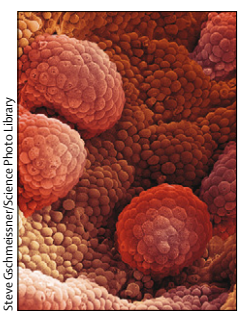
Comment

PSA testing for prostate cancer improves survival—but can we do better?



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Published Online
July 1, 2010
DOI:10.1016/S1470-2045(10)70152-2

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Prostate-specific antigen (PSA) testing remains controversial because it detects some cancers that will never present during the patient's lifetime (over-diagnosis[1]) and it results in unnecessary treatments that can damage men's quality of life (over-treatment).[2] However, in this issue of *The Lancet Oncology*, Hugosson and colleagues[3] show that although these points have validity, PSA testing reduces death from prostate cancer in some circumstances.

Hugosson and colleagues[3] report that 14 years after randomisation, on an intention-to-treat analysis, PSA testing almost halved the risk of death from prostate cancer (absolute risk reduction 0·4%, from 0·9% in the control group to 0·5% in the screening group); the number needed to screen to prevent one death was 293, and number needed to diagnose or treat was 12. These outcomes compare favourably with well-established screening programmes for breast and colorectal cancer and add further evidence to the outcomes of the European Randomised Study of Screening for Prostate Cancer (ERSPC).[4] In the ERSPC study, at a median follow-up of 9 years, a 20% decrease in prostate-cancer deaths was reported. The other screening study, Prostate, Lung, Colon and Ovarian cancer screening (PLCO) trial[5] included 76 000 men, but reported no benefit. However in PLCO, contamination from PSA testing was significant, increasing from 40% in year one to 52% in year six, making this study very difficult to interpret.

There are, however, important caveats about the Göteborg study. The study is small, with 20 000 men, a significant proportion (11 852 of 20 000) of which have already been reported in ERSPC.[4] The reduction in mortality (RR 0·56) is greater than that found in ERSPC (RR 0·80); why are there these differences between ERSPC and Göteborg?

There is a risk that subgroup analysis of the ERSPC has produced these significant results by chance, although the protocol and the date of analysis in the Göteborg trial were predetermined. The follow-up is more mature in the Göteborg study and the outcomes at 9 years were similar to those reported by ERSPC at that time-point. However, although the time since randomisation was 14 years, the median time since diagnosis was much shorter—6·7 years for screened men versus 4·3 years in the control group. These results are surprising because the conventional wisdom suggests that time periods of about 10 years are needed to show benefit from early detection and early treatment.[6] The median age in the Göteborg study was 4 years younger than in the ERSPC, which is important because younger men are likely to benefit more from early diagnosis than older men. The PSA threshold was slightly lower in the Göteborg study than in ERSPC, although it changed over time (from 3·4 ng/mL to 2·5 ng/mL); in men younger than 50 years of age the PSA threshold must be less. The screening interval in the Göteborg study was lower (2 years) than that of the ERSPC (4 years). Probably the most important points are the longer length of time since randomisation and the younger age at screening than in the ERSPC, in a national context of a low baseline rate of PSA testing before the study.

The effect of PSA screening on stage migration in countries with low levels of pre-existing PSA testing has been well described in Tyrol, Austria, and in the UK.[7,8] The study by Hugosson and colleagues[3] might be generalisable to populations that have not had prior extensive PSA testing, but probably not generalisable to populations that have had such testing—eg, in the Göteborg study only 56% of cancers were low-risk according to the D'Amico criteria, by contrast with tumours found in the second or additional rounds of screening in the ERSPC, and particularly with tumours found in the course of PSA testing in the USA, where typically low-risk cancers would be found in 75% of patients.

One important finding of this study is that diagnosis of prostate cancer did not automatically result in men taking up radical treatment. About 40% of men in the screening group were placed on active monitoring protocols; 28% remained on these protocols. Moreover, the results show that in certain circumstances, PSA testing and early diagnosis reduces death from prostate cancer. It does not imply that PSA screening programmes should now be

introduced internationally. Men should be aware of the benefits associated with the early detection of prostate cancer. Current programmes that raise awareness and provide balanced information about the pros and cons of screening seem to be the right way forward.

How can we improve the identification of men with intermediate and high-risk prostate cancers? Biomarkers such as insulin-like growth factor or kallikrein family members might improve sensitivity and specificity. Would this multiplexed biomarker approach, coupled with genetic testing for the 31 predisposition alleles,[9] be more effective in identifying men at high-risk of future progression? We need research programmes that properly address this question, now that we know for certain that early detection and treatment of some prostate cancers can save lives.

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Bevacizumab in lung cancer: hurdles in clinical development

Targeted treatments focusing on inhibition of angiogenesis and epidermal-growth-factor-receptor-mediated signal transduction offer new treatment options for patients with advanced non-small-cell lung cancer (NSCLC).[1] Clinical benefits have been shown for bevacizumab,[2,3] cetuximab,[4] gefitinib,[5] and erlotinib.[6] Overall, however, the clinical development of targeted therapies for NSCLC has been associated with several difficulties. Toxic effects have been a greater than anticipated problem in the development of many targeted agents. For bevacizumab, risk of bleeding was of particular concern, but could be mostly reduced by careful patient selection and exclusion of patients with squamous-cell histology in phase 3 trials.[2,3] Nevertheless, safety concerns led to the SAiL trial, a phase 4 trial assessing side-effects and benefits of bevacizumab over a long follow-up in a large population that was representative of patients seen in routine practice.

As reported by Crinò and colleagues[7] in *The Lancet Oncology*, the results of the SAiL trial have confirmed that bevacizumab added to different chemotherapy protocols is reasonably well tolerated in patients with advanced NSCLC. Main side-effects were thromboembolic events, hypertension, proteinurea, and bleeding. No unexpected toxic effects were reported. These safety data are reassuring for several reasons. First, careful patient selection according to the criteria used in SAiL and surveillance during treatment should guarantee the safe use of bevacizumab in routine practice. Second, bevacizumab seems to be safe in patients with brain metastasis. This finding is relevant because brain metastases either are present at diagnosis or will develop during the course of the disease in many patients. Additionally, brain imaging before treatment with bevacizumab is no longer required. Third, that SAiL did not reveal any previously unknown toxic effects or risks shows that results obtained in phase 3 trials are relevant for a broad patient population.

As shown for bevacizumab, toxicity management strategies should be addressed early during the clinical development of any targeted agent and should be continued after approval of the drug. This strategy will guarantee patient safety and the long-term success


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Published Online
July 21, 2010
DOI:10.1016/S1470-2045(10)70173-X

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