WHAT'S HOT IN... MEDICINE, January/February 2010

Two Studies Continue Debate on Prostate Cancer Screening

by David W. Sharp

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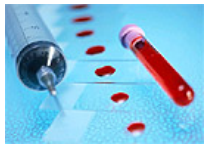
Screening does tend to attract controversy, and prostate cancer is no exception. Evidence that screening for this cancer meets the strict criteria for a valid screening test (see *Science Watch*, Nov/Dec, 2008) has been hard to come by. A systematic review published in 2006 found only two acceptable randomized trials of screening compared with no screening or routine care. The relative risk and confidence interval for mortality then was 1.01 (0.80 – 1.29) (D. Ilic, *et al.*, *Cochrane Database Syst. Rev.*, 3: CD004720, 2006). Many clinicians, patients, and health economists, among others, will have been hoping that two major trials reported in the March 26, 2009, issue of the *New England Journal of Medicine* would settle the controversy (paper #10 and G. L. Andriole, *et al.,* 360[13]: 1310-9, 2009, at #11 with total cites 49 and latest count 38).

As reported in paper #10, the European Randomized Study of Screening for Prostate Cancer (ERSPC) was conducted in seven countries with some variations in methodology between participating centers. A PSA above 3 or 4 ng/mL was an indication for prostate biopsy. The principal endpoint was death from prostate cancer. Cancer was detected in 8.2% of those screened and in 4.8% of controls. For the first six years of follow-up, mortality rates from prostate cancer remained much the same in the two groups, but then a divergence in favor of screening began and the rate ratio for death from prostate cancer was significantly reduced at 0.80. A 20% reduction in prostate cancer mortality sounds important but, put another way, the data mean that 48 additional men would need to be treated to prevent 1 death from cancer of the prostate. Furthermore, in 75.9% of the men who did have a biopsy because of a raised PSA , the PSA result turned out to be a false positive. Overdiagnosis and overtreatment remain major obstacles in the path to any official policy of PSA screening. The smaller U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO, paper #11) is looking negative, at least so far. Although screening picked up prostate cancer at a 22% higher rate, no significant difference in prostate cancer mortality emerged.



Neither the U.S.A. nor the U.K. has a national screening program for this cancer. In both countries the emphasis is on full disclosure of information to men who ask for a PSA test, and last summer the U.K.'s information pack was altered to take into account the two papers now under discussion. Nonetheless there is a wide perception that PSA testing is more established in the U.S.A. than on the other side of the Atlantic. Surveys suggest that most men over 40 in the U.S.A. will have had a PSA test (L.E. Ross, *et al.*, *J. Natl. Med. Assoc.*, 10[4]: 316-24, 2009) and that 87% of U.S. male physicians over 50 seek testing (E.C. Chan, *et al.*, *J. Gen. Intern. Med.*, 21[3]: 257-9, 2006). This complicates the interpretation of the American study (#11) because controls can hardly be barred from asking for the test outside the trial. Indeed, 44% of all those taking part had already been tested before the trial began and many controls were tested later. This unavoidable complication of the trial's design (known as contamination) could have diluted a real benefit of screening. Such dilution, however, happened in the European study also. When the ERSPC data were re-analyzed with adjustment for both contamination and non-attendance at the initial screening round, the benefit of screening in respect of prostate cancer death increased to 29-31% (M.J. Roobol, *et al.*, *Eur. Urol.*, 56[4]: 584-91, 2009). Of other explanations that might account for the apparent lack of screening benefit, the most important in the opinion of the U.S. trialists (#11) could be improved treatment for prostate cancer, leading to fewer deaths in both groups.

