PSA mass screening: is there enough evidence?

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ABSTRACT

Prostate cancer plays an important role in widely understood aspects of men's health, and is becoming a growing problem in terms of public life. Prostate cancer is one of the most common neoplasms among men. Male patients can live with prostate cancer for a long time so it is important to offer appropriate males adequate diagnostic tools and treatments. Prostate cancer and PSA potentially represent a "pair" of a disease and an appropriate indicator to be used in mass screening, but regardless of that there is still active debate about it. Extensive use of PSA screening has modified epidemiology of the diseases. Randomized controlled studies provided sufficient results regarding a reduction in mortality through PSA mass screening, while all agreed on risks of overdiagnosis and overtreatment. New and accurate screening tools are necessary, along with adequate counseling and risk stratification.

The purpose of oncology mass screening is not increasing diagnosis for a specific disease, but reducing the disease related mortality. Not all illnesses are subject to mass screening: rare diseases, incurable diseases, or diseases that are easily treatable even if diagnosed later, wouldn't benefit from a screening test. However, an illness that would largely benefit from being mass screened needs a proper screening tool. It should be easily applicable, non invasive, standardizable, and inexpensive.

Prostate cancer and PSA potentially represent a "pair" of a disease and an appropriate indicator to be used in mass screening, but regardless of that there is still active debate about it. Prostate cancer is the most common neoplasm and the third cause of cancer deaths amongst men. Prostate cancer incidence in EU is 380 000 per year and prostate cancer related mortality is estimated to be 80 000, and in Poland 8.000 and 4.000 respectively [1, 2].

Since its Food and Drug Administration (FDA) approval as a screening tool in 1986, PSA has revolutionized history of prostate cancer. Increased PSA testing has led to increased diagnoses of earlier stage neoplasms, and younger age of affected population. Metastatic disease at diagnoses shifted dramatically from 19.8% in 1989 to 3.3% in 1998 [2].

This observation was initially accepted with widespread enthusiasm. C.J. Mettlin published the considerations of the National Cancer Institute on "Cancer", in 1998: mortality for prostate cancer in USA between 1990 and 1995 had reduced, underlying the probable connection in diagnosis and treatment of prostate cancer after PSA screening had been introduced in the mid-80's [3].

However, what at first appeared as obvious evidence, was criticized in a number of studies published in the following years. Specifically, SE. Oliver analyzed frequency of PSA tests in USA *vs.* England and Wales: he found that male population that underwent testing was 19% in USA while 1.4% in England and Wales [4]. Regardless of this, the drop in mortality rate that raised enthusiasm in C.J. Mettlin and other authors spread to countries where PSA was not even systematically tested.

S.E. Oliver found it difficult to link the decreased mortality rate registered in "PSA free" areas to a specific factor, and speculated that it was related to a possible higher efficacy of medical and surgical treatments, or different nutrition in those areas; however, his conclusions were that PSA screening and decreased prostate cancer-specific mortality rate didn't relate as strongly as previously suggested [4]. In order to define whether PSA would be the proper tool to perform prostate cancer mass screening, G. Andriole and his team in USA and F. Schroeder with his team in Europe carried out two massive randomized perspective studies, and their results were published on the same issue of NEJM in 2009 [4, 5].

PLCO study included 76.000 pts., aged 55-74, randomized between 1993 and 2001. PSA was measured yearly. Follow-up in PCLO study reached 11.5 years, however it was planned to last 13 years after two major protocol changes were done in 1996 and it is only 67% complete for mortality after 10 years. ERSPC study included 162.243 pts., aged 55-69, randomized between 1991 and 2003, PSA was measured variably between 2 and 7 years and follow-up reached 9 years. PLCO showed no increase survival in PSA-tested group over control group, while ERSPC showed a 20% reduction in risk of prostate cancer-related mortality. Furthermore, the ERSPC results showed that Number Needed to Screen (NNS) and Number Needed to Treat (NNT) for PSA screening and prostate cancer mortality were 1410 and 48 patients respectively (Tab. 1).

