Screening for prostate cancer: updated experience from the Tyrol study

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Objectives: *The aim of this study was to monitor the impact of prostate cancer screening in a natural experiment by comparing prostate cancer mortality in Tyrol, Austria, where prostate-specific antigen (PSA) testing was made available at no charge, with the rest of Austria, where this screening was not introduced.*

Methods: *In 1993, PSA testing was made freely available to men aged 40 to 79 years old living in the Federal State of Tyrol, Austria. In the first 10 years of this study, at least 70% of all men in this age range had PSA tests done at least once. Initially, only total PSA was measured, but free PSA measurement was added in 1995, and complexed PSA was added in 2001. Digital rectal examination (DRE) was not part of the screening examination.*

Results: *Significant migration to lower clinical as well as pathological prostate cancer stages has been observed in patients undergoing radical prostatectomy since the introduction of this screening program. A reduction in mortality rates from prostate cancer in Austria occurred from 1993 onward, with a much greater reduction in Tyrol; mortality remained fairly constant between 1993 and 1995 and subsequently fell. From 1993 to 2000 (the most recent data), there was a significantly greater decrease in the rate of prostate cancer mortality in Tyrol compared to the rest of Austria (P value = 0.006). Based on age-specific death rates for men aged 40 to 79, the difference between the number of expected and observed deaths from prostate cancer in Tyrol was 22 in 1998 (a 42% decrease), 18 in 1999 (a 33% decrease) and 25 in 2000 (a 44% decrease).*

Conclusions: *These findings are consistent with the hypothesis that a policy of making PSA testing freely available, and wide acceptance by men in the population, is associated with a reduction in prostate cancer mortality in an area in which urology services and radiotherapy are available freely to all patients. It is our opinion that most of this decline in mortality is likely to be due to aggressive downstaging and successful treatment and that any contribution from detecting and treating early cancers will only become apparent in the years to come.*

Key Words: prostate cancer, PSA screening, prostate cancer mortality

Introduction

In the early 1990s a remarkable increase in the incidence of prostate cancer was observed in many countries, notably the United States.[1] This observation can be attributed to the widespread use of prostate-specific antigen (PSA) testing, which was first approved for the detection of recurrent disease in patients with established prostate cancer in 1986. The potential of this test for early diagnosis of prostate cancer was quickly recognized. From 1984 to 1994, the use of PSA testing for diagnostic purposes increased dramatically. In 1984, 5.1% of all newly diagnosed prostate carcinomas were detected by PSA testing; by 1994 this had increased to 60.6% of cases.[2] It has been shown that a great number of cancers detected by PSA testing are clinically significant and potentially curable.[3-6] The introduction of PSA testing in prostate cancer screening programs has, however, also led to controversy surrounding several distinct

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issues, including the sensitivity and specificity of the screening test, the treatment of early prostate cancer—and, indeed, whether some cancers will do equally well if left untreated — and the side effects of therapy, particularly radical prostatectomy. The two most common cancer screening programs, mammographic examination for breast cancer and Papanicolaou smears for cervical cancer, came into common use and acceptance through widely different mechanisms: the results of randomized trials of mammographic screening for breast cancer, and the observation of the decrease in incidence and mortality from cervical cancer after the policy to introduce cervical cancer screening to populations.

The present study reports the incidence and mortality rates of prostate cancer in the Federal State of Tyrol, Austria, where PSA testing has been made freely available to the population since 1993 and where use of the test has been high. This population is also characterized by being particularly stable. PSA testing was not freely available in the rest of Austria, although it was used, probably evolving in a similar manner to the use in many Western countries. A comparison of the mortality rates between Tyrol and the rest of Austria allowed evaluation of the outcome of this natural experiment.

Materials and methods

In 1993, a mass prostate cancer screening project using the PSA test as the only screening test was launched in the Federal State of Tyrol (one of nine federal states of the Republic of Austria). Previously (1988 to 1992), both PSA tests and digital rectal examination (DRE) were available and used in the diagnostic work-up of symptomatic patients and also in a limited way for asymptomatic men. Since 1989, urologists at the Innsbruck University Hospital have promoted the concept of early prostate cancer detection using PSA and DRE. In 1989 to 1992, the number of PSA tests performed in this hospital rose from 2360 to 5878.

