Peer reviewed article

Screening for prostate cancer: Results of a prospective trial in Canton Aargau, Switzerland

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Summary

Introduction: Prostate cancer is the most commonly diagnosed cancer in Swiss men and the second leading cause of cancer related death among them (e.g. CH: 1,267 in year 1998). With the population at risk constantly growing these absolute numbers are expected to further increase. While there is no question that aggressive treatment of localised tumour is required for definitive cure of prostate cancer, the application of screening for early stage disease remains controversial. Since 1998 the Clinic of Urology in Kantonsspital Aarau has participated in the ERSPC (European Randomised Study of Screening for Prostate Cancer) study, which is designed to provide data on prostate cancer screening within a prospective randomised controlled setting.

Methods: Men aged between 55 and 70 years were enrolled in the study. From n = 18,361 men invited by a letter to participate, 7,124 (38.8%) agreed and gave their informed consent to be randomised in either a PSA measurement (n = 3,562, group 1) or a control group (n = 3,562, group 2). Men in group 1 with a PSA level ≥3.0 ng/ml, n = 372 (10.5%) then underwent ultrasound guided transrectal sextant biopsy of the prostate.

Results: Prostate cancer was detected at presentation in every fourth man biopsied (n = 89). Neither the free-to-total PSA ratio nor the PSA density could significantly spare biopsies while sustaining a high sensitivity level. The overall cancer detection rate amounted to 2.5% in PSA tested men. In 7% (n = 5) distant disease was already present. 93% of men with clinically organ confined disease underwent prostatectomy (n = 59) or radiotherapy (n = 22), whilst only (n = 3) chose to follow a policy of watchful waiting. In 92% the histology of the prostatectomy specimens revealed aggressive cancer characteristics according to the criteria of Epstein et al.

Conclusions: Although the clinically relevant tumour characteristics and the relatively low cancer detection rate of 2.5% (less than the lifetime mortality risk of 3% and the morbidity risk of 8%) seem to justify screening in terms of adequate diagnosis and treatment, follow-up until 2008 is needed to prove the benefit in mortality for the prostate cancer screening group over the control group. Furthermore, information from the ongoing ERSPC study is needed in order to assess uncertainties i.e. the degree of overdiagnosis caused by repeated screening and the quality of life adjusted gain in life years. For daily practice a "PSA grey zone" of 4–10 ng/ml can no longer be postulated as only 70% of men in this range presented with organ confined disease. Once the PSA level exceeds 4.0 ng/ml. prostate biopsy should be performed immediately

Key words: prostate cancer; screening; randomised prospective study

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Introduction

Prostate cancer (Pca) is a major health care problem throughout the world. Estimates for the year 2000 indicate a cancer incidence of 542,990 new cases and 204,313 deaths [1]. In Western countries the risk of death from prostate cancer is about 3% for a 50 year old man. This is the second leading cause of cancer specific death, the most common still being pulmonary malignancies. The

risk of suffering from prostate cancer related morbidity amounts to 8%. Limited data on the disease related morbidity of men undergoing no treatment in curative intent (natural history, dying "with prostate cancer") are available [2, 3]. In order to cure the cancer the tumour must be detected in the organ confined state. However, the natural history of cancer specific survival of localised disease at 10 years varies between 30–90% depending on the initial Gleason score and the disease stage [4]. The long natural history of prostate cancer implies that a screening-related decrease in mortality should not become evident until many years after initiation of screening. Thus, a life expectancy of more than 10 years is usually needed to document a survival benefit from early detection and consecutive curative treatment of organ confined disease. As a consequence the core age group for initial screening was between 55 and 70 years. There is no doubt that early detection followed by curative treatment is beneficial for individual men [5–9]. Yet there are uncertainties whether screening of the whole population will contribute to significant reduction of prostate cancer related mortality. Earlier diagnosis of prostate cancer by screening will produce a lead-time effect establishing a certain "survival benefit" in comparison to historical groups. Thus only a prospective randomised trial including a control group can provide accurate data. As contamination (spontaneous PSA testing and resulting consequences in the control group) is possible (estimated maximal 20% in the ERSPC), a high number of participants is necessary to maintain sufficient statistical power of the study (90% at the 0.05 one-sided significance level) and to detect a 20% prostate cancer mortality reduction. This has been taken into account in the ERSPC trial. The anonymised data of the ERSPC contributing hospitals/areas of Rotterdam, Gothenburg, Tampere/Helsinki, Florence, Antwerp, Getafe-Madrid, Toulouse/Montpellier and Aarau are collected in the independent central database in Edinburgh. A detailed description of the ERSPC study and the preliminary results from all centres has been published recently [10].

