

20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

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TO DETERMINE THE NEED FOR treatment of localized prostate cancer, patients and physicians must understand the natural history of this disease. A recent study by Johansson et al¹ documented 20-year outcomes for a population-based cohort of 223 men diagnosed with localized prostate cancer between 1977 and 1984. The authors noted a substantial increase in prostate cancer mortality among the 49 men who were alive more than 15 years following diagnosis.

In 1998, we published a competing risk analysis of 767 men aged 55 to 74 years with clinically localized prostate cancer at diagnosis who were treated with observation or androgen-withdrawal therapy alone.² The purpose of that analysis was to provide an estimate of the natural progression of prostate cancer if treated conservatively. Because these men have been followed up continuously by the Connecticut Tumor Registry (CTR), we had an opportunity to extend our follow-up to 20 years to determine whether prostate cancer mortality rates declined, remained constant, or increased after 15 years.

For editorial comment see p 2149.

Context The appropriate therapy for men with clinically localized prostate cancer is uncertain. A recent study suggested an increasing prostate cancer mortality rate for men who are alive more than 15 years following diagnosis.

Objective To estimate 20-year survival based on a competing risk analysis of men who were diagnosed with clinically localized prostate cancer and treated with observation or androgen withdrawal therapy alone, stratified by age at diagnosis and histological findings.

Design, Setting, and Patients A retrospective population-based cohort study using Connecticut Tumor Registry data supplemented by hospital record and histology review of 767 men aged 55 to 74 years with clinically localized prostate cancer diagnosed between January 1, 1971, and December 31, 1984. Patients were treated with either observation or immediate or delayed androgen withdrawal therapy, with a median observation of 24 years.

Main Outcome Measures Probability of mortality from prostate cancer or other competing medical conditions, given a patient's age at diagnosis and tumor grade.

Results The prostate cancer mortality rate was 33 per 1000 person-years during the first 15 years of follow-up (95% confidence interval [CI], 28-38) and 18 per 1000 person-years after 15 years of follow-up (95% CI, 10-29). The mortality rates for these 2 follow-up periods were not statistically different, after adjusting for differences in tumor histology (rate ratio, 1.1; 95% CI, 0.6-1.9). Men with low-grade prostate cancers have a minimal risk of dying from prostate cancer during 20 years of follow-up (Gleason score of 2-4, 6 deaths per 1000 person-years; 95% CI, 2-11). Men with high-grade prostate cancers have a high probability of dying from prostate cancer within 10 years of diagnosis (Gleason score of 8-10, 121 deaths per 1000 person-years; 95% CI, 90-156). Men with Gleason score of 5 or 6 tumors have an intermediate risk of prostate cancer death.

Conclusion The annual mortality rate from prostate cancer appears to remain stable after 15 years from diagnosis, which does not support aggressive treatment for localized low-grade prostate cancer.

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METHODS

Study Population

Patients followed up in this analysis were the same patients described in our 1998 study.² The original study population consisted of 767 men identified

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from the CTR database who were Connecticut residents when diagnosed with prostate cancer between January 1, 1971, and December 31, 1984. Of these men, 610 died before March 1, 1997, after a median follow-up of 15.4 years. Since then, 107 patients have died. The year of last contact for the remaining 50 men was 1987 (n=1), 1998 (n=2), 2001 (n=1), 2002 (n=2), 2003 (n=41), 2004 (n=3). The final censoring date was October 8, 2004.

The original research was approved in 1990 to 1992 with a waiver of informed consent by the institutional review boards of the Connecticut Department of Public Health (DPH), as well as 24 acute care hospitals and the 2 Veterans Affairs medical centers in Connecticut that had institutional review boards at the time. Administrative approval waiving informed consent was obtained in the remaining 11 hospitals. This study was approved in 2004 by the Connecticut DPH Human Investigation Committee and the institutional review board of the University of Connecticut Health Center.

