

Evaluation of Prostatic Specific Antigen and Digital Rectal Examination as Screening Tests for Prostate Cancer

Bernard Candas,^{1*} Lionel Cusan,¹ Jose-Luis Gomez,¹ Pierre Diamond,¹ Raul E. Suburu,² Jacques Lévesque,² Ghislain Brousseau,² Alain Bélanger,¹ and Fernand Labrie¹

¹*Prostate Cancer Clinical Research Unit, Department of Medicine and Laboratory of Molecular Endocrinology, Laval University Medical Center (CHUL) and Laval University, Quebec, Canada*

²*Department of Radiology, Laval University Medical Center (CHUL), Quebec, Canada*

BACKGROUND. The 11,811 first visits and 46,751 annual follow-up visits performed since 1988 were analyzed in order to assess the efficacy of serum prostatic specific antigen (PSA) and digital rectal examination (DRE) for diagnosis of prostate cancer.

METHODS. At first visit, screening included DRE and measurement of PSA using 3.0 ng/ml as upper limit of normal, demonstrated as optimal value in the course of the study. Transrectal echography of the prostate (TRUS) was performed only if PSA and/or DRE was abnormal. For elevated PSA, biopsy was performed only if PSA was above the value predicted from prostatic volume measured by TRUS. At follow-up visits, it was decided during the course of the study to use PSA alone.

RESULTS. PSA was above 3.0 ng/ml in 16.6% and 15.6% of men at first and follow-up visits, respectively. Prostate cancer was found in 2.9% of men invited for screening at first visit and in only 0.4% of men at follow-up visits for a 7.1-fold decrease at follow-up visits done up to 11 years. PSA alone allowed to find 90.5% and 90.0% of cancers at first and follow-up visits, respectively, compared to 41.1% and 25.0% by DRE alone. In the presence of normal PSA, 344 and 1,919 DREs are needed to find one prostate cancer at first and follow-up visits, respectively. A significant improvement in stage of the disease is found at follow-up (215 cancers) compared to first visits (337 cancers). Comparison made between men invited for screening and those who were not invited but screened showed no significant difference in terms of incidence and prevalence of prostate cancer as well as diagnosis of cancer as a function of age or as a function of PSA, DRE, and TRUS data. The cost for finding one case of prostate cancer is estimated at Can \$2,420 and Can \$7,105 (first and follow-up visits, respectively, when PSA is used as prescreening).

CONCLUSIONS. PSA used as prescreening and followed by DRE and TRUS when PSA is abnormal is highly efficient in detecting prostate cancer at a localized (potentially curable) stage since 99% of the cancers diagnosed were at such a localized stage, thus practically eliminating the diagnosis of metastatic and noncurable prostate cancer. The approach used is highly reliable, sensitive, efficient, and acceptable by the general population. The detection of

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*Correspondence to: Dr. Bernard Candas, Oncology and Molecular Endocrinology Research Center, Le Centre Hospitalier de l'Université Laval (CHUL), 2705 Laurier Blvd., Quebec, G1V 4G2, Canada. E-mail: fernand.labrie@crchul.ulaval.ca

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INTRODUCTION

When the diagnosis of prostate cancer is made at the metastatic stage, even the best treatment can only prolong life with minimal hope of a cure [1–6]. Consequently, the only possibility for a major impact on prostate cancer mortality is treatment of localized disease before cancer reaches the bones, which are the usual site of distant metastases and where the cancer usually develops resistance to treatment. It is thus clear that if prostate cancer is not treated at a localized stage, it will remain the second cause of cancer death in men [7]. In fact, it was predicted that 37,800 men would die from prostate cancer in the United States in 1999. Prostate cancer is thus a major medical and social problem in urgent need of a significant improvement in diagnosis and treatment.

Since prostate cancer usually develops insidiously for many years without signs or symptoms until it reaches the noncurable stage of metastases in the bones, screening in asymptomatic men is essential. The absence of data showing the efficacy of early treatment was erroneously interpreted as being equivalent to negative results. Most fortunately, five prospective randomized trials have recently demonstrated for the first time that prolongation of life is achieved in patients with localized prostate cancer treated with androgen blockade [8–12].

