

Editorial

Prostate specific antigen (PSA)-based screening

'The Japanese Urological Association guidelines on prostate specific antigen (PSA)-based screening for prostate cancer and ongoing cluster cohort study in Japan' is published on pages 763–768 in the present issue of *International Journal of Urology*. Currently, there is controversy surrounding PSA-based screening in clinical practice. In order to widely discuss PSA-based screening, this Editorial was planned. In the first section, summaries of the five most recent articles on prostate cancer screening in *International Journal of Urology* are introduced. The second section is 'AUA-JUA joint statement on screening for prostate cancer' accompanied by an additional comment from Professor Robert C Flanigan (Loyola University Stritch School of Medicine, Chicago, IL, USA). The third section has been published as an Appendix in the Japanese Urological Association guidelines on screening for prostate cancer. The answers and opinions follow as Guest Editorials. *International Journal of Urology* is inviting submissions in response to any part of this Editorial, including views that oppose this Editorial. You are invited to submit Letters to the Editor by 31 January 2009.

Please submit at: <http://mc.manuscriptcentral.com/iju>.

Hiro Yoshi Suzuki MD
Deputy Editor

Recent articles on prostate cancer screening published in *International Journal of Urology*

Lower urinary tract symptoms and risk of prostate cancer in Japanese men

Matsubara A, Yasumoto H, Teishima J, Seki M, Mita K, Hasegawa Y, Yoshino T, Kato M, Usui T
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Matsubara *et al.* investigated whether or not men, in the Japanese population, with lower urinary tract symptoms are at increased risk of prostate cancer. Symptomatic Japanese men are not at higher risk of prostate cancer despite their higher prostate-specific antigen values compared with asymptomatic men of the same age group.¹ (*Int. J. Urol.* 2006; **13**: 1098–102)

Willingness to pay for mass screening for prostate cancer: A contingent valuation survey

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In an internet questionnaire survey by Yasunaga *et al.*, 400 men aged 50–59 years in Japan were randomly split into two groups: the ill-informed group ($n = 207$), which was provided with information about the detection rate, and the well-informed group ($n = 193$), which was given additional information about false positive/negative results, latent cancer, and the yet-to-be-demonstrated mortality-reducing effect of the test. The mean willingness to pay was yen 1670 (\$15.2). Giving

sufficient information would not decrease willingness to pay for prostate-specific antigen screening.²

(*Int. J. Urol.* 2008; **15**: 102–5)

Ten year trend in prostate cancer screening with high prostate-specific antigen exposure rate in Japan

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Okihara *et al.* evaluated the tendency of the results and quality control of prostate cancer screening serially performed for 10 years in an area of Japan. Clinically localized prostate cancer increased by 17%, and locally advanced and metastatic cancers decreased by 12% in the second compared with the first 5 years of the 10-year period. Serial prostate cancer screening showed a tendency of stage migration in the screened cancer patients.³

(*Int. J. Urol.* 2008; **15**: 156–60)

Economic evaluation of prostate cancer screening with prostate-specific antigen

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Economic issues cannot be ignored in conducting prostate cancer screening using prostate-specific antigen (PSA). Through an electronic search, Imamura *et al.* reviewed five descriptive cost studies and nine cost-effectiveness/cost-utility analyses concerning PSA screening. Most of the existing evidence was based on mathematical model analysis and the results are enormously disparate. At present, patients should be thoroughly informed of the limitations of PSA screening and, in consultation with urological specialists, make the personal decision of whether to receive it.⁴

(*Int. J. Urol.* 2008; **15**: 285–8)

Development of a new nomogram for predicting the probability of a positive initial prostate biopsy in Japanese patients with serum PSA levels less than 10 ng/mL

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Kawamura *et al.* developed a predictive model for Japanese males with a prostate-specific antigen (PSA) < 10 ng/mL to guide decision-making for prostate biopsies in order to provide more precise risk-analysis information for individual patients. Age and the independent predictors of a positive biopsy result (elevated PSA, decreased free to

total PSA ratio, small prostate volume, and abnormal digital rectal examination findings) were used to develop a predictive nomogram based on 1037 Japanese patients' data.⁵ (*Int. J. Urol.* 2008; 15: 598–62)

AUA-JUA joint statement



Fig. 1 AUA-JUA joint statement on screening for prostate cancer (20 June 2007).