Charts were abstracted onsite to confirm the date of diagnosis, metastatic evaluations completed, method of treatment, and any associated comorbidities. Patients who had undergone surgery, received either radiation therapy or brachytherapy, or who were known to have metastatic disease were excluded. In addition, patients with concomitant cancers and those surviving less than 6 months after diagnosis were also excluded. Study personnel performing chart abstraction were blinded to the long-term outcome of the patients as recorded by the CTR. Original histology slides that were used to secure the patients' diagnoses were retrieved from hospital pathology departments and mailed to a referee pathologist who was also blinded to the long-term outcome.² Standardized grading was performed using the Gleason classification system. This system grades prostate cancers into 1 of 5 morphological patterns according to the tumors' glandular differentiation and growth pattern as assessed under low-

power magnification, with 1 indicating well-differentiated disease and 5 indicating poorly differentiated disease. The Gleason score represents the sum of the pattern numbers of the 2 most common patterns by volume. Scores range from 2 to 10, with a Gleason score of 10 being the most poorly differentiated and aggressive tumors.³

Accurate staging information was lacking for many men. Bone scan tests were performed on only 30% of patients and serum acid phosphatase levels were confirmed as normal in only 53% of patients. The proportion of patients without evidence of testing for metastatic disease ranged from 33% for men with a Gleason score of 2 to 4 disease to 15% for men with a Gleason score of 7 and 8 to 10 disease. No information was available concerning prostate-specific antigen (PSA) levels at diagnosis because this population had prostate cancer diagnosed before the clinical application of this test. Approximately 71% of patients were diagnosed with prostate cancer following transurethral resection or open prostatectomy, 26% of patients were diagnosed by needle biopsy of the prostate, and 3% of patients were diagnosed by other or unknown methods.

Outcome Assessment

On March 1, 1997, and again on October 8, 2004, the vital status of each patient was obtained from the CTR, which is located in the Connecticut DPH. The CTR is the oldest state cancer registry and has functioned as one of the sites of the National Cancer Institute's Surveillance, Epidemiology, and End Results program since 1973. The CTR uses a variety of sources to obtain follow-up data for registered patients, including hospital tumor registrars who rely on hospital records and physician and patient contact, as well as periodic searches of the DPH Vital Records Section files. The CTR database is linked annually with files of the Center for Medicare & Medicaid Services, formerly the Health Care Financing Administration, to ascertain deaths of men enrolled in Medicare. If a man

is not known to be dead, a date of last contact is assigned that corresponds with the date of the last Center for Medicare & Medicaid Services/Health Care Financing Administration linkage. The Connecticut Department of Motor Vehicles files are linked annually and the National Death Index Plus files are linked every 1 or 2 years to obtain cause of death for patients known to be dead.

For all men who died since the last analysis, information coded from death certificates was obtained to classify them as having died from prostate cancer or another cause. A patient was determined to have died from prostate cancer if any of the 3 causes listed on part 1 of the death certificate reported prostate cancer. If prostate cancer did not appear on 1 of these 3 lines, the patient's death was attributed to competing medical conditions. For some patients, only information concerning the date of death was available. Patients who were not followed up until death were considered alive until the date of last contact and their subsequent survival time was censored.

Statistical Analysis

The primary outcomes of our study were probability of mortality from prostate cancer or other competing causes, given a patient's age at diagnosis and tumor grade. For the competing risk analysis, we tabulated the numbers of men with each of the 3 outcomes of interest (alive, deceased from prostate cancer, and deceased from other causes) for each of the 20 age-histology combinations. Because of the variable length of follow-up and the small numbers in some cells, we also performed a second competing risk analysis based on 2 inputs: the rate of mortality from prostate cancer and from other causes, both fitted as smooth functions of age at diagnosis, Gleason score, and year of follow-up. These smoothed estimates were derived from regression models and incorporated the duration of follow-up and the patterns of outcomes in neighboring cells to allow more stable estimates for all cells.

The regression models used to construct the smoothed competing risk analysis required information concerning both the date of death and the cause of death for all patients. For 25 (3.5%) of the 717 men who died, only the date of death was available. We imputed the cause of death for each of these 25 men separately for each histology score category according to the ratio of the deaths of known causes for the other men with the same histology scores.² The rates of mortality from prostate cancer and other competing medical conditions were estimated respectively using separate Poisson regression analyses from the 7429 person-years of follow-up by using the Poisson link in the GENMOD procedure in SAS statistical software version 6.12 (SAS Institute, Cary, NC), which allowed non-integer numbers of events. *P* < .05 was considered statistically significant.

