It's time to depolarise the unhelpful PSA-testing debate and put into practice lessons from the two major international screening trials

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ABSTRACT

- Two recently reported large-scale trials conducted in the United States and western Europe have provided evidence that coordinated screening programs will not reduce mortality in countries or regions where prostate-specific antigen (PSA) testing is already highly prevalent, but will reduce mortality in places where PSA testing prevalence is low.
- The trials also produce evidence that coordinated screening will cause over-diagnosis and over-treatment.
- The instigation of a national screening program should be delayed until a more specific marker for aggressive disease than PSA level becomes available. In the meantime, results of the two trials can be used to inform the development of regional testing policies in Australia.
- These policies should encourage regular PSA testing in regions with low testing prevalence, but must also embrace methods of dealing with over-diagnosis and over-treatment.
- "Active surveillance" programs (whereby men with early-stage cancers are monitored regularly by PSA testing and digital rectal examinations) and development of counselling services should be encouraged.

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Opinion is sharply divided on the value of prostate-specific antigen (PSA) testing for prostate cancer.[1] Up to now, the ascendant point of view has been that there is little evidence of benefit from PSA testing but much evidence of morbidity from treatment of slowly progressing cancers.[2-4] At the other end of the spectrum is the view that early diagnosis of all cancers that can be cured in their localised stages is beneficial. At times, both sides of the debate have been expressed with a vigour that has left observers thinking they are mutually exclusive. This has resulted in a state of confusion that, we contend, has done much to paralyse the provision of helpful guidance to the public.

In March 2009, the *New England Journal of Medicine* published the results of two large-scale prostate cancer screening trials that commenced in the early 1990s.[5,6] In the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial in the United States, 76 693 men aged between 55 and 74 years were randomly allocated to either take part in an annual screening program involving PSA testing and digital rectal examination or to receive routine medical care. In the European Randomized Study of Screening for Prostate Cancer (ERSPC) in western Europe, centres in seven countries pooled data from regional trials involving 182 016 men aged between 55 and 74 years who were randomly assigned to undergo2–4-yearly screening or routine medical care. Although the results of the trials are not yet mature, we believe that they have produced sufficient data to depolarise the PSA-testing debate and provide a framework for helpful public guidelines.

Lessons from the PLCO trial and ERSPC

At first sight, it appears that the two trials present conflicting results. After 7 years' follow-up, results of the PLCO trial indicated that an annual screening program did not reduce the number of advanced cancers detected or the number of deaths due to prostate cancer (Box).[5] After a median follow-up period of 9 years, the ERSPC showed that screening at less frequent intervals reduced the number of advanced cancers that were detected by half, and deaths from prostate cancer by 20%, statistically[6] (or 31% when adjusted for "contamination" (informal self-screening arrangements).[7]

How can these different results be reconciled? We believe that the two trials are not producing conflicting results, but rather, among other things, they are reflecting the different "starting positions" of the sampled populations. When a cancer screening test is applied to a large enough number of subjects in an appropriate age range, it will cause an increased number of cancers at all stages of advancement to be detected. If the testing process is repeated within a relatively short period, fewer advanced cancers will be detected by subsequent tests. Therefore, over a given period of time, the total number of advanced cancers detected in the screened population will be lower than the number detected in an unscreened population. In contrast, the number of *early* cancers detected in the screened population will be higher than in an unscreened population over the same time period. This "stage shift" is exactly what was seen in the ERSPC (Box). In the screening arm, 725 of the 6039 cancers detected (12.0%) were advanced or metastatic (ie, Stage T3, T4 or M1). In the control arm, the corresponding proportion was more than double this figure (1209/4611 [26.2%]).

However, if a well coordinated screening program is commenced in a population that has already been heavily exposed to the screening test on an ad hoc basis,[8,9] it is unlikely that a large number of advanced cancers will be newly detected. Thus there will be no large stage shift. This scenario closely reflects what happened in the PLCO trial (Box). In the 3 years before participation in the trial, 44% of men had had one or more PSA tests, and 55% had had a digital rectal examination. As a result, only 135 of the 2940 cancers detected (4.6%) in the control arm of the PLCO trial were advanced or metastatic (ie, Stage 3 or 4) (Box). In addition, half of the men in the "unscreened" control arm of the PLCO trial organised PSA testing for themselves, which weakened the power of the PLCO trial to demonstrate a reduction in mortality. The authors emphasised the point by stating that the cumulative death rate from prostate cancer at 10 years in the intervention and control groups combined was 25% lower in participants who had undergone two or more PSA tests at baseline than in those who had not been tested.

