The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 27, 2004 VOL. 350 NO. 22

Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤4.0 ng per Milliliter

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ABSTRACT

BACKGROUND

The optimal upper limit of the normal range for prostate-specific antigen (PSA) is unknown. We investigated the prevalence of prostate cancer among men in the Prostate Cancer Prevention Trial who had a PSA level of 4.0 ng per milliliter or less.

METHODS

Of 18,882 men enrolled in the prevention trial, 9459 were randomly assigned to receive placebo and had an annual measurement of PSA and a digital rectal examination. Among these 9459 men, 2950 men never had a PSA level of more than 4.0 ng per milliliter or an abnormal digital rectal examination, had a final PSA determination, and underwent a prostate biopsy after being in the study for seven years.

RESULTS

Among the 2950 men (age range, 62 to 91 years), prostate cancer was diagnosed in 449 (15.2 percent); 67 of these 449 cancers (14.9 percent) had a Gleason score of 7 or higher. The prevalence of prostate cancer was 6.6 percent among men with a PSA level of up to 0.5 ng per milliliter, 10.1 percent among those with values of 0.6 to 1.0 ng per milliliter, 17.0 percent among those with values of 1.1 to 2.0 ng per milliliter, 23.9 percent among those with values of 2.1 to 3.0 ng per milliliter, and 26.9 percent among those with values of 3.1 to 4.0 ng per milliliter. The prevalence of high-grade cancers increased from 12.5 percent of cancers associated with a PSA level of 0.5 ng per milliliter or less to 25.0 percent of cancers associated with a PSA level of 3.1 to 4.0 ng per milliliter.

CONCLUSIONS

Biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.

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N Engl J Med 2004;350:2239-46.

When first described in 1979, prostate-specific antigen (PSA) was considered a useful marker for assessing treatment responses and follow-up among patients with prostate cancer.[1] After the publication of reports on several series in which the need for a biopsy of the prostate was based on the results of PSA tests, the potential of the PSA level as a screening tool was recognized.[2,3] Further experience led to the consensus that a PSA level of more than 4.0 ng per milliliter had predictive value for the diagnosis of prostate cancer.[4] Disease detection subsequently increased dramatically.[5] More recent data suggest that a PSA level of more than 2.5 ng per milliliter has a predictive value similar to that of a value of 4.0 ng per milliliter or greater.[6,7] There are no prospective data on the predictive value of PSA in the range of 0.0 to 4.0 ng per milliliter.

We recently reported the results of the Prostate Cancer Prevention Trial, which investigated whether finasteride could prevent prostate cancer.[8] Owing to the finasteride-related decrease in PSA levels, and thus the drug's effect on the rate of detection of prostate cancer over the seven-year study period, an essential element of the study was an end-of-study biopsy in men receiving finasteride or placebo. Here, we report the prevalence of prostate cancer among men in the placebo group of the Prostate Cancer Prevention Trial who had a PSA level of 4.0 ng per milliliter or less.

METHODS

The Prostate Cancer Prevention Trial was a phase 3, randomized, double-blind, placebo-controlled study designed to determine whether treatment with 5 mg of finasteride per day could reduce the prevalence of prostate cancer during a seven-year period. The study was sponsored by the National Cancer Institute and conducted by the Southwest Oncology Group. A total of 18,882 men underwent randomization. Eligibility criteria included a serum PSA level of no more than 3.0 ng per milliliter, a normal digital rectal examination, an age of at least 55 years, an American Urologic Association symptom score of less than 20 (scores can range from 0 [no symptoms] to 35 [severe symptoms]), and no clinically significant coexisting conditions. Men underwent annual measurement of PSA and digital rectal examination. All PSA measurements were performed in a central laboratory with the use of the Tandem E assay (Hybritech) until 2000 and the Access assay (Beckman Coulter) subsequently. During the seven-year study, a PSA level of more than 4.0 ng per milliliter or an abnormal digital rectal examination prompted a recommendation for prostate biopsy. At the end of seven years, participants without a diagnosis of prostate cancer were scheduled to undergo an end-of-study prostate biopsy in which a minimum of six samples were obtained. All participants gave written informed consent. The details of the study have been provided previously.[8-10]

Prostate-biopsy specimens were reviewed by a pathologist at the Core Pathology Laboratory (University of Colorado Health Science Center, Denver), as well as by a pathologist at the participant's institution. Disagreements were resolved by a third pathologist, and consensus was achieved.

