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Original Contribution

Reduction of Prostate Cancer Mortality in Tyrol, Austria, after Introduction of Prostate-specific Antigen Testing

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The objective of this study was to analyze in detail the time trend in prostate cancer mortality in the population of Tyrol, Austria. In Tyrol, prostate-specific antigen tests were introduced in 1988–1989 and, since 1993, have been offered to all men aged 45–74 years free of charge. More than three quarters of all men in this age group had at least one such test in the last decade. The authors applied the age-period-cohort model by Poisson regression to mortality data covering more than three decades, from 1970 to 2003. For Tyrol, the full model with age and period and cohort terms fit fairly well. Period terms showed a significant reduction in prostate cancer mortality in the last 5 years, with a risk ratio of 0.81 (95% confidence interval: 0.68, 0.98) for Tyrol; for Austria without Tyrol, no effect was seen, with a risk ratio of 1.00 (95% confidence interval: 0.95, 1.05). Each was compared with the mortality rate in the period 1989–1993. Although the results of randomized screening trials are not expected until 2008–2010, these findings support the evidence that prostate-specific antigen testing offered to a population free of charge can reduce prostate cancer mortality.

Austria; mortality; prostate-specific antigen; prostatic neoplasms

Abbreviations: APC, age-period-cohort; ASR age-standardized rate; PSA, prostate-specific antigen.

Prostate cancer is the second-leading cause of male cancer death in most industrialized countries. Thus, the discussion about whether prostate-specific antigen (PSA) testing should be offered in organized screening programs acquires great public health importance. Very large, randomized studies with more than 100,000 cases and controls per study are still ongoing in Europe and the United States; to our knowledge, only one smaller randomized study in Quebec has been concluded (1). These large studies reflect the exceptional interest in scientifically proven evidence on whether organized PSA screening reduces prostate cancer mortality. Until now, screening healthy men for prostate cancer has been shown to be feasible and acceptable in large studies (2). However, conclusive results are not anticipated until 2008–2010 (3), and one must bear in mind that randomized studies are expected to entail some problems with contamination of control groups (2).

PSA tests were introduced in Tyrol, Austria, in 1988–1989 and, since 1993, have been offered to all men aged 45–74 years (4). In Tyrol, where PSA testing is free of charge and is widely accepted, more than three quarters of men in this age group had at least one PSA test in the period 1993–2003, and some of them have PSA tests regularly. In addition, free annual health checks, including a digital rectal examination, are offered not only in Tyrol but also in all of Austria. Roughly one fifth of men accept this offer of a general medical examination. However, in Austria without Tyrol, PSA tests are not included in the free annual checks

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and must be paid for by the patient. Consequently, in Tyrol, the prostate has taken the lead among incident cancer sites for men, accounting for one third of all incident cancer cases, although, in terms of mortality, lung cancer is still much more frequent and accounts for one fourth of male cancer deaths. Prostate cancer is responsible for 12 percent of such deaths. The number of incident prostate cancer cases has more than doubled in the last decade, with up to 600 incident prostate cancer cases diagnosed annually in recent years (5–8).

These facts prompted us to conduct an in-depth analysis of time trends in cancer mortality. Our objective was to examine the time trend in prostate cancer mortality by using an age-period-cohort (APC) model to determine whether there was a significant change in the trend and to compare the results for Tyrol with those for Austria without Tyrol.

MATERIALS AND METHODS

Mortality data, which are collected by Statistics Austria (9), were analyzed for Tyrol and for Austria without Tyrol. In Austria, death certificates are issued by official, specially trained medical physicians, pathologists, and forensic medical experts. Specialists at Statistics Austria, the federal institution for statistics in Austria, follow international guidelines and select one main diagnosis that led to death and assign it one *International Classification of Diseases* code (using the Ninth Revision until 2001, the Tenth Revision since 2002). All procedures concerning death certificates, data collection, and coding are applied uniformly throughout Austria and are not state specific. We analyzed all cases for whom prostate cancer was coded as the cause of death, as described above.

Population data are also collected by Statistics Austria. Census data are available for the years 1971, 1981, 1991, and 2001; for intercensus years, population figures are extrapolated based on births, deaths, and migration information. At the time of our analysis, we had no access to population data for 2003 and thus used the population data from 2002 for 2003 (the difference in population for 1 year is very small: about 0.6 percent for states in western Austria and even less in the eastern states, namely, about 0.2 percent). The male population of Tyrol in census year 2001 was 328,323. In Austria without Tyrol, it was 3,559,913.