Staging and prostate cancer deaths among men participating in the PLCO and ERSPC trials[5,6]

	Control arm	Screening arm	
STAGE OF CANCER AT DIAGNOSIS			
PLCO Trial	*n* = 2940	*n* = 3437	RD (%)*
Stage 1	15 (0.5%)	18 (0.5%)	+ 2.6%
Stage 2	2790 (94.9%)	3297 (95.9%)	+ 1.1%
Stage 3	56 (1.9%)	49 (1.4%)	– 25.2%
Stage 4	79 (2.7%)	73 (2.1%)	– 21.0%
ERSPC	*n* = 4611	*n* = 6169	RD (%)*
Stage T1a,b	277 (6.0%)	212 (3.4%)	– 42.8%
Stage T1c	1805 (39.1%)	3477 (56.4%)	+ 44.0%
Stage T2	1320 (28.6%)	1755 (28.4%)	– 0.6%
Stage T3	749 (16.2%)	509 (8.3%)	– 49.2%
Stage T4	156 (3.4%)	67 (1.1%)	– 67.9%
Stage M1	304 (6.6%)	149 (2.4%)	– 63.4%
CAUSE OF DEATH (in men diagnosed with prostate cancer)			
PLCO Trial			Rate ratio†
Prostate cancer	82	92	1.11
Other causes‡	225	312	—
ERSPC			
Prostate cancer	326	214	0.80
Other causes	ns	ns	ns

ERSPC = European Randomized Study of Screening for Prostate Cancer. ns = not specified. PLCO = Prostate, Lung, Colon and Ovarian. RD = relative difference.

* The relative difference is the percentage increase or decrease in cases of a given stage of prostate cancer detected by screening, using the formula RD = {[(proportion in screened arm ÷ proportion in control arm) × 100] – 100}%. eg, for the PLCO Trial, Stage 3, RD = {[(49/3437 ÷ 56/2940) × 100] – 100}% = –25.2%.

† Rate ratio = adjusted value given by the authors.[5,6] ‡ Men with prostate cancer dying of other causes.

Unfortunately, if treatment is not efficacious, all that will be achieved by a stage shift is an apparent prolongation in survival time resulting from earlier diagnosis (a lead-time bias). However, a large body of uncontrolled and randomised controlled clinical data now indicate that survival can be prolonged by radical prostatectomy or radiation[10-13] and by the use of adjuvant androgen suppression therapy.[14-18]

The differences in testing practices between the two continents arose as informal, ad hoc (opportunistic) PSA testing became highly prevalent in the US before the PLCO trial started. In 2002, the age-standardised detection rate of prostate cancer in the US was 124.8 per 100 000 men — much higher than anywhere else in the world,[16] including Australia (76.0 per 100 000). The situation in western Europe (and Australia) was quite different. Opportunistic testing rates were generally much lower than in the US, and advanced cancers were detected more frequently.[8,9,19,20] Not surprisingly, age-standardised detection rates in 2002 in the countries that contributed to the ERSPC (ranging from 35.9 to 90.9 per 100 000 per annum) were far lower than in the US.[21]

On the negative side, it must be pointed out that the ERSPC screening programs increased the number of early-stage cancers detected, which, in the opinion of the trial investigators, resulted in an increase in the diagnosis of "harmless" cancers (over-diagnosis). This, in turn, leads to unnecessary treatment (over-treatment). They estimated that, for every life saved by screening, 1410 would have needed to be tested and 48 additional men would have required curative treatment.[6] Although more deaths will be prevented and these ratios will fall as time passes, these estimates should be seen in context. For example, Rembold estimated that, in mammography breast cancer screening trials with 9 years of follow-up (ie, similar to the PLCO trial and ERSPC), one life would be saved in 4576 women aged 40–49 years, 1532 aged 50–59 years and 695 aged 60–69 years.[22]

Translating the data into policy applicable in Australia

The results of these two trials make it clear that both sides of the PSA testing debate are correct. Organised PSA population screening programs will result in over-diagnosis and over-treatment and will not save lives in places where PSA testing is already highly prevalent. However, they will save lives in countries where detection rates are low.