Since Switzerland has one of the highest rates of prostate cancer mortality in Europe there is a special interest in screening studies. The data from canton Aargau in Switzerland (Kantonsspital Aarau and, since 1999, Kantonsspital Baden) are presented in the following.

Subjects and methods

The local study protocol presented below was accepted by the ethical committee. The privacy act commissioner of Canton Aargau accepted the study as conform to the laws on privacy protection in Switzerland.

The study protocol is outlined below (see also Fig. 1):

1. Mail invitation (males, 55–70 years old living in Canton Aargau).

2. Upon signed informed consent – randomisation 1:1 to the active screening or to the control arm.

3. Measurement of the total prostate specific antigen (t-PSA) concentration in the active screening arm and follow-up without any intervention in the control arm.

4. In participants with t-PSA above or equal to 3.0 ng/ml, a digital rectal examination (DRE) and transrectal ultrasound (TRUS) guided sextant biopsy (incl. targeted biopsy of suspicious lesions) was offered.

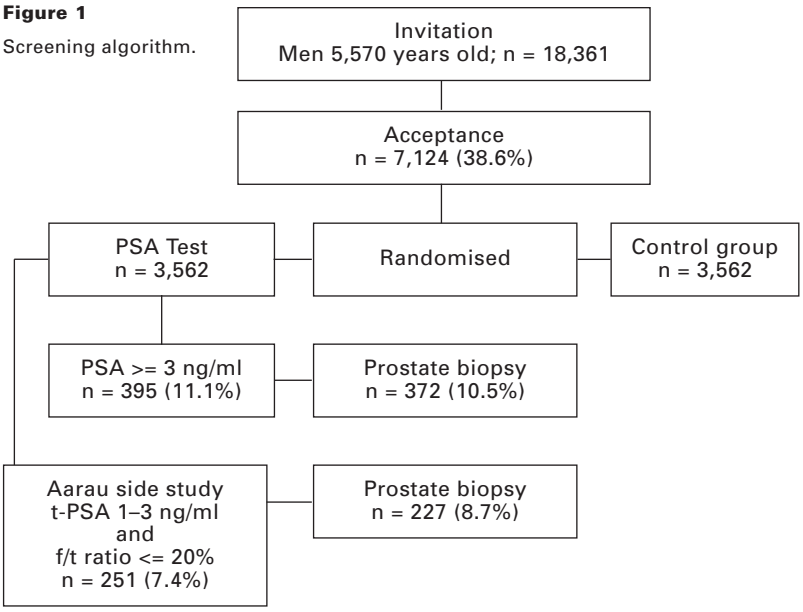
Additionally, prostate biopsy was also offered to participants, if the PSA was in the 1–3 ng/ml range and the free-to-total PSA ratio in this range was below 20% (side study protocol, performed solely at the Swiss study site. For the rationale and preliminary results for this study see ref. 11).

5. Re-screening of those with PSA <3 ng/ml after 4 years and 8 years (including those with negative biopsy results at the first screen).

6. Follow-up of the major study end-point (difference in prostate cancer mortality between the groups) is guaranteed. Both the active screening group and the control group are being followed by means of regular data linkage with the Cantonal Bureau of Statistics. If a participant dies, the death certificate and the available medical data are evaluated to define the cause of death. For this purpose a Causes of Death Committee was established [10].

Screening started in August 1998. Blood sampling was carried out at 2 institutions (Kantonsspital Aarau and Kantonsspital Baden) with no prior prostatic manipulation. The sera were frozen at –70 °C within 2 hours of sampling. Samples were thawed immediately prior to measurement. The PSA measurement was done within 2 weeks of blood sampling using immunoassays. Total PSA was measured by the Abbott AxSym (Abbott Laboratories, Abbott Park, Illinois) assay from September 1998 until June 2000 and by the Access (Beckmann-Coulter Hybritech) assay from July 2000 onwards (as Hybritech Assay is used uniformly across all ERSPC study centres). In order to provide uniform results, data presented are based on the use of the Abbott AxSym Assay.

