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PROSTATE CANCER MORTALITY AFTER INTRODUCTION OF PROSTATE-SPECIFIC ANTIGEN MASS SCREENING IN THE FEDERAL STATE OF TYROL, AUSTRIA

GEORG BARTSCH, WOLFGANG HORNINGER, HELMUT KLOCKER, ANDREAS REISSIGL, WILHELM OBERAIGNER, DIETER SCHÖNITZER, GIANLUCA SEVERI, CHRIS ROBERTSON, AND PETER BOYLE, ON BEHALF OF THE TYROL PROSTATE CANCER SCREENING GROUP

ABSTRACT

Objectives. To monitor the impact of screening in a natural experiment by comparing prostate cancer mortality in Tyrol, where prostate-specific antigen (PSA) testing was introduced at no charge, with the rest of Austria, where it was not introduced.

Methods. In 1993, PSA testing was made freely available to men aged 45 to 75 years in the Federal State of Tyrol, Austria. At least two thirds of all men in this age range have been tested at least once during the first 5 years of the study. Initially, only total PSA was measured, but free PSA measurement was added in 1995. The IMX assay was used. Digital rectal examination was not part of the screening examination.

Results. Significant migration to lower stages has been observed since the introduction of this screening program. A reduction in mortality rates in the rest of Austria from 1993 onward has occurred, with the reduction in Tyrol much greater; the mortality remained fairly constant between 1993 and 1995 and subsequently fell. The trends in prostate cancer mortality rates since 1993 differ significantly between Tyrol ($P = 0.006$) and the rest of Austria. On the basis of the age-specific death rates averaged from 1986 to 1990, the difference between the number of expected and observed deaths from prostate cancer in Tyrol was 22 in the group aged 40 to 79 years in 1998 and 18 the following year.

Conclusions. These findings are consistent with the hypothesis that the policy of making PSA testing freely available, and the 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 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. UROLOGY **58:** 417–424, 2001.

In the early 1990s, a remarkable increase occurred in the incidence of prostate cancer in many countries, particularly in the United States.[1] It can largely be attributed to the widespread introduction of prostate-specific antigen (PSA) testing, which was first approved for the detection of recurrent disease in patients with established prostate cancer in 1986. Thereafter, the potential of this test for early detection was soon recognized. From 1984 until 1994, PSA was increasingly used for diagnostic purposes. In 1984, PSA testing was used in 5.1% and in 1994 in 60.6% of all newly diagnosed prostate carcinomas.[2] It has been shown that a great number of cancers detected by PSA testing are clinically significant and potentially curable.[3–6]

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A complete list of the Tyrol Prostate Cancer Screening Group is provided in the Appendix.

From the Department of Urology, University of Innsbruck; Tyrol Cancer Registry; Institute of Immunology and Transfusion Medicine, University of Innsbruck, Innsbruck, Austria; and Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy

Reprint requests: Peter Boyle, Ph.D., Division of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, Milan 20141, Italy

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However, the introduction of PSA testing for use in prostate cancer screening programs has also led to controversy surrounding several distinct issues, including the sensitivity and specificity of the screening test, 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, Papanicolaou smears for cervical cancer and mammographic examination for breast 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 regular PSA testing has been made freely available to the population in 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 will have been used, probably evolving in a similar manner to 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.

MATERIAL AND METHODS

In 1993, a mass screening project using PSA as the only screening test was launched in the Federal State of Tyrol (one of the nine federal states of the Republic of Austria). Previously (1988 to 1992), both PSA and the digital rectal examination (DRE) were available and used in the diagnostic workup of patients with suspected prostate cancer and in a limited way for asymptomatic men. Since 1989, urologists at the Innsbruck University Hospital have promoted the concept of prostate cancer early 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, at 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 to Innsbruck, the capital, where the central health care unit is located, are not too great (infrequently more than 100 kilometers). This geographic situation, as well as the willingness of the general population to participate in preventive medical programs, caused us to launch a statewide mass screening program with PSA as the single screening test for the 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 who were inhabitants of Tyrol. Of the 307,249 male inhabitants, 65,123 were between 45 and 75 years of age. All men in this age range were advised and encouraged to undergo PSA testing, and information to this effect was distributed to all Tyrollean men by press, radio, and television.