The analysis of mortality time trends was based on APC modeling by fitting separate models for Tyrol and for Austria without Tyrol (10, 11). APC models allow separate effects to be estimated for age (A), period or year of death (P), and cohort (C) by means of Poisson regression. In a more formal sense, we fit a series of models as follows:

$$\log(\rho_{APC}) = \alpha_A + \beta_P + \gamma_C, \text{ where } C = P - A,$$
$$\rho \text{ denotes the mortality rate.}$$

The model is often written in antilogs as follows:

$$\rho_{APC} = \alpha_A{}' \beta_P{}' \gamma_C{}',$$
$$\text{where } \alpha_A{}' \text{ denotes the antilog of } \alpha_A \text{ or}$$
$$\alpha_A{}' = \exp(\alpha_A), \text{ and so forth.}$$

As suggested by Clayton and Schifflers (10, 11), a series of models is fit until model fit is adequate. We start with A alone and proceed by including P and/or C in the model if the model fit is not sufficient without the extra term and inclusion of the term substantially improves goodness of fit. Goodness of fit is measured by deviance, which should be equal to or close to the degrees of freedom if the model fit is reasonably good.

For statistical analysis, the number of prostate cancer deaths was aggregated in 5-year age groups, 5-year period groups, and consequently 5-year cohort groups. In Tyrol, there are very few prostate cancer deaths in men less than age 60 years (3.3 percent of all prostate cancer deaths). We thus decided to build the model for age groups beginning with age 60–64 years and to continue by using 5-year age groups. We had access to mortality data beginning in 1970, so our first period group was 1970–1973. The others continued in 5-year period groups and ended with the period group 1999–2003. Our hypothesis was that the mortality rate decreases following PSA testing, so the reference category for period was 1989–1993. Consequently, because $C = P - A$, cohort groups began with 1882–1886 and continued in 5-year groups.

The analysis was performed with Stata version 8 software, using procedure poisson for Poisson regression (12).

RESULTS

We fitted separate models for prostate cancer mortality for Tyrol and for Austria without Tyrol according to the method suggested by Clayton and Schifflers (10, 11). If a model fits well, the deviance is chi-square distributed with degrees of freedom as given by the model. Therefore, if the deviance is equal to or near the degrees of freedom, the model fits rather well. For Tyrol, the AP model had 30 df and deviance 50.3; the AC model had 25 df and deviance 69.0. After adding period and cohort terms, the APC model reached 20 df with deviance 27.1, which seems reasonably good. For Austria without Tyrol, the AP model had 30 df and deviance 243.7, the AC model had 25 df and deviance 80.8, and the APC model had 20 df and deviance 61.4. We also applied the likelihood ratio test for parameters to test whether the effect of a new parameter was different from zero. For every step in model extension, the likelihood ratio test showed that the parameter effect was different from a zero effect. Thus, it was justified to add each parameter step by step.

One characteristic of the applied model is that period and cohort effects were divided into linear effect (called drift) and nonlinear effect (called nondrift). For Tyrol, we found that neither the AP model nor the AC model reached sufficient model fit, but the APC model fit fairly well. We could not distinguish between drift in period and drift in cohort because, when we modeled drift in cohort terms, we found a strong nondrift period effect, and when we modeled drift in period terms, we found a strong nondrift cohort effect. For Austria without Tyrol, none of the models reached sufficient model fit, so conclusions drawn from the model are to be interpreted with great caution. We modeled drift in period

TABLE 1. Model estimators for period and cohort given by the age-period-cohort model, drift in period, for Tyrol and for Austria without Tyrol, mortality data for Austria, 1970–2003

	Tyrol		Austria without Tyrol	
	Estimator	95% CI*	Estimator	95% CI
Age (years)				
60–64	1	Reference	1	Reference
65–69	2.08	1.63, 2.65	2.29	2.15, 2.43
70–74	4.99	3.93, 6.34	4.62	4.35, 4.92
75–79	8.73	6.72, 11.33	8.96	8.38, 9.57
80–84	14.93	11.07, 20.12	15.44	14.31, 16.66
≥85	23.83	17.06, 33.30	24.59	22.61, 26.74
Period				
1970–1973	0.71	0.53, 0.96	0.88	0.82, 0.95
1974–1978	0.66	0.51, 0.85	0.90	0.84, 0.96
1979–1983	0.81	0.66, 0.99	0.87	0.83, 0.92
1984–1988	0.83	0.71, 0.97	0.91	0.87, 0.95
1989–1993	1	Reference	1	Reference
1994–1998	0.94	0.81, 1.10	0.99	0.95, 1.03
1999–2004	0.81	0.68, 0.98	1.00	0.95, 1.05
Cohort				
1882–1886	1	Reference	1	Reference
1887–1891	1.50	0.94, 2.39	1.22	1.09, 1.38
1892–1896	1.62	1.07, 2.46	1.25	1.12, 1.39
1897–1901	1.80	1.22, 2.65	1.34	1.21, 1.48
1902–1906	1.65	1.13, 2.40	1.41	1.28, 1.55
1907–1911	1.52	1.04, 2.21	1.45	1.32, 1.59
1912–1916	1.57	1.07, 2.30	1.45	1.32, 1.60
1917–1921	1.31	0.87, 1.99	1.27	1.15, 1.41
1922–1926	1.13	0.72, 1.77	1.18	1.05, 1.32
1927–1931	1.02	0.62, 1.67	1.17	1.04, 1.33
1932–1936	1.06	0.60, 1.87	1.23	1.07, 1.41
1937–1941†				