Figure 1
Screening algorithm.



All men completed the International Prostate Symptom Score (IPSS) questionnaire.

The prostate biopsies were done under ultrasound guidance. Sextant biopsies were taken in the more lateral part of the peripheral zone of the prostate. Each biopsy was separately processed and evaluated. The Gleason score was used for tumour grading. The tumour volume in radical prostatectomy specimens was measured and tumours larger than 0.5 ccm were considered to be clinically relevant [12].

All specimens positive for cancer and those suspicious for but without definitive diagnosis of cancer were re-examined by an independent review pathologist. Upon diagnosis of prostate cancer, three treatment options: radical prostatectomy (RP), radiotherapy (RTx) or "watchful waiting" for localised cancer and (whenever applicable) immediate/deferred androgen deprivation for advanced cancer were thoroughly discussed. The family physicians were heavily involved in this decision.

The patient was offered a free choice for treatment and no further randomisation at this level was done, as the study hypothesis is to evaluate the benefit of screening but not the benefit of any treatment modality. The detailed outline of the ERSPC study is described elsewhere [10].

Results

Figure 1 outlines the screening process. Within the first 3 years of screening, of 18,361 men invited, 7,124 agreed to participate (38.8% acceptance rate). Total PSA ≥3.0 ng/ml was found in 395 (11.1%) of all men. 94% of these participants accepted further evaluation, thus 372 (10.5% of all screened men) underwent prostate biopsy (Fig. 1). In 89 cases prostate cancer was found (24% of men undergoing biopsy). In relation to all screened participants a PCa detection rate of 2.5% was calculated. 93% of tumours found were clinically localised and thus potentially curable, 7% were already advanced (Table 1). The distribution of PSA values above 3 ng/ml and cancer cases are shown in Table 2. In the group with a total PSA range between 3–3.9 ng/ml, 25 of 138 men (18.1%) had prostate cancer determined by biopsy. 17 men underwent R.P. and 15 (88%) of these cancers were pathologically organ confined. With increasing PSA values, the incidence of PCa also increased but the percentage of organ confined cancers decreased (Table 2). Overall, 59 PCa patients underwent RP (Table 3). On the basis of the postoperatively measured tumour volume in the prostate specimens, a clinically relevant PCa was found in 55 (92%) cases (median tumour volume 2.5 ccm) [2–3]. Four men (8%) had a tumour volume below 0.5 ccm (median 0.17 ccm), thus presenting with clinically insignificant cancer [2–3]. The follow-up after external beam radiation therapy is too short to be fully comparable (according to ASTRO-American Society of Therapeutic Radiology and Oncology criteria) to the results of tumour curability rates after surgery.

Of the 59 patients who underwent RP, 55 were completely continent within 6 weeks (no pad) postoperatively, four men had grade I stress incontinence (1 pad per day as a precaution). 22 men underwent external radiotherapy and three settled for the option of watchful waiting. Two of five men with advanced disease were treated with immediate androgen deprivation.

International prostate symptom score (IPSS) according to PSA distribution and PCa diagnosis showed no significant difference between PCa and benign groups (Table 4).

Table 1

Results of screening investigations.

	n	%
screened	3562	100.0
Prostate Biopsy	372	10.5
Prostate cancer diagnosis	89	24.0
Prostate cancer detection rate	89 / 3562	2.5
Treatment in curative intentt	84	93.0
Palliative treatment	5	7.0

Table 2

The number of prostate biopsies, prostate cancer detection rates and percent of pathologically organ confined cancers (pT2) according to PSA distribution.

PSA Interval (ng/ml)	number and percent (in brackets) of biopsied participants	(%) men with PCa PPV (n = 89)	(%) of pT2 R.P. (n = 59)
3–3.9	138 (3.9)	18.1	88
4–9.9	193 (5.4)	20.6	70
10–19.9	31 (0.9)	50	60
≥20	10 (0.3)	100	14

Table 3

Treatment distribution of PCa.