Tyrol is an alpine region in Western Austria with, in the 1991 census, 631,410 inhabitants (324,161 women and 307,249 men) in an area of 12,647 square kilometers. The region is dominated by the mountains of the Central Alps, and the distances from outlying towns to Innsbruck, the capital, where the central health-care unit is located, are not too far (infrequently more than 100 kilometers). This geographic situation, as well as the willingness of the general population to participate in preventive medical programs, led us to launch a state-wide mass screening program with PSA as the only screening test for early detection of prostate cancer. PSA testing was made freely available by the Social Insurance Company of the Federal State of Tyrol and the University Hospital of Innsbruck to all men aged 45 to 75 years. All men in this age range were advised and encouraged to undergo PSA testing, and information to this effect was distributed to all Tyrolean men by press, radio, and television.

The screening project was performed in collaboration with general practitioners, medical examiners, urologists, and technicians working in medical laboratories and the Tyrol Blood Bank of the Red Cross. Informed consent was obtained from all volunteers participating in the program. All individuals involved in PSA testing were fully informed of the guidelines for blood sample procurement and centrifugation, storage and shipping of serum samples. PSA was assessed immediately on arrival of the serum samples in the laboratory. Until 2001, PSA was determined using the Abbott IMX assay; since then, the Bayer ADVIA Centaur assay was used. All volunteers and/or referring physicians were informed of the PSA test results. In the case of elevated PSA levels, the men were invited to undergo additional urologic evaluations; men with normal PSA levels were invited to have a repeat PSA test 12 months later. More than 80% of all men found to have an elevated PSA level consented to an additional evaluation, which included DRE, transrectal ultrasound (TRUS), and prostate biopsy. At the time of the initial screening, blood was drawn for PSA measurement, but no DRE was performed. Several scientific studies[7-11] have been published describing this screening program. This mass screening program was provided free of charge to men from 40 to 79 years old. Initially, the biopsy criteria was an elevated age-referenced total PSA level[12] in combination with free PSA of less than 22%. Since October 1995, the biopsy criteria was an elevated "bisected" PSA levels[13] (one half the age-specific reference ranges, Table 1) together with free PSA levels of less than 18%. Since 2001, complexed PSA was also included in our diagnostic work-up. Screened volunteers with a PSA level greater than 10 ng/mL were recommended to

TABLE 1. **Bisected age specific reference ranges for total PSA**

Age (years)	Normal range (ng/ml)
45-49	0 – 1.25
50-59	0 – 1.75
60-69	0 – 2.25
70-75	0 – 3.25

undergo biopsy irrespective of their percent free PSA. Since March 1996, PSA transition-zone density[11] has been introduced as an additional diagnostic parameter in selecting patients for biopsy, to decrease the number of unnecessary biopsies. All men who, according to bisected age-referenced levels and free PSA concentrations, had an elevated PSA concentration were invited to undergo additional urologic evaluation, including DRE and ultrasound-guided biopsies. Urologists performed the DREs and TRUS examinations.

Sextant biopsies were initially made using ultrasound guidance with an automatic biopsy gun and an 18-gauge needle; since 1995, 10 systematic biopsies and since 2000 additional contrast enhanced color Doppler targeted biopsies have been performed.

Patients presenting with organ-confined lesions (T1 and T2) underwent radical prostatectomy or external beam radiotherapy if surgery was not acceptable to them (70.2 Gy, single fraction 1.8 Gy, four-box technique); those with Stage T3 lesions underwent external beam radiotherapy (70.2 Gy, single fraction 1.8 Gy, four-box technique); and those with metastatic disease underwent androgen deprivation therapy. Every patient with N1 or M1 disease received hormonal therapy. The policy was such that no patient was treated primarily by surveillance ("watchful waiting").