To estimate the proportions of men who died from prostate cancer or other competing medical conditions, or who were still alive 20 years following diagnosis, we applied the fitted rates of prostate cancer death and other causes of death to the proportion of men still alive at the beginning of each successive follow-up interval. This was plotted for each age-histology stratum. Prostate cancer mortality rates in each of the 5-year intervals after diagnosis were calculated using the numbers of deaths divided by the number of person-years of follow-up in the interval; rates were expressed as the number of prostate cancer deaths per 1000 person-years. The confidence intervals (CIs) for these mortality rates were calculated by multiple imputation. Because the distribution of tumor histology among survivors after 15 years was more favorable than the entire cohort at the time of diagnosis, we also compared the mortality rates before and after 15 years of follow-up, adjusting for tumor grade and age at diagnosis using Poisson regression.

RESULTS

The median observation period was 24 years (range, 16-33 years); for 87% of the men, it was longer than 20 years.

Of the 107 men who died since our previous study, we determined the date of death for all 107 men and the cause of death for 95 men. We were able to obtain the cause of death for an additional 44 men for whom this informa-

tion was unavailable at the end of the first study.² A description of the original study population, including information gathered concerning cause of death during the past 6 years, is shown in TABLE 1.

Table 1. Characteristics of Patients With Clinically Localized Prostate Cancer (N = 767)

Characteristics	No. (%) of Patients*
Age at diagnosis, median (range), y	69 (55-74)
Year of diagnosis, median (range)	1980 (1971-1984)
Years from diagnosis to 2004 or earlier loss to follow-up, median (range)	24 (16-33)
Follow-up	
Until death	717 (94)
Alive for 15-20 y	18 (2)
Alive for >20 y	32 (4)
Digital examination	
Not indicative of cancer	394 (51)
Indicative, confined within prostate	116 (15)
Indicative, extending through capsule	35 (5)
Indicative, no further information	184 (24)
Not performed or result unknown	38 (5)
Method of diagnosis	
Transurethral resection of prostate	460 (60)
Simple open prostatectomy	81 (11)
Needle biopsy of prostate	202 (26)
Other or unknown	24 (3)
Total acid phosphatase	
Normal	402 (53)
Elevated, ≤2 × upper limit of normal	46 (6)
Elevated, >2 × upper limit of normal	23 (3)
Elevated, magnitude unknown	18 (2)
Performed, but result unknown	23 (3)
Not performed	255 (33)
Bone scan performed: no metastases	229 (30)
Metastatic survey performed: no metastases	208 (27)
No test for metastatic disease performed	164 (21)
Treatment within 6 mo of diagnosis	
None	441 (58)
Orchiectomy	126 (16)
Estrogen therapy	169 (22)
Both	31 (4)
Concurrent medical conditions†	
Myocardial infarction	92 (12)
Congestive heart failure	64 (8)
Peripheral vascular disease	42 (6)
Cerebrovascular disease	55 (7)
Chronic pulmonary disease	149 (20)
Diabetes mellitus	78 (10)
Peptic ulcer disease	84 (11)
Vital status at last contact	
Alive	50 (6)
Deceased due to causes other than prostate cancer	470 (61)
Deceased due to prostate cancer	222 (29)
Deceased, unable to ascertain cause	25 (4)

*Unless otherwise specified.
 †If present in more than 5% of the patients.

Table 2. Age Distribution, Comorbidity Scores, and 20-Year Outcome of 767 Patients With Clinically Localized Prostate Cancer Followed Up for a Median of 24 Years

