Urological Oncology

Tyrol Prostate Cancer Demonstration Project: early detection, treatment, outcome, incidence and mortality

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Accepted for publication 30 November 2007

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Study Type – Therapy (cohort study)
Level of Evidence 2b

OBJECTIVE

To evaluate the effectiveness of a well-controlled programme of early detection and treatment of prostate cancer in the population of Tyrol, Austria, where such a programme of early detection and treatment was initiated in 1988 and where prostate-specific antigen (PSA) testing was offered for free to all men aged 45–75 years from 1993.

SUBJECTS AND METHODS

Comparison of prostate cancer mortality rates in Tyrol and the rest of Austria was accomplished through a generalized additive model. A piecewise linear change-point Poisson regression model was used to compare mortality rates in Tyrol and the rest of Austria. Standardized mortality ratios were calculated with reference to the mortality rates in 1986–1990.

RESULTS

In all, 86.6% of eligible men have been tested at least once since 1993. Cancer deaths in Tyrol in 2005 were 54% (95% confidence interval [CI] 34–69%) lower than expected compared with 29% (95% CI 22–35%) in the rest of Austria. The decreasing trend in prostate cancer mortality was significantly greater in Tyrol compared with the rest of Austria ($P = 0.001$). A significant migration to lower stage disease occurred and radical prostatectomy was associated with low morbidity.

CONCLUSIONS

In the Tyrol region where treatment is freely available to all patients, where widespread PSA testing and treatment with curative intent occurs, there was a reduction in prostate cancer mortality rates which was significantly greater than the reduction in the rest of Austria. This reduction in prostate cancer mortality is most probably due to early detection, consequent down-staging and effective treatment of prostate cancer.

KEYWORDS

prostate cancer, early detection, treatment, mortality

INTRODUCTION

Since PSA testing for prostate cancer became available, both incidence and mortality rates have changed profoundly; between 1989 and 2002, the age-standardized incidence rate of prostate cancer in the USA increased by 21.3% [1]. Prostate cancer is now the most frequently diagnosed noncutaneous cancer in Europe and in the USA [2]. Widespread implementation of prostate cancer screening in the USA has led to stage migration with more cancers being detected at a lower stage. There has been a 75% reduction reported in the proportion of cases presenting with

metastatic disease at diagnosis and a corresponding 32.5% decrease in the age-adjusted mortality rate from 1993 to 2003 [3,4].

Randomized, controlled trials evaluating the efficacy of PSA and DRE screening in reducing prostate cancer mortality are underway [5–7], but the results will not be available for several years. Furthermore, the randomized design of these trials may be compromised if nonadherence to the assigned intervention group is extensive, i.e. widespread contamination of the control group from members seeking PSA testing [8]. The consequences on the statistical power of these trials could be considerable [9].

It is essential to separate the question of efficacy of screening from the effectiveness of a well-controlled screening and treatment programme. The present study reports the incidence and mortality rates of prostate cancer in the Federal State of Tyrol, Austria, where PSA testing started in 1988 and has been made freely available to the population of men aged 45–75 years since 1993. Incidence, stage migration and mortality rates of the Tyrol study are reported. The issues of diagnoses, how PSA can be used intelligently, the value of anatomical radical prostatectomy (RP) and the problem of over-diagnosis are discussed concerning the qualitative effects of prostate cancer screening. PSA testing was not available free of charge in the rest of Austria, although it was used, probably developing in a similar manner to use in many Western countries. Comparing mortality rates between Tyrol and the rest of Austria allows evaluation of the outcome of this natural experiment.

SUBJECTS AND METHODS

STUDY DESIGN

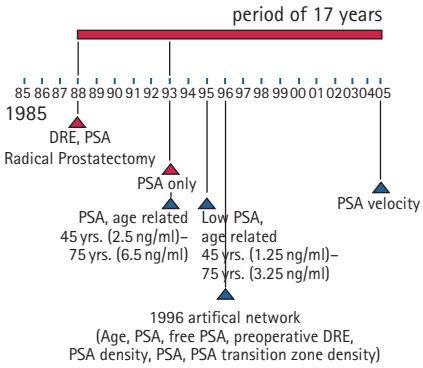
Since 1988, early prostate cancer detection has been promoted by the Department of Urology of the University of Innsbruck, Austria, using both PSA and DRE in the diagnostic evaluation of asymptomatic healthy men. Since 1993, this early prostate cancer detection programme has been carried out in the Federal State of Tyrol (one of the nine Federal States of the Republic of Austria) with prospective data collection and documentation, as well as with the development of an associated biorepository. Details of all individual PSA test results and biopsies, with a unique identifier for the individual man, are recorded so that the cancer registry in Tyrol is able to ascertain which men have had at least one PSA test and hence calculate the numbers of men who have not been tested.