Treatment	n	(%)
Radical Prostatectomy (RP)	n = 59*	(66.3)
Radiotherapy	n = 22	(24.7)
Watchful Waiting	n = 3	(3.4)
Palliative treatment	n = 5	(5.6)

* clinically significant cancers (n = 55), median tumour volume 2.5 ccm), clinically insignificant cancers (n = 4, median tumour volume 0.17 ccm)

Table 4
Micturition/QoL International Prostate Symptom Score (IPSS) parameter for BPH vs. PCa cases according to PSA interval.

PSA interval (ng/ml)	IPSS (min. 0 – max. 35)		Obstructive (min. 0 – max. 20)		Irritative (min. 0 – max. 15)		QoL (min. 0 – max. 6)	
	BPH	PCa	BPH	PCa	BPH	PCa	BPH	PCa
3–3.9	5.0	6.0	3.0	3.0	2.0	3.0	1.0	1.0
4–9.9	6.0	7.0	3.0	3.0	3.0	3.0	2.0	1.0
10–19.9	6.0	7.0	2.0	5.0	4.0	3.0	1.0	3.0
≥20	–	3.0	–	1.0	–	2.0	–	1.0

Discussion

The acceptance rate of nearly 40% in a prospective randomised study shows that PSA screening is feasible in Switzerland. The validity of the results is underlined by the low drop out rate as demonstrated by the fact that 94% of the men with PSA elevation agreed to prostate biopsies. Using a PSA cut-off of >3.0 ng/ml the overall cancer detection rate of 2.5% in one screening round amounts to less than the expected cancer specific mortality rate of 3% or the morbidity rate of 8% [1]. In order to assess the clinical relevance of the detected tumours, the tumour morphology and the individual life expectancy must be considered. Classical studies from Stamey and McNeal revealed that 8% of tumours that later become clinically relevant have a tumour volume >0.5 ccm [13, 14]. In our study 92% of the tumours operated had a volume >0.5 ccm (median 2.5 ccm). However follow-up until 2008 is expected to be necessary to prove a cancer related mortality reduction of 20–25%. In addition the question arises as to whether some cancers with marginal tumour volume could have been allowed to await detection at a later, but still curable time point. In addition, 8% of prostatectomies where a tumour volume of less than 0.5 ccm was found in the specimen could have been avoided. Predictive models addressing this issue, combining PSA, PSA (zone) density, Gleason score, tumour extent in the biopsy, clinical stage and life expectancy/comorbidity in order to evaluate candidates for watchful waiting are necessary. On the other hand the 7% of men who presented with distant disease would have benefited from earlier screening. Thus, when to start screening and the subsequent time intervals for a repeat test are important topics for the future. Of clinical importance is the fact that with rising tPSA fewer cancers are organ confined (Table 2). Thus, a PSA "grey zone" within 4–10 ng/ml range can no longer be postulated. Only about 70% of the men with PSA values in this range presented with organ confined cancer, which is associated with the lowest recurrence rates and the best chance of biochemical no evidence of disease (bNED = no measurable PSA) after 10 years. If, after receiving information on the risk of prostate cancer, treatment options and possible side effects, a man agrees to early detection, a transrectal prostate biopsy has to be done immediately when the total PSA level exceeds 4.0 ng/ml. The ratio of free-to-total PSA (f/t ratio) gives no additional support in this situation, because an elevated benign glands in the transition zone of the prostate with a higher production of free PSA can mask the tumour in the peripheral zone. Increasing specificity is combined with a loss in sensitivity for organ confined disease [15]. The value of the f/t ratio seems to be more relevant in determining the extent of the cancer search (e.g. decision for second biopsy). The lower the f/t ratio by smaller prostate size the more probable is the presence of a cancer, especially in younger men [11].

What data are available on prostate cancer screening at the moment?