	Age at Diagnosis, y				Total No. (%)
	55-59	60-64	65-69	70-74	
Gleason Score at Diagnosis of 2-4					
Sample size	11	35	42	50	138 (100)
Charlson score*					
0-1	10	30	29	35	104 (75)
≥2	1	5	13	15	34 (25)
No. of patients deceased due to					
Prostate cancer	0	1	3	6	10 (7)
Other causes	8	25	32	38	103 (75)
Unknown causes†	0	2	2	4	8 (6)
No. of patients alive	3	7	5	2	17 (12)
Gleason Score at Diagnosis of 5					
Sample size	8	24	43	43	118 (100)
Charlson score*					
0-1	8	19	36	33	96 (81)
≥2	0	5	7	10	22 (19)
No. of patients deceased due to					
Prostate cancer	1	3	6	6	16 (14)
Other causes	3	16	32	35	86 (73)
Unknown causes†	1	1	1	1	4 (3)
No. of patients alive	3	4	4	1	12 (10)
Gleason Score at Diagnosis of 6					
Sample size	25	45	84	140	294 (100)
Charlson score*					
0-1	18	37	65	103	223 (76)
≥2	7	8	19	37	71 (24)
No. of patients deceased due to					
Prostate cancer	5	13	24	39	81 (27)
Other causes	11	25	53	98	187 (64)
Unknown causes†	0	2	3	3	8 (3)
No. of patients alive	9	5	4	0	18 (6)
Gleason Score at Diagnosis of 7					
Sample size	8	22	43	64	137 (100)
Charlson score*					
0-1	6	17	33	48	104 (76)
≥2	2	5	10	16	33 (24)
No. of patients deceased due to					
Prostate cancer	4	18	14	26	62 (45)
Other causes	2	3	29	36	70 (51)
Unknown causes†	2	0	0	1	3 (2)
No. of patients alive	0	1	0	1	2 (2)
Gleason Score at Diagnosis of 8-10					
Sample size	2	15	30	33	80 (100)
Charlson score*					
0-1	2	13	17	27	59 (74)
≥2	0	2	13	6	21 (26)
No. of patients deceased due to					
Prostate cancer	1	13	18	21	53 (66)
Other causes	0	1	11	12	24 (30)
Unknown causes†	1	1	0	0	2 (3)
No. of patients alive	0	0	1	0	1 (1)
All Gleason Scores at Diagnosis					
Sample size	54	141	242	330	767 (100)
Charlson score*					
0-1	44	116	180	246	586 (76)
≥2	10	25	62	84	181 (24)
No. of patients deceased due to					
Prostate cancer	11	48	65	98	222 (29)
Other causes	24	70	157	219	470 (61)
Unknown causes†	4	6	6	9	25 (3)
No. of patients alive	15	17	14	4	50 (7)

*Charlson score of 0 to 1 indicates no or minor comorbidities and a score of at least 2 indicates patients who have significant comorbidities.

†Unknown causes could be prostate cancer or a cause other than prostate cancer.

The distributions of outcomes at the end of this follow-up are shown in TABLE 2. The table stratifies men by 2 key factors that influence long-term survival: age at diagnosis and the histology score of the biopsy specimen classified according to the Gleason system. To standardize the follow-up and provide more stable estimates of the mortality rates from prostate cancer or other competing conditions, smoothed estimates are presented as 20-year outcomes as a function of time from diagnosis (FIGURE). The results follow the same trends as noted in 1998. Few men with low-grade tumors identified by prostate biopsy had progression leading to prostate cancer death within 20 years, although most men with high-grade tumors died from the cancer regardless of their age at diagnosis. Among men with a comorbidity score of 0 to 1, 26%, 15%, and 8% survived at least 15, 20, and 25 years, respectively. Among men with a comorbidity score of more than 1, 11%, 6%, and 3% survived at least 15, 20, and 25 years, respectively.

Prostate cancer-specific mortality rates were unchanged after 15 years of follow-up (TABLE 3). The prostate cancer mortality rate was 33 per 1000 person-years during the first 15 years (95% CI, 28-38) and 18 per 1000 person-years after 15 years of follow-up (95% CI, 10-29). These rates were not statistically different after adjusting for the more favorable histology profiles among men who survived more than 15 years from diagnosis (rate ratio, 1.1; 95% CI, 0.6-1.9).

COMMENT

Considerable controversy surrounds the appropriate treatment of newly diagnosed prostate cancer. Widespread testing for PSA has introduced lead time and length time effects that further complicate the task of determining the efficacy of treatment. Although some of the cancers identified by contemporary biopsy techniques are destined to progress to clinically significant disease, trends in population-based incidence and mortality rates suggest that

a significant number of prostate cancers identified by PSA testing are unlikely to be clinically symptomatic.⁴

Johansson et al¹ recently published 20-year follow-up data of a population-based cohort of men diagnosed with prostate cancer between 1977 and 1984, a period of time very similar to our patient series. They reported an unexpected 3-fold increase in prostate cancer mortality rates for the 49 patients who were still alive 15 years after diagnosis. A 20-year analysis of our cohort does not support that finding. Two factors may contribute to this difference: histology classification and cause of death determination.