The screening project was performed in collaboration with general practitioners, medical examiners, urologists, medical laboratories, and the Tyrol Blood Bank of the Red Cross. Informed consent was obtained from all volunteers participating in the program. All coworkers were fully informed of the guidelines for withdrawal, storage, and shipping of the blood samples. PSA was assessed immediately on arrival of the blood or serum sample. All volunteers and/or referring physicians were informed about the results in writing. In the case of elevated PSA levels, the volunteers were invited to undergo additional urologic evaluations, and the men with normal PSA levels were invited to have a repeated PSA test 6 or 12 months later. More than 80% of all volunteers found to have an elevated PSA level consented to an additional evaluation, which included DRE, transrectal ultrasonography (TRUS), and prostate biopsy. At the time of drawing blood for PSA measurement, no DRE was performed. Several scientific projects[7–11] have been published describing this screening program.

TABLE I. *Bisected, age-specific reference ranges for PSA levels*

Age Range (yr)	PSA Range (ng/mL)
40–49	0–1.25
50–59	0–1.75
60–69	0–2.25
70–79	0–3.25

KEY: PSA = prostate-specific antigen.

This mass screening program was provided free of charge to men between 45 and 75 years old and to younger men with a family history of prostate cancer. In all laboratories, the PSA concentration was assessed using the Abbott IMX assay.

Age-referenced PSA levels,[12] in combination with percent free PSA of less than 22%, were used as the biopsy criteria. Since October 1995, bisected PSA levels[13] (one half the age-specific reference ranges, Table I) together with percent free PSA levels of less than 18% were used. Screened volunteers with a PSA level greater than 10 ng/mL were recommended to 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 transrectal ultrasound examinations. Sextant biopsies were initially made using ultrasound guidance with an automatic biopsy gun and an 18-gauge needle; since 1995, 10 systematic 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 N+ or M+ 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. Men aged 40 to 44 years in 1993 were eligible for screening during the period of follow-up and thus this age group was included. In the case of mortality, it was assumed that in the 5 years of the study period, PSA screening could affect the death rates in the age group beyond the screening age (75 to 79 years) and so truncated rates were extended to age 79. 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 from 1993 and (b) whether the trends in the prostate cancer mortality rates in Tyrol differed from those in the rest of Austria from 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 $\geq$ 1993)" is an indicator that permits a different slope from 1993 onward compared with before 1993. The parameter β_0 gives the estimated log mortality rate in the rest of Austria in 1993; β_3 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 β_1 in the rest of Austria and $\beta_1 + \beta_4$ in Tyrol; thus β_4 represented the difference in slopes before 1993. The parameter β_2 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 $\beta_2 + \beta_5$. Thus β_5 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 at which the practice was different with regard to PSA testing in Tyrol compared with 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 Tyrollean men between 45 and 75 years old underwent PSA screening, and more than two thirds of this population were tested at least once during the first 5 years of the study. At the laboratory of the Department of Urology, Innsbruck University, more than 76,000 men were screened at least once. Of these, 7100 were aged 45 to 49 years and 2900 were aged 40 to 44 years. Thus, a substantial number of men aged 40 to 44 were screened, justifying the inclusion of this age group in the analysis of the incidence and mortality rates.

The incidence of prostate cancer in men aged 40 to 79 in Tyrol increased from 1988 to 1993 and has essentially remained constant since (Fig. 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 (Fig. 2). The stage reported to the Cancer Registry is a mixture of clinical and pathologic stages.

