Natural History of Early, Localized Prostate Cancer

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Context Among men with early prostate cancer, the natural history without initial therapy determines the potential for survival benefit following radical local treatment. However, little is known about disease progression and mortality beyond 10 to 15 years of watchful waiting.

Objective To examine the long-term natural history of untreated, early stage prostatic cancer.

Design Population-based, cohort study with a mean observation period of 21 years.

Setting Regionally well-defined catchment area in central Sweden (recruitment March 1977 through February 1984).

Patients A consecutive sample of 223 patients (98% of all eligible) with early-stage (T0-T2 NX M0 classification), initially untreated prostatic cancer. Patients with tumor progression were hormonally treated (either by orchiectomy or estrogens) if they had symptoms.

Main Outcome Measures Progression-free, cause-specific, and overall survival.

Results After complete follow-up, 39 (17%) of all patients experienced generalized disease. Most cancers had an indolent course during the first 10 to 15 years. However, further follow-up from 15 (when 49 patients were still alive) to 20 years revealed a substantial decrease in cumulative progression-free survival (from 45.0% to 36.0%), survival without metastases (from 76.9% to 51.2%), and prostate cancer–specific survival (from 78.7% to 54.4%). The prostate cancer mortality rate increased from 15 per 1000 person-years (95% confidence interval, 10-21) during the first 15 years to 44 per 1000 person-years (95% confidence interval, 22-88) beyond 15 years of follow-up ($P=.01$).

Conclusion Although most prostate cancers diagnosed at an early stage have an indolent course, local tumor progression and aggressive metastatic disease may develop in the long term. These findings would support early radical treatment, notably among patients with an estimated life expectancy exceeding 15 years.

JAMA. 2004;291:2713-2719 www.jama.com

WITHOUT UNDERSTANDING the natural history of prostate cancer diagnosed at an early, localized stage, patient counseling and clinical management are difficult. The challenge is to maximize the possibilities for survival without extensive overtreatment. Even without initial treatment, only a small proportion of all patients with cancer diagnosed at an early clinical stage die from prostate cancer within 10 to 15 years following diagnosis.[1-3] However, to our knowledge, no study has hitherto adequately analyzed whether patients who escaped metastasis and death during those 10 to 15 years without treatment continue to have an indolent, nonfatal disease course or whether in the long term, tumor progression takes a more aggressive course. Recently, a randomized trial[4] demonstrated that radical prostatectomy may further reduce the low-death rate in early prostate cancer by approximately 50%. Because it takes several years after operation for this benefit to emerge, age at diagnosis, comorbidity that influences life expectancy, and long-term natural history will determine the potential advantage with radical primary treatment.

For editorial comment see p 2757.

This study focuses on information that aids clinical decision making, namely the association between prognostic factors available at diagnosis and the long-term natural history in patients without initial treatment. Such knowledge can help us understand whether there are men with prostate cancer and a long life expectancy in whom early radical treatment might be justified despite the fact that they have favorable prognostic signs seen from a perspective of 5 to 10 years of follow-up. We studied these issues prospectively in the largest population-based cohort ever impaneled to analyze survival following watchful waiting of patients with early prostate cancer. Complete fol-

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Table 1. Characteristics of 223 Patients With Early Prostate Cancer (T0-2 NX M0) Who Received No Initial Treatment According to Age, Tumor Stage, and Grade at Time of Diagnosis in 1977-1984*

Category	Total No. of Patients	Progression, No. (%)			Cause of Death, No. (%)	
		T3	M1	Total	Prostatic Cancer	Other Cause†
Age, y						
<61	13	6 (46)	4 (31)	6 (46)	3 (23)	3 (23)
61-70	86	40 (46)	22 (26)	46 (53)	19 (22)	59 (69)
71-80	96	26 (27)	13 (14)	29 (30)	12 (12)	79 (82)
≥81	28	8 (29)	0 (0)	8 (29)	1 (4)	27 (96)
Tumor stage‡						
T0l	72	14 (19)	11 (15)	17 (24)	10 (14)	55 (76)
T0d	34	14 (41)	8 (24)	17 (50)	8 (24)	26 (76)
T1-T2	117	52 (44)	20 (47)	55 (47)	17 (15)	87 (74)
Grade§						
1	148	42 (28)	18 (12)	45 (30)	14 (9)	118 (80)
2	66	35 (53)	16 (24)	38 (58)	16 (24)	46 (70)
3	9	3 (33)	5 (56)	6 (67)	5 (56)	4 (44)
Total, No. (%)	223	80 (36)	39 (17)	89 (40)	35 (16)	168 (75)

