent free PSA can be used to enhance the specificity of PSA testing for prostate cancer.

Although the test that measures total prostate-specific antigen (PSA) has been valuable for early detection of prostate cancer, it is limited by a lack of specificity when the total PSA level is in the so-called diagnostic gray zone of 4 to 10 ng/mL. In this range, 75% of men who undergo biopsy are reported not to have cancer but rather a benign prostate condition that has caused an elevated PSA level.[1] This situation has resulted in many unnecessary biopsies being done in men who did not have prostate cancer. In a recent study conducted at seven university medical centers, men with total PSA levels of 4 to 10 ng/mL were tested for free PSA, and free-to-total PSA ratio was calculated.[2] This study showed that if the total PSA level is in the diagnostic gray zone, a test measuring the percent free PSA could eliminate 20% of unnecessary biopsies and still detect 95% of the men with cancer by using a free PSA cutoff of 25%.[2]

We conducted a study at two Kaiser Permanente hospitals to determine whether the percent free PSA could be as effective in reducing the need for biopsy in a managed care setting as in an academic setting.

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The abstract of this paper is available at ecp.acponline.org.

Methods

This prospective blinded study was performed at two clinical sites: Kaiser Permanente Northwest Region (Portland, Oregon) and Kaiser Permanente Oakland/Berkeley (California). Hybritech Tandem PSA and Hybritech Tandem free PSA assays (Beckman Coulter, Inc., Fullerton, California) were used.

Eligibility

Figure 1 shows how patients were chosen for the study. The inclusion criteria were age older than 40 years, total PSA levels between 4 and 10 ng/mL, and a definitive diagnosis of cancer or no cancer established by transrectal ultrasonography–guided sextant biopsies. Some patients were excluded because of urologic instrumentation before blood draw, acute prostatitis, or use of PSA-altering drugs (such as finasteride or saw palmetto, an herb). All men meeting the inclusion criteria were consecutively enrolled in the study and underwent a test measuring the percent free PSA. Neither urologists nor pathologists had access to the results, and laboratory scientists did not have access to the diagnosis. The study was performed in compliance with the guidelines of Kaiser Permanente's institutional review board.

Total PSA testing was performed, and all samples were frozen at –20 °C for less than a month. Freeze and thaw cycles do not affect total and free PSA measurement.[3] If the patient met the eligibility criteria, the sample was sent to the Kaiser Berkeley laboratory, where free PSA assays were performed.

Statistical analysis

Because study results were not normally distributed, nonparametric analysis was used when appropriate. The Wilcoxon test was used for comparison between group medians. The percent free PSA was calculated as the free PSA level divided by the total PSA level and multiplied by 100. A cutoff value was selected so that the test would detect most cases of cancer while avoiding unnecessary biopsies. The probability of cancer was calculated by dividing the number of patients with positive biopsy results by the total number of patients in each of three ranges of percent free PSA (0% to 15%, 15% to 25%, and ≥ 25%).

Results

A total of 250 men (63 with prostate cancer and 187 with benign prostate disease) with PSA levels between 4 and 10 ng/mL were enrolled. No significant difference (Wilcoxon test) in median total PSA levels was found between the patients with cancer (PSA level, 6.6 ng/mL) and those without cancer (PSA level, 6.4 ng/mL) ($P > 0.2$). However, as shown in **Figure 2**, a significant difference was found in the median percent free PSA between the patients with cancer (free PSA, 13%) and those without cancer (free PSA, 17%) ($P = 0.001$).

Figure 3 shows that the probability of cancer in this study was similar to that in the multicenter trial[2] in each of the three ranges of percent free PSA. The lower the percent free PSA, the higher the probability of cancer. In the current study, the probability of prostate cancer was 33% when the percent free PSA was less than 15%, and it was 7% when the percent free PSA was greater than 25%.