To ensure that the analysis of the prevalence of prostate cancer among men with a PSA level of 4.0 ng per milliliter or less would be applicable to the general population, only the placebo group of the Prostate Cancer Prevention Trial was used for this analysis. We selected participants in the placebo group who during the trial never had a PSA level of more than 4.0 ng per milliliter or an abnormal digital rectal examination and never underwent a prostate biopsy or a transurethral resection of the prostate over the course of the seven-year study, but who did undergo a biopsy at the end of the study. A PSA test must have been performed either on the day of the end-of-study biopsy, but before the biopsy itself, or within 90 days before the biopsy.

Associations between base-line characteristics and prostate cancer were assessed with the use of chi-square tests with Yates' correction. Student's t-test was used to compare PSA values between men with biopsy-proved prostate cancer and men without prostate cancer on biopsy. Logistic-regression analyses of the risk of prostate cancer and high-grade disease (as defined by a Gleason score of 7 or greater) were performed with the use of the following variables: age in years, presence or absence of a family history of prostate cancer (considered to be present if the man's brother, father, or son had prostate cancer), race (black or other), and PSA level. The positive predictive value of the PSA level for the detection of prostate cancer (or high-grade disease) was defined as the probability that prostate cancer (or high-grade disease) would be found if the PSA level was within a prespecified range, such as 3.1 to 4.0 ng per milliliter.

RESULTS

Of the 9459 men who were randomly assigned to the placebo group, 2 had received a diagnosis of prostate cancer before enrollment and 1242 men either had died before the end of the study or had never undergone an end-of-study biopsy because of the early closure of the trial. Among the remaining 8215 men, 1187 were excluded from the analysis because they had at least one PSA value above 4.0 ng per milliliter, and 3460 men were excluded because they had at least one abnormal digital rectal examination, underwent a transurethral resection of the prostate during the trial, had off-study use of finasteride, or underwent an end-of-study biopsy or had a final PSA measurement neither of which met the timing requirements of the study. Of the remaining 3568 men who were potentially eligible, 618 (17.3 percent) declined to undergo the biopsy. Thus, 2950 men (age range, 62 to 91 years) were included in the analysis.

Table 1 lists the characteristics of the participants, including the men who did not undergo an end-of-study biopsy but otherwise met all criteria for the analysis. A significantly higher proportion of men who declined to undergo biopsy than who consented were older than 75 years of age (P<0.001). The average number of PSA measurements for the 2950 men in the analysis was 7.9 (median, 8), and 96.2 percent of the men had 7 or more PSA measurements. The average number of PSA measurements among the 618 men who declined to undergo the end-of-study biopsy but who met all other criteria for the analysis was 7.7 (median, 8), and 91.3 percent of these men had 7 or more PSA measurements.

Of the 2950 men, 449 (15.2 percent) had prostate cancer on the end-of-study biopsy (Table 1). The percentage of cancers found among men who underwent a sextant biopsy — in which six samples were obtained and which was performed in 84.5 percent of the men — did not differ significantly from the percentage of cancers found in men whose biopsy included more than six samples (15.0 percent and 16.6 percent, respectively). A family history of prostate cancer was significantly associated with an increased risk of prostate cancer, but the age at biopsy and race or ethnic group were not (Table 1). Our inclusion only of men who were at least 62 years old (eligibility for the Prostate Cancer Prevention Trial required an age of at least 55 years)

Table 1. Characteristics of the Men According to Whether They Underwent the End-of-Study Biopsy and to the Findings on Biopsy.

Characteristic	All Men, with or without End-of-Study Biopsy* (N=3568)	Men Who Underwent End-of-Study Biopsy (N=2950)	Men with Cancer on End-of-Study Biopsy (N=449)	P Value†
	no. of men (%)		*no./total no. (%)*	
Age at time of biopsy‡				0.25
62–65 yr§	745 (20.9)	638 (21.6)	94/638 (14.7)	
66–70 yr	1154 (32.3)	957 (32.4)	132/957 (13.8)	
71–75 yr	957 (26.8)	814 (27.6)	140/814 (17.2)	
>75 yr¶	712 (20.0)	541 (18.3)	83/541 (15.3)	
Race or ethnic group				0.42
White	3340 (93.6)	2768 (93.8)	427/2768 (15.4)	
Black	104 (2.9)	81 (2.7)	12/81 (14.8)	
Hispanic	88 (2.5)	69 (2.3)	8/69 (11.6)	
Other	36 (1.0)	32 (1.1)	2/32 (6.2)	
Family history				0.004
Positive (affected brother, father, or son)	573 (16.1)	477 (16.2)	94/477 (19.7)	
Negative	2995 (83.9)	2473 (83.8)	355/2473 (14.4)	