Data on cancer incidence have been available from the population-based Tyrol Cancer Registry since 1988. Cancer mortality data have been available, independently, from the Austrian Central Statistics Office since 1970. The underlying cause of death was attributed from the death certificates of all deaths in Austria by the Central Statistical Office in Vienna, where they were unaware of the study being performed in Tyrol. The numbers of cases and population estimates are available, annually, in 5-year classes of age. PSA tests were available at no charge for men aged 45 to 75 years, although use among men on either side of these age limits also occurred.

All incidence and mortality rates were calculated for the truncated age range (40 to 79 years) using the world standard population as the reference.[14]

The principal hypotheses tested were:

a) whether the prostate cancer mortality rates in Tyrol decreased starting in 1993 and
b) whether the trends in the prostate cancer mortality rates in Tyrol differed from those in the rest of Austria starting in 1993. The trends in the mortality rates in Tyrol and the rest of Austria were compared within a Poisson regression model:

$$\log(\text{rate}) = \beta 0 + \beta 1(\text{year} - 1993) + \beta 2(\text{year} - 1993)I(\text{year} \geq 1993) + \beta 3\text{Tyrol} + \beta 4\text{Tyrol} \times (\text{year} - 1993) + \beta 5\text{Tyrol} \times (\text{year} - 1993)I(\text{year} \geq 1993).$$

This is a "change-point" model in which the term "I(year ≥ 1993)" is an indicator that permits a different slope from 1993 onward compared with before 1993. The parameter β0 gives the estimated log mortality rate in the rest of Austria in 1993; β3 represents the difference from this value in Tyrol. A priori, no difference was anticipated. The slope of the relationship between the log mortality rates and time was given by β1 in the rest of Austria and β1 + β4 in Tyrol; thus β4 represented the difference in slopes before 1993. The parameter β2 gave an estimate of any change in slope from 1993 onward compared with 1992 and before in the rest of Austria. If no change occurred, the estimated value would be about 0; if treatment advances have occurred, a negative estimate would be expected. In Tyrol, the change in the slope from 1993 onward was given by β2+ β5. Thus β5 was the crucial parameter in the analysis, as it measured the different slope in Tyrol compared with the rest of Austria from 1993 onward. The goodness of fit of the model was established on the basis of residual plots, and the hypothesis tests were based on changes in the deviance.[15] All statistical analysis was carried out using Splus 2000.[16]

In this analysis we used 1993 as the reference year. This was the beginning of the period when the policy of PSA testing in Tyrol was different from the rest of Austria and so represents the earliest time at which any changes in the trend associated with the mass screening program might theoretically begin. Any other choice of reference year, such as 1995, could be open to criticism on the basis of a post hoc choice, even though one might argue that the earliest time one might begin to see a real benefit from screening would be about 2 years after the introduction. This is because the median survival time for metastatic prostate cancer is about 18 months. If the mass screening program had an effect on the mortality rates, using the earlier date would tend to give conservative results, because no difference in the rates in the two regions should occur for a certain period after the introduction of the mass screening program. The estimated benefit of the mass screening program was calculated by comparing the observed and expected numbers of deaths in Tyrol and by examining the prostate cancer mortality trends in the two regions. The expected numbers of cases and deaths for each year in Tyrol were calculated using the average of the rates from 1986 to 1990 as the reference. The effect of using the data for 1988 to 1990 in the calculation of the expected values should be conservative for

incidence and have no influence on mortality.

Results

During 1993, when PSA testing became freely available, 32.3% of all Tyrolean men between 45 and 75 years old underwent PSA screening; during the first 10 years of the study more than 70% of this population was tested at least once. At the laboratory of the Department of Urology, Innsbruck University, more than 96,000 had PSA tests done at least once. Of these, 10100 were aged 45 to 49 years old and 4900 were aged 40 to 44 years old. Since a substantial number of men aged 40 to 44 were screened, this age group was included in the analysis of the incidence and mortality rates.

From 1993 to 2001, a total of 6024 transrectal prostate needle biopsies — as described above — were performed. The overall prostate cancer detection rate was 30.2%. Table 2 summarizes the major and minor complications of these transrectal biopsies.

