

Prostate Cancer Screening: The Only Way to Early Treatment and a Major Impact on Survival

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Summary

Although combined androgen blockade can prolong life in advanced metastatic prostate cancer, a major impact on survival requires early diagnosis. Using PSA as first line screening test, 99% of cancers can be diagnosed at the clinically localized stage and are thus potentially curable. PSA alone can be used as a highly efficient screening test. In a prospective screening trial started in 1988 in Quebec City, among 46,480 men aged 45 to 80 years, the follow-up at 10 years shows a 68% decrease in prostate cancer deaths among those who were screened and treated early compared to standard medical practice. This is well supported by the finding of a 40 to 80% decrease in deaths from prostate cancer when long-term and continuous androgen blockade is applied at the localized stage of the disease.

Introduction

Although prostate cancer is the most frequently diagnosed cancer and the second most common cause of cancer death in men, death from this disease has decreased in the United States and in the province of Quebec by up to 22% since 1991. Since even the best treatment for advanced metastatic disease, namely combined androgen blockade can only prolong life by a few months^{1, 2}, the recent decrease in death rates from

prostate cancer can only be due to the treatment of early disease which, on the other hand, requires early diagnosis or screening.

An important observation based on overwhelming scientific evidence is that prostate-specific antigen (PSA) can be efficiently used as a pre-screening test for prostate cancer, thus keeping the more costly and less well-tolerated digital rectal examination (DRE) and transrectal ultrasonography (TRUS) as second step procedures³⁻⁶. Using this approach, practically 100% of prostate cancers can be diagnosed at a clinically localized or potentially curable stage, therefore practically eliminating the diagnosis of metastatic disease^{3, 4}.

Definitive proof of the benefits of early diagnosis, however, can only be obtained from prospective and randomized studies which compare the incidence of death from prostate cancer in a group of men screened and treated early with a parallel group of men receiving standard medical care. Accordingly, the Laval University Prostate Cancer Screening Program (LUPCSP) was started in November 1988. In this study, men aged 45 to 80 years were randomly selected for screening tests from the electoral rolls of Quebec City and surrounding area. The men in the control group not invited for screening were followed according to current medical practice for prostate cancer diagnosis and treatment. Deaths from prostate cancer for all invited and non-invited men were identified using the Québec Cancer Death Registry up to December 1998.

From November 1988 to December 1998, a total of 7,302 men (>99% Caucasians) in the invited group of the electoral rolls were examined at first visit, and 35,909 follow-up visits were performed. Of the 15,350 non-invited men, 14,264 were not screened and constituted the control group^{7, 8}. Other men (4,616) not invited for screening as part of the LUPCSP but who had not undergone any prior screening procedure received the same screening tests at first visit while 15,860 follow-up visits were performed in this group of not invited men. Those men were not part of the analysis on the impact of screening on survival^{7, 8}.

Participants had measurement of serum PSA and all underwent DRE at first visit. The PSA and DRE tests were performed independently. Serum samples were taken before DRE for measurement of PSA by immunoradiometric assay (Tandem-R PSA, Hybritech Inc. or its equivalent). TRUS was performed only in cases with positive PSA (>3.0 ng/ml) and/or positive DRE, except for the first 1,002 men who all had the three procedures, as previously reported⁹. At follow-up visits, TRUS was done if serum PSA already above 3.0 ng/ml had increased by more than 20% compared with the value measured one year earlier (the interassay coefficient of variation [c.v.] being 9.6%, we accepted 10% as a possible increase attributable to the interassay c.v.), leaving a 10% increase attrib-

unable to changes in PSA secretion, or if the measured PSA was increased by more than 20% above the predicted PSA^{10, 11}.

Results

As shown in Figure 1, 16.6% of 11,811 men at first visit had serum PSA >3.0 ng/ml (PSA⁺) while, at 46,751 follow-up visits, PSA was abnormal in 15.6% of cases. Thus, at first (11,811) and follow-up (46,751) visits, 83.4% and 84.4% of men had serum PSA at or below 3.0 ng/ml, respectively. Serum PSA was at or below 2.0 ng/ml in 72.5% of men at first visits and 73.6% of them at follow-up visits.