Figure 4 shows our calculations of sensitivity and specificity. When a free PSA cutoff of 25% was used, 97% (95% CI, 92% to 100%) of the cases of cancer would have been detected for men with total PSA levels of 4 to 10 ng/mL, and 13% (CI, 8% to 18%) of men with benign disease would have been spared from biopsy. In the mul-

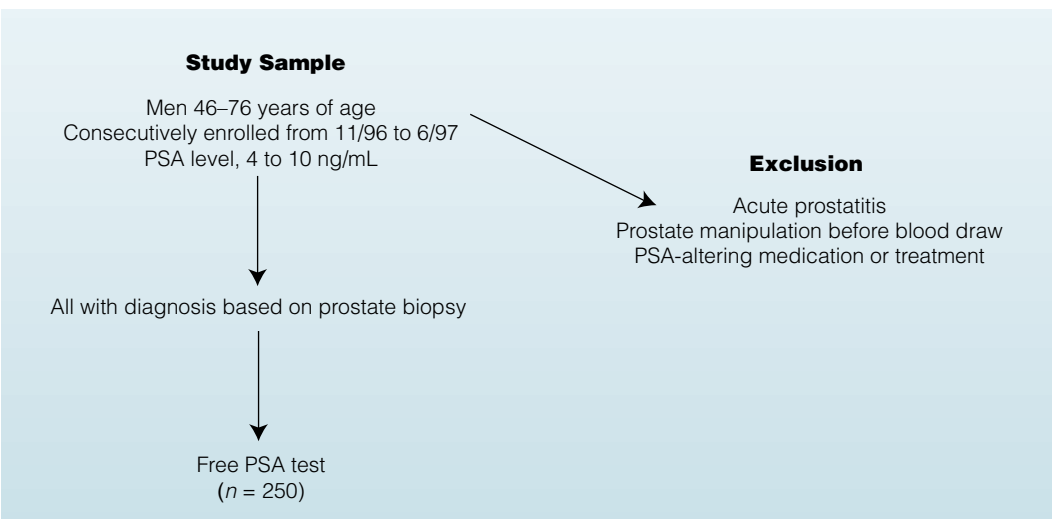
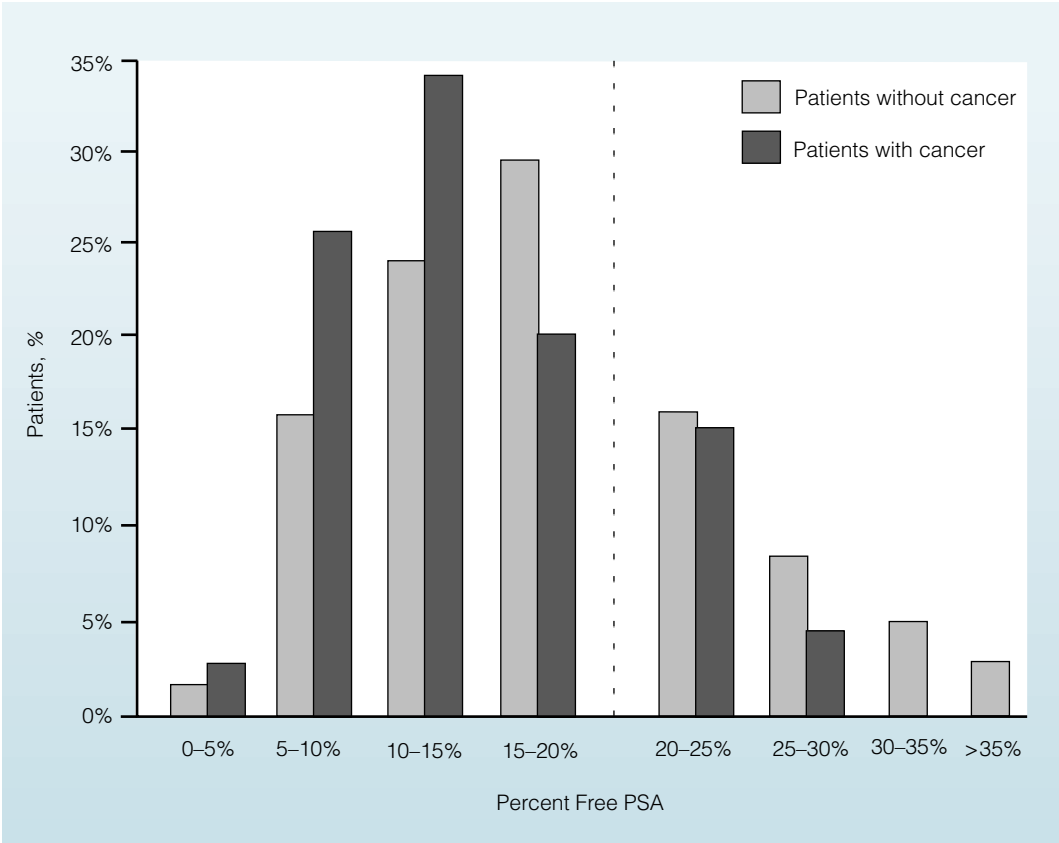