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 km^2. At the same census, the total population of Austria was 7.81 million with 4.05 million women and 3.76 million men. Tyrol 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 great (infrequently >100 km). This geographical situation, as well as the willingness of the general population to participate in preventive medical programmes, is well suited for a state-wide mass screening programme, with PSA as the first-line 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 45–75 years who were inhabitants of Tyrol. Of the 307 249 male inhabitants in 1993, 86 067 were aged 45–75 years. All men in this age range were advised and encouraged to undergo PSA testing; the information of advantages and disadvantages was distributed to all Tyrolean men by press, radio, and television. All these releases were approved by the Review Board of the Prostate Centre at the Department of Urology, University of Innsbruck.

The Screening Demonstration Project was performed in collaboration with GPs, medical examiners, urologists, medical laboratories, and the Tyrol Blood Bank of the Red Cross. The study protocol was approved by the Review Board of the Prostate Centre at the Department of Urology, University of Innsbruck. Informed consent was obtained from all volunteers participating in the programme. All co-workers were fully informed of the guidelines for withdrawal, storage, and shipping of the blood samples. The PSA level 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 urological evaluations at no cost, and the men with normal PSA levels were invited to have a repeated PSA test 6 or 12 months later. At the time of drawing blood for PSA measurement, no DRE was performed.

FIG. 1. Tyrol Prostate Cancer Demonstration Project: development of the early detection algorithm.



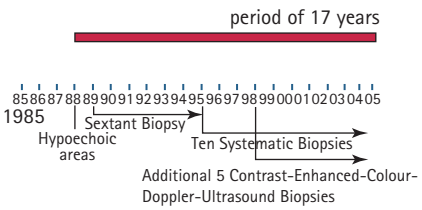
PSA testing was provided free of charge to men aged 45–75 year and to younger men (40 years) with a family history of prostate cancer. In all laboratories, the PSA concentration was assessed using the Abbott IMx assay (Abbott Park, IL, USA).

DIAGNOSIS

From September 1993 to September 1995, age-referenced PSA levels [10] (40–49 years: 0–2.5 ng/mL, 50–59 years: 0–3.5 ng/mL, 60–69 years: 0–4.5 ng/mL, 70–79 years: 0–6.5 ng/mL) in combination with percentage-free PSA levels of <22%, were used as the criteria for recommending biopsy. Since October 1995, lower PSA levels [11] (45(40)–49 years: 0–1.25 ng/mL, 50–59 years: 0–1.75 ng/mL, 60–69 years: 0–2.25 ng/mL, 70–79 years: 0–3.25 ng/mL), together with percentage-free PSA levels of <18% were used. In March 1996, an artificial neural network was constructed, using total PSA, free PSA, age, DRE and TRUS variables. Using this neural network the probability of having cancer could be estimated. In 2005, the concept of PSA-velocity [12] was incorporated in the diagnostic evaluation to further enhance the specificity of the programme (Fig. 1).

All men who met the above-mentioned biopsy criteria, were invited to undergo additional urological evaluation, including DRE and TRUS-guided biopsies of the prostate. Urologists performed the DRE and TRUS

FIG. 2. Tyrol Prostate Cancer Demonstration Project: development of the diagnostic evaluation.



examinations. Sextant biopsies were initially taken using US-guidance with an automatic biopsy gun; since 1995, 10 systematic biopsies have been taken, and since 1998 additional contrast-enhanced colour Doppler-targeted biopsies have been taken by specialized uroradiologists [13] (Fig. 2).

TREATMENT OF MEN WITH PROSTATE CANCER

In men presenting with a clinically localized tumour (clinical T1 and T2 lesions), surgical removal of the prostate was recommended. In 1988, anatomical RP [14] was introduced into the therapeutic concept for localized prostate cancer.

Patients with a clinical stage T3 lesion were treated with external beam radiotherapy (EBRT) alone. Since 2001, androgen-deprivation therapy was used combined with EBRT (70.2 Gy, single-fraction 1.8 Gy, four-field technique). Patients with metastatic disease were treated with androgen-deprivation therapy.

The Austrian Social Insurance System as well as the establishment of a Prostate Centre at the Department of Urology ensured that every man diagnosed with prostate cancer has access to medical care of the highest quality available in both diagnosis and treatment, free of charge.

CLINICAL FOLLOW-UP

All surgically treated patients had a routine follow-up by the treating physician. In all, 1517 patients (91.2%) had a follow-up of ≥1 year and were specifically questioned about their urinary continence and any complications of treatment by an independent investigator. Since 2000, the potency status of 512 men who were potent before RP and aged <65 years was also assessed by an independent investigator. Continence was defined as no need for protective pads, potency was defined as the ability of having intercourse 2 years after RP with or without phosphodiesterase type 5 inhibitors.