The incidence of prostate cancer in men aged 40 to 79 in Tyrol increased from 1988 to 1994 and since then has remained constant Figure 1. The incidence of organ-confined disease (stages I and II) continued to increase from 1988 until 1998, although the incidence of extraprostatic disease (stage III) declined following a peak in 1994. The incidence of metastatic disease (stage IV) has been declining since 1993 Figure 2. The stage reported to the Cancer Registry is a mixture of clinical and pathologic stages.

After the screening project started, a significant migration to lower total PSA levels in patients undergoing radical prostatectomy has been observed. Subsequently the rate of organ- confined diseases in radical prostatectomy increased from 28.7% in 1993 to over 80% in 2002 Table 3.

TABLE 2. **Complications of 6024 transrectal needle prostate biopsies**

n = 6024	
Gross haematuria > 1 day	12.5%
Haemospermia	29.8%
Significant pain	4.0%
Rectal bleeding	0.6%
Nausea	0.8%
Fever > 38.5°C	0.8%
Epididymitis	0.7%
Sepsis	0.3%

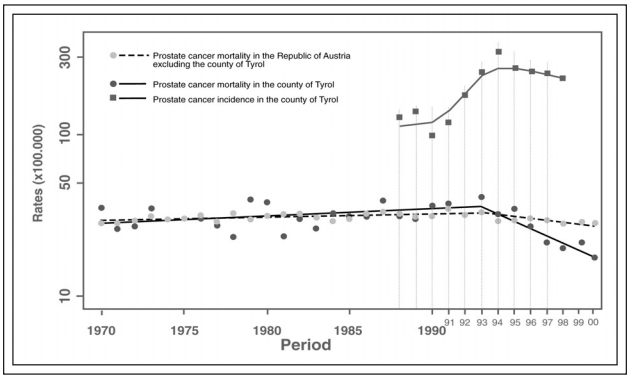

Figure 1. Prostate cancer incidence rates in Tyrol and prostate cancer mortality rates in Tyrol and in the rest of Austria.

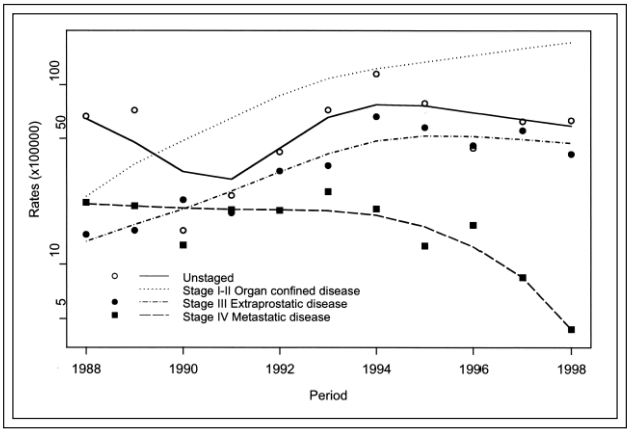

Figure 2. Prostate cancer incidence rates in Tyrol by stage in men aged 40 to 79.

TABLE 3. **Total-PSA and stage migration in radical prostatectomies since 1993**

Year	**Mean PSA ng/ml**	**Stage % of organ confined prostate cancer**
1993	14.9	28.7
1994	14.2	27.6
1995	12.7	25.1
1996	9.7	55.8
1997	8.6	65.7
1998	6.3	67.2
1999	6.2	79.1
2000	5.8	82.1
2001	5.3	82.0
2002	4.8	81.0

The mortality from prostate cancer in Tyrol decreased significantly between 1993 and 2000, in contrast to the modest downward trend in prostate cancer death rates observed in the rest of Austria Figure 1. In Tyrol, based on age-specific prostate cancer mortality rates (in the age range 40 to 79), 22 fewer prostate cancer deaths than expected occurred in 1998, 18 fewer deaths than expected occurred in 1999, and 25 fewer deaths than expected occurred in 2000 Table 4.