The mortality from prostate cancer in Tyrol decreased significantly between 1993 and 1999, in contrast to the modest downward trend in prostate cancer death rates observed in the rest of Austria (Fig. 1). On the basis of the age-specific prostate cancer mortality rates in Tyrol between 1986 and 1990, 22 fewer prostate cancer deaths in the age range 40 to 79 occurred in 1998 than were expected and 18 fewer deaths than expected occurred in 1999 (Table II). A trend was found for the decrease of the standardized mortality ratio from 1995 in the truncated age range (Table II). We had some difficulty in interpreting the expected deaths in the *all ages* group because they were heavily weighted by the numbers of deaths observed in the age groups older than 80 years. The median age at death from prostate cancer in the European populations is in the late 70s.[17]

The fitted values of the model, described above, are shown in Figure 1. No significant difference was found between the trends in Tyrol and the rest of Austria before 1993 ($\chi^2 = 1.12$, 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 ($\chi^2 = 12.74$, 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

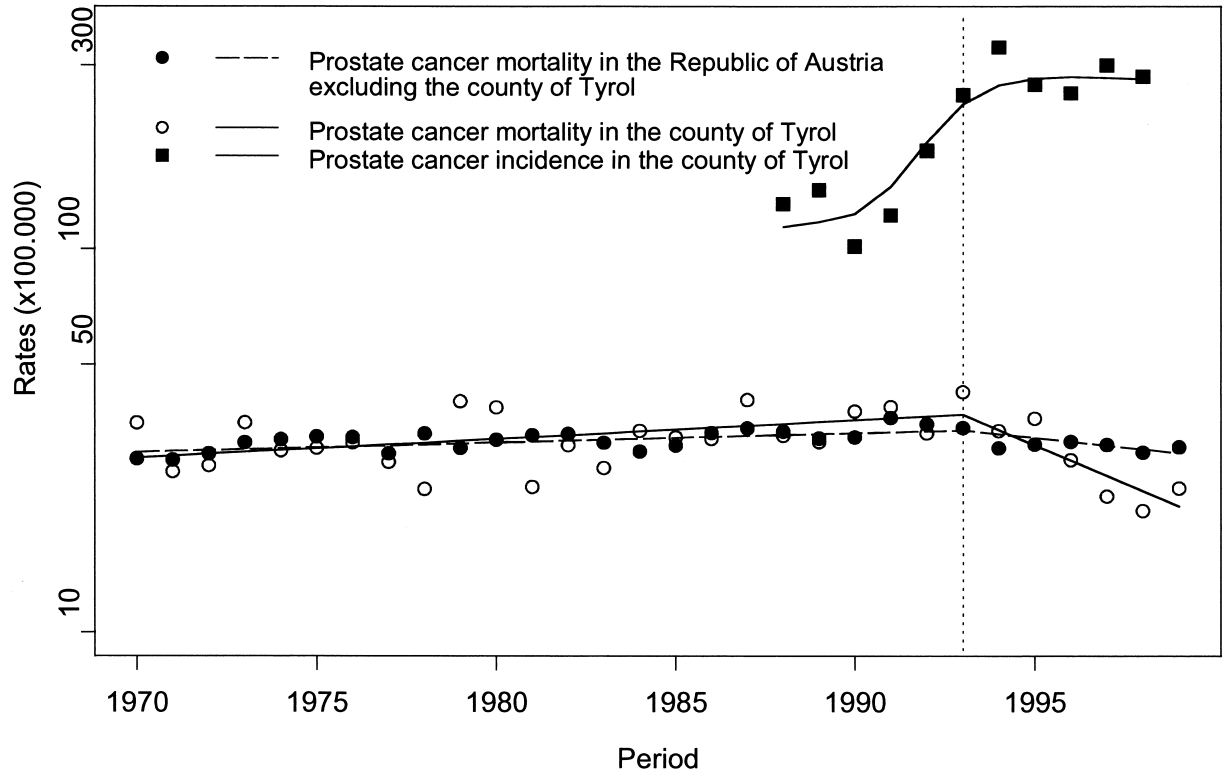

FIGURE 1. *Prostate cancer mortality rates in Tyrol and in the Republic of Austria (excluding Tyrol), and prostate cancer incidence rates in Tyrol in men aged 40 to 79.*

1993 onward, the trends in the rates show a significant difference between Tyrol and the rest of Austria ($\chi^2 = 7.55$, 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 (Fig. 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 β_3 and β_4 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 $\chi^2 = 5.38$, $P = 0.02$. 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 ($\chi^2 = 7.99$, $P = 0.0047$). 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 ($P = 0.0098$).