The essential objective of screening for prostate cancer is detection of the cancer at a localized and thus curable stage before the cancer reaches to the bones where the success of treatment is only temporary. In order to be useful and applicable in the general population, however, the screening tests used must be simple, noninvasive, reliable, efficient, and of low cost. It thus becomes particularly important to obtain precise information on the performance of the two tests most currently available for screening, namely PSA and digital rectal examination (DRE). It is clear that such information can only be obtained from large-scale studies. The interest in this area is particularly high following the decision of the European Randomized Study Screening for Prostate Cancer (ERSPC) not to use DRE for screening when PSA is normal (≤ 3.0 ng/mL) [13]. It will also be of interest to compare the results obtained in the groups of men invited and not invited for screening.

SUBJECTS AND METHODS

As part of the prospective, randomized, and controlled Laval University Prostate Cancer Detection Program (LUPCDP), men aged 45–80 years were randomly selected for screening tests from the electoral rolls of Québec City and its vicinity. Men in the control group not invited for screening are followed according to current medical practice for diagnosis and treatment of prostate cancer and are identified during follow-up in the Quebec Cancer Death Registry, while the men selected for screening were invited to participate by letter and are followed by annual visits at the prostate cancer clinic. To minimize bias, no public announcement was made through the media. From November 1988 to December 1998, a total of 7,195 men (>99% Caucasians) in the invited group of the electoral rolls were examined at first visit; and 30,891 follow-up visits were performed. The number of men selected in each age group was proportional to that in the general male population. Other men (4,616) not invited for screening as part of the LUPC Detection Program received the same screening tests at first visit, while 15,860 follow-up visits were performed in this group of noninvited men.

Participants completed a questionnaire on familial incidence of prostate cancer and provided information on genitourinary history and present symptomatology. They then had measurement of serum PSA and underwent DRE. The PSA and DRE tests were performed independently. TRUS was performed only in cases with positive PSA and/or DRE, except for the first 1,002 men who all had the three procedures, as previously reported [14]. 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 attributable to changes in PSA secretion or if the measured PSA was increased by more than 20% above the predicted PSA [15]. Serum samples were taken before DRE for measurement of PSA by immunoradiometric assay (Tandem-R PSA, Hybritech Incorporated, San Diego, CA, or its equivalent).

The following classification of prostate cancer staging was used at diagnosis: B₀ (T2a) (one localized pal-

TABLE I. Correlation Between Serum PSA Levels and the Presence of Detectable Prostate Cancer in 45- to 80-Year-Old Invited Men at 7,195 First Visits (A) and 30,891 Follow-Up Visits (B). Similar data are presented for 4,616 first visits and 15,860 follow-up visits in a similar population of uninvited men.

(A)												
First visit												
PSA (ng/ml)	Not invited				Invited				All subjects			
	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)
0.0-1.0	2,090	45.3	5	0.24	3,086	42.9	3	0.10	5,176	43.8	8	0.15
1.1-2.0	1,236	26.8	3	0.24	2,153	29.9	6	0.28	3,389	28.7	9	0.27
2.1-3.0	445	9.6	8	1.80	838	11.7	12	1.43	1,283	10.9	20	1.56
3.1-4.0	259	5.6	12	4.63	427	5.9	29	6.79	686	5.8	41	5.98
4.1-5.0	162	3.5	13	8.02	212	3.0	18	8.49	374	3.2	31	8.29
5.1-7.0	184	4.0	19	10.33	218	3.0	37	16.97	402	3.4	56	13.93
7.1-10.0	111	2.4	23	20.72	120	1.7	29	24.17	231	2.0	52	22.51
10.1-20.0	90	2.0	18	20.00	98	1.4	41	41.84	188	1.6	59	31.38
>20.1	39	0.8	25	64.10	43	0.6	36	83.72	82	0.7	61	74.39
Total	4,616	100	126	2.73	7,195	100	211	2.93	11,811	100	337	2.85

