The value of screening for prostate cancer has been a contentious issue within the medical literature for several decades. At the crux of the matter lies a judgment call of whether the potential benefits of screening, a reduction in prostate cancer and all-cause mortality, outweigh the limitations, overdiagnosis and overtreatment. The study by Schröder et al. reports 9, 11 and 13-year follow-up data on men participating in the European randomized study of screening for prostate cancer (ERSPC). While the authors report a significant reduction in prostate cancer mortality, they conclude that potential harms associated with screening currently circumvent any recommendation for a population-based approach to screening for prostate cancer.

The most recent Cochrane systematic review in 2013 identified five randomized controlled trials that have to date investigated the effectiveness of screening on prostate cancer mortality. Of those five studies, only two (the US-based prostate lung colorectal and ovarian [PLCO] cancer screening trial, and the ERSPC study) have been assessed as having a low risk of bias with respect to their methodology.1 Relying on the results from these two quality trials to guide recommendations in clinical practice has been problematic, as the PLCO trial reports no benefit in screening for prostate cancer in a 10–13 years follow-up period, while the ERSPC study has consistently reported a significant reduction in prostate cancer mortality.1,3

The ERSPC was initiated in 1993 in the Netherlands and Belgium as a screening trial to examine the effectiveness of screening on prostate cancer mortality. Between 1994 and 1998 five additional study centers (Finland, Italy, Sweden, Switzerland and Spain) joined the study; with French study sites joining the ERSPC study from 2000 onwards. Men aged 50–74 years at the time of randomization were eligible for inclusion in participating sites, with primary analysis assessing prostate cancer mortality in men within a "core" age group of 55–69 years.

Measurement of prostate-specific antigen (PSA) in serum was utilized as the primary screening test among all sites, yet significant variation exists with respect to uniformity within the trial protocol. A PSA threshold of 3.0 ng ml⁻¹ was predominantly used as an indicator for further investigation with biopsy amongst sites. The Belgium and the Netherlands sites initially used a threshold of 4.0 ng ml⁻¹ and positive results from supplementary tests as prerequisites for biopsy. This protocol was changed in 1997 when a PSA cut-off of 3.0 ng ml⁻¹ was implemented as an indicator for biopsy. Both the Finnish and Italian sites implemented ancillary tests and PSA thresholds of 3.0–3.90 ng ml⁻¹ as prerequisites for biopsy.

Screening interval differed; occurring every 4 years at six of the sites, with Sweden adopting a 2 years screening interval. France ceased screening after two rounds, with Belgium, Finland and Spain ceasing screening after three rounds. Screening continued for up to five rounds in the Netherlands and ten in Sweden.4

In the current publication, Schröder et al. report data truncated for the first time at 9, 11 and 13 years follow-up postrandomization. Participants’ mean age at randomization was 60.2 years, with men allocated to the screening group receiving a mean of 2.3 screens. A total of 66% of prostate cancer cases were screen detected, with the remaining 34% interval cancers (i.e. detected between screening rounds) or detected in nonattenders. The rate ratio (RR) of prostate cancer mortality was reported to be 0.85 (95% confidence interval [CI] 0.70–1.03) at 9 years follow-up; 0.78 (0.66–0.91) at 11 years follow-up and 0.79 (0.69–0.91) at 13 years follow-up. No difference in the relative effect of screening is noticeable between the 1 and 11 versus 13 years periods; which the authors attribute to possible noncompliance in the intervention group, and contamination in the control group. The absolute risk reduction in prostate cancer mortality was reported to be 0.11 prostate cancer deaths per 1000 person-years.

The authors note that all-cause mortality did not differ between screening and control groups. This is an important outcome to note, as disease-specific mortality rests on the assumption that cause of death can accurately be determined, which is not always the case.4 Given that deaths ascribed to prostate cancer make up 2.3% of deaths in the screening group and 2.7% in the control group, any inaccuracies associated with the reporting of mortality could draw a significant impact upon the results. In 2013, the authors reported that any reduction in prostate cancer mortality in the ERSPC was not attributed to bias in cause of death adjudication.7 Conversely, all-cause mortality only requires an accurate ascertainment of mortality and when it occurs. All-cause mortality can also capture lethal adverse events associated with medical care – an important issue given the impact of...
overdiagnosis and overtreatment in prostate cancer.6,8–10

While the authors report a significant reduction in prostate cancer mortality in men across all ages (RR = 0.83, 95% CI 0.73–0.94) and the “core” age group (RR = 0.79, 95% CI 0.69–0.91), it is important to highlight that a statistically significant reduction in prostate cancer mortality was only observed in the 65–69 years age group (RR = 0.69, 95% CI 0.55–0.87). Other age groups, including men aged below 54, 55–59 and 60–64 years do not report any statistically significant reduction in prostate cancer mortality. The results clearly indicate that screening is not beneficial in men aged 70 years and over (RR = 1.17, 95% CI 0.82–1.66). In addition, prostate cancer mortality in the “core” age groups was demonstrated to be significantly reduced in only two arms of the ERSPC study – the Swedish (RR = 0.62, 95% CI 0.41–0.92) and the Netherlands sites (RR = 0.67, 95%CI 0.51–0.88). The largest site, Finland, reported no significant difference (RR = 0.91, 95% CI 0.75–1.10), with Switzerland reporting an effect (RR = 1.14, 95% CI 0.56–2.33) opposite to all sites.

The authors acknowledge the limitations of the study, including the heterogeneity between centers with respect to screening protocol, performance, contamination and follow-up. Further detail is required to ascertain whether the variation in prostate cancer mortality amongst study sites can be attributed to these issues or other confounding factors such as geographic location. The rate of overdiagnosis in the ERSPC study is estimated to be 41%, which would require that further detailed information about adverse events (both mental and physical) associated with screening is required. What this study does confirm is that population-based screening for prostate cancer is not warranted. Rather, an informed discussion between patient and physician should occur in which any potential benefits and harms associated with screening should be clearly outlined.1

The use of decision aids and risk calculators may further promote patient education and their ability to make an informed choice.4,11,12

COMPETING INTERESTS

The author declares no competing interests.

REFERENCES

1 Illic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; 1: CD004720.
2 Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104: 125–32.
3 Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366: 981–90.
4 Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, et al. Screening and prostate cancer mortality: results of the European randomised study of screening for prostate cancer (ERSPC) at 13 years of follow-up. Lancet 2014.
5 Schröder FH, Roobol-Bouts M, Vis AN, van der Kwast T, Krans R. Prostate-specific antigen-based early detection of prostate cancer – validation of screening without rectal examination. Urol Int 2001; 57: 83–90.
6 Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. J Natl Cancer Inst 2002; 94: 167–73.
7 van Leeuwen PJ, Krans R, Hakulin T, Hugosson J, Tammela TL, et al. Impacts of a population-based prostate cancer screening programme on excess total mortality rates in men with prostate cancer: a randomized controlled trial. J Med Screen 2013; 20: 33–8.
8 Pashayan N, Duffy SW, Pharoah P, Greenberg D, Donovan J, et al. Mean sojourn time, overdiagnosis, and reduction in advanced stage prostate cancer due to screening with PSA: implications of sojourn time on screening. Br J Cancer 2009; 100: 1198–204.
9 Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Perison DF, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol 2014; 65: 1046–55.
10 Loeb S, Vellekoop A, Ahmed HU, Catte J, Emberton M, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013; 64: 876–92.
11 Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014; 1: CD001431.
12 Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, et al. Assessing prostate cancer risk: results from the prostate cancer prevention trial. J Natl Cancer Inst 2006; 98: 529–34.