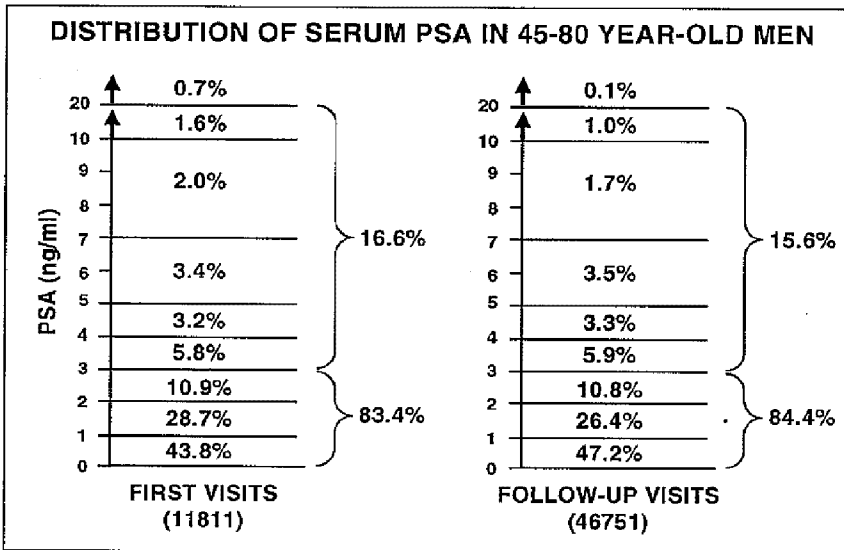


Figure 1. Distribution of serum PSA at first and follow-up visits in 45-80 year old men.

The most significant changes observed between first and annual follow-up visits are seen in the percentage of men with serum PSA values above 20 ng/ml where a 6.3-fold reduction was seen between the first and follow-up visits (the incidence rate decreasing from 0.69% to 0.11%).

Since a major concern about screening is a potential increase in the number of clinically not significant cancers detected, it is important to observe that only 215 cancers were found at 46,751 follow-up visits for an incidence of 0.46% compared to a prevalence of 2.85% (337 cancers in 11,811 men) at first visit. The percentage of men found as having

prostate cancer at follow-up visits is thus 6.2 times lower compared to first visits.

Another important finding is that the percentage of men showing serum PSA >3.0 ng/ml who were found as having prostate cancer decreased from 15.3% at first visits to 2.8% at follow-up visits. There was thus a 5.5-fold decrease in the incidence of diagnosed prostate cancer at follow-up compared to first visits in men having abnormal PSA. In other words, prostate cancer was found in 1 out of 6.5 men having serum PSA above 3.0 ng/ml at first visits compared to only one out of 35.5 men at follow-up visits.

Table 1 describes the relative sensitivity of serum PSA and DRE to detect prostate cancer at first visits and at annual follow-up visits. Since DRE was eliminated from follow-up visits in January 1993, the data are presented only for the visits where both PSA and DRE were performed. These data do not include the cancers found by TRUS in the presence of normal PSA and DRE in the early phase of the detection program (first 1002 men)⁹. At first visits, 97 of the 282 (34.4%) cancers were both PSA⁺ and DRE⁺; 158 cancers (56.0%) were PSA⁺ and DRE⁻ while only 27 cancers (9.6%) were PSA⁻ and DRE⁺. At follow-up visits, 15 of the 74 cancers (20.3%) were PSA⁺ and DRE⁺; 53 (71.6%) were PSA⁺ and DRE⁻ while only 5 (6.8%) were PSA⁻ and DRE⁺. Thus, 255 of the 282 cancers (90.4%) detected at the first visits were PSA⁺ while only 124 (44.0%) were DRE⁺. At the follow-up visits, 68 of the 74 cancers (91.9%) were PSA⁺, but only 20 (27.0%) were DRE⁺. It is important to mention that of the 74 prostate cancers diagnosed at follow-up visits in invited men who had DRE and PSA at all visits, 68 were PSA positive and only 6 (8.1%) were missed by PSA and found by DRE, thus demonstrating the unique efficacy of serum PSA to detect prostate cancer, especially at annual follow-up screening visits (Table 1).

The present data show that 344 DREs are required to find one case of prostate cancer at first visit while 1,919 DREs are required at follow-up visits. On the other hand, 36 and 141 PSA measurements are required at first and follow-up visits to diagnose one case of prostate cancer.