(B)												
Follow-up visits												
PSA (ng/ml)	Not invited				Invited				All subjects			
	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)
0.0-1.0	7,554	47.6	1	0.01	14,490	46.9	1	0.01	22,044	47.2	2	0.01
1.1-2.0	4,016	25.3	2	0.05	8,345	27.0	1	0.01	12,361	26.4	3	0.02
2.1-3.0	1,672	10.5	4	0.24	3,392	11.0	1	0.03	5,064	10.8	5	0.10
3.1-4.0	909	5.7	12	1.32	1,847	6.0	31	1.68	2,756	5.9	43	1.56
4.1-5.0	536	3.4	16	2.99	1,023	3.3	19	1.86	1,559	3.3	35	2.25
5.1-7.0	609	3.8	21	3.45	1,042	3.4	33	3.17	1,651	3.5	54	3.27
7.1-10.0	346	2.2	22	6.36	467	1.5	20	4.28	813	1.7	42	5.17
10.1-20.0	193	1.2	9	4.66	257	0.8	18	7.00	450	1.0	27	6.00
>20.1	25	0.2	0	0.00	28	0.1	4	14.29	53	0.1	4	7.55
Total	15,860	100	87	0.55	30,891	100	128	0.41	46,751	100	215	0.46

pable nodule and/or a TRUS positive lesion < 1 cm in diameter), B₁ (T2b) (one localized palpable nodule and/or TRUS lesion with a diameter between 1.0 and 1.5 cm), B₂ (T2C) (more than one palpable nodule or TRUS lesion and/or palpable nodule or TRUS lesion with a diameter > 1.5 cm), C₁ (T3a, b) (minimal palpable extracapsular extension or invasion of prostate capsule at biopsy), C₂ (T3c, T4) (extension of tumor to seminal vesicles and/or bladder neck at biopsy), D₁ (Tx, N1, 2 M0) (lymph node metastases), and D₂ (Tx, M1) (distant lymph node or bone metastases). Of the 339 invited men diagnosed as having prostate cancer, 330 agreed to be staged at our clinic.

RESULTS

Since the population of invited men is exclusively composed of previously unscreened men, we have the

opportunity to obtain information specific for each visit, and thus compare the findings at first visit with those obtained at annual follow-up visits. As shown in Table IA, 15.5% of the 7,195 men invited for screening and examined at first visit had serum PSA above 3.0 ng/ml, the optimal cut-off value previously determined by receiver operator curve analysis [14]. Comparable results were obtained in the 4,616 noninvited men where 18.3% of men had serum PSA above 3.0 ng/ml and were thus candidates for TRUS at their first visits.

On the other hand, at 30,891 follow-up visits in the invited group, 15.1% of men had serum PSA above 3.0 ng/ml. Comparable results were obtained in the 15,860 follow-up visits in the group of men not invited for screening where 16.5% had serum PSA above the cut-off value of 3.0 ng/ml (Table IB).

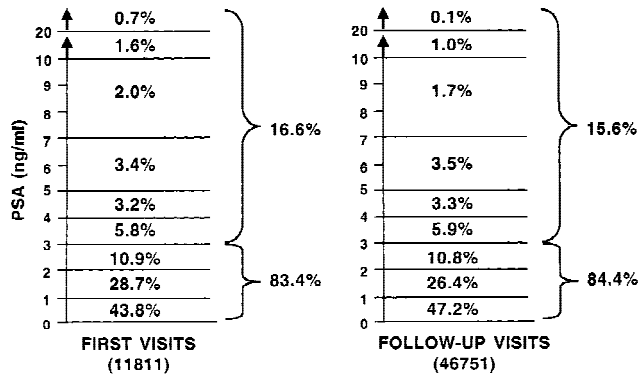


Fig. 1. Distribution of serum PSA at first and follow-up visits in 45- to 80-year-old men.