* A total of 618 men declined to undergo the end-of-study biopsy and thus were excluded from subsequent analyses.
† P values denote the significance of the correlation of each variable with a risk of prostate cancer for the 2950 participants who underwent an end-of-study biopsy.
‡ The median age was 69.4 years.
§ One participant was younger than 62 years.
¶ Significantly more men who declined to undergo the end-of-study biopsy than men who consented were older than 75 years (P<0.001).

and our exclusion of men with PSA levels above 4.0 ng per milliliter may have made it impossible to detect any associations between age and the risk of cancer, since both PSA levels and the risk of prostate cancer increase with age. Detecting associations between race and ethnic group and the risk of cancer may have been prevented by the limited numbers of blacks and members of other minority groups in our study. The inability to assess black men adequately is an important limitation of our study because of differences in the natural history of prostate cancer: the disease occurs earlier among blacks than whites and is at a more advanced stage when it is detected, but the stage-specific prognoses are similar between blacks and whites.

All 449 prostate cancers for which information on the stage was available were stage T1; however, such information was missing for 30 cancers (6.7 percent). Of the 449 cancers, 12 (2.7 percent) had Gleason scores of 2 to 4, 349 (77.7 percent) had scores of 5 or 6, 67 (14.9 percent) had scores of 7 to 9, and 21 (4.7 percent) were not graded. None of the tumors had a Gleason score of 10.

The mean (±SD) PSA value was 1.78±0.92 ng per milliliter among the 449 men with prostate cancer and 1.34±0.86 ng per milliliter among the 2501 men without cancer (P<0.001). Figure 1 shows the distribution of PSA levels in the two groups. The annual increase in the PSA level during the seven years of the study, which was computed by means of linear regression (range, 0.32 to 0.46 ng per milliliter per year), was positively associated with the risk of prostate cancer (P<0.001). The mean ratio of the PSA level to the volume of the prostate was slightly higher among men with cancer (0.06±0.03) than among men without cancer (0.04±0.06), but the association was not significant.

Table 2 shows that the risk of prostate cancer increased from 6.6 percent for PSA values of 0.5 ng per milliliter or less to 26.9 percent for PSA values of 3.1 to 4.0 ng per milliliter. Logistic-regression analysis showed that the PSA level had a significant effect on the risk of prostate cancer (odds ratio for prostate cancer, 1.66 per unit increase in the PSA level; 95 percent confidence interval, 1.50 to 1.85; P<0.001). Figure 2 shows the relation between the PSA level and the risk of prostate cancer. In a multivariate analysis, a family history of prostate cancer was significantly associated with the risk of prostate cancer (odds ratio, 1.39; 95 percent confidence interval, 1.07 to 1.79; P=0.01), as was an increase in the PSA level (odds ratio, 1.65 per unit increase; 95 percent confidence interval, 1.48 to 1.83; P<0.001).

The relation between the PSA level and the Gleason score is shown in Table 2 and Figures 1, 2, and 3. Although the risk of high-grade disease increased with increasing PSA levels, there was considerable overlap in the distributions of PSA levels among the grades. Figure 2 shows predictions of the risk of high-grade disease on the basis of a logistic model. There was a significant correlation between the PSA level and high-grade disease (odds ratio, 2.10 per unit increase in the PSA level; 95 percent confidence interval, 1.66 to 2.65; P<0.001). The association persisted when cancers with a Gleason score of 7 (3+4 — the sum of the primary [most prevalent] grade and the highest secondary grade) were excluded (odds ratio for high-grade disease, 1.80 per unit increase in the PSA level; 95 percent confidence interval, 1.17 to 2.77; P=0.02). In a multivariate analysis, there was an additional significant association with black race (odds ratio for high-grade disease, 4.14; 95 percent confidence interval, 1.77 to 9.68; P=0.001). The odds ratio for high-grade disease in the multivariate analysis was 2.08 per unit increase in the PSA level (95 percent confidence interval, 1.64 to 2.64; P<0.001).