CANCER INCIDENCE AND MORTALITY DATA

Population-based data on cancer incidence have been available from the Tyrol Cancer Registry, since 1988, and also from the Austrian National Cancer Registry. Cancer mortality data have been available, independently, from the Austrian Central Statistics Office since 1970. 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. Annual numbers of cases and population estimates are available in 5-year age categories. PSA tests were available at no charge for men aged 45–75 years, although PSA testing was used among men in other age groups. Men who were 40–44 years of age in 1993 were eligible for screening during the follow-up interval of this study.

During the 5-year study period, it was assumed that PSA screening could affect death rates in the age group beyond screening age range (75–79 years); therefore, truncated mortality rates were considered to age 79 years. Incidence and mortality rates for the age range of 40–79 years were calculated, using the World Standard Population as reference [15].

The principal hypotheses to be tested can be expressed as follows: (i) do prostate cancer mortality rates in Tyrol decrease from 1993; (ii) do trends in prostate cancer mortality rates in Tyrol differ from those in the rest of Austria from 1993 onwards. Trends in the mortality rates, for age group, i, and year, y, in Tyrol and the rest of Austria were compared within a Poisson regression model:

$$\begin{aligned}\log(rate_{iy}) = {} & \beta_{0i} + \beta_1(y-1993) \\ & + \beta_2(y-1993)I(y \geq 1993) \\ & + \beta_3 Tyrol + \beta_4 Tyrol(y-1993) \\ & + \beta_5(y-1993)I(y \geq 1993)\end{aligned}$$

This is a 'change-point' model in which the term $I(y \geq 1993)$ is an indicator that permits there to be a different slope from 1993 onwards compared with before 1993. The parameter (β_{0i}) gives the estimated log mortality rate in the rest of Austria in 1993 for age group i, and β_3 represents the difference from this value in Tyrol. A priori, no difference is anticipated in any age group. The slope of the relationship between log mortality rates and year is given by β_1 in the rest of Austria and $\beta_1 + \beta_4$ in Tyrol; thus, β_4 represents the difference in slopes, before 1993. The parameter β_2 gives an estimate of any change in slope from 1993 onwards compared with 1992 and before in the rest of Austria. If there is no change then the estimated value will be about zero, if there have been treatment advances then a negative estimate would be expected. In the Tyrol the change in the slope from 1993 onwards is given by $\beta_2 + \beta_5$. Thus, β_5 is the crucial parameter in the analysis as it measures the different slope in the Tyrol compared with the rest of Austria from 1993 onwards. The goodness-of-fit of the model was established based on residual plots and hypothesis tests were based on changes in the deviance [16]. In particular, interaction tests were used to test if the parameters $\beta_1, \ldots, \beta_5$ depended upon age group. The interactions tests are secondary hypotheses and the effects are only included in the final model if significant at the 1% level.

A possible criticism of this analysis is that it assumes a change-point model with linear trends for year. As there is a much longer follow-up relative to our previous analysis, we relaxed this assumption using a generalized additive model [17] where the linear trends are replaced by smooth splines:

$$\begin{aligned}\log(rate_{iy}) = {} & \beta_{0i} + s_1(y-1993) + \beta_3 Tyrol \\ & + s_2(Tyrol(y-1993))\end{aligned}$$

In this model, $s_1(\,)$ represents the trend in the rates in the rest of Austria, while $s_2(\,)$ represents the trend in Tyrol. All statistical analysis was carried out using *Splus* 7.0 [18].

As previously reported [19], the estimated benefit of the mass-screening programme was calculated by comparing the observed and expected numbers of prostate cancer deaths in Tyrol and by comparing the prostate cancer mortality trends in Tyrol with the rest of Austria. The expected numbers of deaths for each year in Tyrol were calculated using the age-specific averages of the rates from 1986 to 1990 as the reference. This calculation was carried out for men aged 40–79 years and for men aged ≥80 years.

RESULTS

During 1993, when the Tyrol Prostate Cancer Demonstration Project was formally launched, 11.0% of Tyrolean men aged 45–75 years had undergone PSA screening, and 86.6% of eligible men have been tested at least once during the study period. From 1988 to 2005, 454 356 PSA measurements were performed in all laboratories in the county of Tyrol (Table 1). About 85% of all volunteers who, according to reference levels used at the time of their test, had an elevated PSA level, consented to additional evaluation, including DRE, TRUS, and needle biopsy of the prostate.