Acknowledging regional variations in detection and mortality

In a country like Australia, where survival rates for men with prostate cancer are among the highest in the world,[23] the reader will be forgiven for wondering whether the PSA testing debate matters and, more importantly, whether the results of the screening trials are relevant. But substantial regional variations in incidence and mortality rates for prostate cancer provide good reason to answer "yes" to both questions. As Coory and Baade have shown, the prevalence of PSA testing varies significantly between regions.[24] Moreover, they found that these variations translated into mortality differences, in much the same way, we contend, that they did in the PLCO trial and ERSPC. For example, 5-year data from the New South Wales Central Cancer Registry between 2002 and 2006 indicate that age-adjusted mortality rates for prostate cancer were about 40% higher in the NSW Cancer Council's Hunter region than in its Central and Southern Sydney regions (standardised mortality ratios, 16.0 v 11.4 per 100 000; $P < 0.01$), but that age-adjusted incidence rates were about 7% lower (standardised incidence ratios [SIRs], 69.9 v 75.1 per 100 000). Furthermore, the cancers detected in the Hunter region were more advanced than those in the Central and Southern Sydney regions (SIRs for "localised" cancer, 25.2 v 41.7 per 100 000; SIRs for "distant" cancer, 3.4 v 2.8 per 100 000).[25]

The implications are that, in some regions, over-diagnosis and over-treatment will be commonplace. In these regions, exhorting all men to get tested annually will achieve no more than was achieved in the screening arm of the PLCO trial. But in regions where belated diagnosis and poor access to specialised medical services are significant problems, discouraging testing will serve to increase belated diagnoses and deaths. Viewed in this way, it is obvious that the PSA-testing debate serves no-one properly.

What can Australia learn from these variations in incidence, mortality and survival rates? We believe that a national population-based screening program using PSA testing is not warranted at the present time. However, if a better screening test becomes available — one that is highly specific for prostate cancers that are likely to cause harm within 15–20 years and thus will reduce over-diagnosis and over-treatment — then the concept of a national screening program will need to be revisited. In the meantime, we need to recognise that regional problems do exist.

Development of regionally based policy

A concept that deserves serious consideration is the development of a prostate cancer awareness policy that is designed to meet the needs of different regions. For example, in a region that already has a high prevalence of PSA testing and good access to medical services, the major problems to deal with are over-diagnosis and over-treatment. Even though there are already means of avoiding biopsies (eg, by obtaining confirmatory PSA levels in the ensuing months, one or two of which include free to total PSA ratios) in every man with a PSA level of 4 ng/mL or more, the introduction of more specific tests is a long way off, and over-diagnosis will continue to be a problem. Over-treatment is likely to remain a problem until biomarker staining of biopsy specimens becomes a reliable means of differentiating between aggressive and indolent cancers.[26-28]

In the meantime, we need to develop other strategies for avoiding over-treatment. The most promising of these is the "active surveillance" concept,[29-33] whereby men with early-stage, low-grade cancers are monitored regularly with PSA testing and digital rectal examinations. In some of these programs, biopsies are repeated every 12–24 months. The goal is to delay curative therapy as long as possible (which in many cases will be indefinitely), but not long enough to make cure impossible. This approach differs significantly from the concept of "watchful waiting", whose goal is to use palliative interventions only when cancer-related symptoms develop. Disadvantages of active surveillance are that it is resource-intensive and that the trigger points for initiating curative interventions are rather arbitrary. In two larger studies,[32,33] men with PSA-level doubling times of less than 3 years or with very low free PSA to total PSA ratios underwent earlier interventions than those without.

In a region where PSA testing prevalence is low, where cancers are detected at advanced stages and access to specialist medical services is poor, a well coordinated PSA testing program could reduce the incidence of advanced cancer. Most new cancers diagnosed under such a program would be impalpable, low-grade, indolent cancers that could be managed in active surveillance clinics. The program would need to be accompanied by improved access to specialised monitoring and treatment services.

Finally, we envisage a valuable role for specially trained counsellors. Many of the decisions relating to prostate cancer detection and the need for treatment require lengthy discussions, and usually involve the wife or partner of the man at risk.[34] General practitioners and specialists rarely have the time to explain the complexity of important issues such as "who should be tested and how often," and "who should undergo or avoid treatment." This is certainly not a novel concept. Breast cancer counsellors have been appointed in most health districts in the past 15 years and play an important role in helping women to understand the complexities of breast cancer treatment.

Competing interests

None identified.

