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**EDITORIAL**

# Screening for prostate cancer: Defining critical issues

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Several facts point towards that prostate cancer in theory is a suitable goal for secondary prevention with screening. It is a common disease in many countries with often a malignant course when detected clinically. Clinical symptoms are unspecific or few and clinical diagnosis often means late diagnosis in a stage where medical interventions cannot today claim to be curative. There is presently no clearly identifiable life style risk factor that could be changed to influence the incidence substantially. There is a long preclinically identifiable phase where the disease is limited and with a low probability of having produced clinically viable micrometastases during that time. For the last 5–10 years there has been increasing evidence that locally radical intervention at a stage where the disease is limited can save lives [1,2].

However, we already knew when the randomised studies to evaluate the efficacy of prostate cancer screening [3,4] started that two major obstacles stand in our way to realise expectations of a successful screening program: First, the current means to detect prostate cancer in a symptomatic stage – PSA testing followed by biopsies – will diagnose a substantial number of men with cancer that would not have surfaced clinically during their lifetime, thus causing overdiagnosis [5,6]. Our hope to find a reliable method to distinguish the patients that benefit from treatment from those that do not remains unfulfilled. Second, a local radical intervention for prostate cancer is still despite many remarkable improvements in surgical technique associated with a clinically significant risk of side-effects that may be unacceptable given the potentially indolent course of disease. These two obstacles combine in an unfortunate way to risk of overtreatment with severe consequences that then threatens the cost-benefit balance certainly for small, but even for modest and clearly clinically relevant eventual mortality reductions by screening.

We now have the first evidence from two large randomised trials in prostate cancer screening, the ERSPC [4] and the PLCO [3] trial. In this section of the proceedings of the WHO consultation on prostate cancer, further evidence than those already published in the New England Journal of Medicine will be presented and discussed. Furthermore, the trialists set the empirical findings in a context of the discussions emerging from the first publications. Given what we know hitherto from the publications, a first priority is to understand the very basic fact: is there a mortality reduction to expect from PSA screening or not? This task is not trivial. Mass screening trials are extremely complex to undertake, analyse and interpret. A multiprofessional, multidisciplinary, careful, realistic and sincere approach free from irrational conflicts of interest – be they commercial, political, academic or any – is needed from all stakeholders. We need to understand that we are only in the beginning of the follow-up and of this discussion. It is sobering to think that the first randomised data in breast screening now came some 40 years ago, and still, though a majority of experts and reviews are very clear about a mortality reduction following mammography screening, new debates pops up from time to time and health care providers many times get confused. The same is true for screening for colorectal cancer, where as in mammography screening the randomised data are so much richer and older than for prostate cancer screening. The medical community should show that we have a collective memory and learning so that we in the prostate cancer debate avoid the sometimes irrational and emotional overtones in

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cancer screening history, which have hindered people's understanding of the screening issues.

A second task is to define the most important and pressing questions that rise from the current problem situation. We suggest that rather than using a number of critical questions only as criticisms and dismissal of trial data, they should be brought forward as important research issues to be solved either with data from the current trials or in other research in existing datasets or in prospective trials. For such an approach to give answers sooner than later, the ERSPC and PLCO trialists need support for their efforts and others have to collaborate constructively in focused efforts. Some such questions are obvious and are already on the research agenda for many groups, i.e. finding a way to distinguish potentially lethal cancer from the very slow growing or improving the screening test itself. However, such a magic bullet may not be found for many years and if screening continues, we need to engage in large studies of immediate clinical problems: Is active surveillance a safe option? Is there a low-toxic intervention that could be offered for men with low volume disease with beneficial prognostic markers? Such studies need to be done in large, collaborative networks. In this section of the proceedings there is an important discussion about the possible contribution from genetic biomarkers to solve these problems.

If the results of these two tasks can be clearly formulated it will go a long way to help us with the ultimate goal: to have science inform men and health care providers what the current state of affairs tells us about prostate cancer screening, what is known, which are the great enigmas and what are the possible clinical implications. We cannot in the long run shy away from trying to solve one of the most important medical and ethical dilemmas today: should screening with PSA for prostate cancer be stopped, should it be encouraged on a large population scale, or should it only be offered after a very careful individual information including an informed consent? This problem solving requires a lot of very good, honest collaborative teamwork.

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