FIGURE 1. The Kaiser Permanente study. Although free PSA was measured after prostate biopsy, the observers were blinded to the biopsy results. In clinical practice, the order of testing would be reversed.

FIGURE 2. Distribution of the percent free PSA by diagnosis.



ticenter study, a free PSA cutoff of 25% was associated with a sensitivity of 95% and a specificity of 20%. The multicenter results and the results from our study did not significantly differ ($P \geq 0.05$). **Figure 5** shows the individual patient data in the current study.

We examined results from patients with more than one biopsy to see whether the percent free PSA could have predicted which patients would be appropriate candidates for repeated biopsy. Of the 85 men with negative results on more than one previous biopsy, a free PSA cutoff of 18% would have detected 17 of 17 (100% [CI, 97% to 100%]) cases of cancer and avoided 30 of 68 (44% [CI, 31% to 57%]) unnecessary biopsies.

For patients with prostate cancer, the probability of favorable pathologic findings (determined from surgical specimen and defined as organ-confined disease, Gleason sum of 6 or less, and negative nodes) correlated with the percent free PSA. The higher the percent free PSA in the presence of cancer, the more favorable the pathologic findings. The lower the percent free PSA, the more unfavorable the pathologic results. Patients with a percent free PSA value greater than 15% had a 57% chance of favorable pathologic results, compared with a 23% chance in patients with a free PSA percentage less than 15%.

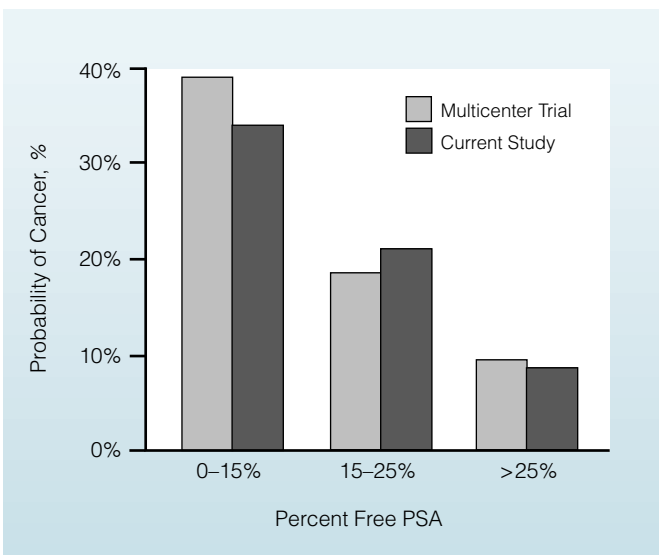


FIGURE 3. Probability of cancer in the multicenter trial[2] and the current study.