The first study of screening was initiated in 1988 in the Quebec area of Canada and reported a PCA specific mortality reduction of 69% [16]. However, there was a clear evidence of a self selection bias. Only 23% of the potential screening group agreed to participate. On the other hand, 7% of the control group had had PSA test performed and were included in the screening group. Furthermore, large and unexplained differences in the follow-up times of both groups were noticed [17]. A more important study was carried out in the area of Innsbruck, Austria. Since 1993 a free of charge PSA test has been available to every man between the ages 50 and 70 years. Until 1999 a PCa specific mortality reduction of 42% (calculated as the difference between the observed and expected mortality rates) was reported [18, 19]. Critics of the validity of these preliminary results stated that due to the lead-time effects (bringing diagnosis forward by screening), the benefit in mortality reduction is seen too early to be the result of the screening itself. An intensive follow-up in the next years will be helpful in explaining this early effect and contribute to the topic of screening benefit. Interesting observations are presented by the SEER (Surveillance Epidemiology and End Results) study in which men were observed from the moment of diagnosis until death. A decrease in age related PCa specific mortality of 27% was documented from 1991 until 1999, possibly due to the decrease in the incidence of primary distant disease stages [20]. The authors stated that this was the consequence of an increased use of PSA testing since 1986. Considering the widespread use of

PSA testing in the USA with a punctum maximum in 1992, the further course of age related mortality in the SEER program is of great importance. The ongoing prospective randomised screening trials are: PLCO (prostate, lung, colorectal and ovarian, including 74,000 men) study from the National Cancer Institute and the ERSPC study. This last trial has already included 180,000 men in Europe and is designed to detect a mortality reduction of 20–25% with a statistical power of about 90% [10, 21, 22]. These trials are also expected to bring clearer answers especially in respect to the prognostic value of different risk factors (age, PSA level, tumour volume, Gleason score, tumour extent in biopsies, etc.) as well as to the choice of the best treatment option for the individual.

Conclusions

At the moment it is premature to recommend a mass screening programme. For men at risk (50–70 years) an "individual well-informed decision" on PSA testing is most suitable. The decision making process should involve both the family physician and the patient and it should be structured as following:

1. The previously mentioned general risks of mortality and morbidity on prostate cancer have to be addressed.
2. If a positive family history of prostate cancer is present, the lifetime risk increases by the factor 2.5 (one relative) or 3.5 (two relatives), thus screening at younger ages, e.g. at the age of 40 (two or more relatives) or 45 years (one relative), should be considered [23].
3. Treatment options (radical prostatectomy, radiotherapy and watchful waiting) and outcomes must be discussed. It should be mentioned that prostate cancer is a curable disease if detected early in the organ-confined stage.
4. At the same time, the possible treatment side effects, i.e. incontinence after surgery (0–5%) or radiotherapy (0–5%) should also to be mentioned. Loss of spontaneous erection (but not of orgasm, which is present but becomes dry) is expected to occur in 20–80% cases after surgery depending on the intraoperative possibility of nerve sparing. Similarly, erectile dysfunction following radiotherapy ranges from 30% and 70% increasing over time.
5. If an individual agrees to PSA testing, further diagnostic procedures using TRUS guided prostate biopsy should be performed immediately if the PSA level exceeds 4.0 ng/ml.

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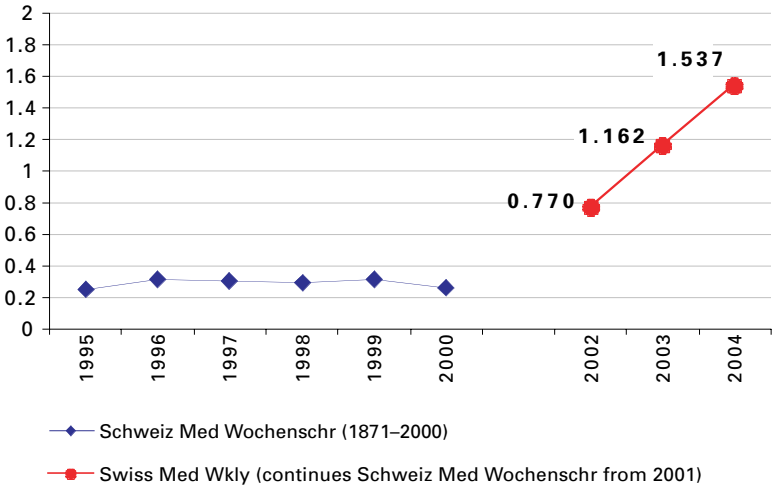

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