COMMENT

Three possibilities could lead to a reduction in the mortality rate from prostate cancer: (a) prevention of the disease, (b) detection of the disease at a stage when it is more likely to be curable, and (c) improvement in the outcome of therapy for metastatic disease. A fourth possibility, that screening would bring forward the time of death in some individuals, is very unlikely to explain the differences observed. Currently, screening for prostate cancer is in a phase of rapid development, with

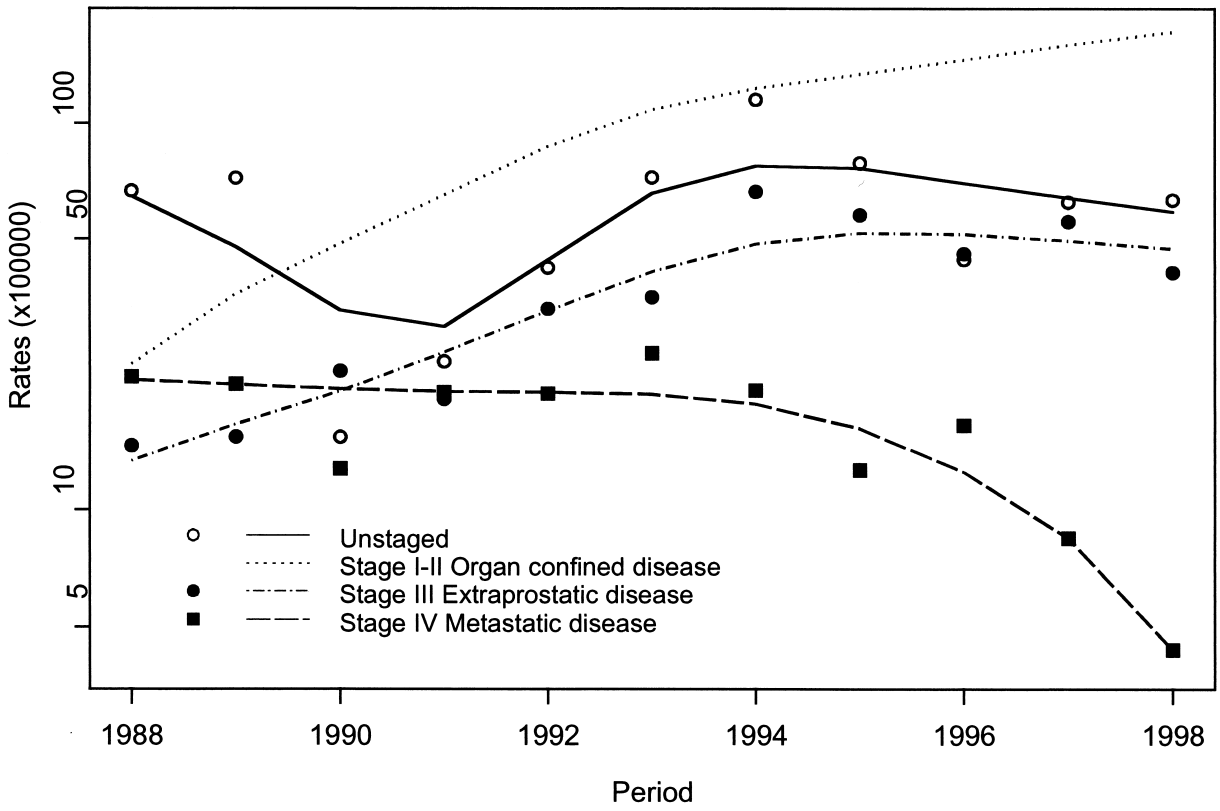

FIGURE 2. *Prostate cancer incidence rates in Tyrol by stage in men aged 40 to 79.*