The group of noninvited men included men listed in the electoral rolls and who were originally part of the control group of our randomized screening study as well as men from outside the metropolitan area of Quebec City who came to our clinic on their own without being invited by letter. When all data are pooled (Table IA,B), 16.6% of 11,811 men at first visit had abnormal PSA while, at 46,751 follow-up visits, PSA was abnormal in 15.6% of cases (Fig. 1). Thus, at first (11,811) and follow-up (46,751) visits, 83.4% and 84.4% of men have serum PSA within normal limits or below 3.0 ng/ml. It can also be seen on the same figure that 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.

The most significant changes observed between first and annual follow-up visits of invited men are seen at serum PSA values above 20 ng/ml where a 6.7-fold reduction was seen at follow-up visits in the percentage of men having a serum PSA above 20 ng/ml, the incidence rate decreasing from 0.69% at first visit to 0.09% at follow-up visits of invited men. Similarly, in the group of noninvited men, there was a 5.4-fold reduction in the number of men who had serum PSA above 20 ng/ml at follow-up compared to first visits.

Since a major concern about screening is a potential increase in the number of clinically not significant cancers detected, it is important to see in Table I and Figure 2 that only 128 cancers were found at 30,891 follow-up visits in invited men for an incidence of 0.41% compared to a prevalence of 2.93% (211 cancers in 7,195 men) at first visit. The percentage of men found as having prostate cancer at follow-up visits is thus 7.1 times lower than at first visits. In the noninvited men, 126 cancers were found at 4,616 first visits for a prevalence of 2.73% while at 15,860 follow-up visits, 87 cancers were found for an incidence of 0.55% (Table I). The percentage of noninvited men diag-

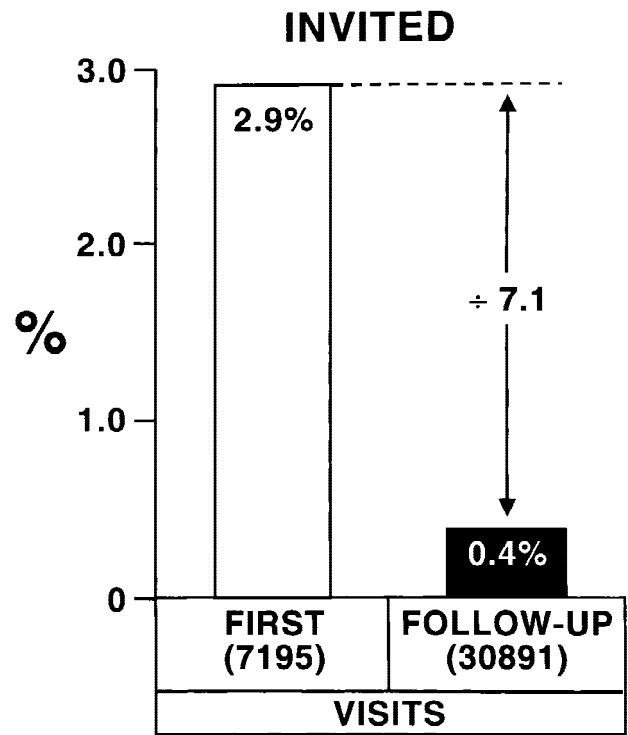


Fig. 2. Percentage of men diagnosed with prostate cancer at first and follow-up visits.

nosed with prostate cancer is thus 5.0 times lower at follow-up compared to first visits.

When the 6,136; 5,498; 5,207; 3,503; 3,358; 3,248; 2,742; 1,005; 162; and 32 men not found to have prostate cancer at first visits (7,195) were similarly examined by serum PSA at their second, third, and until their eleventh annual visit, the incidence of prostate cancer was found to be much lower at 0.46, 0.56, 0.48, 0.57, 0.21, 0.15, 0.36, 0.20, 0, and 0%, respectively (Fig. 3). It can be seen in Table I that similar results were found in the group of noninvited men.