Despite recent advances in genomics, tumor histology still remains the most powerful predictor of disease progression. Patients in the study by Johansson et al¹ underwent an aspiration biopsy and the results were classified according to the World Health Organization grading system. Our study used the Gleason score grading system, which relies on glandular architecture to classify specimens. Although both systems show good correlation between grade and survival, they are based on fundamentally different criteria and may result in different classifications, especially among men with moderately differentiated disease.^{3,5}

Both studies agree that men with well-differentiated tumors rarely die from their disease and that men with poorly differentiated tumors frequently die within 5 to 10 years of diagnosis, often despite aggressive interventions. Men with moderately differentiated tumors have the greatest variation in outcomes. Based on only 8 prostate cancer deaths from years 15 to 20, Johansson et al¹ reported that the prostate cancer mortality rate for the entire cohort increased from 15 to 44 deaths per 1000 person-years. We found that men with Gleason scores of 5, 6, and 7 had mortality rates of 12, 30, and 65 deaths per 1000 person-years, respectively, during a 20-year follow-up. These rates were unchanged from those rates at 15 years. The increased mortality rate reported by

Johansson et al¹ may therefore reflect a classification artifact involving a small number of patients.

A second distinction between these 2 studies is cause of death determination. Prostate cancer mortality statistics rely on an accurate determination of whether a patient died of his disease or from a competing medical condition. This can be difficult to determine when patients have multiple chronic diseases, such as heart disease

or other malignancies (eg, lung cancer or colon cancer).

Johansson et al¹ relied on medical record review to determine cause of death and validated their findings with information recorded in the Swedish Death Register. We relied on information reported on part I of the death certificate to classify patients as having died from prostate cancer or a competing medical condition. Although death certificates are often an unreliable source

Figure. Survival and Cumulative Mortality From Prostate Cancer and Other Causes Up to 20 Years After Diagnosis, Stratified by Age at Diagnosis and Gleason Score

