Chapter 2

The Value of Prostate-Specific Antigen Screening in Several & Differents Studies. Conclusions: Questions that are born

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Prostate cancer has become the most common non-skin cancer neoplasm amongst men in Europe, with an estimated 382,000 cases occurring in 2008 [1]. Incidence has increased rapidly over the past two decades, and rates are influenced by early diagnosis by prostate specific antigen (PSA) testing amongst men, with or without symptoms, as well as by the detection of latent cancer in prostate surgery.

The mortality rate is less affected by early diagnosis of asymptomatic cancers, and consequently the high death rates in the Nordic countries are five times those seen in several Central and Eastern European countries, where rates have been relatively low for decades.

The age-standardized incidence of prostate cancer in the European Union (EU) was 65/100 000 men in 2008, ranging in different member states from 18 per 100 000 in Greece to 126 per 100 000 in Ireland depending pre-

dominantly on the prevalence of prostate-specific antigen (PSA) screening [2]. Age standardized mortality rates are predominantly between 15 and 37 per 100 000 [3]. It is the most common cancer in men with an estimated 382 000 cases occurring during 2008 in Europe. The mortality in the EU is 30.6/100 000 men/year and almost 90 000 deaths from prostate cancer occurred in Europe in 2008, making it the third most common cancer death in men [3]. Subclinical prostate cancer is common in men >50 years. Population-based screening of healthy men between 55 and 69 years old using PSA testing reduces prostate cancer mortality by an estimated 20%. Six trials and a meta-analysis have been published evaluating the role of screening, of which three were originally designed to evaluate prostate cancer mortality [4,5]. After a median follow-up of 11 years the European screening trial demonstrated a relative reduction in the risk of prostate cancer mortality of 21% for the screened population (29% if adjusted for non-compliance). However, 1055 men needed to be invited for screening and 37 patients needed to be treated to prevent one patient from dying from prostate cancer. At 11 years follow-up, there was no reduction in overall mortality between the screened and non-screened population. In a further evaluation of the European screening study, it was shown that the benefit of screening was diminished by loss of quality adjusted life years [6]. Recommendation: population-based screening for prostate cancer reduces prostate cancer mortality at the expense of a high over-treatment rate [2].

According to a new study which has published in the New England Journal of Medicine on March 2014, after 10 to 18 years of follow-up, the number needed to treat to prevent one death decreased from 20 to 8 in the whole cohort, and from 8 to 4 among men younger than 65 years of age.

An updated search of numbers of incident prostate cancer cases (ICD-10 C61) and the corresponding population figures were obtained from recently published reports from population-based cancer registries in Europe, with data commonly obtained from the Institutions' websites [7]. Also based on the basis of ERSPC follow-up data, we used Microsimulation Screening Analysis (MISCAN) and other analysis which include criteria for a PSA test and DRE within 1 year of the biopsy as well as an additional PSA measurement during the 3 years before the biopsy to compute PSA velocity, to predict the number of prostate cancers, treatments, deaths, and quality adjusted life-years (QALYs) gained after the introduction of PSA screening. Various screening strategies, efficacies, and quality-of-life assumptions were modeled [8-10].

For a further six countries, numbers of incident prostate cancer cases and corresponding population data were obtained from the Cancer Incidence in Five Continents Plus (CI5Plus) Dataset (ci5.iarc.fr) by registry, year of diagnosis and 5-year age group.

In another study, a total of 76 685 men, aged 55–74 years, were enrolled at 10 screening centers between November 1993 and July 2001 and randomly assigned to the intervention (organized screening of annual PSA testing for 6 years and annual DRE for 4 years; 38 340 men) and control (usual care, which sometimes included opportunistic screening; 38 345 men) arms. Screening was completed in October 2006 [11]. All incident prostate cancers and deaths from prostate cancer through 13 years of follow-up or through December 31, 2009, were ascertained. Relative risks (RRs) were estimated as the ratio of observed rates in the intervention and control arms, and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution for the number of events. Poisson regression modeling was used to examine the interactions with respect to prostate cancer mortality between trial arm and age, comorbidity status, and pretrial PSA testing. All statistical tests were two-sided.

Finally, we based on the AUA guidelines on detection of prostate cancer involved a systematic literature review of >300 studies that evaluated outcomes important to patients (prostate cancer, incidence/mortality, health-related quality of life, diagnostic accuracy and harms of testing) [13-16].

To determine whether screening for prostate cancer reduces prostate cancer-specific mortality or all-cause mortality and to assess its impact on quality of life and

adverse events [17].