A particularly important finding illustrated in Figure 4 is that the percentage of men showing serum PSA above 3.0 ng/ml who were found to have prostate cancer decreased from 17.0% at first visits (1,118) to 2.7% at follow-up visits (4,664) in the group of invited men. There was thus a 6.3-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 5.9 men having serum PSA above 3.0 ng/ml at first visits compared to only one out of 37 men having similar PSA levels at follow-up visits. In the group of noninvited men having an abnormal PSA at first visits (> 3.0 ng/ml), 110 cancers were diagnosed in 845 men with abnormal PSA for an incidence rate of 13.0% and cancer was thus found in one out of 7.7 men (Table I). At follow-up visits, on the other hand, the percentage

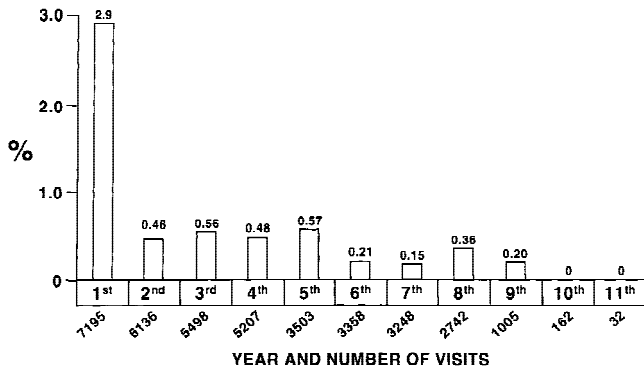


Fig. 3. Prevalence (first visits) and incidence (follow-up visits) of prostate cancer in men invited for screening.

of men with abnormal PSA found with cancer decreased to 3.1% (80 cancers in 2,618 men with abnormal PSA). A cancer was thus found in 1 out of 33 noninvited men having abnormal PSA at follow-up visits, thus showing a 4.3-fold decrease compared to first visits.

In a total of 38,086 visits of invited subjects, 339 cancers were detected by abnormal serum PSA and/or DRE. Five of these cancers were detected only by TRUS in the first 1,002 men, when TRUS was performed in all men independently of the results of serum PSA and DRE [14]. In fact, the results of our initial study [14] meant that the general use of TRUS could not be justified as a first-line procedure for detection of prostate cancer. This technique was then subsequently limited to the subpopulation of men with abnormal serum PSA and/or DRE. This decision was based on the need to develop a strategy for the diagnosis of early stage and curable prostate cancer that would be sensitive, efficient, precise, require minimal health professional labor, and be acceptable by the general population as well as being in line with the optimal cost-effectiveness required by the health care system.

Table II thus 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 1,002 men [14]). At first visit of the invited men, 53 of the 168 (31.5%) cancers were both PSA⁺ and DRE⁺; 99 of 168 (58.9%) cancers were PSA⁺ and DRE⁻ while only 16 cancers (9.2%) were PSA⁻ and DRE⁺. At follow-up visits, 8 of the 40 cancers (20.0%) were PSA⁺ and DRE⁺; 30 (75.0%) were PSA⁺ and DRE⁻ while only 2 (5.0%) were PSA⁻ and DRE⁺. Thus, 152 of the 168 cancers (90.5%) detected at the first visits were PSA⁺

while 69 (41.1%) DRE⁺ (Fig. 5). At the follow-up visits, 38 of the 40 cancers (95.0%) were PSA⁺, but only 10 (25.0%) cancers were DRE⁺. Combining all 11,970 visits, 190 of the 208 cancers (91.3%) were PSA⁺ and 79 (38.0%) were DRE⁺. Thus showing that PSA has a 2.4-fold higher sensitivity than DRE at first visit. At first visits, PSA detects 2.2 times more cancers than DRE while at follow-up visits, 3.8 times more cancers are PSA positive than DRE positive.