DISCUSSION

PSA was first described in 1979, and its use suggested for the evaluation of treatment responses in men with prostate cancer. Early observations suggested that the PSA level might not be useful for screening,[11] and a level of 2.6 ng per milliliter was proposed as the upper limit of the normal range.[12-15] Because of concern about the specificity of the test, other early reports suggested that the upper limit of the normal range for prostate-cancer screening should be 7.5 to 10.0 ng per milliliter.[16,17]

Before the advent of the PSA test, prostate cancer was usually diagnosed by means of digital rectal examination, which often detected cancer after the disease had spread.[18] If a digital rectal examination was abnormal, prostate biopsy with digital guidance was usually performed, often with four or fewer biopsy samples obtained. The morbidity associated with the procedure was substantial.[19] In the mid-1980s, the use of ultrasound-guided biopsies with an automated, 18-gauge biopsy "gun" increased the safety and speed of the technique.[20,21]

In one of the first reported evaluations of PSA screening (in 1653 men), prostate cancer was de-

tected in 22 percent of the men (19 of 85) who underwent a biopsy because of a PSA level of 4.0 to 9.9 ng per milliliter and in 67 percent of the men (18 of 27) who underwent a biopsy because of a PSA level of more than 10.0 ng per milliliter.[2] In a subsequent study of 1249 men, prostate cancer was found in 26 percent of the men (23 of 87) who underwent a biopsy because of a PSA level of 4.1 to 10.0 ng per milliliter and in 50 percent of the men (9 of 18) who underwent a biopsy because of a PSA level of more than 10.0 ng per milliliter.[3] After these initial reports of PSA screening, there was a dramatic increase in the detection of prostate cancer.

The positive predictive value of a PSA level of less than 4.0 ng per milliliter is not well defined. A multi-institutional, prospective study of PSA levels and digital rectal examination in 6630 men who were 50 years of age or older suggested that a value of 4.0 ng per milliliter should be used as the upper limit of the normal range.[22] In that study, only men with a PSA level of more than 4.0 ng per milliliter were offered a prostate biopsy unless they had an abnormal digital rectal examination. There are limited data on the prevalence of prostate cancer among men with a PSA level of 4.0 ng per milliliter or less and, in particular, among men with levels below 2.5 ng per milliliter. One study showed that the rate of detection of clinically important prostate cancer among men with a PSA level of 2.6 to 4.0 ng per milliliter was the same as that among men with PSA values of more than 4.0 ng per milliliter.[7] The determination of an appropriate upper limit of the normal range for PSA screening for prostate cancer has been further confounded by changes in prostate-biopsy procedures. Although the initial standard for ultrasound-guided prostate biopsy was to obtain 6 samples, more recent studies have shown that obtaining 10 to 12 samples increases the detection rate.[23]

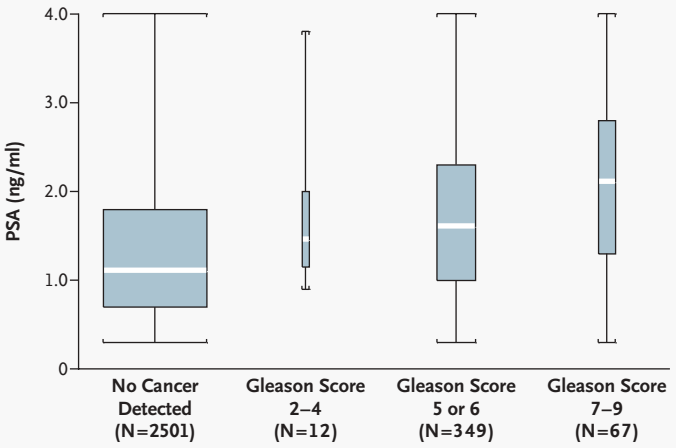

Figure 1. Distributions of Prostate-Specific Antigen (PSA) Values According to the Gleason Score among Men with Prostate Cancer Detected on End-of-Study Biopsy and Men with No Cancer Detected on Biopsy.

The horizontal white lines within the boxes denote the medians, and the boxes span the 25th and 75th percentiles of the distributions. The vertical lines above and below each box indicate the range of the distribution. The width of each box is proportional (although not directly) to the number of men in the corresponding group. Twenty-one cancers were not graded.