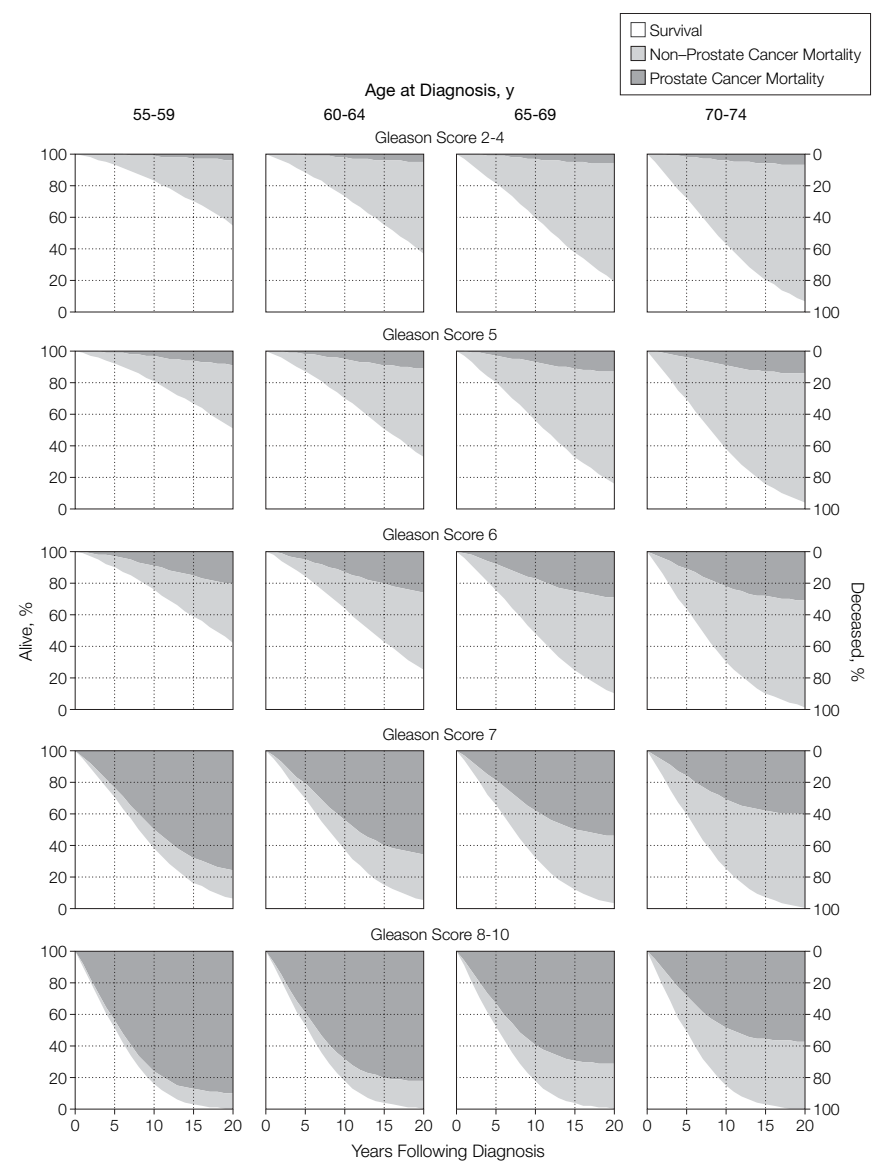


Table 3. Unadjusted Prostate Cancer Death Rates by Period of Follow-up, Age at Diagnosis, and Tumor Grade at Diagnosis

	No. of Person-Years	No. of Prostate Cancer Deaths*	Mortality Rate (95% CI)†
Follow-up, y			
1-5	3287.0	98.9	30 (24-36)
6-10	2050.6	67.8	33 (25-42)
11-15	1148.2	45.6	40 (28-52)
16-20	651.7	11.1	17 (8-29)
21-31	291.9	6.2	21 (7-43)
1-15	6485.8	211.3	33 (28-38)
16-31	943.6	17.3	18 (10-29)
Age at diagnosis, y			
55-59	783.2	12.8	16 (8-27)
60-64	1849.1	49.6	27 (19-36)
65-69	2275.3	66.2	29 (22-37)
70-74	2521.7	99.9	40 (31-48)
Gleason score‡			
2-4	1784.9	10.7	6 (2-11)
5	1413.7	16.6	12 (6-19)
6	2803.2	83.4	30 (23-37)
7	976.3	63.4	65 (49-83)
8-10	451.2	54.4	121 (90-156)
Overall	7429.3	228.6	31 (26-35)

Abbreviation: CI, confidence interval.

*The numbers include fractions because the 25 deaths for whom the cause of death was unavailable are attributed to deaths from prostate cancer and deaths from other causes in the same proportions as were observed for the deaths in each Gleason score category in which the cause was available. Thus, the overall 228.6 deaths from prostate cancer include 222 men for whom cause of death information was available, plus 6.6 of the 25 men for whom it was not. Confidence intervals incorporate the uncertainty involved in this imputation.

†Deaths per 1000 person-years.

‡For a description of Gleason scores, see the "Methods" section in the text.

for identifying a specific cause of death, we have determined through 2 independent validation studies that prostate cancer mortality can be classified reliably (concordance with medical record review of 87%-96%) when cause of death is recorded as a dichotomous variable (ie, the patient died from prostate cancer or a competing medical condition).^{6,7} The misclassification of a small number of patients in either study may explain the different findings at years 15 and 20. Overall, the prostate cancer mortality rates determined in both studies are remarkably similar.

The clinical implications of both studies should be the same. Men with well-differentiated disease rarely require treatment, while men with poorly differentiated disease treated with androgen deprivation alone will usually die from prostate cancer. Radical prostatectomy may reduce disease-specific mortality by half.⁸ However, for those men who have PSA recurrence follow-

ing surgery, there is a high probability of disease progression during a period of 10 to 15 years; this most commonly occurs in men who have poorly differentiated disease.⁹

Counseling men who have moderately differentiated disease (Gleason score of 5-6 and/or World Health Organization grade 2) and a life expectancy of more than 15 years poses the greatest challenge. A majority of these men will die from competing medical conditions during a period of 15 to 20 years. Until better prognostic markers are developed, physicians will continue to recommend aggressive treatments at the time of diagnosis.