In the United States, we have seen a decline in prostate cancer mortality that has occurred after the use of PSA screening became more widespread. The factors for this decline in mortality remain undefined but many experts believe that PSA screening with earlier detection of prostate cancer at a lower stage has been a major contributing factor. There has also simultaneously been a shift in our use of PSA, including lower threshold levels for young patients, the use of isoforms of PSA and PSA kinetics. I personally put a great deal of stock in the findings of the Tyrol Prostate Program of Austria that has suggested that PSA screened men are less likely to be under-diagnosed and less likely to have extra-prostatic disease.

Therefore, I personally continue to advocate yearly PSA screening (along with digital rectal examination) for men beginning at age 50 years and ending at 75 years (I begin earlier in men at increased risk of disease, including those with a positive family history or in African American men). The formal proof of this practice awaits the results of large screening studies, but in the interim I believe that this practice is very justifiable.

Robert C Flanigan MD
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Appendix in the Japanese Urological Association guidelines on screening for prostate cancer

Question: Is it acceptable to conduct a population-based screening for prostate cancer based on a well-balanced fact sheet including updated reviews on screening, diagnostic procedure and treatment for prostate cancer?

Akihiko Okuyama MD
Editor-in-Chief

Guest Editorials (Answers)

Comment from Professor Fernand Labrie MD

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In response to your question 'Is it acceptable to conduct a population-based screening for prostate cancer based on a well-balanced fact sheet including updated reviews on screening, diagnostic procedures and treatment for prostate cancer?' The answer is YES.

Since metastatic prostate cancer is and will remain for a long time non curable, it is essential, in order to decrease deaths from prostate cancer, to diagnose the cancer at the localised stage when cure is a possibility in the majority of cases.

With this well known scientific evidence that early diagnosis is a necessity, it remains important to explain to the patient the precision of the available diagnostic procedures (including detection of some cases of slow – growing cancer) and also the efficacy and side effects of the various treatments available for prostate cancer.

It most also be clearly stated to the patient that the important reduction of the death rate from prostate cancer observed during the last of 15 years is due to early diagnosis coupled with efficient treatment while no cure exists for metastatic disease found in most cases if no screening is performed. The patient must decide between a small percentage of cases with potential overtreatment compared to the large number of lives saved with early diagnosis and appropriate treatment. It thus remains to the patient well informed by his physician and otherwise to decide to be screened or not to be screened but the answer is very clear for me: it is YES for annual screening with PSA followed by other techniques if abnormal PSA.

Comment from Professor Francesco Montorsi MD

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The EAU are producing a guideline on prostate cancer for publication in 2009; 'Screening and early detection'. Population or mass screening is defined as the examination of asymptomatic men (at risk). Usually, screening takes place within the framework of a trial or study and is initiated by a screener. Contrary to that, early detection or opportunistic

screening represents individual case findings. It is initiated by the screenee (patient) and/or his physician. The primary endpoint of both is two-fold: first, the reduction of CaP-specific mortality. The goal is not to detect more and more carcinomas, nor is survival the endpoint because survival is heavily influenced by lead-time. Second, quality of life is important as expressed by quality of life adjusted gain in life years (QUALY).

The trends in mortality from CaP show a wide variety from country to country all over the industrialized world. A decrease in mortality rates due to CaP is currently seen in the USA and Austria, but also in the UK and France, which share a similar decrease in CaP mortality rates. Similarly, in Sweden, the relative 5-year survival rates increased in the period from 1960 to 1988, which was attributed to increased diagnostic activities and the detection of more non-lethal tumours. However, this trend could not be confirmed in a similar study from the Netherlands.

