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Prostate Cancers in Men with Low PSA Levels — Must We Find Them?

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Prostate cancer is the second leading cause of death from cancer among men in the United States. In the era before prostate-specific antigen (PSA) screening, most prostate cancers were identified at a stage (T2 or T3) that could not be cured. Today, with the widespread use of PSA screening, most prostate cancers are identified at an earlier stage, which can be treated effectively with surgical or nonsurgical approaches. Once PSA screening became widespread in the United States, the rate of death from prostate cancer declined — for example, in 1997 it fell below the rate recorded in 1986, a year in which PSA testing was rarely performed.¹ Although the initial decline could have been the result of improved treatments or other population-screening effects (e.g., a misclassification artifact),² it is difficult to believe that earlier detection has had no effect on the continued decline in mortality, given the 50 to 70 percent decline in the incidence of distant disease between 1986 and 1999 among men 50 years of age or older.³

There is general agreement among clinicians that the PSA test has the highest predictive value for prostate cancer, that PSA screening can detect early-stage cancers, and that most cancers detected by PSA screening appear to be clinically important when their pathological characteristics are used as a surrogate for biologic potential. There is, however, disagreement as to what level of PSA should prompt a prostate biopsy. The controversy stems from the following: the use of higher PSA thresholds risks missing an important cancer until it is too late for a cure, whereas the use of lower PSA thresholds increases not only unnecessary biopsies but also the proportion of biopsies that identify clinically insignificant disease (disease that would not have been detected in the absence of screening). The use of a PSA threshold of 4.0 ng per milliliter for men over the age of 50 years has been accepted by most clinicians as striking a reasonable balance between these tradeoffs. However, information on the prevalence of biopsy-detectable prostate cancer among men with PSA values of 4.0 ng per milliliter or less and no other indication for biopsy (e.g., an abnormal prostate examination) is limited.

In this issue of the *Journal*, Thompson et al.⁴ report the prevalence of prostate cancer among men in the control group of the Prostate Cancer Prevention Trial. During a seven-year period, none of the men in this analysis had PSA levels above 4.0 ng per milliliter or any abnormality on digital rectal examination. All participants underwent a prostate biopsy at the end of the study. Of almost 3000 men in the group, 15 percent had a prostate cancer on the end-of-study biopsy, and of these cancers, 15 percent were high grade (a Gleason score of 7 to 9). The prevalence of cancer increased with the PSA level, from 7 percent among men with PSA values of 0.5 ng per milliliter or less to 27 percent among men with PSA values of 3.1 to 4.0 ng per milliliter. Furthermore, the prevalence of high-grade disease also increased with the PSA level, from 13 percent when the PSA level was 0.5 ng per milliliter or less to 25 percent when the PSA level was 3.1 to 4.0 ng per milliliter. Given this report of the risk of prostate cancer — and the risk of high-grade disease — at PSA levels below the threshold of 4.0 ng per milliliter, which has traditionally been used to prompt prostate biopsy, should we now recommend lowering the threshold for biopsy?

I believe not, for the following reasons. First, it should not be surprising that 10 to 27 percent of the men with PSA values of 4.0 ng per milliliter or less, who ranged in age from 62 to 91 years, were found to have prostate cancer in the study by Thompson et al. On the basis of the results of 5250 autopsies reported in the U.S. literature, the prevalence of prostate cancer was 15 to 60 percent among men 60 to 90 years of age and increased with age.⁵ Ninety percent of men 50 to 90 years of age have PSA values of 4.0 ng per milliliter or less.⁶ Thus, quite a few men with PSA levels of 4.0 ng per milliliter or less must harbor a prostate cancer.

