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European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 43–51 of this issue

Solid Science for the Upside but Lack of Solid Science for the Downside—Towards Cutting-edge Prostate-cancer Screening

Gunnar Steineck^{a,b,*}, Olof Akre^{c,d}, Anna Bill-Axelsson^e

^a Division of Clinical Cancer Epidemiology, Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Sweden; ^b Department of Oncology and Pathology, Division of Clinical Cancer Epidemiology, Karolinska Institutet, Stockholm, Sweden; ^c Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; ^d Department of Pelvic Cancer, Karolinska University Hospital, Sweden; ^e Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden

The results of the study by Hugosson et al. [1] in this month's issue of *European Urology* show that screening for prostate cancer saves lives. The SPCG-7 [2] and SPCG-4 [3] studies, recruiting men in the pre-prostate-specific antigen (PSA)-testing era, have previously given convincing evidence that radical treatment reduces prostate-cancer mortality among men diagnosed with localized or locally advanced prostate cancer. We learn from these new data that, by screening for prostate cancer, it is possible to push some men from being incurable to a therapeutic window within which their disease trajectory can be altered significantly.

Hugosson et al. [1] report data from nine different centers with varying validity and effect-modifying factors. Centers in Sweden, Finland, and the Netherlands have population-based registries that enabled nearly complete follow-up, whereas others report more losses to follow-up. The screening interval varies. Men in the screening arm were invited for retesting every 2 yr in Sweden and France, and every 7 yr in Belgium. Even the duration of the screening varied; it was longest in Sweden and the Netherlands—18 yr. These differences are reflected in the metrics of the calculated effects on mortality. Sweden (rate ratio of prostate-cancer mortality [RR] = 0.63) and the Netherlands (RR = 0.67) report lower figures than the average effect of 0.80.

Table 3 in Hugosson et al.'s [1] paper shows increased absolute effects of screening over time. The number of men with prostate cancer needed to be diagnosed to save one man from a premature death was estimated to be 76, 34, 26,

and 18 after 9, 11, 13, and 16 yr of follow-up, respectively. Moreover, the impression from Figure 2 of this study is that the trial arms continue to diverge over the entire follow-up period. In SPCG-4, events of prostate-cancer deaths have continued to accumulate throughout the 29 yr of follow-up [3], indicating that we have to wait many years for the final results of the European screening trial.

The list of harmful effects of testing for and treating prostate cancer, afflicting men whether they benefit from screening or not, is long. It includes discomfort and pain during biopsies, infections secondary to biopsies, and psychological effects of being told that they have cancer. After being diagnosed with prostate cancer, a greater number of men commit suicide than men in the same age groups without a diagnosis [4]. Moreover, if the diagnosis leads to a radical prostatectomy or radiotherapy, lifelong treatment-induced survivorship diseases and states may follow. Surgery and irradiation frequently lead to erectile dysfunction and urinary leakage. Men who have recovered continence may still leak a large portion of urine at orgasm after removal of the internal urinary sphincter during surgery. Pain during orgasm may occur in preserved seminal vesicle stumps during surgery. Inguinal hernia may be a consequence of surgery. Lymphedema in the legs may be caused by a lymph node dissection, and the perceived penile length may be shortened. Irradiation (but not surgery) may induce close to 30 different lifelong symptoms that reduce the intestinal health [5]. These symptoms can be grouped into an anal-leakage syndrome, an urgency

DOI of original article: <https://doi.org/10.1016/j.eururo.2019.02.009>.

* Corresponding author. Division of Clinical Cancer Epidemiology, Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Box 100, 405 30 Gothenburg, Sweden. Tel. +46 70 7387461.

E-mail address: Gunnar.Steineck@gu.se (G. Steineck).

<https://doi.org/10.1016/j.eururo.2019.03.043>

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syndrome, excessive mucus discharge, uncontrollable and odorous flatulence, and blood discharge. In research, the use of scores blurs our possibilities for disentangling specific symptoms. Some authors euphemistically cite symptoms that may be devastating for the quality of life as grade 1. Psychometrically validated quality-of-life instruments seldom give us a high resolution of symptoms such as urinary leakage during orgasm or frequent loose stools. To improve pretreatment information to the patient, we need instruments measuring the concrete symptoms and data from a neutral third party [6].

Preparedness for a specific adverse effect reduces, to a large extent, the distress from the same adverse effect [7]. We can reduce the harm to the patient through better information before diagnosis and treatment. In SPCG-4, the levels of self-assessed quality of life were assessed to be as low among those who were allocated to radical prostatectomy as among those who were allocated to watchful waiting. Moreover, of equal importance, the level in both groups was lower than the levels among men without a diagnosis (population controls) [8]. Some part of this reduction is likely to be purely psychological. The dramatic difference in the reduction of self-assessed quality of life after castration speaks for this explanation; the reduction was seen almost exclusively among men in the watchful-waiting group [9]. Our possibility to develop and implement psychological techniques to make progress regarding these observations would reasonably benefit from directing men scheduled for screening to specialized centers where psychological aspects are being studied as much as other aspects.

Hugosson et al. [1] emphasis screening, as performed in the European trial, implies overdiagnosis and, as a consequence, overtreatment. A large part of the current research activities in the prostate-cancer field aims at lowering overdiagnosis and overtreatment by the use of other kallikreins than PSA, genetic tests, magnetic resonance-guided precision biopsies and studies with magnetic resonance imaging or positron emission tomography/computed tomography, and active monitoring programs. In a perfect world, a man who asks for screening for prostate cancer is referred to a specialized center that first inform the man of the upsides and downsides of screening. If required, the center then offers modern technology according to prespecified rules and a suggested length of the screening period based on the man's age. If diagnosed with prostate cancer, the center again offers cutting-edge counseling concerning active surveillance or treatment. Of equal importance, in such a center with a defined screening program, researchers can accumulate knowledge about the upside and downside of undergoing screening.

We live in a society with demand for screening, and certainly some part of the demand can be dismissed as grounded on illusions or unjustified marketing of tests [10]. However, the strong drive among some men to undergo a test for prostate cancer will not be halted easily and must be handled. The data in the latest report from the European screening trial suggest that we should not handle “prostate-cancer screening” as one entity. In

Supplementary Table 2 of Hugosson et al. [1] paper, we read that 65 men are needed to be diagnosed with prostate cancer in Switzerland and seven in Sweden, to save one man from death due to prostate cancer. Screening is not “screening”; when we discuss prostate-cancer screening, we must specify all the details of a program. Unstructured PSA testing without careful pretest information, without modern diagnostics and prespecified decision rules for diagnostic means and allocation to treatment strategies such as active surveillance, is ineffective according to the European screening trial in terms of prostate-cancer mortality and may give the man the downside of screening only. Hugosson et al. [1] give us solid science concerning the upside; our challenge now is to utilize modern technology to reduce overdiagnosis and overtreatment, to structure the healthcare system and find resources for symptom-focused and psychological research so that we can get solid science also regarding the downside and for communicating the balance between the upside and the downside.

Conflicts of interest: Professor Steineck is on the board of AroCell AB. Otherwise, there are no conflicts of interest.

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