The reduction in mortality seen lately in the USA is often attributed to the widely adopted aggressive screening policy. However, there is still no absolute proof that the concept of prostate-specific antigen (PSA) screening is the cause for reduced mortality due to CaP.

A non-randomized screening project in Tyrol (Austria) may support the hypothesis that screening can be effective in reducing CaP mortality. The early detection programme in combination with the availability of free treatment was used as an explanation for the 33% decrease in the CaP mortality rate seen in Tyrol as compared with the rest of Austria (level of evidence: 2b). In addition, Labrie and co-workers from Quebec (Canada) claim lower mortality rates in men randomized to active CaP screening, even though these results have been challenged. Other studies have contradicted the positive findings attributed to screening, with a comparative study between the Seattle area (highly screened population) and Connecticut (seldom screened population) by Lu-Yao and co-workers showing that, notwithstanding the very large diversity in PSA testing and in use of curative treatments, there was no difference in the reduction in the rate of CaP mortality (level of evidence: 2b).

In order to be able to really evaluate the efficacy of CaP screening, prospective, preferably population-based, randomized trials are needed. Two large trials are underway, the PLCO (Prostate, Lung, Colorectal and Ovary) trial in the USA and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe. The first analysis of the main endpoint of these trials—differences in CaP mortality is scheduled for 2008 (level of evidence: 1b).

Thus, at the present time, there is a lack of evidence to support or disregard widely adopted, population-based screening programmes for early detection of CaP aimed at all men in a given population (level of evidence: 3).

Less controversial, and recommended in most guidelines, is the use of PSA in combination with digital rectal examination (DRE) as an aid to early diagnosis (11) (see chapter 5) (level of evidence: 3). The group has also produced a shorter version for publication in *European Urology* (*Eur. Urol.* 2008; **53**: 68–80).

Comment from Professor Robert C Flanigan MD

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I am very pleased to support the concept that it is acceptable to conduct a population – based screening for prostate cancer based on a well – balanced fact sheet including updated reviews on screening, diagnostic procedures and treatment for prostate cancer.

Prostate cancer remains a major killer of men across the world. It is clear to me that early detection of this disease has led to the decreased death rate from prostate cancer that we have been experiencing in our country over the past several years. I am therefore personally very happy to support this proposed effort. I will send this note to you on my stationery.

Comment from Professor Kenneth Lin MD

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Prostate cancer is the most common non-skin cancer in men in the United States; 1 in 6 men will be diagnosed during their lifetimes. However, the vast majority of men diagnosed with prostate cancer (218 890 in the US in 2007) do not die from it (27 350 deaths in 2006).^{6,7} These statistics suggest that our current methods for detecting prostate cancer that is clinically important (e.g. with the potential to cause health problems during a patient's lifetime) leave much to be desired. Prostate-specific antigen (PSA) screening in men over the age of 50 has been the norm in the United States since the early 1990s. PSA screening is also one of the few preventive benefits paid for by the US Medicare program for patients aged 65 and older, despite the lack of evidence from randomized trials showing that such screening reduces prostate cancer mortality⁸ and ample evidence that screening and treatment lead to significant psychological and physical harms.^{9–11}

Why is this so? Ransohoff *et al.* have suggested that prostate cancer screening is 'a system without negative feedback'; patients are likely to be grateful for early detection and rationalize adverse effects from treatment.¹² A recent case report in the *New England Journal of Medicine*¹³ regarding a 54 year-old man with early-stage prostate cancer that was detected after multiple PSA tests and benign biopsies illustrated two points: (i) the harder you look for prostate cancer, the more you will find; and (ii) once confronted with a prostate cancer diagnosis, virtually all men in reasonably good health will choose invasive therapy.