Table 1: Number of TRUS-guided biopsies and positive biopsies according to serum PSA and DRE in men who had both exams at all visits at first and follow-up visits.

PSA	DRE	First Visit						Follow-up Visits							
		Visits #	TRUS #	% Visits	Biopsies #	% TRUS	CaP #	% Biopsies	Visits #	TRUS #	% Visits	Biopsies #	% TRUS	CaP #	% Biopsies
-	-	7,281						7,674	45	0.6	15	33.3	1	6.7	
-	+	404	381	94.3	246	64.6	27	11.0	189	115	60.8	59	51.3	5	8.5
+	-	1,379	1,298	94.1	494	38.1	158	32.0	1,662	584	35.1	224	38.4	53	23.7
+	+	232	220	94.8	173	76.6	97	56.1	68	43	63.2	32	74.4	15	46.9
Total		9,296	1,899	20.4	913	48.1	282	30.9	9,593	787	8.2	330	41.9	74	22.4

Based upon 18,889 visits where men had both PSA and DRE, the present data show that PSA is about 10 times more efficient than DRE to detect prostate cancer at a clinically localized and potentially curable stage. Such data support our previous findings¹²; and those of Schröder *et al.*^{5,6} which demonstrate the high efficacy of PSA used alone for prostate cancer screening.

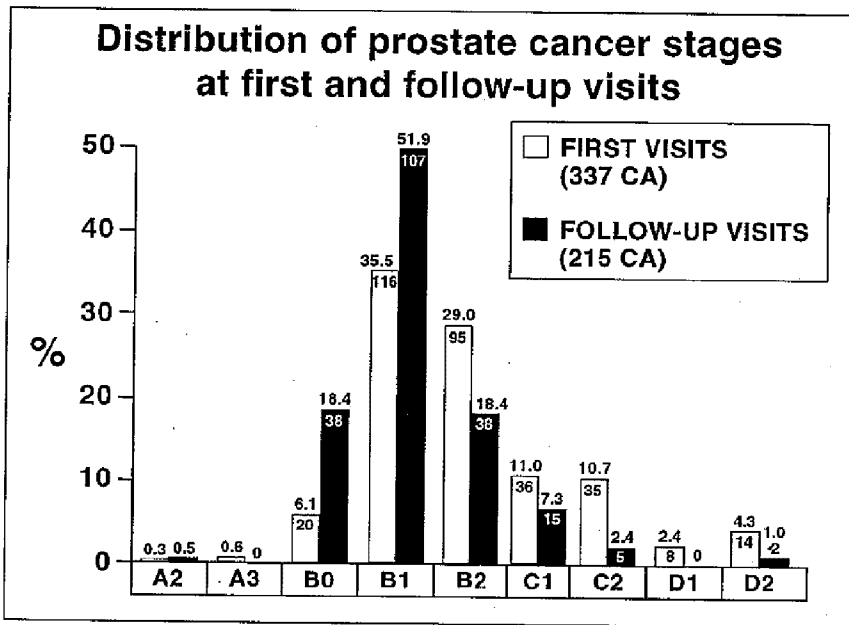


Figure 2. Distribution of clinical stages of 337 and 215 (327 and 206 staged) prostate cancers diagnosed at first and follow-up screening visits, respectively. Data are expressed as percentage of total number of staged cancers in each group to facilitate comparison.

A most important finding is that only two out of 215 (1.0%) cancers diagnosed at 46,751 follow-up visits were metastatic compared with 6.7% at first visit (Fig. 2). It can be also be seen that stage C₂ prostate cancers decreased from 10.7% at first visit to only 2.4% at follow-ups. Stages B₀, on the other hand, increased from 6.1% at first visit to 18.4% at follow-up visits while stage B₁ disease increased from 35.5% to 51.9% and stage B₂ cancers, on the other hand, decreased from 29.1% to 18.4%.

As clearly suggested in our previous reports^{3,4} and well demonstrated by the present update and extension of the previous data, the most cost-effective strategy is measurement of serum PSA as first line approach as

recently concluded by Schröder et al., 1998⁵ and Schröder et al., 2001⁶ in another large-scale screening study. Following this strategy, the costs for finding one case of prostate cancer at first visits and follow-up visit are estimated at \$2,418.75 and \$7,105.00, respectively.