The fitted values of the model, as described above, are shown in Figure 1. No significant difference was found between the trends in Tyrol and the rest of Austria before 1993 (c2 = 1.12, 1 degree of freedom, P = 0.29). The log mortality rates increased at a rate of 0.0113 (standard error [SE] 0.005) per year in Tyrol and 0.0057 (SE 0.0014) in the rest of Austria from 1970 up to and including 1992. No significant difference was found between the estimated rates in 1993 in the two regions of Austria (P = 0.13). A decrease in mortality occurred in Tyrol after 1993 (c2 = 12.74, 1 degree of freedom, P = 0.0004), where the log mortality rates decreased at a rate of 0.092 (SE 0.024) per year from 1993 onward. In the rest of Austria, the decrease was 0.0229 (SE 0.0064) per year. From 1993 onward, the trends in the rates show a significant difference between Tyrol and the rest of Austria (x2 = 7.55, 1 degree of freedom, P = 0.006). In the analysis, we assumed linear trends between the log mortality rates and year, permitting changes in slopes from 1993 onward in Tyrol and in the rest of Austria. We tested whether the change in the slope from 1993 onward was the same in Tyrol as in the rest of Austria. This hypothesis was rejected. Although no statistically significant differences were observed between Tyrol and the rest of Austria before 1993, the fitted value in Tyrol in 1993 was slightly higher than in the rest of Austria Figure 1, and this may have some implications for the change in the slope. To investigate the effect of this, we constrained the line before 1993 to be exactly the same in Tyrol as in the rest of Austria. This was achieved by setting b3 and b4 both equal to 0 in the model. The rate of increase in the log mortality rate was 0.0061 (SE 0.0013) per year, which was very similar to that for the rest of Austria, as Tyrol is a small part of Austria. In the rest of Austria, the rate of decrease from 1993 onward was 0.0246 (SE 0.0063) per year, and in Tyrol, it was 0.0709 (SE 0.0197) per year. The test statistic for the comparison of the slopes from 1993 onward was c2 = 5.38, P = 0.02. Thus, our conclusions were only slightly tempered.

Taking 1995 as the year at which the first change can be reasonably expected yielded a rate of decrease in the rest of Austria from 1995 onward of 0.0309 (SE 0.0104) per year, in Tyrol, it was 0.1505 (SE 0.0410) per year. The latter figure was almost double the corresponding decrease from 1993 and the rate of decrease in the rest of Austria, was one third greater. These rates of decrease are significantly different (c2 = 7.99, P = 0.0047). Constraining the lines to be identical in Tyrol and the rest of Austria before 1995 yielded very similar results. In the rest of Austria, the rate of decrease was 0.0328 (SE 0.0103) per year, and in Tyrol, it was significantly greater at 0.1259 (SE 0.0355) per year (P = 0.0098).

TABLE 4. **Expected and observed numbers of prostate cancer deaths in the Federal State of Tyrol**

Year	Deaths expected	Deaths observed	SMR (95% CI) %
1991	44	50	114 (84-150)
1992	43	44	101 (74-136)
1993*	43	52	121 (90-159)
1994	43	42	97 (70-132)
1995	45	45	101 (74-135)
1996	47	37	79 (56-109)
1997	49	33 (-32%)	67 (46-94)
1998	52	30 (-42%)	58 (39-82)
1999	55	37 (-33%)	
2000	57	32 (-44%)	

SMR: standardized mortality data

Discussion

Three likely possibilities could lead to a reduction in the rate of mortality from prostate cancer: 1) better prevention of the disease, 2) earlier detection of the disease, at a stage when it is more likely to be curable, or 3) improved outcomes from therapy for metastatic disease. Currently, screening for prostate cancer is in a phase of rapid development, and several different approaches are being used. The general acceptance of prostate cancer screening as a part of public health-care programs can only be expected if benefits such as decreased mortality can be demonstrated.