* CI, confidence interval.
† Because there was drift in period, there is no estimator for this last cohort.

terms, so what we report here as estimators for period is the linear plus the nonlinear time trend.

Effects from the APC model are described in table 1. The reference category for age was 60–64 years; for period, the reference category was 1989–1993; and for cohort, the reference category was 1882–1886. Figures 1 and 2 show observed age-specific rates and predicted rates in an age-period graph and in an age-cohort graph, respectively.

Age effects were comparable for Tyrol and Austria without Tyrol. Compared with the age group 60–64 years, effects were about 2, 5, 9, 15, and 24 for the age groups 65–69, 70–74, 75–79, 80–84, and ≥85 years, respectively.

Period effects, each compared with years of death 1989–1993, were about 0.7–0.8 for the 1970s and 1980s in Tyrol and about 0.9 for both decades in Austria without Tyrol. Details are shown in table 1 and figure 3. For the years after 1993, which means after optional PSA testing was introduced for all men in Tyrol, Tyrol showed an effect of 0.94 (95 percent confidence interval: 0.81, 1.10) for 1994–1998 and a significantly reduced effect of 0.81 (95 percent confidence interval: 0.68, 0.98) for 1999–2003. For Austria without Tyrol, the effects were 0.99 for 1994–1998 and 1.00 for 1999–2003.

For Tyrol, cohort effects were about 1.5 until 1916, after which we found a decrease over the next decade, reaching 1.0 in 1927. For Austria without Tyrol, cohort effects were rather stable, with estimators of 1.20–1.40.

DISCUSSION

Our analysis was based on an observational study conducted among the population of Tyrol, where PSA testing has been offered to men free of charge since it was introduced in the early 1990s. Note that PSA testing is offered in

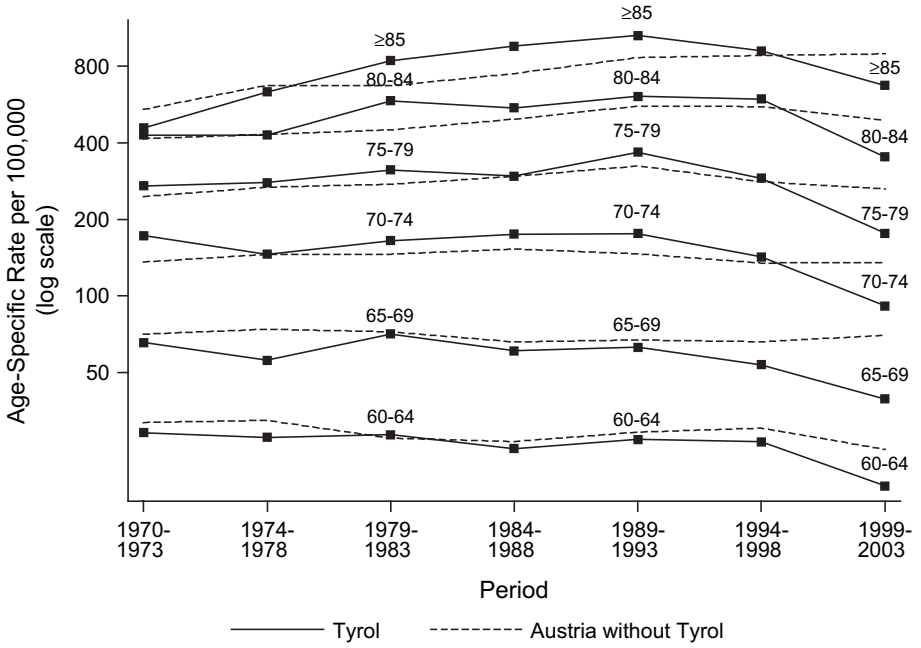

FIGURE 1. Predicted period effects, by age group (years), of prostate cancer mortality in Tyrol and in Austria without Tyrol, mortality data for Austria, 1970–2003.

an opportunistic way, not in the framework of an organized screening program. In addition, without a system of invitation and reinvitation, about three quarters of men aged 45–74 years underwent at least one PSA test for screening purposes in 1991–2003 (4). It seems justified to compare the time trend in prostate cancer mortality in Tyrol with that in the other Austrian states (detailed figures are given in table 2) because time trends in prostate cancer mortality were quite comparable until 1990, and health services in general, as well as diagnosis and therapy for cancer patients, are