*The number of patients with progression of the tumor manifested by local growth (T3) or distant metastases (M1) and the number and causes of death are shown.
†Three patients died of cardiovascular disease during treatment with estrogens.
‡T0 indicates clinically occult, incidental; T01, T0pT localized (cancer <25% of the total specimen); T0d, T0pT diffuse (cancer ≥25% of the total specimen); T1-2, confined to prostate gland (T1, nodule surrounded by normal prostatic tissue; T2, large nodule or multiple nodules; and T3, localized to periprostatic area). These grades correspond to the TNM classification from 1978.[5] In the classification from 2002, T1 is considered no evidence of clinical disease and T2 is considered palpable disease.
§Grade 1 indicates highly differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. These grades refer to the World Health Organization classification of malignant diseases.[6] They are not directly translatable to the Gleason grading system. However, in an earlier report,[1] grade 1 was compared with Gleason score 2 to 4, grade 2 with Gleason score 5 to 7, and grade 3 with Gleason score 8 to 10.

low-up of this cohort has now been achieved during an average of 21 years, and only 9% of the patients are still alive.

METHODS

Patients

The patients comprised a population-based cohort of patients with early, initially untreated prostate cancer as previously described in detail.[3] The TNM system[5] and the World Health Organization[6] classification of malignant diseases were used. At the time of diagnosis, all patients underwent a clinical examination, excretory urography, chest radiography, bone scan, and skeletal radiography (if needed) and had routine blood samples taken. The nodal status was not known for any of the patients. Prostate-specific antigen (PSA) testing was not available, and no screening activities for prostate cancer took place during the period when this cohort was recruited.

From March 1977 through February 1984, a total of 654 new cases of prostate cancer were diagnosed among residents in the regionally well-defined catchment area in central Sweden. Patients were given no initial treatment if the tumor growth was localized to the prostate gland as judged by digital rectal examination (T0-T2) and no distant metastases were present (306 patients). This was in accordance with the standard management at the time in Sweden. The following restrictions were applied, however, among those with palpable tumors (T1-T2). From March 1977 through February 1979, only patients with a highly differentiated tumor (grade 1) were included in the untreated group. From March 1979 through the end of the recruitment period, patients younger than 75 years at diagnosis and with moderately or poorly differentiated tumors (grades 2-3) were randomly allocated to receive local radiation (10 patients) or no treatment, and only the latter group was included in this cohort study. Patients 75 years or older were not treated and included in the study.

Among the 227 eligible patients, 4 (2%) were given initial treatment and had to be excluded from the analyses. The distribution of the study group of 223 patients by age, stage, and grade at the time of diagnosis is shown in TABLE 1. The mean age at diagnosis was 72 years (range, 41-91 years). Altogether 106 (48%) cases were detected by histopathologic examinations of specimens obtained at operations for suspected benign prostatic hyperplasia. The remaining 117 patients had a palpable clinical disease localized to the prostate gland. A review by an experienced histopathologist confirmed the initial diagnosis in all cohort members. Approximately two thirds of patients had highly differentiated tumors, whereas only 9 (4%) had a poorly differentiated tumor (Table 1).

Procedures

All 223 patients were followed up from diagnosis until death or the end of the observation period (September 1, 2001). No patient was lost to follow-up. Clinical examination, laboratory tests, and bone scans were performed every 6 months during the first 2 years after diagnosis and subsequently once a year during the first 10 years of observation and thereafter at least once every second year. Those in whom the cancer progressed to symptomatic disease were treated with exogenous estrogens or orchidectomy.

Local progression was defined as tumor growth through the prostate capsule (T3) as judged by digital rectal examination. Development of distant metastasis (M1) was classified as generalization. If both local progression and metastatic disease were present, the patient was classified as having generalized disease.

During the first 6 years of follow-up, all patients who were still alive and consented underwent a new fine-needle biopsy every other year. We obtained such biopsy specimens from 178 (80%) of the 223 patients. Although this procedure has lower than 100% sensitivity, notably for impalpable tumors, remaining cancer growth was con-

firmed cytologically in most patients: 45 (73%) among those with T01 disease, 24 (92%) among those with T0d disease, and 90 (100%) among those with T1-2 disease. Altogether 31 (17%) of 178 patients showed evidence of dedifferentiation. Twenty-one patients (18%) changed from high to moderate differentiation, 7 (13%) from moderate to low differentiation, and 3 (3%) from high to low differentiation.