From 1993 to 2005, 7074 TRUS-guided needle biopsies were taken at the Innsbruck University Hospital, and prostate cancer was detected in 24% of men with a PSA level of 2–4 ng/mL and 40.2% with a PSA level of 4–10 ng/mL. The morbidity associated with TRUS-guided biopsy was low, with major complications in <1% of patients and 0.5% of patients required hospitalization, most commonly for fever. Among patients diagnosed with T1–T2 disease, 89.3% were treated with anatomical RP, 5.7% were treated with brachytherapy and 4.7% were treated with EBRT; 0.3% of patients were managed with a watchful-waiting protocol.

The great majority of RPs were performed at the Department of Urology of the University of Innsbruck, Austria. Between 1988 and 2005, 1765 RPs were performed mostly by two surgeons (G.B., W.H.). RP was associated with a low morbidity rate; the 30-day mortality was zero, and none of the patients had a ureteric injury. The rectal injury rate decreased from 0.6% before the year 2000 to 0.1% thereafter. Of the patients, 0.7% had postoperative bleeding requiring intervention. At 3 months after RP, 80.6% of men had recovered urinary continence (no pads), which increased to 95.1% by 1 year, and erectile potency was preserved in 78.9% of men aged <65 years.

The incidence rate of prostate cancer in men aged 40–79 years in Tyrol increased from 1988 until 1999/2000 and has remained essentially constant since. In the Tyrol, the incidence rate of organ-confined disease (clinical stage T1–T2, M0) increased from 1988 until 2000, when the rate leveled off. In the rest of Austria, the incidence rate for T1–T2, M0 prostate cancer, which was lower than that in the Tyrol from 1990, has increased gradually and in 2003 was at the same level as Tyrol (Fig. 3). The incidence of metastatic prostate cancer (M1) was lower in the Tyrol, especially since ≈1995/6, but there is now evidence that the rates are converging (Fig. 3).

The age-standardized rates (World Standard Population weights for ages 40–79 years) and fitted values of the additive model are shown in Fig. 4A with those from the piecewise-linear model in Fig. 4B. In both cases, there is evidence of good agreement between the model and the observed age-standardized rates. The deviance test of the more restrictive piecewise linear change-point model against the additive model yields a nonsignificant change of deviance of 2.95 (4.0 d.f.) suggesting that the simpler piecewise-linear model is an adequate description of the trends. Of note from the additive model, Fig. 4A, is that the general trend of the rates in the rest of Austria is of a smooth curve peaking around 1990. Before 1990 there was a similar trend in Tyrol as in the rest of Austria but in the last 10 years, especially the rate of decrease of the mortality rates has been much steeper in Tyrol compared with the rest of Austria. The predicted line in Tyrol is lower than that for the rest of Austria from 1995 onwards.

TABLE 1
Annual uptake rates of PSA testing in Tyrol in men aged 45–74 years

Year	No. men with PSA screening	Male population, *n*	Testing rate, %	Cumulative testing rate, %
1993	9 474	*86 067*	11.0	11.0
1994	14 147	*88 342*	16.0	23.3
1995	20 309	*90 153*	22.5	34.6
1996	23 839	*91 497*	26.1	44.1
1997	26 796	*92 607*	28.9	51.0
1998	30 228	*93 719*	32.3	56.8
1999	36 366	*95 000*	38.3	63.3
2000	41 860	*96 692*	43.3	70.1
2001	44 400	*98 638*	45.0	75.1
2002	50 370	*100 740*	50.0	80.2
2003	51 658	*102 904*	50.2	84.0
2004	52 503	*105 216*	49.9	86.1
2005	46 591	*107 600*	43.3	86.6

FIG. 3. Prostate cancer incidence rates per 100 000 by tumour stage in the county of Tyrol and the Republic of Austria excluding the county of Tyrol.

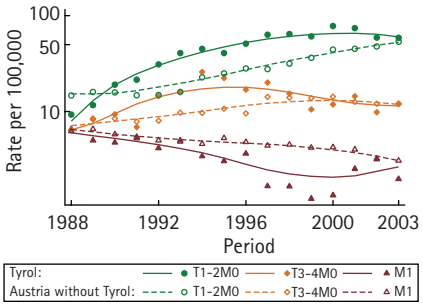


FIG. 4. Prostate cancer mortality rates of men aged 40–79 years in the county of Tyrol and in the Republic of Austria excluding the county of Tyrol. Age-standardised mortality rates and predictions from: (A) a generalized additive model – separate smoothing trend in Tyrol and rest of Austria and (B) based upon a linear change-point model with age interactions.