several different approaches used. The general acceptance of prostate cancer screening as a part of public health care programs can only be expected if the benefits in terms of mortality can be demonstrated. The intermediate endpoints of cancer screening include migration to lower cancer stages at the time of diagnosis and lower 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 the 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 (eg, 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, there is usually a discrepancy between the sensitivity and specificity. In the case of prostate cancer, the cutoff for PSA as a biopsy criterion has to be lowered to improve sensitivity; however, that entails a great number of negative biopsies. Because of its low cost and complete standardization and automation, it would be very attractive to use 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] With the help of these two diagnostic tests, approximately 54% of negative biopsies could be avoided.[11] In evaluating this program, one should bear in mind that an "aggressive" screening policy has been combined with a complex decision algorithm to maximize prostate cancer detection without unacceptable biopsy rates. Agreement is general 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

TABLE II. *Observed and expected numbers of prostate cancer cases and deaths in the Federal State of Tyrol*

	Deaths				New Cases			
			SMR				SIR	
Year	Expected (n)	Observed (n)	%	95% CI	Expected (n)	Observed (n)	%	95% CI
All ages								
1991	84	96	115	93–140	203	199	98	85–113
1992	85	91	107	86–131	205	288	140	125–158
1993*	86	96	111	90–136	208	367	177	159–196
1994	88	95	108	87–132	211	483	228	209–250
1995	90	93	104	84–127	216	384	178	160–196
1996	91	91	100	80–123	221	371	168	151–186
1997	93	88	95	76–117	226	436	193	175–212
1998	95	60	63	48–82	231	393	170	154–188
1999	97	79	81	64–101				
Age range 40–79 yr								
1991	44	50	113	84–150	150	149	99	84–117
1992	44	44	101	73–135	150	212	141	123–162
1993*	43	52	120	90–158	150	294	196	174–219
1994	43	42	97	70–131	153	400	262	237–289
1995	45	45	100	73–134	158	326	207	185–230
1996	47	37	79	55–108	165	325	197	176–219
1997	50	33	66	46–93	173	389	225	203–248
1998	52	30	57	39–82	181	368	204	183–226
1999	55	37	68	48–93				

KEY: SMR = standardized mortality data; SIR = standardized incidence ratio; PSA = prostate-specific antigen.
** PSA testing freely introduced to population of men aged 45 to 75 years in Tyrol.*
Expected numbers were based on the age-specific rates for 1986–1990 for mortality data and 1988–1990 for incidence data.

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 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 precisely what is expected if a large proportion of men are screened. The continued increase in local disease incidence, indicating that PSA testing picks up early disease, and the constant decline in the incidence of prostate cancer that has distant spread at diagnosis in the population are encouraging. The fall in prostate cancer mortality rates in Tyrollean men contrasts with the more modest change taking place among all men of the same age in the rest of Austria (Fig. 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. Mortality rates from cervical cancer in Nordic countries fell after screening became widely available, but not in Norway, where it was not available.[28] In addition, the mortality rates from breast cancer in The Netherlands and the United Kingdom have both fallen since the introduction of mammographic screening programs,[29] in both cases too quickly to be due to the diagnosis and treatment of 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 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, for which screening was available to all its members, that the policy of making PSA testing universally available and at no cost may have led to a reduction in death from prostate cancer in that population. Many aspects of prostate cancer screening require better definition by randomized trials, including screening interval, issues relating to lead time, cutoff 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, the gap between the absolute numbers of deaths observed and those expected by the pre-PSA testing age-specific mortality rates has been growing in the age range liable to have been screened.

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REFERENCES

1. Stanford JL, Stephenson RA, Coyle M, *et al: Prostate Cancer Trends 1973–1995, SEER Program.* NIH Publication No. 99-4543. Bethesda, National Cancer Institute, 1999, pp 7–15.

2. Jones GW, Mettlin C, Murphy GP, *et al:* Patterns of care for carcinoma of the prostate gland: results of a national survey of 1984 and 1990. J Am Coll Surg **180:** 545–554, 1995.