Although it would be desirable to detect the small proportion of high-grade cancers — cancers that are likely to be life threatening — in men with low PSA levels, the identification of such cancers will require the development of new biomarkers, because high-grade cancers actually produce less PSA than low-grade cancers, after correction for cancer volume.⁷ The increasing prevalence of high-grade cancer with increasing PSA levels reflects the finding that higher-grade cancers are more often larger in volume than low-grade cancers, and the PSA level is directly related to the volume of the cancer.⁷

Second, prostate cancers detected at lower PSA levels are more likely to have a small volume (less than 0.5 ml) and to be low-grade⁸ and are thus more likely to represent clinically insignificant disease, because cancer volume and grade are surrogates for biologic potential.⁹ McNeal et al. found that only cancers that were much larger than 1 ml in volume and poorly differentiated were associated with metastatic disease.⁹ Furthermore, prostate cancers with a volume of less than 1 ml do not usually result in PSA levels above 4.0 ng per milliliter,¹⁰ so that the unexpected detection of cancer at lower PSA levels is more likely to identify disease for which treatment not only may be unnecessary but also may fail to improve survival.¹¹ Thompson et al. could provide information about the estimated cancer volume in their population because the PSA density (PSA level divided by prostate volume) and the features of the cancer on biopsy (the grade, the number of cores with cancer, and the percentage of the core that is cancerous) are predictive of the cancer volume determined pathologically after surgery.¹²

Third, there is no convincing evidence that, with contemporary therapy, men who are treated when their cancers are detected at PSA levels at or below 4.0 ng per milliliter have better outcomes than men who are treated when the PSA is slightly higher than 4.0 ng per milliliter. In short, detection of prostate cancer at a PSA threshold lower than 4.0 ng per milliliter has not been shown to improve the disease-free outcome. With a PSA level in the range of 2.6 to 6.0 ng per milliliter, younger men are more likely than older men to have curable prostate cancer¹³ and a disease-free outcome¹⁴ — observations that are probably driven by the fact that older men are more likely to have high-grade cancers. Hence, the weight of the evidence suggests that the detection of prostate cancer at younger ages should have a greater effect on the likelihood of being free from disease after treatment than would the detection of prostate cancer at a PSA level of 4.0 ng per milliliter or less.

Fourth, in an investigation similar to that of Thompson et al., Gann et al. have shown that men with baseline PSA levels between 1.0 and 4.0 ng per milliliter are at significantly higher risk for a diagnosis of prostate cancer over the next 10 years than are men whose baseline PSA level is below 1.0 ng per milliliter.¹⁵ They found that a cutoff value of 3.3 ng per milliliter resulted in optimal sensitivity and specificity, but the gain was minimal as compared with that afforded by a cutoff value of 4.0 ng per milliliter. In addition, Morgan et al.¹⁶ have shown that the PSA cutoff value that results in 95 percent sensitivity (the detection of 95 percent of cancers) is close to 4.0 ng per milliliter for men between the ages of 50 and 70 years and 2.5 ng per milliliter for men in the fifth decade of life. Because most of the variability in PSA levels is due to benign prostate enlargement that occurs with age,

and men below the age of 50 years are unlikely to have such enlargement, a threshold of 2.5 ng per milliliter seems reasonable for men below the age of 50 years.

Gann et al.¹⁵ pointed out that the “dichotomization of PSA results into normal and abnormal obscures important information contained in levels below the usual cutoff.” The data of Thompson et al. provide a framework for the risk assessment of men with PSA values of 4.0 ng per milliliter or less and should prompt careful consideration of the likelihood of cancer at these lower PSA levels in men at particularly high risk, such as those with a strong family history of the disease. Given that the risk of a clinically significant prostate cancer increases incrementally with PSA levels between 0 and 4 ng per milliliter, it makes sense to track the rate of rise in PSA values (the PSA velocity), which has previously been shown to correlate directly with the risk of cancer¹⁷ and was significantly associated with the risk of cancer in the current study.

Finally, considering that the lifetime risk of death from prostate cancer is 3 percent and the lifetime risk of a diagnosis of prostate cancer is 16 percent, it is apparent that any approach that finds more cancers without quantifying the clinical significance of the detected disease will only increase overdiagnosis and overtreatment, as alluded to by Thompson et al. This, together with the absence of proof that PSA screening saves lives, should cause physicians to be circumspect about routinely recommending a prostate biopsy for men over the age of 50 years who have a PSA level of 4.0 ng per milliliter or less.

Although the value of PSA screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test, so that they can make an informed decision about the need for routine screening. The enthusiasm for screening in general in the United States suggests that most men will decide to be tested.¹⁸

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