The medical records of all deceased patients were reviewed. In most instances, the cause of death determined in real time was obvious on clinical grounds alone. An autopsy was performed if the cause of death was not clear. Prostate cancer was recorded as the underlying cause of death, a contributory cause of death, or unrelated to death as described in detail in a previous report.[3] If treatment of the prostate cancer was related to death (chiefly due to cardiovascular complications following estrogen administration), prostate cancer was recorded as a contributory cause. As a validation, we compared our own classification of causes of death with those recorded in the Swedish Death Register. This information was obtained through record linkage between our study cohort and the Swedish Death Register based on the individually unique national registration number assigned to all Swedish residents. There was agreement in 90% of the patients and no evidence of systematic overascertainment or underascertainment of prostate cancer as cause of death in our data. Although based on small numbers, there was no evidence that the disagreement was larger in older than in younger patients.

Statistical Methods

We estimated various measures of patient survival using the actuarial (life-table) method.[7] Cause-specific survival was estimated by considering only deaths due to prostate cancer as events of interest (deaths due to other causes were considered censored), observed survival by considering deaths due to any cause as events, and progression-free survival by considering progression as the event of interest. We also estimated relative survival, defined as the ratio of observed survival to the expected survival of a comparable group from the general population assumed to be free of prostate cancer. We estimated expected survival using the Hakulinen method[8] based on Swedish population life tables stratified by age, sex, and calendar time. We also calculated prostate cancer–specific mortality rates (deaths per 1000 person-years at risk) and associated 95% confidence intervals (CIs).[9] We estimated Poisson regression models[9] to study the association between prostate cancer mortality and time since diagnosis while adjusting for age at diagnosis, stage, and grade. Relative survival was estimated using software developed at the Finnish Cancer Registry.[10] All other analyses were performed using Stata statistical software (Stata Corporation, College Station, Tex). All reported *P* values are 2-sided. Statistical significance was $P<.05$.

Table 2. Rates per 1000 Person-Years for Progression to Metastatic Disease and Death Due to Prostate Cancer by Years of Follow-up, Age, Stage, and Grade at Diagnosis*

	Progression		Prostate Cancer Death	
Category	No. of Events	Rate (95% CI)	No. of Events	Rate (95% CI)
Follow-up, y*				
0-4	18	20 (13-32)	11	12 (7-22)
5-9	9	15 (8-30)	11	18 (10-33)
10-14	5	16 (7-38)	5	15 (6-36)
≥15	7	41 (20-87)	8	44 (22-88)
Age, y				
≤70	26	24 (16-35)	22	19 (13-29)
≥71	13	15 (9-26)	13	15 (8-25)
Stage				
T01	11	17 (9-30)	10	15 (8-28)
T0d	8	31 (15-62)	8	28 (14-57)
T1-2	20	19 (12-30)	17	16 (10-25)
Grade				
1	18	13 (8-21)	14	10 (6-17)
2	16	29 (18-47)	16	27 (17-44)
3	5	242 (101-581)	5	194 (81-466)
Total	39/223 (17)	20 (14-27)	35/223 (16)	17 (12-24)

Abbreviation: CI, confidence interval.
*Numbers of patients alive after 5 years were 150; 91 after 10 years; and 48 after 15 years.

RESULTS

Overall Findings

During a mean observation period of 21 years, 89 patients (40%) experienced progression of disease, and of these 39 (17% of the entire cohort) developed generalized disease. A total of 203 patients (91% of the entire cohort) died during follow-up, with prostate cancer considered the cause of death in 35 (16% of the entire cohort; Table 1). Among patients who were 70 years or younger at diagnosis, 22 (22%) died from prostate cancer during follow-up, whereas this proportion decreased markedly at higher ages. The proportion of patients dying from prostate cancer was strikingly similar among those with nonpalpable (T0) tumors detected at transurethral resection (18 patients [17%]) and those with a palpable tumor (17 patients [15%]). In contrast, poor differentiation was a strong predictor of prostate cancer–specific death (Table 1).