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References

1 MacKenzie R, Chapman S, Barrett A, Holding S. "The news is [not] all good": misrepresentations and inaccuracies in Australian news media reports on prostate cancer screening. *Med J Aust* 2007; 187: 507-510.
2 Royal Australian College of General Practitioners. Prostate screening: policy endorsed by the 51st RACGP Council 6 May 2009. http://www.racgp.org.au/policy/Prostate_screening.pdf (accessed Dec 2009).
3 Cancer Council Australia. Position statement: prostate cancer screening. http://www.cancer.org.au/File/PolicyPublications/Position_statements/PS-Prostate_cancer_screening_Apr08.pdf (accessed Dec 2009).
4 Urological Society of Australia and New Zealand. USANZ PSA testing policy 2009. http://www.usanz.org.au/uploads/29168/ufiles/USANZ_2009_PSA_Testing_Policy_Final1.pdf (accessed Dec 2009).
5 Andriole GL, Grubb RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009; 360: 1310-1319.
6 Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomised European study. *N Engl J Med* 2009; 360: 1320-1328.
7 Roobol MJ, Kerkhof M, Schröder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol* 2009; 56: 584-591.
8 Ross LE, Berkowitz Z, Ekwueme DU. Use of the prostate-specific antigen test among US men: findings from the 2005 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 636-644.
9 Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States. *JAMA* 2003; 289: 1414-1420.
10 Nilsson S, Norlén BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. *Acta Oncol* 2004; 43: 316-381.
11 Hammad FT. Radical prostatectomy. *Ann N Y Acad Sci* 2008; 1138: 267-277.
12 Zhou EH, Ellis RJ, Cherullo E, et al. Radiotherapy and survival in prostate cancer patients: a population-based study. *Int J Radiat Oncol Biol Phys* 2009; 73: 15-23.
13 Potters L, Klein EA, Kattan MW, et al. Monotherapy for stage T1–T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 2004; 71: 29-33.
14 D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004; 292: 821-827.
15 Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002; 360: 103-106.
16 Pilepich MV, Winter K, Lawton C, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma — long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005; 61: 1285-1290.
17 Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group protocol 92-02. *J Clin Oncol* 2003; 21: 3972-3978.
18 Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol* 2005; 6: 841-850.
19 Bouchardy C, Fioretta G, Rapiti E, et al. Recent trends in prostate cancer mortality show a continuous decrease in several countries. *Int J Cancer* 2008; 123: 421-429.
20 Smith DP, Supramaniam R, Coates MS, Armstrong BK. Prostate cancer in New South Wales in 1972 to 1994. Sydney: NSW Cancer Council, 1998.
21 Baade PD, Youlden DR, Krnjacki LJ. International epidemiology of prostate cancer: geographical distribution and secular trends. *Mol Nutr Food Res* 2009; 53: 171-184.

22 Rembold CM. Number needed to screen: development of a statistic for disease screening. *BMJ* 1998; 317: 307-312.
23 Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; 9: 730-756.
24 Coory MD, Baade PD. Urban–rural differences in prostate cancer mortality, radical prostatectomy and prostate-specific antigen testing in Australia. *Med J Aust* 2005; 182: 112-115.
25 Cancer Institute NSW. NSW Central Cancer Registry. Statistical reporting module. http://www.statistics.cancerinstitute.org.au (accessed Dec 2009).
26 Quinn DI, Henshall SM, Sutherland RL. Molecular markers of prostate cancer outcome. *Eur J Cancer* 2005; 41: 858-887.
27 Henshall SM, Horvath LG, Quinn DI, et al. Zinc-alpha2-glycoprotein expression as a predictor of metastatic prostate cancer following radical prostatectomy. *J Natl Cancer Inst* 2006; 98: 1420-1424.
28 Lapointe J, Li C, Higgins JP, et al. Gene expression profiling identifies clinically relevant subtypes of prostate cancer. *Proc Natl Acad Sci U S A* 2004; 101: 811-816.
29 Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol* 2004; 5: 101-106.
30 Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol* 2002; 167: 1231-1234.
31 Klotz L. What is the best approach for screen-detected low volume cancers? — the case for observation. *Urol Oncol* 2008; 26: 495-499.
32 Klotz L. Active surveillance with selective delayed intervention using PSA doubling time for good risk prostate cancer. *Eur Urol* 2005; 47: 16-21.
33 van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol* 2008; 54: 1297-1305.
34 Baade PD, Steginga SK, Pinnock CB, Aitken JF. Communicating prostate cancer risk: what should we be telling our patients? *Med J Aust* 2005; 182: 472-475.

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