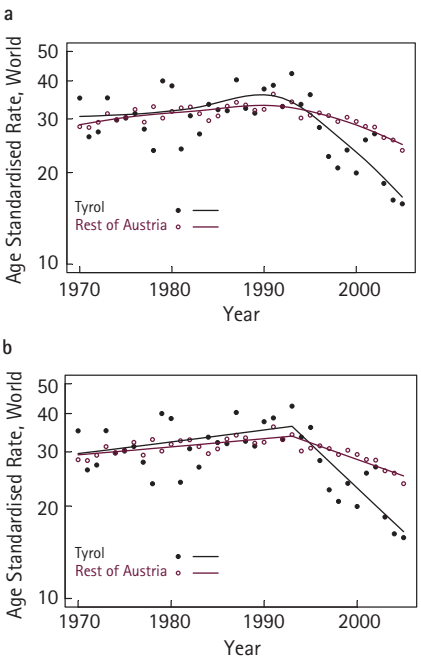


TABLE 2 Observed and expected numbers of prostate cancer deaths in Tyrol and the rest of Austria for men aged 40–79 years and ≥80 years (expected values are based on the application of age-specific rates from 1986 to 1990 to the population)

	Tyrol			Rest of Austria		
Year	Observed deaths, *n*	Expected deaths, *n*	SMR (95% CI)	Deaths, *n*	Expected deaths, *n*	SMR (95% CI)
Aged 40–79 years						
1991	50	44.1	113.4 (84.1–149.5)	606	544.5	111.3 (102.6–120.5)
1992	44	43.6	100.8 (73.3–135.4)	546	538.6	101.4 (93.1–110.3)
1993	52	43.2	120.4 (89.9–157.9)	554	534.7	103.6 (95.2–112.6)
1994	42	43.4	96.8 (69.8–130.9)	489	536.8	91.1 (83.2–99.5)
1995	45	44.8	100.4 (73.2–134.4)	516	552.3	93.4 (85.5–101.8)
1996	37	47.1	78.6 (55.3–108.3)	543	580.2	93.6 (85.9–101.8)
1997	33	49.7	66.4 (45.7–93.3)	559	611.9	91.4 (83.9–99.3)
1998	30	52.3	57.4 (38.7–81.9)	575	641.4	89.6 (82.5–97.3)
1999	37	54.8	67.6 (47.6–93.1)	602	664.6	90.6 (83.5–98.1)
2000	32	56.8	56.4 (38.6–79.6)	606	680.8	89.0 (82.1–96.4)
2001	44	57.5	76.5 (55.6–102.7)	571	679.1	84.1 (77.3–91.3)
2002	44	59.2	74.3 (54.0–99.7)	578	689.2	83.9 (77.2–91.0)
2003	32	61.2	52.3 (35.8–73.8)	537	694.0	77.4 (71.0–84.2)
2004	28	63.3	44.2 (29.4–63.9)	549	714.6	76.8 (70.5–83.5)
2005	30	65.3	45.9 (31.0–65.6)	517	730.0	70.8 (64.9–77.2)
Aged ≥80 years						
1991	46	39.7	115.8 (84.8–154.5)	504	451.7	111.6 (102.0–121.8)
1992	47	41.6	113.0 (83.0–150.2)	502	465.0	107.9 (98.7–117.8)
1993	44	43.3	101.7 (73.9–136.6)	527	479.7	109.9 (100.7–119.7)
1994	53	44.6	118.7 (88.9–155.3)	504	491.5	102.5 (93.8–111.9)
1995	48	44.9	106.9 (78.8–141.7)	593	494.6	119.9 (110.4–130.0)
1996	54	44.1	122.6 (92.1–159.9)	535	484.4	110.4 (101.3–120.2)
1997	55	43.2	127.3 (95.9–165.7)	537	471.1	114.0 (104.6–124.1)
1998	30	42.4	70.8 (47.7–101.0)	504	459.7	109.6 (100.3–119.6)
1999	42	42.7	98.5 (71.0–133.1)	541	457.5	118.2 (108.5–128.6)
2000	47	43.7	107.4 (78.9–142.9)	544	472.6	115.1 (105.6–125.2)
2001	41	42.7	95.9 (68.8–130.1)	528	466.8	113.1 (103.7–123.2)
2002	35	44.0	79.5 (55.3–110.5)	481	486.5	98.9 (90.2–108.1)
2003	36	45.5	79.0 (55.4–109.4)	553	489.8	112.9 (103.7–122.7)
2004	31	47.7	65.0 (44.1–92.2)	531	527.4	100.7 (92.3–109.6)
2005	32	49.9	64.1 (43.8–90.5)	518	556.4	93.1 (85.2–101.5)

SMR, standardized mortality ratio.