Given these realities, it is vitally important for a man to have an informed discussion with his physician about the potential benefits and known harms of PSA testing before deciding whether or not to get the test. Shared decision-making is recommended by most major US medical organizations, including the US Preventive Services Task Force (USPSTF).¹⁴ Many decision aids to assist shared decision-making about prostate cancer screening have been developed and have been shown to improve patient knowledge and involvement in the decision.¹⁵ Unfortunately, recent studies show that few physicians and patients are actually having these discussions, for a variety of reasons.¹⁶

The question posed to me was whether or not it was 'acceptable to conduct population-based screening for prostate cancer based on a well-balanced fact sheet.' I would argue that is not possible to create such a balanced fact sheet until we know more of the facts. The first critical question which will hopefully be answered within the next few years by two ongoing randomized trials,^{17,18} is whether population-based screening actually reduces prostate cancer mortality. If it does,

the next questions will be which men benefit the most from screening, how often should screening be performed, and for how long? Many years (and quite possibly decades) of additional research will be required to answer these questions. In the meantime, there are many other preventive measures that clinicians should be recommending to men over 50 that have much stronger evidence of benefit, such as colorectal cancer screening, smoking cessation counseling, and yearly influenza vaccination. Better to spend one's time at an office visit discussing things that we know help before doing what might help.

The opinions expressed in this commentary are those of the author and do not represent the official position of the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

Comment from Professor William J Catalona MD

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The informed use of PSA and PSA kinetics, together with appropriate and effective treatment, can substantially reduce suffering and death from prostate cancer.

Since 1994, there has been a striking decline in United States (US) prostate cancer mortality rates, a reduction that I believe must be ascribed, at least in part, to early detection through PSA-based screening combined with effective treatment.

A single PSA value provides a powerful risk assessment about the presence and aggressiveness of prostate cancer. The serum PSA concentration correlates with PSA velocity, with the Gleason grade and with prostate-cancer-specific mortality after treatment.

If a man has a PSA of 2.5 to 4 ng/mL, there is a 20 to 25% chance prostate cancer will be found on biopsy, depending on the number of biopsy cores obtained. That risk rises to 25 to 40% if the PSA is 4 to 10 and 60% if the PSA is greater than 10.

Several studies now show that the single PSA value for men in their 30s and 40s can predict later prostate cancer and prostate cancer mortality.

What is less appreciated is prostate cancer risk assessment using as a benchmark the median PSA for the age group in the general population.

In my PSA study that lasted 12 years and enrolled 36 000 volunteers, men in their 40s and 50s had median PSAs of 0.7 and 0.9, respectively. Men in their 60s had PSA values of 1.3, and in their 70s of 1.7. All these numbers are lower than the lowest PSA cutoffs suggested for recommending biopsy (2.5 ng/mL).

For men in their 50s, as the PSA goes up over the median (0.9) to 2.5, there is a 7-fold risk they will develop prostate cancer over the next 12 years. The risk rises to 27-fold if the PSA is between 2.6 and 4, and to 44-fold if the PSA is greater than 4. For men in the 60s and 70s, as PSA values rise above the median for their age group, the risk of being diagnosed with prostate cancer and for having aggressive prostate cancer also increases significantly.

In findings of my PSA Study, similar to those of the Prostate Cancer Prevention Trial, showed that in men with a PSA of less than 4 and a normal digital rectal exam, there was a linear increase in the

percentage who had prostate cancer found on = biopsy as their PSA values rose from 0 to 0.5, from 0.6 to 1, from 1 to 2, from 2 to 3 and from 3 to 4.

As for high Gleason grade cancer, when the PSA was under 2, 10% of cancers detected had a high Gleason grade; when it increased above 2, the percentage that were high grade rose to more than 20%. Accordingly, there is a substantial prevalence of prostate cancer in men who have PSA values of less than 4.

As for cure rates, the most important outcome of PSA screening, in my personal series of now more than 4700 men with radical retropubic prostatectomy, many is that if cancer was detected at a PSAs of 2.5 to 4, the cure rate is almost 90%, falling to 50% if diagnosis occurred at PSAs above 10.