Discussion

Our study at two Kaiser Permanente medical centers had results similar to those from a large study conducted at academic medical centers.[2] In both settings, the percent free PSA was found to increase the specificity of PSA testing for prostate cancer detection. A free PSA cutoff of 25% detected 97% of cases of cancer and spared

Test Result	Disease Status: Cancer	Disease Status: No Cancer
Positive Free PSA ≤25%	61	162
Negative Free PSA >25%	2	25
Total	63	187
	Sensitivity = 61/63 = 97% (95% CI, 92% to 100%)	Specificity = 162/187 = 13% (95% CI, 8% to 18%)

FIGURE 4. A 2 × 2 table showing the test performance of measuring percent free PSA in which a 25% cutoff is used.

8% to 18% of men with benign disease in our Kaiser sample from unnecessary biopsies.

The percent free PSA was also shown to be useful as a predictor of the probability of prostate cancer; the higher the percent free PSA, the lower the probability of cancer. Cancer risk ranged from 7% to 33%, depending on each patient's percent free PSA. Patients with free PSA percentages greater than 25% had the lowest risk for cancer (7%). This risk is only slightly higher than the prevalence of detectable cancer found in the general population of U.S. men older than 50 years of age (4%).[1] If biopsies were performed in men with free PSA percentages of 25% or more, 93% of these findings would be negative for cancer. Although some risk for prostate cancer is present in all men older than 50 years of age, the objective of screening tests is to identify high- and low-risk groups of men before biopsy to maximize cancer detection while ensuring wise use of health care dollars.

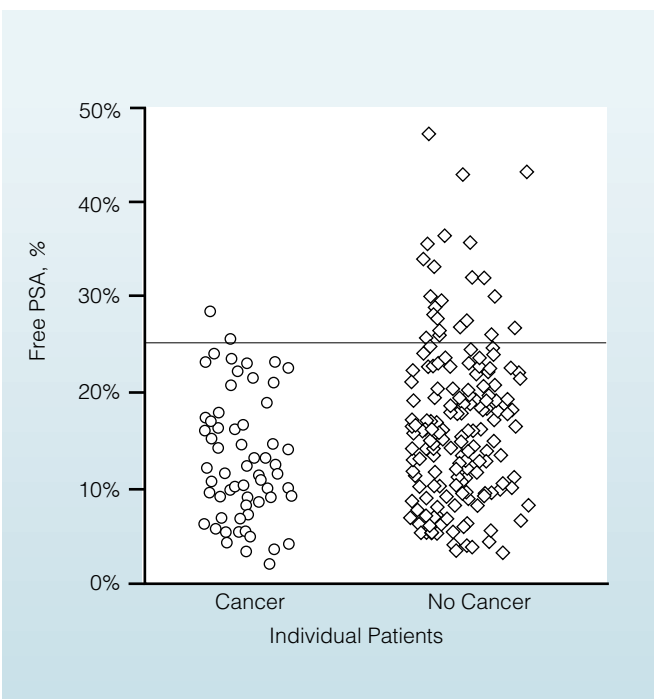


FIGURE 5. With use of a PSA cutoff of 25% (*thin line*), 13% of patients with benign disease would be spared biopsy and 97% of patients with cancer would be identified.

Determination of the percent free PSA may be particularly helpful in men who have previously had negative results on biopsy because a low percent free PSA heightens clinical suspicion in these men, particularly when the percent free PSA is less than 15%. In our study, men with previously negative biopsy results and a lower free PSA percentage had an increased risk for cancer. Published reports have shown that an initial biopsy misses approximately 20% of cases of cancer, which can be detected with repeated biopsy.[4] We examined results from patients with more than one biopsy to see whether the percent free PSA could have predicted which patients would be appropriate candidates for repeated biopsy. Results showed that a free PSA cutoff of 18% would have detected 100% of cases of cancer and avoided 44% of unnecessary repeated biopsies. At Kaiser Permanente Northwest Region, we plan to continue our research on repeated biopsy in patients who previously had negative biopsy findings and to further refine cutoffs for percent free PSA.

