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Author

Cooperberg, Matthew R

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PROSTATE CANCER

Why the prostate arm of the PLCO trial failed and what it has taught us

Matthew R. Cooperberg

Given a recent update from the PLCO trial reporting that over 90% of men in the ‘usual care’ arm underwent some degree of PSA testing, the PLCO can no longer accurately be called a trial of screening versus no screening — nor can it be included as such in meta-analyses or guideline statements.

Refers to Shoag, J. E., Mittal, S. & Hu, J. C. Reevaluating PSA testing rates in the PLCO trial. *N. Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMc1515131> (2016)

The Prostate, Lung, Colon, and Ovarian (PLCO) cancer screening trial comprised a set of randomized trials commissioned by the National Cancer Institute in the early 1990s, and was intended to determine the benefits of screening programmes for each of the cancers named in the title. In the case of prostate cancer, the screening method of interest was PSA testing. The prostate arm of the PLCO trial launched in 1993, and over the next 8 years randomized 76,693 men aged 55–74 years to receive either annual PSA testing or ‘usual care’. The trial first reported its findings in March 2009, concluding that, at the 7–10 years follow-up point, no statistically significant difference in prostate cancer mortality could be identified between the two arms¹. The impact of this first paper cannot be overstated — the results were widely publicized in the popular press and have repeatedly been claimed² to constitute a rebuttal to the positive results shown by the European Randomized Screening Study for Prostate Cancer (ERSPC), which were published in 2009 on the same day³.

Problems with the PLCO trial were evident early on in the study. Recruitment was a challenge. Some of the ERSPC centres

randomized the entire male population and achieved approximately 75% compliance with testing³. In the PLCO, by contrast, fewer than 10% of men recruited in the one center reporting these results accepted randomization⁴. Compliance with PSA testing in the screening arm was good with 85–89% of men undergoing PSA testing⁵. Consistent with standard practice in the USA at the time, 4.0 ng/ml was considered the threshold above which sextant biopsy would be recommended. However, most men with elevated serum PSA levels refused to undergo biopsy; only 30–40% agreed at each time point⁵.

By far the greatest problem facing the prostate arm of the PLCO trial was contamination of the ‘usual care’ arm with PSA testing — because, in fact, screening was becoming part and parcel of standard patient management as the PLCO launched, and in 1993–2001 ‘usual care’ involved an unprecedented amount of screening. Thus, a very large (and largely immeasurable) pool of men with prostate cancer had already been removed from the eligible population by the time the trial launched.

Beyond that issue, even the first report of the results acknowledged problems with

ongoing contamination. In the initially reported ‘usual care’ group, 44% of men had received at least one serum PSA test in the 3 years before randomization¹ — and, of course, this group overrepresented men without cancer as it excluded men diagnosed with cancer by definition. Contamination continued after randomization: between 40% and 52% of men in the ‘usual care’ arm underwent PSA testing in each year after randomization¹.

Not surprisingly, then, the rate of prostate cancer diagnosis was only 20% higher in the screening arm compared with the ‘usual care’ arm, roughly 95% of cancers in both arms were stage I–II (screen-detected by definition), and no difference in cancer-specific mortality was observed between the two arms¹. Despite the fact that these problems did not go unnoticed, the PLCO was still incorporated into meta-analyses, whereby it inappropriately diluted the effects of the positive European trials⁶, and it became ingrained in the eyes of both physicians and the public as a negative trial.

Publications over subsequent years shed more light on the contamination issue. A 2010 paper reported that only 21% of men in the ‘usual care’ arm did not receive a PSA test during the study period; 79% of men received a mean of 2.7 PSA tests⁷. The PLCO investigators acknowledged these limitations in their 2012 update of trial outcomes, concluding that “organized annual screening” offered no apparent benefit over “opportunistic screening, which forms part of usual care.” (REF. 8). However, this more circumspect, and more accurate, conclusion was lost on those opposed to screening — most notably the members of the US Preventive Services Task Force (USPSTF) whose D recommendation against any PSA-based early detection efforts repeatedly referred to PLCO as a negative trial.

“The truth regarding PSA screening is not black or white, but reflects many overlapping shades of grey”

Most recently, a research letter published in the *New England Journal of Medicine* has shed further light on the contamination problem in PLCO⁹. After detailed analysis of data from the

questionnaires used to assess screening behaviours among trial participants, the authors of the letter conclude that the proportion of men in the 'usual care' arm who underwent at least one PSA test before or during the trial was 86%, and — accounting for additional PSA testing during follow-up monitoring after the 6 years of the intervention period — the final rate of contamination is 91%. The letter makes the further, remarkable observation that in fact men in the 'usual care' arm of the PLCO trial actually underwent more cumulative PSA testing than those in the intervention arm.

What, then, can we truthfully conclude from the PLCO trial? Firstly, this study was *not* a trial of screening versus no screening. PLCO offers absolutely no insight into whether PSA testing versus no testing reduces prostate cancer mortality. It cannot be included in meta-analyses on this question, and should not be described in guideline statements as evidence against screening. Secondly, the PLCO trial does clearly demonstrate that annual screening for men in their late 50s to early 70s is not an optimal implementation of PSA testing. In fact, PSA testing should be offered earlier and much less frequently for most men, with lower thresholds for referral for younger men. Thirdly — and perhaps

most importantly — cancer screening trials are highly complex and the final truth is not necessarily evident from the conclusion of the abstract of the initial publication. Prostate cancer testing rates in the USA have plummeted in recent years, an effect that is in no small part due to persistent misinterpretation of the PLCO results¹⁰, along with rates of both low-risk and high-risk prostate cancer. PSA screening was nearly implemented as a negative quality indicator for primary care by the Centers for Medicare and Medicaid Services (CMS)⁹. The truth regarding PSA screening is not black or white, but reflects many overlapping shades of grey. Only through recognition of these subtleties, both in the research and clinical practice settings, can we arrive at a smarter screening paradigm which combines an optimal PSA testing regimen and selective, risk-adapted treatment targeted to those men most likely to benefit.

Matthew R. Cooperberg is at the Departments of Urology and Epidemiology & Biostatistics, UCSF Helen Diller Family Comprehensive Cancer Center, 550 16th Street, Box 1695, San Francisco, California 94143-1695, USA. Matthew.Cooperberg@ucsf.edu

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Competing interests statement

The author declares no competing interests.