To summarize these important trials as positive (#10) and negative (#11) is probably too simple because both will yield more data with longer follow-up and more endpoints (a further six years is planned for PLCO). Indeed, the confidence interval for the principal endpoint in the "negative" U.S. study encompasses the "positive" finding in the European one. *NEJM*'s editorialist, Dr. Michael J. Barry (360[13]: 1351-4, 2009) questions publication of this unfinished business, noting that there was neither a clear declaration of futility in the PLCO trial nor an unambiguous net benefit in the ERSPC trial." When *Science Watch* asked Prof. Fritz. H. Shröder (ERSPC, Erasmus Medical Center, Rotterdam, Netherlands) why the PLCO And ERSPC findings were different, he too drew attention to contamination but also noted the shorter follow-up and smaller sample size of PLCO (ERSPC was more than twice the size). "The power calculation which was a crucial issue of discussion with the editors of *NEJM*, with respect to the ERSPC paper, is not even mentioned in the PLCO paper," Schröder told *SW*. Whether interim findings should (or, indeed, could) be kept under wraps is often controversial. With PLCO it was the independent data and safety monitoring board that urged publication. Either way, evidence from randomized trials is more reliable than the superficially persuasive fact that, compared with U.K. experience, prostate cancer mortality in the U.S.A. fell more rapidly over the decade 1994 to 2004 when PSA testing was introduced into that country (S.M. Collin, *et al.*, *Lancet Oncol.*, 9[5]: 445-52, 2008).

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Medicine Top 10 Papers

Rank	Paper	Citations This Period (Jul-Aug 09)	Rank Last Period (May-Jun 09)
1	J. Yu, *et al.*, "Induced pluripotent stem cell lines derived from human somatic cells," *Science*, 318(5858): 1917-20, 21 December 2007. [Genome Ctr. Wisconsin, Madison; U. Wisconsin, Madison] *243HE	78	3
2	The ACCORD Study Group (H.C. Gerstein, *et al.*), " Effects of intensive glucose lowering in type 2 diabetes," *New Engl. J. Med.*, 358(24): 2545-59, 12 June 2008. [Writing Group: 10 U.S. and Canadian institutions] *311IJ	77	1
3	The ONTARGET Investigators (S. Yusuf, *et al.*), "Telmisartan, ramipril, or both in patients at high risk for vascular events," *New Engl. J. Med.*, 358(15): 1547-59, 10 April 2008. [Writing committee: 5 institutions worldwide] *285NK	67	4
4	The ADVANCE Collaborative Group (A. Patel, *et al.*), "Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes," *New Engl. J. Med.*, 358(24): 2560-72, 12 June 2008. [Writing Group: 18 institutions worldwide] *311IJ	62	2
5	J.M. Llovet, *et al.*, "Sorafenib in advanced hepatocellular carcinoma," *New Engl. J. Med.*, 359(4): 378-90, 24 July 2008. [22 institutions worldwide] *329FK	51	7
6	R.R. Holman, *et al.*, "10-year follow-up of intensive glucose control in type 2 diabetes," *New Engl. J. Med.*, 359(15): 1577-89, 9 October 2008. [6 U.K. institutions] *358FS	45	6
7	R.M. Klevens, *et al.*, "Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States," *JAMA*, 298(15): 1763-71, 17 October 2007. [11 U.S. institutions] *220WF	44	†
8	Cancer Genome Atlas Research Network (L. Chin, *et al.*), "Comprehensive genomic characterization defines human glioblastoma genes and core pathways," *Nature*, 455(7216): 1061-8, 23 October 2008. [60 institutions worldwide] *363FG	44	†
9	S.D. Wiviott, *et al.*, "Prasugrel versus clopidogrel in patients with acute coronary syndromes," *New Engl. J. Med.*, 357(20): 2001-15, 15 November 2007. [8 institutions worldwide] *230RV	39	†
10	F.H. Schröder , *et al.*, "Screening and prostate-cancer mortality in a randomized European study," *New Engl. J. Med.*, 360(13): 1320-8, 26 March 2009. [15 institutions worldwide] *423VP	38	†

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KEYWORDS: PROSTATE-SPECIFIC ANTIGEN, PSA, PSA SCREENING, PROSTATE CANCER, ERSPC, PLCO.

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