Progression and Survival Rates

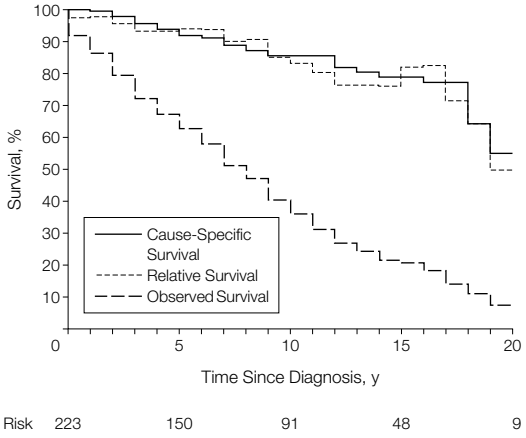
Although based on small numbers, the progression and mortality rates remained fairly constant during the first three 5-year periods following diagnosis (TABLE 2). Averaged over the first 15 years, the rate of progression to metastatic disease was 18 per 1000 person-years (95% CI, 13-25) and the prostate cancer mortality rate was 15 per 1000 person-years (95% CI, 10-21). In

Table 3. The 15- and 20-Year Progression-Free Survival, Observed Survival, Relative Survival, and Cause-Specific Survival Rates by Stage and Grade at Diagnosis*

	Percentage of Survival (95% Confidence Interval)							
	Progression Free		Observed		Relative		Cause Specific	
Category	15 Years	20 Years	15 Years	20 Years	15 Years	20 Years	15 Years	20 Years
Stage								
T01	57.7 (38.9 to 76.5)	52.5 (32.7 to 72.3)	22.2 (12.4 to 32.0)	7.5 (–0.1 to 15.0)	82.1 (45.9 to 118.4)	56.1 (0.6 to 112.8)	81.1 (66.5 to 5.6)	57.9 (28.3 to 87.5)
T0d	35.9 (15.1 to 56.5)	17.9 (–9.5 to 45.3)	14.7 (2.6 to 26.8)	0	63.6 (11.1 to 116.1)	0	69.7 (50.1 to 89.2)	46.4 (6.3 to 86.5)
T1-2	38.4 (26.8 to 50.1)	33.1 (20.9 to 45.4)	23.1 (15.3 to 30.9)	10.3 (4.2 to 16.3)	75.2 (49.8 to 100.6)	61.5 (25.2 to 97.9)	80.3 (69.8 to 90.8)	56.9 (34.9 to 78.9)
Grade								
1	56.0 (44.4 to 67.6)	46.0 (30.9 to 61.0)	24.3 (17.2 to 31.4)	9.7 (4.3 to 15.1)	83.7 (59.4 to 108.0)	63.4 (28.1 to 98.8)	88.9 (81.4 to 96.3)	71.8 (54.9 to 88.7)
2	28.8 (15.2 to 42.3)	24.3 (10.2 to 38.4)	18.2 (8.7 to 27.7)	3.5 (–1.8 to 8.7)	64.7 (30.9 to 98.4)	23.4 (–12.0 to 58.7)	64.5 (47.2 to 81.8)	22.1 (–7.5 to 51.7)
3	15.6 (–12.8 to 43.9)†	0	0	0	0	0	28.6 (5.6 to 62.7)†	0
All patients	45.0 (35.7 to 54.3)	36.0 (24.2 to 47.9)	21.5 (16.0 to 27.0)	7.5 (3.5 to 11.4)	75.9 (56.5 to 95.3)	49.9 (23.4 to 76.4)	78.7 (70.8 to 86.7)	54.5 (37.6 to 71.4)

*For definitions of tumor stages and grades, see Table 1 footnotes.
†After 7 years.

Figure 1. Survival of Prostate Cancer Patients (n = 223)



contrast, an approximately 3-fold higher rate was found both for progression and death during follow-up beyond 15 years (Table 2). This increase was almost statistically significant for progression ($P = .06$) and statistically significant for death ($P = .01$).

