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National Screening Advisory Committee's Review of the Interim Results of the European and U.S. Trials of Prostate Cancer Screening

To Stephen McKernan, Director-General of Health, Ministry of Health
From Ross Lawrenson, Chair, National Screening Advisory Committee

Purpose

1. To review the interim results of two ongoing international trials: the *European Randomized Study of Screening for Prostate Cancer (ERSPC)* and the *Prostate, Lung, Colorectal, and Ovarian (PLCO)* trial. Both trials were published on 18 March 2009 in the *New England Journal of Medicine*.

Background

European Trial: the European Randomized Study of Screening for Prostate Cancer (ERSPC)

2. *Aim:* To evaluate the effect of screening with prostate-specific antigen (PSA) testing on mortality from prostate cancer.
3. *Design:* From 1997 to 2006, 162,387 men between the core ages of 55 and 69 years in seven European countriesⁱ were randomly assigned to either a group that was offered PSA screening every four years (n=72,952) or to a control group that was not offered PSA screening (n=89,435). The average diagnostic cut-off for a positive PSA was 3 ng per mL. The primary outcome measure was cause-specific mortality.
4. *Screening benefits:* After 8.8 to 9.0 years of follow-up, within a core age group of 55 to 69 years, 214 and 326 prostate cancer deaths were observed in the screening group and control group respectively. The unadjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.67 to 0.95 P=0.01). This corresponds with a significant absolute risk difference between groups of 0.71 deaths per 1000 men. This means that 1410 men would have to be screened 1.7 times over 9 years (number needed to screen), and 48

ⁱ In Sweden study investigators included men between the ages of 50 and 54, whereas investigators in the Netherlands, Italy, Belgium and Spain included men up to the age of 74 years.

men would need to be treated (number needed to treat) to prevent one prostate cancer death.

5. *Screening harms:* Of the men who had a PSA test, 16.2% were positive and required diagnostic evaluation (i.e. biopsy). Of the men who underwent biopsy for positive PSA, 78.9% were negative meaning their PSA test was a false positive result.
6. *Conclusions:* PSA screening was associated with a significant absolute reduction of 0.71 prostate cancer deaths per 1000 men after an average follow-up of 8.8 years.

U.S. Trial: the Prostate, Lung, Colorectal and Ovarian (PLCO) Trial

7. *Aim:* To determine the effect of annual prostate-specific antigen (PSA) testing and digital rectal examination (DRE) on mortality from prostate cancer.
8. *Design:* From 1993 to 2001, 76,693 men between the ages of 55 and 74 years were enrolled at 10 centres across the United States and were randomly assigned to receive either annual screening (n=38,343) or usual care (n=38,350). Men in the screening group were offered annual PSA testing for 6 years and DRE for 4 years. The diagnostic cut-off for a positive PSA was 4 ng per mL. The primary outcome measure was cause-specific mortality.
9. *Screening benefits:* After 7 years of follow-up, 50 and 44 prostate cancer deaths were observed in the screening group and control group respectively. The corresponding rate ratio for death from prostate cancer in the screening group was not significant (rate ratio, 1.13, 95% CI 0.75 to 1.70). This means that in spite of a higher chance for men being diagnosed with prostate cancer in the screening group than in the control group, the chance of dying from the disease was the same as in both study groups.
10. *Screening harms:* For those men who had a DRE, the rate of bleeding and pain was 0.3 per 10,000 men screened, whereas for those men who had a PSA test the rate of complications, including dizziness, bruising, and hematoma, was 26.2 per 10,000 men screened. For those men who underwent biopsy for a positive PSA, the rate of complications, including infection, bleeding, clot formation and urinary difficulties, was 68 per 10,000 men. The rate of treatment related complications related to overdiagnosis, including infection, urinary incontinence, and impotence, will be reported separately.
11. *Conclusions:* After 7 to 10 years of follow-up, the rate of death from prostate cancer did not differ significantly between the two study groups.

Discussion

12. The European trial reported a small benefit of for prostate cancer screening, whereas the U.S. trial reported no screening benefit. Both trials, however, reported screening harms including: risks of overtreatment and overdiagnosis.

13. The screening benefit observed in the European trial applied to the core age-group of men aged 55 to 69 years. There was no screening benefit observed for younger men aged 50 to 54 years.
14. Both trials, while of good quality overall, had issues related to the contamination of the control group (i.e. proportion of the men who were assigned to the control condition which had PSA testing anyway). For the U.S. trial, the control group was defined as 'usual care', which by definition, sometimes includes screening. Contamination of the control group by opportunistic PSA screening in the European trial was reported previously (Ciatto et al 2003).
15. For the European trial, there were differences in how the study was carried out in each international jurisdiction including: the protocol used for recruiting and randomizing men, and the diagnostic cut-off used for a positive PSA result.
16. Both trials are ongoing and report interim results after approximately 10 years. A longer follow-up period may produce different results.

Recommendations

The National Screening Advisory Committee recommends that you:

a)	note that the benefits of PSA screening for prostate cancer identified in the European trial were small	Yes / No
b)	note that no benefit of prostate cancer screening was identified in the U.S. trial	Yes / No
c)	note that both trials identified considerable screening harms related to overdiagnosis and overtreatment	Yes / No
d)	note that the benefits of PSA screening identified in the European trial were observed using an average screening interval of four years, whereas a screening interval of one to two years is more commonly used in general practice	Yes / No
e)	note that the utility of prostate screening increases with age	Yes / No
f)	note that a longer study follow-up period may alter trial results and	Yes / No
g)	note that a watching brief of these two prostate cancer screening trials should be kept, including similar trials of prostate cancer treatment effectiveness, to inform men about making prostate screening decisions.	Yes / No

References

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