Several factors can confound PSA values: BPH, prostatitis, ejaculation, rectal exam, differing assay standardizations and normal biological variations in a man's PSA levels, which can vary by up to 15% over two weeks.

Useful but under-utilized tools for adjusting for BPH are PSA density and the percentage of free PSA. If the PSA density is over 0.1, it is suspicious for cancer and PSA density also correlates to tumor volume, Gleason grade, PSA velocity and progression-free survival.

Similarly, if the percentage of free PSA is less than 10%, there is nearly a 60% chance the man has prostate cancer; however, the percentage of free PSA is greater than 25%, there is only an 8% chance the patient has prostate cancer.

As for PSA kinetics, PSA velocity – which is the absolute change in PSA per year – is a simple tool for diagnosing men who have not been previously diagnosed with prostate cancer, because it is independent of the baseline PSA. PSA doubling time is also used for diagnosis and prognosis, but since it is a function of the baseline PSA, the higher the baseline value, the longer it takes for its concentration to double.

For example, consider two hypothetical patients who develop identical prostate cancers that grow for a year. Patient A with a base-line PSA of 1 ng/mL does not have BPH, while patient B with a base-line PSA of 4 ng/mL does. At the end of one year, patient A's PSA has gone from 1 to 2, for a 100% rise and a PSA velocity of 1. Patient B, who has BPH, has gone up 25% to 5 from a baseline of 4, for the same PSA velocity of 1. His doubling time, however, is 4, because it will take four years to double from 4 to 8, if it increases at the same rate. The diagnostic danger is that patient A might be erroneously thought to have a less aggressive tumor and patient B a more aggressive tumor based upon their different PSA doubling times.

PSA velocity is, I think, better for initial diagnosis, while doubling time is better for men who have failed treatment, because patients who have failed radical prostatectomy or radiation usually start out with very low PSAs after treatment – 0.1 or 0.2 – so the baseline PSA is not so critical in the post-treatment setting.

The normal PSA velocity for man with no prostate cancer is 0.1, for an increase of about one tenth of a nanogram per year. In a collaborative study, we found that if PSA increased by 2.0 in the year before diagnosis, it was associated with a nearly 10-fold higher rate of prostate-cancerspecific mortality compared with lower PSA velocities. The PSA velocity cutoff for curable prostate cancer is 0.35, above which there is an increased risk of prostate cancer mortality.

There is as yet no proof from randomized clinical trials that PSA screening saves lives. There are two prospective trials underway in the United States and Europe, but the results will not be available for several years. Furthermore, both of these trials have significant flaws, and it is unlikely that they will answer this question beyond debate.

The strongest population-based epidemiologic evidence for the effectiveness of PSA screening reported to date comes from a study of cancer registry data sampling more than 60% of the US population. This study examined, in more than 30 regions of the US, the relationship between the prevalence of PSA-based screening, the incidence of advanced-stage prostate cancer at diagnosis, and prostate cancer-specific mortality rates in the region. The results showed that the more PSA screening was practiced, the lower the proportion of cases with advanced-stage disease at diagnosis, and the lower the prostate cancer-specific mortality rate in the region.

The benefits of PSA-based screening in the US are also becoming obvious in the national tumor registry data. In the US, where widespread PSA screening was introduced in 1991, there has been a 70% reduction in the percentage of men presenting with metastases at time of diagnosis. That, in turn, has had a profound impact on the five-year survival rate, which is now almost 100% for patients with local or regional disease. There has been a 32.5% reduction in the US age-adjusted prostate cancer mortality rate through 2003.

Globally, the trends are similar. In jurisdictions where PSA screening is common, such as France, the US, Canada, prostate cancer mortality has decreased. The Austrian federal province of Tyrol has seen approximately a 50% per cent decrease in deaths with PSA screening. In countries such as Greece, Venezuela, Spain and Sweden, however, where screening is not recommended for reasons ranging from economics to public-health philosophy, prostate cancer mortality is on the rise.