In patients with cancer in our study, the percent free PSA was also associated with pathologic stage and grade: The higher the percent free PSA, the more favorable the pathologic findings. These results also agree with those of the multicenter study.[2] Patients with cancer whose free PSA percentage was greater than the 25% cutoff were found to have features of less-aggressive cancer. Because prostate cancer is slow-growing and the stage of the

"missed" cancer is early, these tumors could be detected in the future with annual examinations to determine if the PSA level was increasing or the percent free PSA was decreasing.

A frequent criticism of studies performed in large teaching hospitals and academic institutions is that the results are not always applicable to other settings. An important finding of our study is that the percent free PSA results obtained in a managed care setting were almost identical to those obtained in the academic centers. It is encouraging that a new prostate cancer marker (percent free PSA) that increases the specificity of measurement of PSA for screening can successfully be used in either setting. If used only for patients in the diagnostic gray zone (total PSA level, 4 to 10 ng/mL), free PSA testing would be performed in only 9% of men; however, this group represents 35% of all biopsies.[1, 2] Published reports have shown that the cost-effectiveness of prostate cancer screening programs is highly sensitive to changes in test specificity, such that a small increase in specificity (approximately 5%) produces marked reductions (about 50%) in net cost per person screened.[5]

Before use of PSA assays, more than half of the cases of prostate cancer detected were locally advanced or metastatic at the time of diagnosis. With PSA screenings, more than 70% of the cases of cancer detected by these tests are organ-confined, thus giving men a far better chance of curative resection. Various studies have shown that the use of PSA assays, along with digital rectal examination, promotes earlier diagnosis of potentially curable cancer.[6, 7] It is too early to know whether PSA screening reduces prostate cancer mortality rates because the use of PSA for cancer detection began relatively recently (in the early 1990s). However, it is encouraging that the United States has seen an approximate 12% decline (2% per year) in deaths from prostate cancer since the peak in 1991.[8] Continuing long-term studies will eventually provide the definitive answer on reduction of the mortality rate. In the interim, however, a stage shift to earlier disease at detection and decreasing numbers of men with biochemical failure after therapy suggest that further research in this area is warranted.

Methods other than measurement of percent free PSA have also been proposed to enhance the specificity of PSA screening, such as age-specific PSA reference ranges, PSA density, and PSA velocity. However, all of these methods have limitations. Age-specific PSA reference ranges have been shown to miss the cancer in a substantial percentage of cases.[9] PSA density requires a transrectal ultrasonographic estimate of prostate volume; this is a more costly, inconvenient, and technique-dependent procedure than a blood test. PSA velocity requires at least three blood sample measurements over an 18-month period to determine a clinical pattern. Thus, this approach may be invalidated if laboratories change their PSA methods or if samples are tested by different laboratories using different methods. In contrast, use of the percent free PSA maintains a high cancer detection rate, requires only a single blood sample, and is convenient and relatively inexpensive compared with other methods.

The percent free PSA should be used in prostate cancer detection programs in managed care settings among men with total PSA levels of 4 to 10 ng/mL. Men with PSA levels in this range who have a percent free PSA percentage greater than 25% may reasonably choose to forgo biopsy unless family history or other medical information (such as suspicious results on digital rectal examination or an increasing PSA value) indicate otherwise.

Physicians who refer patients for tests measuring total PSA levels and percent free PSA need to be aware of which manufacturers' assays are being used by their laboratory. To ensure accurate results, the total PSA and free PSA assays should be made by the same manufacturer because different values have been obtained from identical serum samples tested with different manufacturers' assays.[10]

Take-Home Points

- **The probability of prostate cancer in men with a moderately elevated PSA level (4 to 10 ng/mL) at screening is about 25%.**
- **The proportion of PSA that is unbound (free PSA) is inversely related to the probability of prostate cancer: A lower percent free PSA indicates a higher risk for cancer.**
- **With use of a 25% cutoff for free PSA, the sensitivity is about 97% and the specificity is about 13%.**
- **If the free PSA is more than 25%, the probability of prostate cancer is only about 7%.**
- **Men with moderately elevated PSA levels and a free PSA percentage of more than 25% may reasonably choose to forgo a second biopsy.**

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