TABLE 3 shows various measures of survival after 15 and 20 years of follow-up. During this 5-year period, the progression-free survival among all patients decreased from 45.0% to 36.0%. The low and rapidly decreasing observed survival reflects chiefly the impact of causes of death other than prostate cancer. Most notably, however, we found a substantial decline by approximately 25 percentage points in both the relative and the cause-specific survival rate during the last 5 years of follow-up. FIGURE 1 further illustrates how a gradual decline in relative and cause-specific survival seemingly occurred more rapidly after approximately 16 years of follow-up. This change seemed to affect tumors regardless of initial stage and also to affect tumors that were both initially highly and moderately differentiated (FIGURE 2). The gloomy outlook among patients with poorly differentiated tumors became manifested already within the first 5 years of follow-up.

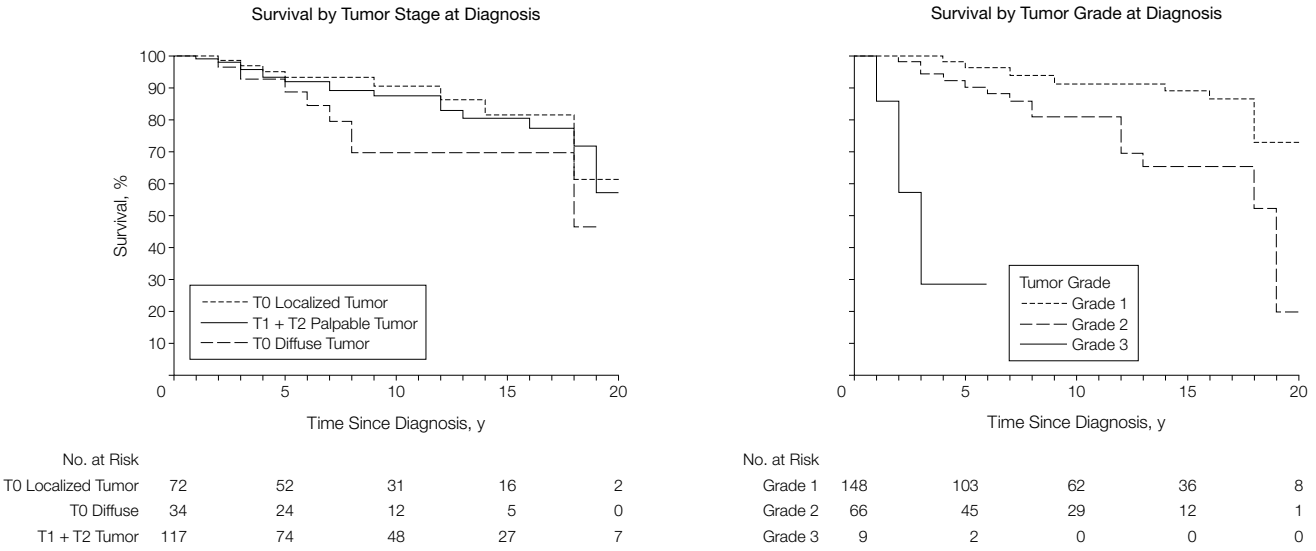
Prostate cancer mortality was slightly higher among patients whose cancer was diagnosed at 70 years or younger than among those whose cancer was diagnosed at older ages (Table 2). Strikingly similar mortality rates were found among patients who had localized nonpalpable cancer compared with those who had a cancer in stage T1 or T2. In contrast, the mortality rate was 70% higher among men with a nonpalpable diffuse cancer. With regard to differentiation, the mortality rate increased drastically from highly to poorly differentiated tumors (Table 2).

Multivariable Analyses

Multivariable Poisson regression models were fitted to quantify the independent effects of follow-up time, age at diagnosis, grade, and stage (TABLE 4). Our analyses showed a significant (approximately 6-fold) higher mortality rate after 15 years of follow-up compared with the first 5 years. The strong prognostic impact of grade, notably of poorly differentiated tumors, was also confirmed. In contrast, neither age at diagnosis nor stage of disease was significantly associated with risk of death due to prostate cancer. Although we had limited power to test interaction, the risk of death due to prostate cancer after 15 or more years of follow-up compared with 0 to 14 years was similar among patients with cancer diagnosed before (relative risk, 4.1) and after (relative risk, 3.1) 70 years of age.

A separate model was fitted in which the event of interest was local progression. In this analysis, we disregarded if and when regional and/or distant progression or metastases were ascertained. Except for age at diagnosis, the pattern for local progression was strikingly different from that of death due to prostate cancer (Table 4). Hence, the

Figure 2. Cause-Specific Survival by Stage of Disease and Tumor Grade at Diagnosis



Disease stages were T0 localized, T0 diffuse, and T1-T2. Grades were as follows: grade 1, highly differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated.

risk of local progression did not increase over follow-up time, and the association with grade was weak. Moreover, compared with T01 tumors, growth beyond the prostate capsule was 2 or 3 times more likely in patients with T0d and T1-2 tumors, respectively.