Repeated PSA testing is exacerbating this dilemma by introducing a lead time of many years. The data from our study and Johansson et al¹ are derived from patients diagnosed with prostate cancer before the advent of PSA testing. Based on data collected by the Rotterdam section of the European Ran-

domized Study of Screening for Prostate Cancer, Draisma et al⁴ have developed models that estimate the impact of PSA testing on lead time and the probability of detecting clinically insignificant disease. These depend on a man's age at screening. For a single PSA screening test at age 55 years, the estimated lead time was 12.3 years (range, 11.6-14.1 years) and the likelihood of detecting clinically insignificant disease was 27% (range, 24%-37%). At age 75 years, the estimated lead time was only 6.0 years (range, 5.8-6.3 years), but the likelihood of detecting clinically insignificant disease increased to 56% (range, 53%-61%). Draisma et al⁴ estimated that annual PSA testing from ages 55 to 67 years would yield insignificant cancers in approximately half of all men diagnosed with localized prostate cancers and would increase a person's lifetime risk of being diagnosed with prostate cancer by 80%.

Thompson et al¹⁰ have recently demonstrated that the pool of subclinical prostate cancer is much larger than prostate cancer mortality statistics would suggest. After analyzing data from a large chemoprevention study comparing finasteride with placebo, they found that the prevalence of prostate cancer was 6.6% among men whose PSA was consistently less than 0.5 ng/mL and as high as 26.9% among men whose PSA was between 3.1 and 4.0 ng/mL. It is unclear whether these tumors will progress at the same rate as described by our study and Johansson et al.¹ Length time bias would result in PSA testing preferentially identifying slower growing tumors. Evidence supporting the impact of length time bias is found in a recent study by Stamey et al¹¹ who reviewed pathology specimens from 1317 consecutive men undergoing radical prostatectomy at Stanford University during the past 20 years. They found that the size of the prostate cancers identified by PSA testing has decreased steadily since 1983 and that an increased PSA level in 2004 more commonly reflects benign prostate enlargement rather than prostate cancer.

A limitation of our study is that many of the patients did not undergo a complete metastatic evaluation and the actual stage of the disease at diagnosis may have been worse than our classification. Before the advent of contemporary transrectal ultrasound-guided biopsies, which often include 10 to 12 cores, 40% of patients with newly diagnosed disease had clinical evidence of extracapsular disease.¹² Catalona et al¹³ have shown that more than half of all patients presenting with a serum PSA level of more than 10 mg/mL have pathological evidence of extracapsular disease. Because none of the patients included in our series underwent PSA testing, there is a high probability that the series contains a number of men with extracapsular disease. Therefore, our results most likely underestimate survival for contemporary patients with localized prostate cancer.

Extended follow-up of our competing risk analysis suggests that prostate

cancer progression rates do not increase after 15 years of follow-up. Men with low-grade prostate cancer have only a small risk of prostate cancer progression even after 20 years of management by observation or androgen withdrawal therapy alone. These results do not support aggressive treatment of localized low-grade prostate cancer. Men with poorly differentiated disease (Gleason scores of 7 and 8-10) have a high risk of death from prostate cancer; only 3 men were alive after 20 years. Men with moderate-grade disease (Gleason scores of 5-6) have an intermediate cumulative risk of prostate cancer progression after 20 years of follow-up. Our data provide what are likely overestimates of prostate cancer progression when men are treated by observation or androgen withdrawal therapy alone. Only through randomized controlled trials designed to measure the efficacy of screening and treatment for prostate cancer can we an-

swer questions concerning which patients may truly benefit. Such trials are currently under way in Sweden, England, and the United States.¹⁴⁻¹⁷

Author Contributions: Dr Albertsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Albertsen.

Acquisition of data: Albertsen, Fine.

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Drafting of the manuscript: Albertsen, Hanley.

Critical revision of the manuscript for important intellectual content: Albertsen, Hanley, Fine.

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