EDITORIALS

Early Detection and Aggressive Treatment of Prostate Cancer

Groping in the Dark

The diffusion of early detection of prostate cancer with the prostate-specific antigen (PSA) test and subsequent aggressive treatment for the cancers discovered, in the absence of randomized trials documenting such screening efforts do more good than harm, has been nothing short of remarkable in the United States.¹ The decade of the 1990s in this country might appropriately be referred to as the "PSA era." The medical and social reasons for the success of this strategy are complex. They include a captivating pathophysiologic rationale, "proof of concept" that early detection saves lives with screening for breast cancer in women, economic incentives for physicians and industries involved with testing and treatment, medicolegal concerns relating to failure to diagnose prostate cancer, positive feedback from grateful patients who feel reassured based on their test results, and even stronger positive feedback from prostate cancer survivors who are sure they have "beaten cancer" as a result of early detection—many of whom would never have even known they had prostate cancer in the "pre-PSA" era. Even the U.S. Postal Service has gotten into the business of screening recommendations in this area with a 1999 postage stamp urging "Annual Check-Ups and Tests" for prostate cancer.²

Advocates of PSA screening point to recent declines in population-based prostate cancer mortality in the United States³ and the state of Tyrol in Austria⁴ as evidence of the effectiveness of this strategy, and they may be right. However, the time course of the mortality drop and the lack of correlation between regional drops in mortality rates and intensity of local screening and treatment efforts raise concerns about attributing causation in these ecological studies.^{5,6} There is no clear consensus regarding when the strength of evidence from population-based cohort studies and case-control studies makes randomized trials of preventive interventions unnecessary and therefore unethical (as is considered the case with cervical cancer screening, albeit with much more consistent evidence of a larger effect than reported for prostate cancer to date).⁷

One particular disadvantage for clinicians trying to grope their way along in this stygian evidence void is that in the absence of strong controlled outcomes data, variations on the theme of both screening and treatment for prostate cancer abound. While urologists virtually unanimously agree that PSA screening should be done,⁸ there are differences in how urologists think it should be done,

to whom, and how often; when a test result should be considered suspicious; and when and how a biopsy should be performed. Current "hot" debates in urologic circles include whether the biopsy threshold should be dropped from the traditional (but arbitrary) PSA level of 4.0 ng/ml to a 2.5 ng/ml^{9,10}; and, recognizing the relative insensitivity of biopsy, how many biopsy cores should be taken per session and how many times sets of biopsies should be repeated when men have suspicious PSA results.^{11,12} And in the treatment arena, we have found that urologists and radiation oncologists generally recommend the prostate cancer treatments they themselves deliver.⁸

A "new kid on the block" in the controversy about when PSA results should trigger a biopsy has been "free PSA" (a medical oxymoron). This test has been introduced to combat the acknowledged nonspecificity of mild elevations in raw PSA ("mild elevation" being in the eye of the beholder, but somewhere between 2.5 or 4.0 ng/ml and 10.0 ng/ml, above which the positive predictive value of PSA is generally greater than 50%). In this issue, Hoffman and colleagues present a careful meta-analysis of the performance of ratios of free-to-total PSA at discriminating prostate cancer from other causes of raw PSA elevation. Although the cut-off date for selection of articles was two years ago, many subsequent publications on free PSA seem in general agreement with the data extracted for this study.

The basic problems with the clinical use of free-to-total PSA measurements, as nicely highlighted by this paper, are the relatively weak likelihood ratios for a negative test, and, due to a relatively high pretest probability of prostate cancer for men with mildly elevated PSAs, a negative predictive value of only about 90%. At what threshold probability of prostate cancer is a biopsy no longer necessary? When men have a suspicious digital rectal exam but a PSA less than 4.0 ng/ml, the probability of prostate cancer at biopsy is about 10%,¹³ and clinicians generally feel obliged to biopsy these men. It would seem inconsistent to forgo biopsy on men with a similar probability of prostate cancer who have an elevated raw PSA simply because of a high free-to-total PSA ratio.

Might free-PSA measurements have a role elsewhere in the screening cascade, where the pre-test probability is low enough for a negative test to drop the post-test probability below the biopsy threshold (whatever that is)? Hoffman and colleagues cite a pre-test probability of prostate cancer of 10% for men with raw PSA levels of 2.0 to 4.0

ng/ml,¹⁴ but other studies have suggested probabilities of cancer of 22% to 26% for men with PSAs in this range, despite negative digital rectal exams^{15,16}—too high, in the editorialist's opinion, to feel comfortable using free PSAs to help make biopsy decisions for such men.

Perhaps free PSA measurements will prove most helpful in deciding how much to reassure men who have a mildly elevated PSA and one negative set of biopsies and whether a second set of biopsies should be considered in the near future. These men have about a 10% pre-test probability of prostate cancer,¹⁷ which would mean a post-test probability of about 2% to 3% with a high free-to-total PSA ratio measured 3 to 6 months after the first biopsy (unfortunately, only a minority of men can be expected to have such a reassuring result). Men with lower free-to-total PSA ratios should at least be aware of their higher residual probability of prostate cancer, lest the biopsy provide false reassurance. In contrast to the situation in breast cancer screening, a negative biopsy is often not great reassurance against a diagnosis of prostate cancer in the near future, and the psychological implications of that stark fact need further study.