COMMENT

Although our cohort of patients with early stage, initially untreated prostate cancer has been previously followed up in great detail during an average of 15 years,[3] the additional 6 years included in this analysis revealed an unexpected change in prognostic outlook; the cause-specific survival rate decreased by almost 25 percentage points, reflecting an approximate 3-fold increase in prostate cancer mortality rate compared with the first 15 years of follow-up. This change occurred consistently across stage and grade except for poorly differentiated cancers in which excess mortality becomes manifest already during early follow-up. We were unable to conceive of any bias that could have spuriously generated these recent findings. Indeed, the internal validity of our population-based study should be high because we achieved complete follow-up and used standardized procedures for clinical examination, ascertainment of disease progression, and classification of death. Moreover, the slight difference between cause-specific and relative survival estimates were largely consistent over time. This argues against any shifting criteria for classification of cause of death, since the relative survival rate reflects excess mortality (compared with mortality in the general population) and is thus unaffected by any subjective judgment. Prostate cancer mortality rates were mirrored closely by rates of disease progression to metastatic disease. Hence, chance is the only realistic alternative to a real deterioration in prognosis after long-term follow-up, and the level of statistical significance argues against this explanation.

If our data reflect a real phenomenon, they would imply that the probability of progression from localized and indolent to metastatic mortal disease increases markedly after long-term follow-up. This progression is not restricted to cancers diagnosed due to clinical symptoms but includes also tumors detected incidentally at transurethral resection due to presumed benign prostatic hyperplasia. Our survival data, supported by biopsy specimens taken during follow-up, would further im-

Table 4. Multivariable Relative Risks of Death From Prostate Cancer and Local Progression (Growth Through the Prostate Capsule) in Relation to Follow-up Time, Age at Diagnosis, Tumor Grade, and Tumor Stage*

Category	Relative Risk (95% Confidence Interval)	
	Death	Local Progression
Follow-up, y		
0-4	1.0	1.0
5-9	2.2 (0.9-5.5)	0.6 (0.3-1.1)
10-14	2.0 (0.6-6.3)	0.6 (0.3-1.3)
≥15	6.4 (2.3-17.8)	0.8 (0.3-2.1)
Age at diagnosis, y		
<70	1.0	1.0
≥70	0.7 (0.3-1.6)	0.9 (0.6-1.5)
Grade		
1	1.0	1.0
2	3.4 (1.6-7.3)	2.5 (1.6-4.0)
3	46.6 (12.3-177.4)	3.3 (0.9-11.9)
Stage		
T01	1.0	1.0
T0d	0.7 (0.2-2.1)	2.0 (0.9-4.4)
T1-2	0.7 (0.3-1.6)	2.7 (1.5-4.9)

*Estimated using Poisson regression where each factor is simultaneously adjusted for all other factors. For definitions of tumor stage and grade, see Table 1 footnotes.

ply that these latter lesions are either incompletely removed or multifocal with malignant clones left at a transurethral resection. Contrary to emerging views,[11,12] our data also suggest that metastases may arise as a consequence of late mutations rather than being determined already by the early mechanisms of malignant transformation. According to a rival interpretation, the phenomenon we observed reflects transformation of new, more aggressive cancer clones rather than progression of those initially detected. Empirical testing of these complementary, but not mutually exclusive, theories seems difficult.

It may be difficult to validate our survival data in any new cohort study of watchful waiting since aggressive treatment of localized prostate cancer has become more routine now than it was 25 years ago when we started to assemble our cohort.[13-16] Indeed, it has been estimated that approximately 60 000 men undergo radical prostatectomy yearly in the United States alone, and the number performed annually in England increased nearly 20-fold between 1991 and 1999.[17] This development toward treatment with a curative intent may further accelerate following recent documentation that radical prostatectomy reduces prostate cancer mortality by approximately 50%.[4] Hence, support for our findings has to be found chiefly in existing studies of watchful waiting. Other such cohorts are, however, few and small, none of them are population based and prospective,[2,18-20] and virtually no follow-up data are available beyond 15 years after diagnosis. Within these constraints, experience during the first 10 years after diagnosis is strikingly similar in existing cohorts of patients with early stage prostate cancer left without initial treatment, with a favorable course of the disease for men with highly or moderately differentiated tumors.[1]