A thorough analysis of the two large and complex studies allowed further interpretations of the results. PLCO was tainted with high contamination: at least 52% of control group subjects underwent PSA screening, and this information is comforted by the finding of only 15% lower incidence of prostate cancer in the control group when compared to the tested group. Furthermore, the wide majority of patients affected by prostate cancer in the control group had initial stage disease. It is self-evident how diag-

Table 1. Description and results from PLCO and ERSPC

PLCO versus ERSPC	Sample size	Age range	Period	PSA interval	Follow-up	Cancer incidence (screening *vs.* control group)	Cancer mortality
PLCO	76.693	55-74	1993-2001	1 year	11.5 years	9% *vs.* 7.8%	Ratio rate of 1.13: 95% CI, 0.75-1.70*
ERSPC	162.387	55-69	1991-2003	2-7 years	9 years	8,2% *vs.* 4.8%	Ratio rate of 0.80; 95% CI, 0.67-0.95, P=.01

noses of prostate cancer in a population that had not undergone any screening tests would be based on progression of the disease, and in some cases on symptoms related to it, and in any case they would be diagnosed at a later stage of the disease.

The counterproof comes from the analysis of compliance to the study found in patients belonging to the control group: 15% of them had not undergone any previous PSA testing. Amongst these patients, the ratio of subjects with advanced disease at diagnosis was higher than that found both in the PSA-screened group and in the control group [6]. It is important to underline also the selection bias that affected this study: 44% of subject selected for the study had already undergone PSA testing at least once. Finally, the mean 11.5 years follow-up was obtained through randomization, while 25% of neoplasms were diagnosed 6 years after the randomization began. PLCO raised strong criticism because of the multiple bias encountered.

ERSPC was criticized mostly on a lack of homogeneity: different centers applied different protocols for biopsy and for screening intervals. Mean follow-up interval was 2.1 yrs. (range: 2-7 yrs.), and mean overall follow-up was limited to 9 yrs. [6, 7]. ERSPC's results showed a significant mortality reduction in the screening arm (20%, RR 0.80). It was also noted that in order to reach this result, the NNS was 1410, and NNT was 48: with similar results there was a relevant risk of researchers leaning towards overtreatment.

In a recent analysis of ERSPC some interesting information was revealed: in a computerized simulation S. Loeb and her team projected the results of ERSPC over time, trying to predict what the results would have been if follow-up had been longer. Her results showed that NNS would drop to 837 at 10 years, and to 503 at 12 years, and that NNT would accordingly decrease to 29 and 18 [8]. Authors concluded that given a longer follow-up, if mortality difference in the two groups would have kept increasing, NNT to save a life with PSA screening would have decreased.

Another important study is the Goteborg Screening Trial, which yielded interesting results [9]. J. Hughson et al. in December 1994 selected 20.000 men born between 1930-1944, who had never undergone PSA screening. They randomized them with a 1:1 ratio in two groups: one underwent PSA screening every 2 years, the control group did not undergo PSA testing [9]. The screening group continued to be screened until they reached age limit (67-71 you.), and only the patients with increased PSA underwent further investigation (DRE, prostate biopsy). The first object was to check cancer-specific mortality in the intended-to-treat group. Preliminary results showed approximately 50% mortality reduction in 14 years. With a 14 years follow-up,

G. Sandblom et al. recently published a study that included the whole male population aged 50-69 of the Swedish town of Norrkoping in 1987 (9026 subjects) [12]. One every 6 men (total 1494) underwent medical visit every 3 years. In 1987 and 1990 patients underwent only DRE, and since 1993 they were also PSA tested. All patients were later followed-up through the South-East Region Prostate Cancer Register and the National Cancer Register, which allowed to keep track of all data regarding diagnosis, treatment and mortality of the patients enrolled in the study. The number of patients who underwent PSA testing in 1987 was 1161 (out of 1492 selected) (78%), 957 in 1990 (70%), in 1996 only 446 men underwent PSA testing. Prostate cancer was diagnosed in 85 patients (5.7%) in the screening group and in 292 patients (3.9%) in the control group. Cancer-specific mortality in screening group patients was 35%, 45% in the control group. Overall mortality in prostate-cancer patients was 81% in the screening group and 86% in the controls. Furthermore, the ratio of patients affected by localized disease (T1-2, N0, M0) was significantly higher in the screening group (56.5%) than in the control group (26.7%). The most interesting fact derived from the study is that, by deploying statistical models such as rank test and Cox proportional hazard analysis, it appears to be no advantage neither in overall survival (P = 0.14) nor in cancer specific survival (P = 0.065) in the screened versus the control groups [12].