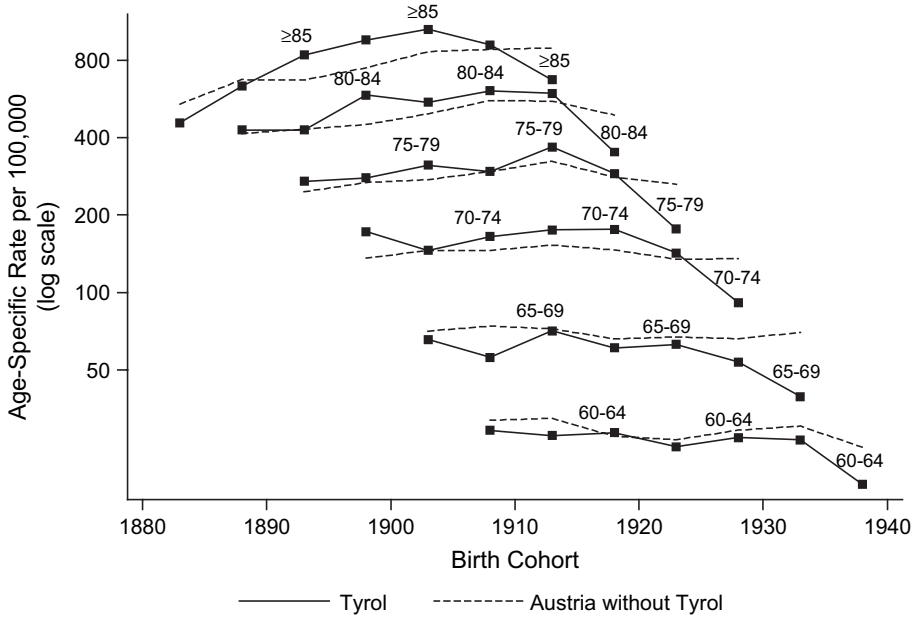

FIGURE 2. Predicted cohort effects, by age group (years), of prostate cancer mortality in Tyrol and in Austria without Tyrol, mortality data for Austria, 1970–2003.

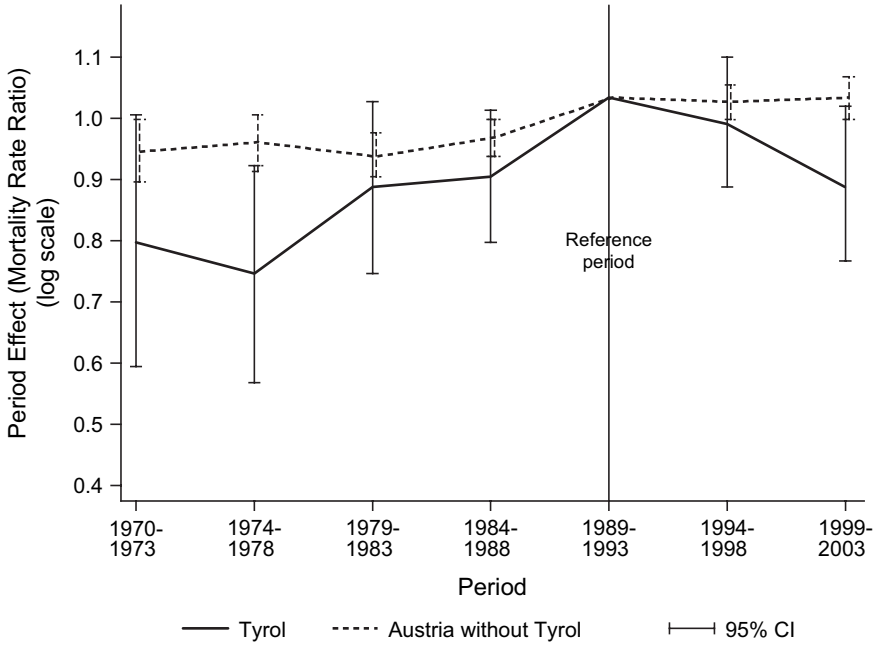

FIGURE 3. Estimated period effects of prostate cancer mortality in Tyrol and in Austria without Tyrol, mortality data for Austria, 1970–2003.

uniform throughout Austria. PSA tests are also conducted in Austria without Tyrol but not on the same scale as in Tyrol.

The results of our model showed a statistically significant reduction in prostate cancer mortality during the last period (1999–2003) in Tyrol, but no reduction in Austria without Tyrol. Our final model for Tyrol fit well and also included cohort as an independent factor, so period effects were adjusted for cohort effects. In contrast, for Austria without Tyrol, model fit was not good.