From a public health perspective, implications of late progression from early stage to mortal disease may not be significant because without PSA testing, average age at diagnosis of prostate cancer is so high that competing causes of death predominate (Table 1). Although it is well established[21,22] that an excess death rate continues long term in population-based cohorts of prostate cancer patients, these data do not enable distinction of deaths generated by patients initially diagnosed as having localized disease. In our entire cohort, 25 (11%) of 223 patients died from prostate cancer within 15 years of diagnosis and an additional 10 during subsequent follow-up until a time when only 9% of all patients in the cohort were still alive and therefore at risk of progression. Assuming that radical prostatectomy prevents approximately 50% of prostate cancer deaths,[4] approximately 18 patients (8%) in our entire cohort (that is, 0.5×35) would have experienced a survival benefit, whereas the remaining 205 would not. However, among elderly men, reducing the risk of death from prostate cancer by a certain amount may have limited impact on their overall survival.

Our data may be important for counseling and clinical management of individual patients. Postponement of death is not the only treatment objective because local progression may create substantial suffering. Indeed, many of our patients experienced symptomatic local growth without generalized disease (Table 1), requiring treatment with estrogens or orchidectomy. Obviously, radical prostatectomy is a major procedure with substantial adverse effects, chiefly impotence and incontinence.[23,24] Because these complications are surprisingly well tolerated,[25] many patients may prefer a radical prostatectomy even if prolonged survival is an uncertain consequence. Our data may be particularly relevant to otherwise healthy men diagnosed as having prostate cancer at an early age. If such patients are in their 60s or younger, disease progression that occurs after 15 or more years may be a real concern, arguing for early local treatment with a curative intent. In patients with a PSA-detected cancer,[26] such counseling is, however, complicated by the fact that a lead time that cannot be individually determined has to be added to the approximately 15 years that may precede more rapid tumor progression.

One important and complicated question is how the findings of this study relate to the current era when many patients are detected by means of PSA testing. The results are directly relevant for patients with clinical disease diagnosed before the PSA era and also to preclinical disease detected at transurethral resection for presumed benign prostatic hyperplasia. Indeed, as shown in Table 4, these 2 categories of patients experienced similar risk of dying from prostate cancer. The natural history we have described reflects also what would happen among PSA-detected cancer if the lead time could be accommodated and the patients were left without early therapeutic intervention. However, a substantial proportion of PSA-diagnosed cancers represents overdetection of subclinical disease. These cancers would never have surfaced clinically during the patient's lifetime, either because they are indolent or because death occurs from competing causes before clinical manifestation of the malignancy. By definition, these cancers do not generate any mortality.

In conclusion, our data indicate that the probability of progression to a more aggressive and lethal phenotype may increase after long-term follow-up of prostate cancers that are diagnosed at an early stage and initially left without treatment. These findings argue for early radical treatment of patients with long life expectancy. Not only would such surgical intervention potentially prevent deaths, it would also convey prevention from disability caused by local tumor growth.

Author Contributions: Dr Johansson, as principal investigator, had full access to all of the data in this study and takes responsibility for the integrity of these data and the accuracy of the data analysis.
Study concept and design: Johansson, Andersson, Adami.
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Analysis and interpretation of data: Johansson, Andersson, Dickman, Holmberg, Magnuson, Adami.
Drafting of the manuscript: Johansson, Andren, Andersson, Magnuson, Adami.
Critical revision of the manuscript for important in-

tellectual content: Johansson, Andrén, Andersson, Dickman, Holmberg, Adami
Statistical expertise: Dickman, Magnuson.
Obtained funding: Johansson.
Administrative, technical, or material support: Johansson, Andrén, Andersson, Adami.
Study supervision: Adami.

Funding/Support: This study was supported by grants from the Örebro County Council Research Committee, the Örebro University Hospital Research Foundation, Öbrebro, Sweden, and the Swedish Cancer Society.
Disclaimer: Study sponsors had no role in data Collection, analysis, manuscript preparation, or authorization for publication.
Acknowledgment: We thank the Örebro County Council Research Committee, University Hospital Research Foundation, and the Swedish Cancer Society.

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