M. Dreier et al. commented Sandblom's study underlying the relevance of an important bias due to lead-time (i.e.: the difference in the moment of diagnosis between the screened and the controls) [11]. In this study screened patients were diagnosed with prostate cancer 1.6 yrs. earlier than the controls (mean age at diagnosis time of controls – mean age at diagnoses time of screened). This leads to a necessary review of the survival curves, which currently are "favoring" the screened groups by 1.6 years [11]. F.H. Schroder expressed on BMJ a few doubts on Sandblom study: first of all he pointed out that the number of men belonging to the screening group was quite limited (only 1161 men out of 1494 invited patients underwent PSA screening). He also stresses the importance of lead-point bias on survival curves [12].

J. Abramowitz, considering the effective number of men who participated in the study and those who got lost throughout the years concluded that probably most of the people belonging to the screening group underwent a single PSA testing. He then asks if one single PSA blood test can be considered as a screening program. J. Aranowitz also criticizes the therapeutic choices adopted because only a quarter of the people diagnosed with prostate cancer were treated with curative intent, therefore the reason for the apparent similar survival curves between screened and non-screened population could be due to under screening and under treatment [13].

European guidelines state that mass screening for prostate cancer is currently not appropriate, while an opportunistic screening should be performed offering the possibility of diagnosis to the well-informed man. Finding a tool to identify high-risk patients is a premier need in order to treat them promptly. This appears to be feasible combining family history of disease, race, and baseline PSA.

The Malmo Preventive Project in 1981 recruited 1167 men aged 60, tested their PSA, and followed them until they were 85 years old [14]. The study shows that PSA levels at 60 y.o.a. have a predictive value regarding prostate cancer-related mortality before turning 85 y.o.a. The majority of prostate cancer deaths (>90%) occurred in men whose PSA at 60 y.o.a. was >2 ng/mL. According to the study, men that have PSA ≤1ng/mL could be informed whether they might develop prostate cancer, however this would not be their cause of death. Therefore, at least 50% of the patients older than 60 could be exempted from further screening and chemoprevention [14].

C. Keto et al. studied men aged 55-74 with a single PSA level <3 ng/mL. In the following 15 years, these patients were 150 times more likely to die for causes different from prostate cancer, and were 10 times less likely to die from prostate cancer than men with baseline PSA >3 ng/mL. Ratio of patients deaths related to prostate cancer was 0.3% for PSA levels between 2 and 2.9 ng/mL, 0.1% with PSA between 1 and 2 ng/mL, and 0.04% with PSA <1 ng/mL; 80% of men selected had baseline PSA <3 ng/mL and therefore belonged to low-risk group [15].

In conclusion, we cannot underestimate prostate cancer, as it stands as the most frequent neoplasm in males, and the third most deadly cancer in Europe. Extensive use of PSA screening has modified epidemiology of the disease, increasing incidence, reducing age, and increasing differences in stage of disease at diagnoses. Randomized controlled studies provided disaccording results regarding real reduction in mortality through PSA mass screening, while all agreed on the risks of overdiagnosis and overtreatment.

We should develop accurate markers that allow distinguishing between high- and low-grade neoplasms. We would then be able to reduce treatment of low risk diseases (consequently reducing NNT). We should also develop tools for adequate patients' information and choice regarding prevention, screening, biopsy, and treatment options.

Current European guidelines support opportunistic screening, not mass screening. New accurate screening tools are necessary, along with adequate counseling and risk stratification.

Baseline PSA appears to be a useful tool in selecting high-risk patients that would benefit from watchful follow-up, avoiding though over diagnosis and overtreatment.

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