Geographical variations in incidence and mortality, trends in incidence and mortality by European region. Relative changes in incidence versus changes in mortality, timing and extent of mortality declines [18], the value of the PSA test to control the disease's progression.

The effect of prostate cancer testing on the observed trends in incidence and mortality can be evaluated here only indirectly, as no information on the extent of PSA testing was available. The relationship between decreasing mortality trends and advances in treatment in combination with early detection by PSA has been the subject of much debate [19]. The testing of men for PSA can affect prostate cancer incidence dramatically, as lead-time has been estimated as 6–12 years and overdiagnosis up to 40% [20]. In the USA, prostate cancer testing is more common than in Europe; Up to 70% of the men in the USA have been tested at least once, which in most European countries figures around 10–20% have been published [21,22], even though no large and systematic analyses have been conducted. In the USA, a sharp increase in the prostate cancer incidence was noted in the 1990's followed by a decline [23]. Almost simultaneously with the increase in incidence, a decrease in prostate cancer mortality also occurred.

Prostate cancer screening did not significantly decrease prostate cancer-specific mortality in a combined meta-analysis of five RCTs. Only one study (ERSPC) reported a 21% significant reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 years. Pooled data currently demonstrates no significant reduction in prostate cancer-specific and overall mortality. Harms associated with PSA-based screening and subsequent diagnostic evaluations are frequent, and moderate in severity. Overdiagnosis and overtreatment are common and are associated with treatment-related harms. Men should be informed of this and the demonstrated adverse effects when they are deciding whether or not to undertake screening for prostate cancer. Any reduction in prostate cancer-specific mortality may take up to 10 years to accrue; therefore, men who have a life expectancy less than 10 to 15 years should be informed that screening for prostate cancer is unlikely to be beneficial. No studies examined the independent role of screening by DRE [17].

According to all these studies, we must focus our attention on two issues. First on the benefit of PSA test as a prognostic factor. In one of these studies, the predicted effects of screening strategies is to show us that the extension of the screening to the age of 74 years resulted in an overall gain of 82 life-years and an increase in the number of prostate-cancer deaths prevented from 9 to 11. However, the model predicts that only 56 QALYs (range, −47 to 111) would be gained, representing a 32% reduction in unadjusted life-years. This reduction in quality of life is mainly due to the large number of overdiagnosed cases (48% of cancers detected on screening) and the 372 additional negative biopsies that would occur. On the other hand, the number who would need to be screened (84) was more favorable than the number associated with screening up to the age of 69 years. Screening at 4-year intervals among men between the ages of 55 and 69 years led to a gain of 52 life-years and 41 QALYs (range, −10 to 69). There was a reduction of 21% in the number of life-years gained after adjustment for quality of life, and the number who would need to be screened rose to 129. Single screening at the age of 55 years, 60 years, or 65 years resulted in the detection of fewer cancers but also in less overdiagnosis, with a reduction of 27 to 31% in steady-state prostate cancer mortality and a gain in life-years of 12 to 25. The number of men who would need to undergo single screenings at 55, 60, or 65 years of age in order to prevent one prostate-cancer death was 490, 249, and 186, respectively Weighing the balance between the benefits and harms of prostate-cancer screening is essential for decision making regarding screening at both the individual and the policy level. Second to the economic cost of the PSA test comparing with the benefit for the patient's life. The next step should be calculating the cost effectiveness of screening. However, to find the optimal screening strat-

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egy, studies should simulate more screening scenarios, including various intervals, starting and stopping ages, and intervals that vary according to age.

In conclusion, these studies, quantifies how much of the benefit of the overall reduction in prostate cancer mortality in the ERSPC must be adjusted when the harms are taken into consideration. It is essential to await longer follow-up data from both, the ERSPC and AUA, as well as longer-term data on how treatment and active surveillance affect long-term quality of life, before more general recommendations can be made regarding mass PSA screening.

The modest reduction in absolute risk in the high-risk group differs from the results of the PIVOT study, which suggested a possible survival benefit only in men with intermediate risk or high-risk tumors [24]. However, there was evidence that a substantial proportion of men in the high-risk group in this new trial had micrometastases at diagnosis (16 had lymph node–positive metastases), and therefore they did not undergo surgery.

Questions

How does a PSA test cost? The benefits of the test are more than the economic cost?

In what ages worth to use the PSA, as a based screening of healthy men? The reduce of the mortality depends on the PSA test as based screening, on the cutting edge ra-

diotherapy techniques, like dynamic IMRT, or both combination? Does the accuracy of the treatment method is enough to immobilize the prostate?

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