Figure 4 and table 2 show an increase in the prostate cancer mortality rate in both geographic areas and higher rates for Tyrol compared with Austria without Tyrol between 1980 and 1990. We observed an increase of about 15 percent in prostate cancer mortality for most central European countries between 1980 and 1990 (13). In Tyrol, the age-standardized rate (ASR) was 11–17 in 1970–1975 and reached a peak between 1987 and 1995, with a mean ASR of 19; in the rest of Austria, the ASR was 13–15 in 1970–1975 and peaked at 18 in 1991. We found no clear reasons for this different increase in Tyrol and in Austria without Tyrol. In the model, we defined the reference category for time as 1989–1993. As a consequence, for both geographic areas, the estimator for this reference time period was 1 and the period estimators for Tyrol were smaller in the 1970s and 1980s than for Austria without Tyrol (figure 3).

A recent publication by Vutuc et al. (14) analyzed prostate cancer mortality data in Austria from 1970 to 2002. That study used a different method, namely, a joined-point regression model, which assumes linear segments and identifies points where the slope changes. Age groups were also defined in a slightly different way. Possibly its greatest difference from our method is that the joined-point regression model did not take cohort effects into account. Finally, Vutuc et al. analyzed mortality data up to 2002, whereas we considered mortality data up to 2003. For Austria without Tyrol, Vutuc et al. found a significant annual decrease of −2.36 for the age group 70–79 years beginning in the year 1989 and a significant annual increase of 1.64 for the age group 80–89 years (we report significant results only). For Tyrol, the authors reported a nonsignificant annual increase of 1.15 for the age group 50–59 years, a nonsignificant annual decrease of −0.60 for the age group 60–69 years, a significant annual decrease of −6.42 for the age group 70–79 years beginning in 1991 (after a nonsignificant annual increase of 1.99), and a nonsignificant annual increase of 1.16 for the age group 80–89 years.

When we looked at the age groups up to 80 years, about two thirds of prostate cancer deaths were found in the age group 70–79 years. However, the Vutuc et al. (14) results also showed a significant decrease.

One might argue that differences in age structure could be responsible for some of the differences in prostate cancer mortality; however, our model considered age groups. In addition, there were only slight differences in age structure between Tyrol and Austria without Tyrol. Whereas in Tyrol the percentages of men aged 65, 75, and 85 years or older were 12.3, 4.7, and 0.9, in Austria without Tyrol, the respective percentages were 10.9, 4.0, and 0.9.

Because we analyzed mortality data, the quality of death certificates was very important to the conclusions we drew. In general, the quality of mortality statistics in Austria has been high for decades (15). Nevertheless, we cannot rule out the possibility that PSA testing has had an influence on death certificates. As mentioned above, coding is performed

TABLE 2. Prostate cancer mortality in Tyrol and in Austria without Tyrol, mortality data for Austria, 1970–2003

Year of death	Tyrol		Austria without Tyrol	
	No.	ASR*	No.	ASR
1970	56	17.1	677	13.5
1971	41	12.6	695	13.5
1972	39	11.0	700	13.8
1973	56	15.9	779	14.9
1974	51	13.8	777	15.1
1975	47	13.3	771	14.7
1976	52	14.7	809	15.4
1977	50	13.7	779	14.2
1978	57	15.2	865	16.3
1979	68	18.0	783	14.4
1980	90	22.9	845	15.3
1981	52	13.4	849	15.3
1982	69	17.1	874	16.0
1983	61	15.2	837	15.1
1984	68	17.1	835	15.0
1985	76	17.7	905	15.5
1986	70	16.7	925	15.8
1987	87	20.9	984	16.9
1988	71	15.7	941	16.2
1989	72	15.3	986	17.0
1990	96	20.3	1,014	16.8
1991	96	21.0	1,110	18.3
1992	91	18.3	1,048	17.1
1993	96	20.4	1,081	17.7
1994	95	19.5	993	16.1
1995	93	19.2	1,109	17.4
1996	91	17.8	1,079	16.9
1997	88	15.9	1,096	16.9
1998	60	11.3	1,079	16.1
1999	79	14.2	1,143	16.9
2000	79	13.7	1,150	16.5
2001	85	14.8	1,099	16.1
2002	79	14.0	1,059	15.2
2003	68	11.6	1,092	15.5

* ASR, age-standardized rate per 100,000 using Segi weights.

by one central institution for the whole of Austria and thus is not state specific. Therefore, the only difference could be in how the death certificates are written. We can imagine a bias in each direction: a tendency to code either more prostate cancer deaths because of great public awareness of prostate cancer or fewer prostate cancer deaths because of more caution in denoting prostate cancer as the cause of death. In summary, although we cannot rule out a bias regarding death certificates attributable to the different time trends, our assessment is that if a bias exists, it is probably small and cannot explain the 19 percent reduction in prostate cancer mortality we observed in our model.