Using the piecewise-linear model, Fig. 4B, there was no evidence of any interactions between age group and the effects of the comparison between Tyrol and the rest of Austria: intercept in Tyrol in 1993, β_3, $P = 0.29$; slope in Tyrol before 1993, β_4, $P = 0.50$; slope in Tyrol after 1993, β_5, $P = 0.35$. There was some evidence that the overall trends in the age groups were not parallel: trend before 1993, β_1, $P = 0.04$; trend after 1993, β_2, $P = 0.01$. These interactions are not important for the main comparison between Tyrol and the rest of Austria and are therefore ignored in the remainder of the paper. The interactions manifest themselves with slightly weaker trends over time among those aged 40–54 years (where there are comparatively few deaths), compared with those aged 55–79 years.

There is no evidence that the trends in the rates in Tyrol and the rest of Austria before 1993 are significantly different (chi-squared 0.42, 1 d.f., $P = 0.52$). In Tyrol the log mortality rates increased at a rate of 0.009 (SE 0.004) per year while in the rest of Austria the increase was 0.007 (SE 0.001) per year. Furthermore, in 1993, there was no evidence of any difference between the estimated rates in the two regions ($P = 0.16$). From 1993 onwards there is strong evidence of a decrease in mortality in Tyrol (chi-squared 39.2, 1 d.f., $P < 0.001$) where the log mortality rates have decreased at a rate of 0.076 (SE 0.012) per year, corresponding to a yearly reduction in mortality rate of 7.3% (95% CI 5.1–9.5%). In the rest of Austria, there is also a significant decrease in the log mortality rates of 0.032 (SE 0.003) per year, corresponding to a decrease of 3.2% per year (95% CI 2.6–3.8%) in the mortality rate. There is very strong evidence that the decrease from 1993 in Tyrol is significantly greater than the decrease in the rest of Austria (chi-squared 12.3, 1 d.f., $P = 0.001$).

Although, there were no statistically significant differences between Tyrol and the rest of Austria before 1993 the fitted value in Tyrol in 1993 is slightly higher than in the rest of Austria (Fig. 4), and this may have some implications for the change in the slope. To investigate the effect of this we constrain the line before 1993 to be exactly the same in Tyrol as in the rest of Austria. This is achieved by setting β_3 and β_4 both equal to zero in the model. Now the rate of increase in the log mortality rates is 0.007 (SE 0.001) per year, which is very similar to that for the rest of Austria above as Tyrol is a small part of Austria. In the rest of Austria the rate of decrease from 1993 onwards is 0.033 (SE 0.003) per year while in the Tyrol it is 0.065 (SE 0.007) per year. The test statistic for the comparison of the slopes from 1993 onwards is chi-squared 21.08 ($P < 0.001$).

The standardized mortality ratios in Table 2 show a reduction in prostate cancer deaths, among men aged 40–79 years, relative to those expected on the basis of the age-specific rates in the immediate pre-screening years (1986–1990). In 2005, in Tyrol there was a 54% (95% CI, 34–69%) reduction compared with 29% (95% CI, 22–35%) in the rest of Austria. Among men aged ≥80 years in the Tyrol, there was no evidence of an increase in prostate cancer deaths from 1991 onwards. Indeed, there were 36% (95% CI, 10–56%) fewer prostate cancer deaths than expected in 2005. In the rest of Austria there was evidence of an increase in prostate cancer deaths among men aged ≥80 years from 1995 to 2003 associated with the increase in men in this age group.

In 1996–2005, there were 567 expected (based on pre-testing rates from 1980 to 1990), but only 347 observed prostate cancer deaths (reduction 38.8%). As shown by the expected and observed deaths rates in men aged >80 years, there was a smaller, yet still substantial, decrease in the prostate cancer mortality rate (2002–2005, men aged >80 years: 187 expected deaths, 134 observed deaths, a reduction of 28.4%).

DISCUSSION

The present report is based on a demonstration project conducted in the population of Tyrol, Austria, where PSA testing has been offered to men free of charge since 1993. Even without a system of invitation and re-invitation, >80% of men aged 45–74 years underwent at least one PSA test for screening in the years 1993–2005 (Table 1).

During the past decade, there has been a dramatic stage migration for newly diagnosed prostate cancer. Currently, 80% of men are diagnosed with prostate cancer while it is pathologically organ-confined, compared with only 20–30% in the 'pre-PSA era' [20]. In the Surveillance, Epidemiology and End Results programme, the rate of distant disease fell by 52% between 1990 and 1994 [21].

A similar favourable stage migration is documented in the Tyrol Project and can almost certainly be attributed, at least in part, to the widespread acceptance of PSA-based prostate cancer screening. Several studies have clearly shown that cancers detected because of a PSA elevation are more likely to be organ-confined than those detected because of an abnormal DRE [20–26].