Concerns have been raised about whether PSA screening largely detects clinically insignificant cancers. However, prostate cancer deaths would not have decreased so much if screening only over-detected harmless prostate cancer.

The current recommendations for prostate cancer screening by US professional medical societies are conflicting. The American Urological Association, the American Cancer Society, and the National Comprehensive Cancer Network all recommend that screening be offered to men over the age of 50 years with a life expectancy of at least 10 years, and at a younger age in high-risk men. In contrast, the American College of Physicians and the US Preventive Services Task Force do not believe there is sufficient evidence at this time to recommend screening. The National Cancer Institute has remained neutral on this issue, pending the results of the prospective screening trials.

My current recommendations for prostate cancer screening are:

Start PSA testing at age 40 to provide a baseline from which to track changes over time and to assign appropriate risk assessment.

Know the standardization of the PSA assays you use – Hybritech (1986) or World Health Organization (WHO) (1999). PSA is more than 20% lower if the WHO standard is used (e.g. PSA 4 = 3.1).

Assess patients' prostate-cancer risk by comparing their PSA values with the median for their age group

Strongly consider prostate biopsy if PSA is higher than 2.5 ng/mL

Use PSA density and percentage of free PSA to evaluate confounding from BPH

Rule out prostatitis with antibiotics and/or by repeat PSA measurements. Studies show that PSAs can drop substantially after antibiotic therapy.

Use a PSA velocity of 0.35 ng/mL/year to identify more aggressive tumors. Velocity >0.35 is associated with an increased risk of death 15 years later.

I would estimate that prostate cancer death rates could be reduced by another one-third with the systematic intelligent use of PSA combined with effective treatment.

Comment from Professor George Bartsch MD

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

The estimates of prostate cancer 'overdiagnosis' (30% to 50%) have been exaggerated in the literature.^{19,20} This may be due in part by the fact that much of the data have been derived from older men, in whom overdiagnosis 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 overdiagnosis are much less frequently met (~15%).²⁰ Nevertheless, a recent study has shown that even men over 65 years of age have a mortality benefit from treatment with radical prostatectomy or radiation therapy.²¹ In the Tyrol study, in which the mean age of screened men was less than 65 years, the estimate of overdiagnosis according to the criteria of Epstein²² was 8.7%.²³ Using the pathology criteria in the prostatectomy specimen for overdiagnosis of pathologic stage T2a, Gleason <7, overdiagnosis in the Tyrol Project was 19.7% in the PSA range of 2 ng/mL to 4 ng/mL and 17.6% in the PSA range of 2 ng/mL to 10 ng/mL. In another screening study, using the Otori criteria for unimportant disease,²⁴ fewer than 10% of men underwent treatment for 'overdiagnosed' prostate cancer.²⁵ Although reduction in prostate cancer mortality rates is important, it is also necessary to consider the effects of prostate cancer screening and treatment on patient quality of life. Potential gains in survival could be more than offset decrements in quality of life that may result from diagnosis and treatment.²⁶

Ecological data suggest that 10% to 30% of the geographic variation in mortality rates may relate to variations in access to medical care.²⁷ A key feature of this 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 programs that detect prostate cancer at an early stage and prevent the tumor acquiring the lethal phenotype. Since PSA screening was widely implemented in 1990, prostate cancer mortality in the United States has decreased dramatically.

The prostate cancer mortality rate has decreased by an average of 2.4% yearly from 1993 to 2003.²⁸ Between 1993 and 2002, the truncated (40–79) age standardised prostate cancer mortality rate in the United States 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.

Data from the Tyrol have been presented here using the same approach as in the previous report²⁹ for the purpose of 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 favorable outcomes, the more rapid accelerated decline in mortality rates in Tyrol compared to 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 programs 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 our study is that screening is only the first step in the optimal management of prostate cancer patients.

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