There are no approximate figures on the volume of PSA testing conducted in Austria without Tyrol. We tried to use sales figures collected by test kit companies, but all information was too imprecise to realistically estimate the PSA testing rate in Austria without Tyrol.

For Tyrol, we collected data from all PSA laboratories and estimated the PSA testing rate based on two assumptions. First, it was for only the Urology Department of Innsbruck Medical University that we knew whether a PSA test was for screening purposes; that is, 85 percent were screening tests, and we assumed the same percentage for all other laboratories. Second, there was no personal identifier for about 500,000 of the PSA tests, and we assumed that the first four digits of the surname and date of birth uniquely identified the person. Details are shown in table 3. After 9 years of intensive PSA testing, we estimated that 75.1 percent of all men aged 45–74 years in Tyrol had had at least one screening PSA test.

Because we had no valid information on the volume of PSA testing conducted in Austria without Tyrol, looking at the time trend in cancer incidence can provide some insight into the amount of such PSA testing. When we compared incidence time trends between Tyrol and Austria without Tyrol, we found an ASR of 40–53 for 1988–1991. Afterward, the incidence rate in Tyrol already had doubled by 1993 (ASR = 87), and we observed an ASR of 100–130 since 1997. In Austria, however, from 1988 to 1991, the ASR was identical to the rates in Tyrol; we observed an increase beginning in 1993 and an ASR of 79–90 since 1998. Details are shown in table 3. Thus, for Austria, we expect a smaller decrease in mortality, and we expect the decrease to begin some 5 years later.

Our estimation of the PSA testing rate shows that, in 1995 and 1997, more than one third and one half, respectively, of all men in the age group 45–74 years in Tyrol had at least one PSA screening test. However, our estimation did not consider PSA tests before 1993. Thus, we tended to underestimate the true PSA screening rate. In other words, the period when half of the men had at least one PSA screening test is likely to be 1 or 2 years earlier. The model shows a decrease in prostate cancer mortality in Tyrol by one third around 2000. These data would fit a screening latency period of 5–7 years, which has been shown for mammography screening programs.

The effect of screening programs depends on the sensitivity and specificity of the detection method but also on the efficacy of the therapy applied for the cases detected in the screening program. This second component should not be underestimated. In fact, in Tyrol, a large proportion of such patients are treated by high-quality radical prostatectomy. This high quality of outcome is also shown by the excellent survival figures, for example, in the EUROCARE study (16).

The reduction in prostate cancer mortality in Tyrol could be due to 1) prevention of the disease, 2) detection of the disease at a stage when it is more likely to be curable, or 3) improved outcome of therapy for metastatic disease (4). We discuss these possibilities in order to explain the

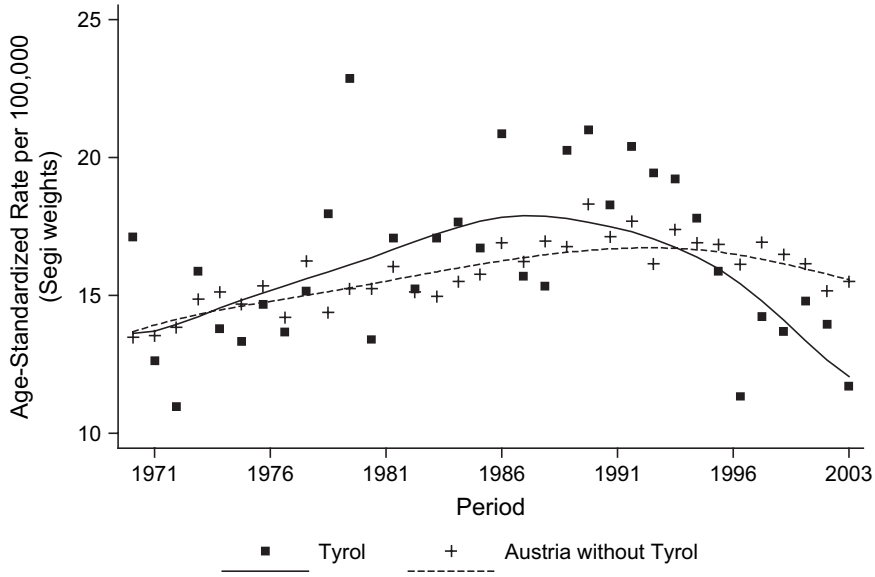

FIGURE 4. Age-standardized rate of prostate cancer mortality in Tyrol and in Austria without Tyrol, mortality data for Austria, 1970–2003. Segi weights, world population according to Segi, modified by Doll.