The prostate cancer incidence data from Tyrol show that the age-standardized rate for metastatic cancer decreased from 5.2 to 2.1 per 100 000 and for advanced cancer (Union Contre le Cancer stage IV) from 7.9 to 3.7 per 100 000 from 1988–1992 to 1998–2002. This is consistent with a population-based, case-control study reporting that among asymptomatic men, the frequency of PSA-testing was significantly lower among men with metastatic prostate cancer [27].

As PSA thresholds lower than the traditional 4 ng/mL for recommending a prostate biopsy were adopted, a highly significant increase in the proportion of patients with pathologically organ-confined disease has been observed: this rose from 23.7% in 1993 to 78.7% in 2005. Similar results were reported in a 12-year PSA-based screening study when the pathological features of prostate cancers detected were compared from three consecutive time intervals [28].

Screening for prostate cancer, viewed as the first step in patient management would not lead to an improved outcome if the cancers detected were either clinically insignificant, already incurable or if the available treatment options were ineffective. For prostate cancer this has been shown not to be the case. The Scandinavian Prostate Cancer Group Study reported on outcomes of 347 men with early, nonscreen-detected prostate cancer randomized to RP, compared to 348 men randomized to watchful waiting [29]. The risk of overall mortality, cancer-specific mortality, distant metastasis, and local progression were all significantly lower in the patients treated with RP after 8 years of follow-up. After 10 years, there also was a significant improvement in overall survival in patients treated with RP [29].

It is probable that treatment with the intention to cure for early prostate cancer has contributed to the decreases in prostate cancer mortality observed in countries such as the USA, where treatment with RP and radiation therapy is widely practised. Extrapolating these findings to a population of men who undergo screening, the removal of small tumours should improve survival by detecting the life-threatening tumours earlier. In the Tyrol screening project, the treatment of patients with clinical stage T1–T2 lesions was RP in 89.3%, performed largely in a high-volume tertiary referral centre by experienced surgeons and was associated with low morbidity [30] (95.1% urinary continence (no pads) 1 year after RP; 78.9% preservation of erectile potency in men aged <65 years). The probability of clinical cancer progression after RP in patients with low PSA levels (<4 ng/mL), a low positive surgical margin rate (4.2%), and a low biochemical recurrence rate (5.7%), is low. Therefore, in the long term, patients with early-stage prostate cancer that is detected through PSA screening, who are treated effectively, should be expected to have a lower prostate cancer mortality rate.

The controversy surrounding screening for prostate cancer with PSA revolves around three key issues. Does PSA identify clinically significant prostate cancer in most cases? Does aggressive intervention with surgery or radiation alter the outcome in men diagnosed with clinically significant disease? Does diagnosis and treatment seriously impinge of quality of life (QoL)?

The estimates of prostate cancer over-diagnosis (30–50%) have been exaggerated in the literature [31,32]. This may be due in part by the fact that much of the data have been derived from older men, in whom over-diagnosis is a greater concern because of their limited life expectancy. In younger men, who are most likely to benefit from early diagnosis and treatment, the criteria for calling over-diagnosis are much less frequently met (≈15%) [32]. Nevertheless, a recent study showed that even men aged >65 years have a mortality benefit from treatment with RP or radiation therapy [33]. In the Tyrol study, in which the mean age of screened men was <65 years, the estimate of over-diagnosis according to the criteria of Epstein *et al.* [34] was 8.7% [35].

Using the pathology criteria in the RP specimen for over-diagnosis of pathological stage T2a, Gleason <7, over-diagnosis in the Tyrol Project was 19.7% for PSA levels of 2–4 ng/mL and 17.6% for PSA levels of 2–10 ng/mL [34]. In another screening study, using the Ohori criteria for unimportant disease [25], <10% of men underwent treatment for over-diagnosed prostate cancer [36].

Although reduction in prostate cancer mortality rates are important, it is also necessary to consider the effects of prostate cancer screening and treatment on patient QoL. Potential gains in survival could be more than offset by decrements in QoL that might result from diagnosis and treatment [37]. Ecological data suggest that 10–30% of the geographical variation in mortality rates might relate to variations in access to medical care [38]. A key feature of the present study setting is that patients in Tyrol have equal access to all therapeutic resources (surgery, radiotherapy and hormonal therapy) and that diagnosis and therapy are free of charge for everyone.