Impact on Survival - (November 15, 1988 - December 31, 1998)

Of the 46,480 eligible men aged between 45 and 80 years included in the prospective randomized study started in 1988, 31,130 were invited by letter to be screened for prostate cancer while 15,350 were allocated to the control unscreened group. Figure 3 shows the breakdown in terms of the number of men, of man-years and deaths from prostate cancer according to original randomization and participation to screening⁸.

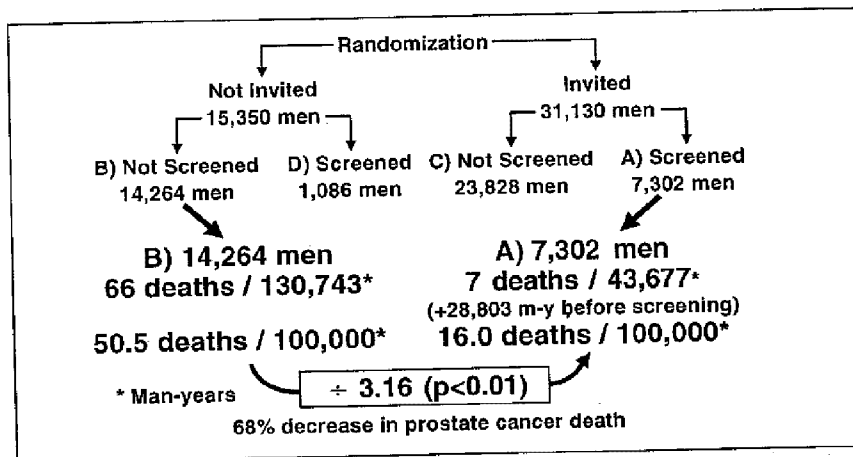


Figure 3. Summary of data of the Laval University prostate cancer screening program (November 15, 1988 to December 31, 1998).

Over the 10-year period, the annual cause-specific death rate incidences are 16.0 (Fig. 3, Group A) and 50.5 (Fig. 3, Group B), per 100,000 man-years in the invited screened and control unscreened groups, respectively (p<0.01). The prostate cancer death incidence rate thus decreased by 68% in men of the screened group.

Conclusion

PSA used as a single test for prescreening and followed by DRE and TRUS when PSA is abnormal is highly efficient in detecting prostate

cancer at a localized (potentially curable) stage in close to 100% of cases, thus practically eliminating the diagnosis of metastatic and non curable prostate cancer^{3,4}. The approach used is highly reliable, sensitive, efficient and acceptable by the general population⁹. With the kits available, PSA measurement is a low cost routine procedure which requires a simple blood sampling and a minimum of expenses. Only 17% of men then need to be referred to specialized prostate cancer clinics when PSA becomes abnormal (> 3.0 ng/ml), thus reducing the costs and optimizing the use of specialized health care personnel and expertise. The detection of clinically non significant as well as metastatic advanced cancers has become an exception. Coupled with treatment of localized disease, the present approach demonstrates, in the first prospective and randomized study, that early diagnosis and treatment permit a dramatic decrease in deaths from prostate cancer. If the present trend continues, the present data suggest that among the male population in the United States, the present approach could save 2.0 million lives of the 3.0 million presently living in the United States and expected to die from prostate cancer if no significant change in diagnosis and/or treatment occurs.

Two other randomized screening trials for prostate cancer are ongoing, namely the Prostate, Lung, Colon, and Ovarian Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). Results from those trials are not expected before year 2005. Moreover, their relatively late start carries the high risk of significant contamination of the control group by screening.

As strong support for the crucial role of early diagnosis and treatment, the Quebec clinical trial that represents the first prospective and randomized prostate cancer screening study shows that early diagnosis combined with treatment of localized disease decreased death from prostate cancer by 68%. The present data are also in agreement with the 42% decrease observed in 1998 in the prostate cancer death rate in the Tyrol area where PSA screening was made available since 1993 compared to the rest of Austria where PSA screening was not offered¹³. Since about two thirds of men were screened in Tyrol during that period, the 42% decreased death rate observed is comparable to the 68% value measured in our study among the men who were screened.

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