TABLE 3. Prostate cancer incidence rates in Tyrol and in Austria without Tyrol, and the PSA* screening rate in Tyrol, mortality data for Austria, 1970–2003

Year	Prostate cancer incidence				PSA screening test in Tyrol in the age group 45–74 years			
	Tyrol		Austria†		No. of men with a PSA screening test	Male population (no.)	Testing rate‡ (%)	Cumulative testing rate§ (%)
	No.	ASR*	No.	ASR				
1988	203	49.2	2,125	44.1				
1989	216	51.9	2,322	48.5				
1990	179	40.6	2,309	47.6				
1991	202	47.2	2,285	46.5				
1992	291	68.4	2,422	48.9				
1993	365	87.3	2,709	54.5	9,474	86,067	11.0	11.0
1994	490	117.3	3,156	63.0	14,147	88,342	16.0	23.3
1995	403	94.2	3,487	68.4	20,309	90,153	22.5	34.6
1996	408	92.4	3,699	71.5	23,839	91,497	26.1	44.1
1997	480	109.1	4,001	76.2	26,796	92,607	28.9	51.0
1998	506	114.9	4,218	79.2	30,228	93,719	32.3	56.8
1999	471	103.5	4,593	84.6	36,366	95,000	38.3	63.3
2000	596	130.1	4,925	89.5	41,860	96,692	43.3	70.1
2001	600	130.9	5,131	91.5	44,400	98,638	45.0	75.1

* PSA, prostate-specific antigen; ASR, age-standardized rate per 100,000 using Segi weights.

† We had data for Austria only as a whole, not for Austria without Tyrol (the male population of Tyrol constitutes 8 percent of the Austrian male population).

‡ We had no unique personal identifier; therefore, we estimated men to be uniquely identified by the first four characters of their surname and date of birth. We had no information on screening intention in the PSA database, so we estimated the screener percentage as 85 on the basis of detailed data in the database of the Urology Department of Innsbruck Medical University; each man is counted only once per year.

§ For the cumulative testing rate, each man was counted only once from 1993 to the end of the respective period.

different results for Tyrol and for Austria without Tyrol. Obviously, as shown in table 3, the disease has not been prevented. PSA testing is known to result in a shift toward earlier stages of the disease (4, 17, 18). Incidence data from Tyrol show that the ASR for metastatic cancer decreased from 5.2 to 2.1 and for advanced cancer (stage IV according to Union International Contre Cancer) from 7.9 to 3.7, whereby each decrease was calculated from the period 1988–1992 to the period 1998–2002. We had only limited data for Austria without Tyrol showing a reduction in disseminated prostate cancers of 20 percent in the last decade (19). Labrie et al. (1) reported that, in the Quebec study, only one of 159 cancers (0.6 percent) was metastatic, and Hugosson et al. (18) found that 97 percent of the cancers detected by screening were clinically localized. Jani et al. (20) also reported stage shifts. Thus, the mortality reduction in Tyrol and the stage shift are in line with observations made in other studies, and the different sizes of stage shift are in line with the different results for Tyrol and for Austria without Tyrol.

With regard to improved outcome of therapy for metastatic disease, all patients in Austria have equal access to therapeutic resources; radiotherapy and hormonal therapy are offered in a similar way throughout Austria. In addition, aside from a small amount of money to be paid by hospital patients beginning recently, diagnosis and therapy are free of charge for everyone. Therefore, it is very unlikely that differences in therapy or differences in improvements in therapy caused the differences in mortality reduction between Tyrol and Austria without Tyrol. In conclusion, the main difference between Tyrol and Austria without Tyrol seems to be the high percentage of men in Tyrol who underwent a PSA test.

Other studies also show benefits of PSA screening. In a very detailed analysis, the Surveillance, Epidemiology, and End Results Program group showed possible benefits of PSA screening, although this study was also population based with known possible biases. The authors concluded that part of the decline in prostate cancer mortality in the United States could be due to PSA screening, although they did not rule out other interpretations (17, 21, 22). An analysis of data for England and Wales also showed a reduction in mortality, but there was little evidence that PSA screening was the main reason for that reduction; figures show that a change in therapy probably influenced mortality there (23).

The main problem with our analysis is that nonrandomized studies are prone to several biases. It is hoped that this problem will be solved by the large, randomized screening studies under way in both Europe (European Randomized Study of Screening for Prostate Cancer (2)) and the United States (24). Up to 2002, the European study—in part population based, in part volunteer based—had enrolled 220,000 men. Neither large study will perform its final analysis before 2008–2010 (25), and there is some concern about contamination of control groups (2). A small study with 46,486 participants was conducted in Quebec, Canada (31,133 men in the intervention arm and 15,353 in the control arm), and its last update showed a relative risk of 0.38 ($p \leq 0.0002$), in other words, a 62 percent reduction in prostate cancer deaths in the screened group. The 33 percent mortality reduction seen in our study 10 years after PSA testing was offered to all men in the age group 45–74 years is in line with findings from the Quebec study if we bear in mind that our result was derived from a population-based analysis.