Population-based reductions in prostate cancer mortality rates may be the only way to assess the impact of prostate cancer

screening. Although androgen-deprivation therapy can slow the progression of prostate cancer, as a curative treatment for advanced disease is not available yet, any reduction in mortality is likely attributable, at least in part, to programmes that detect prostate cancer at an early stage and prevent the tumour acquiring the lethal phenotype. Since PSA screening was widely implemented in 1990, prostate cancer mortality in the USA has decreased dramatically. The prostate cancer mortality rate has decreased by an average of 2.4% yearly from 1993 to 2003 [3]. Between 1993 and 2002, the truncated (40–79 years) age-standardized prostate cancer mortality rate in the USA has decreased by an average of 4.7% per year. In Austria, excluding Tyrol, the decline was 3.2% per year while in the Tyrol it was 7.3%. The dramatic shift of stage in the PSA era followed by effective therapy should translate into a decrease of mortality rates.

Vutuc *et al.* [39] present a join point analysis of prostate cancer mortality rates in Austria from 1970 to 2002 and conclude that there is no evidence of a reduction in prostate cancer mortality which can be attributed to the introduction of the early detection program in the Tyrol in 1993. There are differences in the statistical analysis which can explain this apparent anomaly all related to statistical power. Principally, while this manuscript and Bartsch *et al.* [19] specify a prior hypothesis about a change in slope in the trends in Tyrol and the rest of Austria from 1993, Vutuc *et al.* [39] search for evidence of a change point, with a consequent reduction in power when adjusting for multiple testing. Secondly we expect to find the same trends in all age groups and have carried out a pooled analysis, adjusting for age effects, while Vutuc *et al.* [39] carried out a stratified analysis fitting the same model 8 times. Admittedly most of the power in both analyses comes from the 70–79 age group where most deaths are observed and the interaction tests we carried out to establish if there was any evidence that the trends in the two areas post 1993 were different in the age groups have low power. The analysis presented here and in Bartsch *et al.* [19] is based upon the estimation of effects and it can be concluded that there is evidence that the rates in both areas of Austria have decreased since 1993 and that there is evidence that the rate of decrease is faster in Tyrol. When estimating a change point there is sampling error in this estimation and an associated confidence interval and this is not reported by Vutuc *et al.* [39]. We have carried out a sensitivity analysis from 1991 to 1995 and at each year there was evidence of a change in slope (on our pooled analysis). Furthermore there was evidence that the reduction in mortality in Tyrol is greater than the reduction in the rest of Austria.

Data from the Tyrol have been presented here using the same approach as in the previous report [19] for maintaining longitudinal transparency of our study findings. These findings continue to be consistent with the notion that making PSA testing freely available, and its wide acceptance by men in the population, is associated with a reduction in prostate cancer mortality in a region where potentially curative prostate cancer treatment services are available free of charge to all patients.

Although it is not possible from the available data to separate the individual contributions of PSA testing and curative treatment to the favourable outcomes, the more rapid accelerated decline in mortality rates in Tyrol compared with the rest of Austria is unlikely to be artefactual. The delay between early detection and radical treatment beginning in 1988 (accelerating in 1993) and the decline in mortality in the targeted age range, which started in 1996, is comparable with that seen in other screening programmes with high compliance. It is likely that much of this decline in mortality rates is due to earlier detection and successful treatment of prostate cancer. However, an important corollary implication of the present study is that screening is only the first step in the optimal management of patients with prostate cancer.

Pending the results of the large randomized clinical trials, there is a great public health need to know more details of the potential risks and benefits of PSA testing. However, it is likely that, given the penetrance of PSA testing in communities of men, even null findings from these randomised trials will not deter future PSA testing rates [37].

The study group described here is a well-defined population of Tyrol, where detailed knowledge of PSA testing rates and information on therapy offered to the population exist. Of course, the design of the present study cannot overcome the problems inherent in nonrandomized studies, but it can provide useful information on the potential benefits of early detection in a real-life setting.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the contribution of all participants to this study. This manuscript is published by the list authors on behalf of the Tyrol Prostate Cancer Screening Group comprising GPs in the Federal State of Tyrol, the Urologists: Arno Ebner, Stephan Frank, Otmar Ennemoser, Lorenz Hoeltl, Jörg Joost, Sandor Kovesdi, Heinz Puschban, Wolfgang Schachtner, Karl Scheiber, Ferdinand Walser, Gerhard Weissteiner, Ernst Zangerl, Markus Sandbichler, Josef Girstmaier, Günther Petrischor, the Pathologists Gregor Mikuz, Georg Schäfer and Andrea Brunner, medical laboratories, all doctors, nurses and secretaries of the Department of Urology of the University of Innsbruck, the Blood Bank of the Red Cross, the Innsbruck, Social Security and Health Service of the Federal State 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.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **RP**, radical prostatectomy; **EBRT**, external beam radiotherapy; **QoL**, quality of life.