Table 2. Relationship of the Prostate-Specific Antigen (PSA) Level to the Prevalence of Prostate Cancer and High-Grade Disease.*

PSA Level	No. of Men (N=2950)	Men with Prostate Cancer (N=449)	Men with High-Grade Prostate Cancer (N=67)	Sensitivity	Specificity
		no. of men (%)	*no./total no. (%)*		
≤0.5 ng/ml	486	32 (6.6)	4/32 (12.5)	1.0	0.0
0.6–1.0 ng/ml	791	80 (10.1)	8/80 (10.0)	0.93	0.02
1.1–2.0 ng/ml	998	170 (17.0)	20/170 (11.8)	0.75	0.33
2.1–3.0 ng/ml	482	115 (23.9)	22/115 (19.1)	0.37	0.73
3.1–4.0 ng/ml	193	52 (26.9)	13/52 (25.0)	0.12	0.92

* High-grade disease was defined by a Gleason score of 7 or greater. The population was restricted to men with a PSA level of 4.0 ng per milliliter or less throughout the study. Therefore, the definitions of sensitivity and specificity are restricted to cutoff values of less than 4.0 ng per milliliter (the cutoff values are equal to the lower value of the ranges in the PSA column [0.0, 0.6, 1.1, 2.1, and 3.1 ng/ml]). Sensitivity was defined as the proportion of men with cancer who had a PSA value above the cutoff among all men with cancer who had a PSA value of 4.0 ng per milliliter or less. Specificity was defined in a like manner.

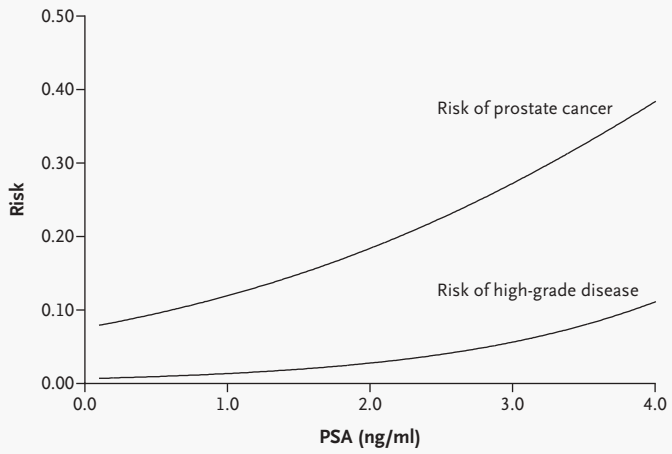

Figure 2. Estimated Risk of Prostate Cancer and High-Grade Disease as a Function of the Prostate-Specific Antigen (PSA) Level.
High-grade disease was defined by a Gleason score of 7 or greater.

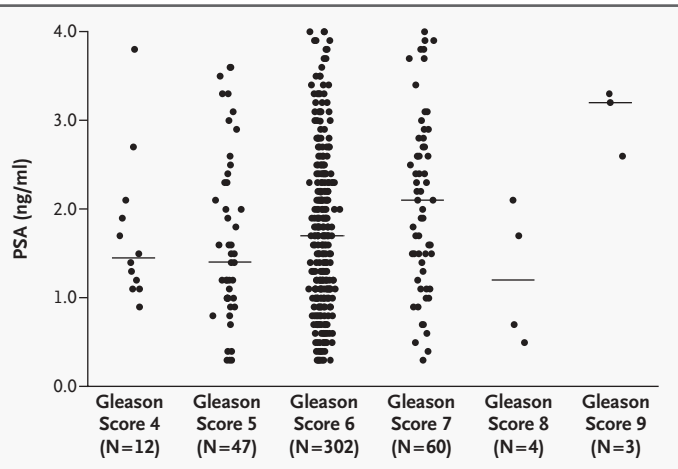

Figure 3. Prostate-Specific Antigen (PSA) Values among the 449 Men with Prostate Cancer, According to the Gleason Score.
Median PSA values are denoted by horizontal lines. A single cancer with a Gleason score of 2 is included in the group with a Gleason score of 4. Twenty-one cancers were not graded. There were no cancers with a Gleason score of 10. Of 60 cancers with a Gleason score of 7, 48 had a Gleason score of 3+4 and 12 a score of 4+3.