While we wait for the conclusive results of the large randomized studies, there is great public health eagerness to know more details of the potential benefit of PSA screening. Our study concerned a well-defined population in Tyrol, where we had detailed knowledge of PSA testing rates and information on therapy offered to the population. The APC model fit well for Tyrol, and, in comparison to Austria without Tyrol, the PSA testing rate seemed to be the main factor explaining the difference in time trends between Tyrol and Austria without Tyrol. Of course, our analysis could not overcome the problems of nonrandomized studies, but it can provide further information on the potential benefits of PSA testing or screening.

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REFERENCES

1. Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004;59: 311–18.
2. de Koning HJ, Auvinen A, Bereguer Sanchez A, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. Int J Cancer 2002;97:237–44.
3. Makinen T, Tammela TL, Stenman UH, et al. Second round results of the Finnish population-based prostate cancer screening trial. Clin Cancer Res 2004;10:2231–6.
4. Bartsch G, Horninger W, Klocker H, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001;58:417–24.
5. Oberaigner W, Mühlböck H, Harrasser L. Biannual report on cancer incidence and mortality in Tyrol/Austria, 1997/1998. (In German). Innsbruck, Austria: IET-Bericht, 2003.
6. Oberaigner W, Mühlböck H, Harrasser L. Biannual report on cancer incidence and mortality in Tyrol/Austria, 1999/2000. (In German). Innsbruck, Austria: IET-Bericht, 2004.
7. Parkin DM, Whelan SL, Ferlay J, et al, eds. Cancer incidence in five continents. Vol VII. Lyon, France: International Agency for Research on Cancer, 1997. (IARC scientific publication no. 143).
8. Parkin DM, Whelan SL, Ferlay J, et al, eds. Cancer incidence in five continents. Vol VIII. Lyon, France: International Agency for Research on Cancer, 2002. (IARC scientific publication no. 155).
9. Hansluwka H. Cancer mortality statistics: availability and quality aspects of mortality data worldwide. Recent Results Cancer Res 1989;114:163–75.

10. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: age-period and age-cohort models. Stat Med 1987;6:449–67.
11. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: age-period-cohort models. Stat Med 1987;6: 469–81.
12. Stata Corporation. Stata statistical software, release 8. College Station, TX: Stata Corporation, 2003.
13. WHO Mortality Database (WHO Statistical Information System (WHOSIS)). Table 1: Numbers and rates of registered deaths, Austria—2002. World Health Organization, 2005. (http://www3.who.int/whosis/mort/table1_process.cfm).
14. Vutuc C, Schernhammer ES, Haidinger G, et al. Prostate cancer and prostate-specific antigen (PSA) screening in Austria. Wien Klin Wochenschr 2005;117:457–61.
15. Holzner JH. The role of autopsy in the control of mortality in Austria. In: Riboli E, Delendi M, eds. Autopsy in epidemiology and medical research. Lyon, France: International Agency for Research on Cancer, 1991:25–35. (IARC scientific publication no. 112).
16. Coleman MP, Gatta G, Verdecchia A, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 2003;(14 suppl 5):v128–49.
17. 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 1999;91: 1017–24.
18. Hugosson J, Aus G, Bergdahl S, et al. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. BJU Int 2003; 92(suppl 2):39–43.
19. Statistics Austria (ed). Annual health statistics for Austria. (In German). Vienna, Austria: Statistics Austria, 2004.
20. Jani AB, Vaida F, Hanks G, et al. Changing face and different countenances of prostate cancer: racial and geographic differences in prostate-specific antigen (PSA), stage, and grade trends in the PSA era. Int J Cancer 2001;96:363–71.
21. Etzioni R, Legler JM, Feuer EJ, et al. Cancer surveillance series: interpreting trends in prostate cancer—part III: quantifying the link between population prostate-specific antigen testing and recent declines in prostate cancer mortality. J Natl Cancer Inst 1999;91:1033–9.
22. Feuer EJ, Merrill RM, 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 1999;91:1025–32.
23. Oliver SE, Gunnell D, Donovan JL. Comparison of trends in prostate-cancer mortality in England and Wales and the USA. Lancet 2000;355:1788–9.
24. Andriole GL, Reding D, Hayes RB, et al. The prostate, lung, colon, and ovarian (PLCO) cancer screening trial: status and promise. Urol Oncol 2004;22:358–61.
25. Auvinen A, Hugosson J. The rationale for the ERSPC trial: will it improve the knowledge base on prostate cancer screening? BJU Int 2003;92(suppl 2):14–16.