3. Catalona WJ, Richie JP, Ahmann FR, *et al:* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol **151:** 1283–1290, 1994.

4. Ohori M, Wheeler TM, Dunn JK, *et al:* The pathological features and prognosis of prostate cancer detectable with current diagnostic tests. J Urol **152:** 1714–1720, 1994.

5. Smith DS, and Catalona WJ: The nature of prostate cancer detected through prostate specific antigen based screening. J Urol **152:** 1732–1736, 1994.

6. Slawin KM, Ohori M, Dillioglugil O, *et al:* Screening for prostate cancer: an analysis of the early experience. CA Cancer J Clin **45:** 134–147, 1995.

7. Reissigl A, Pointner J, Horninger W, *et al:* Comparison of different PSA cutpoints for early detection of prostate cancer: results of a large screening study. Urology **46:** 662–665, 1995.

8. Reissigl A, Pointner J, Horninger W, *et al:* PSA based screening for prostate cancer in asymptomatic younger males: pilot study in blood donors. Prostate **30:** 20–25, 1997.

9. Reissigl A, Ennemoser O, Klocker H, *et al:* Frequency and clinical significance of transition zone cancer in prostate cancer screening. Prostate **30:** 130–135, 1997.

10. Reissigl A, Klocker H, Horninger W, *et al:* Usefulness of the ratio free/total PSA in addition to total PSA levels in prostate cancer screening. Urology **48:** 62–66, 1996.

11. Horninger W, Reissigl A, Klocker H, *et al:* Improvement of specificity in PSA based screening by using PSA transition zone density and percent free PSA in addition to total PSA levels. Prostate **37:** 133–137, 1998.

12. Oesterling JE, Jacobsen SJ, Chute CG, *et al:* Serum prostate specific antigen in a community-based population of healthy men: establishment of age specific reference ranges. JAMA **270:** 860–864, 1993.

13. Reissigl A, Horninger W, Fink K, *et al:* Prostate carcinoma screening in the federal state of Tyrol, Austria. Cancer **80:** 1818–1829, 1997.

14. Boyle P, and Parkin DM: Statistical methods for registries, in Jensen OM, Parkin DM, McLennan R, *et al* (Eds): *Cancer Registration: Principles and Methods, No. 95.* Lyon, IARC Scientific Publication, 1995, pp 126–158.

15. McCullagh P, and Nelder JA: *Generalized Linear Models,* 2nd ed. London, Chapman and Hall, 1989.

16. *Splus 2000: User's Guide.* Seattle, Data Analysis Products Division, Mathsoft, 1999.

17. Boyle P, and Severi G: Epidemiology of chemoprevention of prostate cancer. Eur Urol **35:** 370–376, 1999.

18. Catalona WJ, Smith DS, Ratliff TL, *et al:* Measurement of prostate specific antigen in serum as a screening test for prostate cancer. N Engl J Med **324:** 1156–1161, 1991.

19. Mettlin C, Murphy GP, Babaian RJ, *et al,* for the Investigators of the American Cancer Society National Prostate Cancer Detection Project: The results of a five year early prostate cancer detection intervention. Cancer **77:** 150–159, 1996.

20. Wilson JMG, and Jungner G: *Principles and Practice of Screening for Disease,* Public Health Paper No. 34. Geneva, World Health Organization, 1969.

21. Von Eschenbach A, Ho R, Murphy GP, *et al,* for the American Cancer Society: Guidelines for the early detection of prostate cancer. Cancer **80:** 1805–1807, 1997.

22. Smart CR: The results of prostate carcinoma screening in the U.S. as reflected in the Surveillance, Epidemiology, and End Results Program. Cancer **80:** 1835–1844, 1997.

23. Hankey BF, Feuer EJ, Clegg LX, *et al:* Cancer surveillance series: interpreting trends in prostate cancer—part I: evidence of the effects of screening in recent prostate cancer incidence, mortality and survival rates. J Natl Cancer Inst **91:** 1017–1024, 1999.