Given the lack of a rigorous evaluation of the optimal PSA level for the detection of prostate cancer and the changes in biopsy technique, it is not surprising that the predictive value of the PSA level is not known. The end-of-study biopsies in the Prostate Cancer Prevention Trial provided a unique opportunity to examine the predictive value of the PSA level in the range considered to be normal. We restricted our evaluation to men in the placebo group, because their PSA values were unaffected by finasteride. The design of the Prostate Cancer Prevention Trial, including centralized pathological review and PSA measurement and the planned end-of-study biopsy, permitted this comprehensive, prospective evaluation of the prevalence of prostate cancer among men with a PSA level of 4.0 ng per milliliter or less.

With only six biopsy samples obtained from 84.5 percent of participants and normal PSA levels (4.0 ng per milliliter or less) and digital rectal examinations over a period of seven years in all men, our study cohort had a surprisingly high rate of biopsy-detected prostate cancer: 15.2 percent. The rate of prostate cancer was 10.1 percent among men with PSA levels of 0.6 to 1.0 ng per milliliter and rose to 26.9 percent among men with PSA levels of 3.1 to 4.0 ng per milliliter. High-grade cancers (those with a Gleason score of at least 7) were observed throughout this range of PSA values and had an overall prevalence of 2.3 percent. The majority of cancers identified in men with a PSA level of 4.0 ng per milliliter or less had a Gleason score of 6, a value that is reported to be associated with an increased risk of disease progression in the absence of treatment.[24] Although the risk of a finding of cancer on biopsy is directly related to PSA levels in the range of 0.0 to 4.0 ng per milliliter, there is no PSA value below which a man can be assured that he has no risk of prostate cancer.

A major strength of our analysis is that it is not subject to verification bias, since the study included only men who underwent an end-of-study biopsy, unlike other studies, which included few men with a PSA level of less than 4.0 ng per milliliter who underwent a prostate biopsy.[25] Nevertheless, the implications of our results for current recommendations regarding prostate biopsy are unclear. Our data indicate that high- or intermediate-grade prostate cancer can be present in men with low PSA levels, despite the impression of many clinicians that men with PSA levels of 4.0 ng per milliliter or less (accounting for up to 92.4 percent of all men) have almost no risk of prostate cancer.[26]

A decision to lower the current PSA threshold for biopsy, however, should be considered within the broader context of the PSA-screening debate. Although the use of PSA testing in the United States has led to earlier diagnosis and a marked shift in

the stage at which prostate cancer is identified, it is unclear whether PSA testing reduces the rate of death from prostate cancer.[27,28] This question is being addressed by the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial,[29] a large-scale screening trial with mortality end points. The uncertain benefits of PSA screening have resulted in different recommendations from policymaking organizations. Although clinically important cancers are not always fatal, the large difference between a man's risk of death from prostate cancer (3 to 4 percent) and his lifetime risk of the diagnosis of prostate cancer (16.7 percent) suggests that many prostate cancers detected in routine practice may be clinically unimportant. Lowering the PSA threshold for proceeding to prostate biopsy would increase the risks of overdiagnosing and overtreating clinically unimportant disease.

Our finding that as many as 15 percent of men with a "normal" PSA level had prostate cancer underscores the need to consider fundamental changes in the approach to diagnosing prostate cancer. The dilemma of overtreating the clinically unimportant disease that will be detected if the PSA threshold for biopsy is lowered or undertreating potentially clinically important disease that will go undetected if biopsy is not performed in men with a PSA level of 4.0 ng per milliliter or less must be resolved. Help in resolving this dilemma will come from the results of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and from critically needed studies of prognostic biomarkers. Carefully planned studies of biomarkers, such as those conducted by the Early Detection Research Network of the National Cancer Institute,[30] may identify biomarkers in serum (before diagnosis) and cancer tissue (after diagnosis) that can be used to differentiate biologically important from unimportant prostate tumors, especially with respect to tumors with a Gleason score of 6 or 7, which show marked clinical variability.

Supported in part by Public Health Service grants (CA37429, CA35178, and CA45808) from the National Cancer Institute.

We are indebted to the 18,882 men who participated in this study; to the members of the data and safety monitoring committee; to the steering committee; to the study-site principal investigators and clinical research associates; to collaborators from the Southwest Oncology Group, the Eastern Cooperative Oncology Group, and Cancer and Leukemia Group B; and to Merck for providing the finasteride and the placebo.

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