It is important to mention that of the 40 prostate cancers diagnosed at follow-up visits in invited men who had DRE and PSA at all visits, 38 were PSA positive and only 2 (5.0%) were missed by PSA and found by DRE, thus demonstrating the unique importance of serum PSA to detect prostate cancer, especially at annual follow-up screening visits (Table IIB). On the other hand, at first visits, 90.5% of cancers in invited men were PSA positive while 9.5% were found by DRE in the presence of normal PSA (Table IIA) (Fig. 5).

Similar results were obtained in the group of non-invited men where 44 of the 114 cancers (38.6%) at first visit were both PSA⁺ and DRE⁺; 59 cancers (51.8%) were PSA⁺ and DRE⁻ and only 11 cancers (9.6%) were PSA⁻ and DRE⁺. At follow-up visits in the noninvited group of men, 7 of the 34 cancers (20.6%) were PSA⁺ and DRE⁺ while 67.6% (23 of 34 cancers) were PSA⁺ and DRE⁻. On the other hand, only 3 cancers (8.8%) were PSA⁻ and DRE⁺. Thus, while at first visit, 90.4% of the cancers were PSA⁺, PSA⁺ was positive in 95% of the cancers at follow-up visits of noninvited men. When combining all data of first and follow-up visits, 133 out of 148 cancers (89.9%) were PSA⁺ while 43.9%

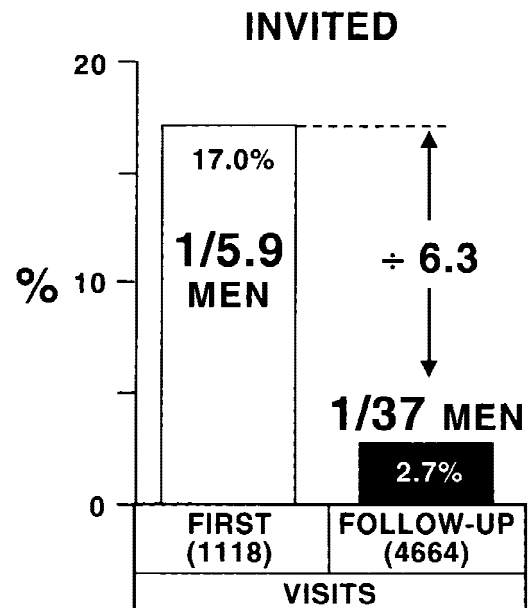


Fig. 4. Percentage of men with abnormal PSA (> 3.0 ng/ml) diagnosed with prostate cancer at first and follow-up visits.

TABLE II. 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 (A) and Follow-up (B) Visits

		(A)																				
		First visit																				
		Uninvited							Invited							All subjects						
		TRUS		Biopsies		CaP			TRUS		Biopsies		CaP			TRUS		Biopsies		CaP		
PSA	DRE	Visits (#)	% of Visits	(#)	% of TRUS	(#)	% of Biopsies	(#)	Visits (#)	% of Visits	(#)	% of TRUS	(#)	% of Biopsies	(#)	Visits (#)	% of Visits	(#)	% of TRUS	(#)	% of Biopsies	
-	-	2,951							4,330							7,281						
	+	172	158	91.9	85	54.8	11	12.9	232	223	96.1	161	72.2	16	9.9	404	381	94.3	246	64.6	27	11.0
+	-	620	576	92.9	210	36.5	59	28.1	759	722	95.1	284	39.3	99	34.9	1,379	1,298	94.1	494	38.1	158	32.0
	+	125	115	92.0	85	73.9	44	51.8	107	105	98.1	88	83.8	53	60.2	232	220	94.8	173	76.6	97	56.1
Total		3,868	849	21.9	380	44.8	114	30.0	5,428	1,050	19.3	533	50.8	168	31.5	9,296	1,899	20.4	913	48.1	282	30.9
		(B)																				
		Follow-up visit																				
		Uninvited							Invited							All subjects						
		TRUS		Biopsies		CaP			TRUS		Biopsies		CaP			TRUS		Biopsies		CaP		
PSA	DRE	Visits (#)	% of Visits	(#)	% of TRUS	(#)	% of Biopsies	(#)	Visits (#)	% of Visits	(#)	% of TRUS	(#)	% of Biopsies	(#)	Visits (#)	% of Visits	(#)	% of TRUS	(#)	% of Biopsies	
-	-	2,296	20	0.9	5	25.0	1	20.0	5,378	25	0.5	10	40.0	0	0.0	7,674	45	0.6?	15	33.3	1	6.7
	+	80	53	66.3	30	56.5	3	10.0	109	62	56.9	29	46.8	2	6.9	189	115	60.8	59	51.3	5	8.5
+	-	641	218	34.0	89	40.8	23	25.8	1,021	366	35.8	135	36.9	30	22.2	1,662	584	35.1	224	38.4	53	23.7
	+	34	22	64.7	19	86.4	7	36.8	34	21	61.8	13	61.9	8	61.5	68	43	63.2	32	74.4	15	46.9
Total		3,051	313	10.3	143	45.7	34	23.8	6,542	474	7.2	187	39.5	40	21.4	9,593	787	8.2	330	41.9	74	22.4