24. Feuer J, Merrill RM, and Hankey BF: Cancer surveillance series: interpreting trends in prostate cancer—part II: cause of death misclassification and the recent rise and fall in prostate cancer mortality. J Natl Cancer Inst **91:** 1025–1032, 1999.

25. Etzioni R, Legler JM, Feuer EJ, *et al:* Cancer surveillance series: interpreting trends in prostate cancer—part III: quantifying link between population prostate specific antigen testing and recent declines in prostate cancer mortality. J Natl Cancer Inst **91:** 1033–1039, 1999.

26. Jacobsen SJ, Bergstralh EJ, Katusic SK, *et al:* Screening digital rectal examination and prostate cancer mortality: a population-based case-control study. Urology **52:** 173–179, 1998.

27. Boyle P: Prostate specific antigen (PSA) testing as screening for prostate cancer: the current controversy. Ann Oncol **9:** 1263–1264, 1998.

28. Laara E, Day NE, and Hakama M: Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programs. Lancet **1:** 1247–1249, 1987.

29. van den Akker-van Marle E, de Konig H, Boer R, *et al:* Reduction in breast cancer mortality due to the introduction of mass screening in The Netherlands: comparison with the United Kingdom. J Med Screen **6:** 30–34, 1999.

30. Messing EM, Manola J, Sarosdy M, *et al:* Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med **341:** 1781–1788, 1999.

APPENDIX

The Tyrol Prostate Cancer Screening Group was composed of the following: the General Practitioners in the Federal State of Tyrol, the Medical Examiners, Urologists (Arno Ebner, Stephan Frank, Wilfried Glantschnig, Gunter Hoeltl, Jorg Joost, Herbert Kollensperger, Sandor Kovesdi, Helmut Madersbacher, Hans Marberger, Heinz Puschban, Wolfgang Schachtner, Karl Scheiber, Ferdinand Walser, Gerhard Weissteiner, and Ernst Zangerl), Pathologists (Gregor Mikuz, Hermann Rogatsch, and Gunter Weisser), medical laboratory per-

sonnel (Gerda Holzl, Petra Dertschnig, Elmar Jarosch, Richard Rohrer, Wolfgang Gutter, Christian Schmoigl, Horst Philadelphy, Franz Schmalzl, Klaus Gattringer, Karl Maly, Peter Baumgartl, Peter Lechleitner, and Engelhard Frischmann), all the doctors, nurses, and secretaries of the Department of Urology of the University of Innsbruck, the Blood Bank of the Red Cross, Innsbruck, the Social Security and Health Service of the Federal State of Tyrol, Military Hospital Innsbruck, Staffregiment No. 6 of the Austrian Military Forces, Landeck, Works' Medical Officers of the Post and Telecom, Innsbruck, Austria, Plansee Company, Swarovski Company, Social Security Board of Kematen and Jenbach, District Commission of Schwaz, Innsbruck University Hospital, and Dipl.Vw. Max Laimböck.

EDITORIAL COMMENT

PSA testing was introduced and rapidly accepted by physicians despite the lack of evidence from randomized trials that early detection and treatment reduce prostate cancer mortality. In the absence of randomized trials, incidence and mortality trends after the introduction of a screening test can provide useful evidence with respect to the benefits of screening. If the test has benefit, one would expect that cancer mortality reductions would be greater in areas where the screening test had high penetration in the population compared with those areas with lower penetration. Cervical cancer screening programs are, in part, supported by the inverse relationship between disease-specific mortality and the prevalence of screening.[1] Are similar convincing data available to support PSA screening?

The authors describe population trends in incidence and mortality after the initiation of a mass PSA screening effort in Tyrol, Austria. In this "experiment," men between ages 45 and 75 years were offered free PSA screening beginning in 1993, and prostate cancers were aggressively treated with curative intent. Opportunistic screening (early detection using PSA and DRE) was started at the Department of Urology, University of Innsbruck, Austria in 1988. They noted stage migration to lower stages and reductions in the incidence of advanced disease with screening (their Fig. 2)—trends previously reported in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.[2] In addition, when compared with the rest of Austria, where no organized screening effort was undertaken, the county of Tyrol had a greater decline in prostate cancer mortality (their Fig. 1). What do these data suggest?