The intermediate endpoints of cancer screening include migration to lower cancer stages at the time of diagnosis with lower rates of cancer progression and higher survival rates. The endpoint of screening programs and the ultimate goal of all cancer research and treatment has to be a reduction in disease-related

mortality and improvement in quality of life. The latter is of particular concern when a screening program could result in more men living longer with cancer and the side effects of the disease and its treatment. Screening programs may help control prostate cancer. The term "screening" should only be used if tests suitable for early detection are applied in a clearly defined program (e.g., in the form of population screening). In terms of the costs associated with this type of screening, only primary PSA screening would be acceptable. However, the sensitivity, specificity, and positive predictive value of PSA must be known and must be superior to other diagnostic tools suitable for screening.[18,19]

With screening procedures, a test that has a high sensitivity might not have a high specificity, and vice versa. In the case of prostate cancer, when the cut-off level for abnormal PSA as a biopsy criterion is lowered to improve detection rates, this can lead to a greater number of negative biopsies. Because of its low cost and complete standardization and automation, it would be very attractive to use a certain value of total PSA as the only biopsy criterion. However, to reduce the number of negative biopsies, additional diagnostic tests such as the assessment of percent free PSA and PSA transition-zone density should be performed.[11] It is estimated that with the help of these two diagnostic tests, approximately 54% of negative biopsies could be avoided.[11] In evaluating the prostate cancer screening program in Tyrol, one should bear in mind that an "aggressive" screening policy was combined with a complex decision algorithm to maximize prostate cancer detection without unacceptable biopsy rates. It is generally agreed that a number of prerequisites have to be fulfilled before a screening program can be introduced as a health policy. These requirements have been described by Wilson and Jungner[20] in a classic paper.

No evidence is yet available from randomized trials that PSA-based screening can decrease prostate cancer mortality rates.[21] Nevertheless, the results obtained from the population-based Surveillance, Epidemiology, and End Results Program[22-25] show that the incidence of prostate cancer and the mortality rates have declined in recent years. The results of another study[26] suggest that screening for prostate cancer by DRE may be beneficial; screening by DRE was found to be much less common among men who died of histologically confirmed prostate cancer than among age-matched population controls. Currently two large, prospective studies are underway to examine the impact of PSA-based screening on prostate cancer mortality, but to date, neither study has a sufficiently long follow-up to document a reduction in mortality as a direct result of PSA-based screening.[27]

The results reported here are from a unique natural experiment. The increase in incidence of prostate cancer after the introduction of a uniformly available and free testing program is what is expected if a large proportion of men are screened. The continued increase in local disease incidence indicates that PSA testing picks up early disease. This outcome and the constant decline in the incidence of prostate cancer that has distant spread at diagnosis in this population are encouraging findings. The fall in prostate cancer mortality rates in Tyrolean men contrasts with the more modest change taking place among all men of the same age in the rest of Austria Figure 1 and coincides from the temporal point of view with the introduction of PSA testing. The differences we report between the mortality rates in Tyrol and the rest of Austria bear strong similarities to two other phenomena. After PAP screening became widely available in Nordic countries, mortality rates from cervical cancer fell in those countries; but rates did not fall in Norway, where this screening was not available.[28] In addition, mortality rates from breast cancer in The Netherlands and the United Kingdom have both fallen since the introduction of mammographic screening programs in those countries;[29] in both cases, the quick drop in mortality rates was likely due to the diagnosis and treatment of previously clinically undetectable cancers. The absence of a watchful waiting strategy in Tyrol has meant that some patients with stage T3/4 disease will have been treated with hormonal therapy earlier than is usual in the disease course. Recent evidence suggests that earlier hormonal therapy may have a beneficial effect on survival.[30] The decline in mortality from prostate cancer seen in the Tyrol study population — men in the age range for which PSA testing was made available, and where acceptance of testing was high — is the first evidence from a geographically defined population that the policy of making PSA testing universally available and at no cost may have led to a reduction in death from prostate cancer. Many aspects of prostate cancer screening require better definition by randomized trials, including screening interval, issues relating to lead time, cut-off limits for a PSA test to be considered positive, and estimation of the benefits. Our study was not designed to investigate the important issues relating to economics and psychological impact. Although these necessary data are becoming available, the current demonstration of a decline in mortality

from prostate cancer supports, but does not prove, the hypothesis that the policy of making PSA testing available to the population of Tyrol has led to a reduction in prostate cancer death rates. Also, in the eligible age group, the gap between the absolute numbers of deaths observed and those expected by the pre-PSA testing age-specific mortality rates has been growing. □

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