If a prostate biopsy reveals cancer, then men face what may often seem to them a bewildering array of treatment options. The interesting paper by Holmboe and Concato in this issue presents the results of a clinimetric analysis of patient likes and dislikes for the candidate treatment options. As is sometimes the case in the political arena, the two traditional active treatment candidates, radical prostatectomy and external beam radiotherapy, despite long track records, seem to suffer from few "likes" and many "dislikes" in the minds of the voters. Brachytherapy, the new "independent candidate," is seen as logistically easier with fewer side effects and therefore preferable in the eyes of many of the electorate. Relatively few are bothered by its meager record of long-term effectiveness.

The popularity of brachytherapy in this small cohort from several specialty practices appears to reflect the growing national popularity of this treatment, particularly now that insurance carriers are more often providing coverage for this option. Interestingly, as clinicians performing brachytherapy are often combining this treatment with external beam radiotherapy to afford better cancer control, studies carefully documenting the side effects of brachytherapy as delivered in community practices are urgently needed. Although patients may often perceive that brachytherapy is "risk free," this perception needs careful verification.

Holmboe and Concato also document how difficult it is for most American men not to "do something" when they have prostate cancer, perhaps to avoid a feeling of regret in the event of future cancer progression. Their physicians are generally no more enthusiastic about watchful waiting as a treatment option,⁸ despite relatively similar outcomes to surgery and radiation in nonexperimental

studies for the moderately differentiated prostate cancers that most commonly turn up in PSA-based screening programs.¹⁸ Interestingly, while our earlier decision model did not take into account the "disutility" of knowing one has cancer and not taking action,¹⁹ a subsequent re-exploration of our model by Kattan and colleagues incorporated a substantial utility penalty for "life with untreated prostate cancer," suggesting that alleviating this situation with treatment contributed substantially to the expected benefit of surgery in the model,²⁰ a benefit that would presumably persist even if treatment were ineffective at prolonging survival.

In the final analysis, it is disturbing that randomized trials of prostate cancer screening and treatment were not initiated in the late 1980s when the PSA test first became available. Why so many trials of breast cancer screening were initiated early while none were initiated early for prostate cancer screening is a fascinating question. The price of delay is not only that we do not know whether any one particular strategy of early detection and treatment of prostate cancer saves lives, but also, because of contamination of control groups due to widespread screening and treatment in "usual care," we may be condemned never to find the answer, at least in trials conducted in the United States. Are you afraid of the dark?—**MICHAEL J. BARRY, MD**, *Massachusetts General Hospital, Boston, Mass.*

REFERENCES

1. Fowler FJ, Bin L, Collins MM, et al. Prostate cancer screening and beliefs about treatment efficacy: a national survey of primary care physicians and urologists. *Am J Med.* 1998;104:526–32.
2. Woloshin S, Schwartz L. The U.S. Postal Service and cancer screening—stamps of approval? *N Engl J Med.* 1999;340:884–7.
3. Tarone R, Chu K, Brawley O. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. *Epidemiology.* 2000;11:167–70.
4. Bartsch G, Horninger W, Klocker H, et al. Decrease in prostate cancer mortality following introduction of prostate specific antigen (PSA) screening in the federal state of Tyrol, Austria. *J Urol.* 2000; 163:88.
5. Brawley O. Prostate carcinoma incidence and patient mortality. The effects of screening and early detection. *Cancer.* 1997;80: 1857–63.
6. Etzioni R, Legler J, Feuer E, Merrill R, Cronin I, Hankey B. Cancer surveillance series: interpreting trends in prostate cancer—Part III: quantifying the link between population prostate-specific antigen testing and recent declines in prostate cancer mortality. *J Natl Cancer Inst.* 1999;91:1033–9.
7. U.S. Preventive Services Task Force. Screening for cervical cancer. In: U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services*, 2nd ed. Baltimore, Md: Williams and Wilkins; 1996: 105–18.
8. Fowler F, Collins MM, Albertsen P, Zietman A, Elliott D, Barry M. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. *JAMA.* 2000;283:3217–22.
9. Catalona W, Ramos C, Carvalhal G, Yan Y. Lowering PSA cutoffs to enhance detection of curable prostate cancer. *Urology.* 2000; 55:791–5.
10. Carter H. A PSA threshold of 4.0 ng/mL for early detection of prostate cancer: the only rational approach for men 50 years old and older. *Urology.* 2000;55:796–9.

11. Babian R. Extended field prostate biopsy enhances cancer detection. *Urology*. 2000;55:453-6.
12. Terris M. Extended field prostate biopsies: too much of a good thing? *Urology*. 2000;55:456-60.
13. Catalona WJ, Richie JP, Ahmann FR. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol*. 1994;151:1283-90.
14. Schroder FH, van der Cruisjen-Koeter I, de Koning HJ, Vis AN, Hoedemaker RF, Kranse R. Prostate cancer detection at low prostate specific antigen. *J Urol*. 2000;163:806-12.
15. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. *JAMA*. 1997;277:1452-5.
16. Babaian R, Ayala A, Bhadkamkar V, Naccarato W, Fritsche H. The incidence of prostate cancer in the PSA reflex range of 2.5 and 4.0 ng/mL. *J Urol*. 2000;163:88.
17. Djavan B, Zlotta A, Remzi M. Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. *J Urol*. 2000;163:1144-9.
18. Lu-Yao G, Yao S-L. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet*. 1997;349:906-10.
19. Fowler FJ, Roman A, Barry MJ, Wasson J, Lu-Yao G, Wennberg JE. Patient-reported complications and follow-up treatment after radical prostatectomy. The national Medicare experience; 1988-1990. *Urology*. 1993;42:622-9.
20. Kattan M, Cowen M, Miles B. A decision analysis for treatment of clinically localized prostate cancer. *J Gen Intern Med*. 1997;12: 299-305.

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