Men who receive no treatment for localized prostate cancers die of their disease only after a protracted course. Therefore, a mortality reduction from treatment of localized prostate cancer is not likely to appear early after detection. The observed mortality reductions in Tyrol began almost immediately after the initiation of mass screening (their Fig. 1 and Table II). Therefore, it seems exceedingly unlikely that these reductions were a result of early treatment of surgically curable prostate cancer that was discovered after the initiation of the screening program. If surgery and/or radiation therapy delay the progression of incurable disease, an early reduction in mortality could occur by prolonging the survival of those men who were found through screening to have incurable cancers, even though death from the disease—if not another cause—was a certainty. The authors suggest that earlier hormonal treatment of noncurable disease may have led to a decrease in mortality. Although there is controversy regarding the benefits of early hormonal therapy, I believe that a change in the timing of hormonal therapy is an unlikely explanation for these findings.

Their Figure 1 demonstrates that the increase in prostate cancer incidence in Tyrol began long before the initiation of the screening program that started in 1993. Their Figure 2 shows that the steepest increase in the incidence of surgically staged disease (organ confined and extraprostatic) occurred before mass PSA screening began in 1993 and the incidence of metastatic disease fell most dramatically after the onset of mass PSA screening. These data suggest that surgical treatment for clinically localized prostate cancer in Tyrol was prevalent and increasing long before the screening project began. Thus, the mortality reductions described after the onset of screening in Tyrol may have been due to the treatment of prostate cancer that occurred long before organized screening began.

There is a reasonable explanation for the observations in Tyrol and the mortality reductions described in the SEER data from the National Cancer Institute. A surgical treatment for prostate cancer associated with lower morbidity was initially described in the early 1980s,[3] and this increased patient and physician acceptance of radical prostatectomy as a management option. Increased case finding as a result of the availability of this improved treatment option may have resulted in some of the stage migration that occurred before the introduction of PSA testing.[4] In addition, before the introduction of PSA testing in the United States, the proportion of patients with localized prostate cancer treated by radical prostatectomy was increasing dramatically[5]—especially in younger men who are more likely to have surgically curable disease. The data presented by the authors suggest that this same trend occurred in Tyrol, perhaps to a greater extent than in other areas in Austria. Thus, we may be observing an initial decline in prostate cancer mortality 20 years after the description of a surgical technique that led to increases in the proportion of patients undergoing effective treatment. If so, one would expect prostate cancer mortality to continue to decline if PSA testing is not uncovering a large pool of cancers that were never destined to cause harm.

I believe—as do most urologists—that PSA testing saves lives. The careful monitoring of population trends in incidence and mortality as described in the Tyrol project may provide strong evidence in the future to support our current use of the PSA test.

REFERENCES

1. Laara E, Day NE, and Hakama M: Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programs. Lancet **1:** 1247–1249, 1987.

2. Hankey BF, Feuer EJ, Clegg LX, *et al:* Cancer surveillance series: interpreting trends in prostate cancer—part I: evidence of the effects of screening in recent prostate cancer incidence, mortality and survival rates. J Natl Cancer Inst **91:** 1017–1024, 1999.

3. Walsh PC, Lepor H, and Eggleston JC: Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate **4:** 473–485, 1983.

4. Gilliland F, Becker TM, Smith A, *et al:* Trends in prostate cancer incidence and mortality in New Mexico are consistent with an increase in effective screening. Cancer Epidemiol Biomarkers Prev **3:** 105–111, 1994.

5. Mettlin C, Murphy GP, and Menck H: Trends in treatment of localized prostate cancer by radical prostatectomy: observations from the Commission on Cancer National Cancer Database, 1985–1990. Urology **43:** 488–492, 1994.

H. Ballentine Carter, M.D.
Johns Hopkins Hospital
Baltimore, Maryland

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