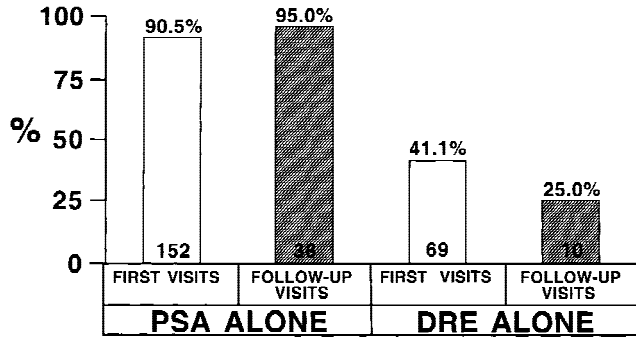


Fig. 5. Percentage of prostate cancer diagnosed by PSA or DRE alone at first and follow-up visits.

of cancers (65 out of 148 cancers) were DRE+ and 9.5% of cancers were DRE+ in the presence of normal PSA.

Based on the above-described data, it seems appropriate to combine the results obtained in the invited and noninvited men. It can be seen in Tables IIA and IIB that the major difference between first and follow-up visits is the decrease in the percentage of both PSA+ and DRE+ cancers from 34.4% at first visit to 20.3% at follow-up visits with a corresponding increase in the percentage of PSA+ and DRE- cancers from 56.0% at first visit to 71.6% at follow-up visits. DRE+ PSA- cancers, on the other hand, decreased from 9.6% at first visit to 6.8% at follow-up visits. The percentage of PSA+ DRE+ in the total population decreases from 2.45% at first visit to 0.71% at follow-up visits. The percentage of PSA+ DRE-, on the other hand, increases from 14.8% to 17.3%. All cancers diagnosed at first visits with both negative PSA and DRE were removed from the present calculations. In fact, 78.3% of men at first visit and 80.0% of men at follow-up visits had both normal PSA (≤ 3.0 ng/ml) and normal DRE.

It then becomes of interest to calculate the number of DREs and PSA measurements required to find one case of prostate cancer at first and follow-up visits in men who had both PSA and DRE at all visits. As can be seen in Table IIA, 27 (9.6%) of the 282 cancers diagnosed at all first visits (9,296) were found by DRE+ in PSA- patients. At follow-up visits (9,593), on the other hand, 5 (6.8%) of 74 cancers were diagnosed in PSA- and DRE+ patients. Thus, 344 DREs are needed to find one case of prostate cancer at first visit while 1,919 DREs are needed at follow-up visits (Fig. 6). On the other hand, 36 and 141 PSA measurements are needed at first and follow-up visits to diagnose one case of prostate cancer.

If only PSA above 3.0 ng/ml had been used to identify the population of men at high risk and selected for TRUS, 27 cancers (9.6%) would have been missed at first visit, and 5 (6.6%) cancers would have been missed at follow-up (Fig. 7). On the other hand, if only DRE had been used, 158 cancers (56.0%) would have

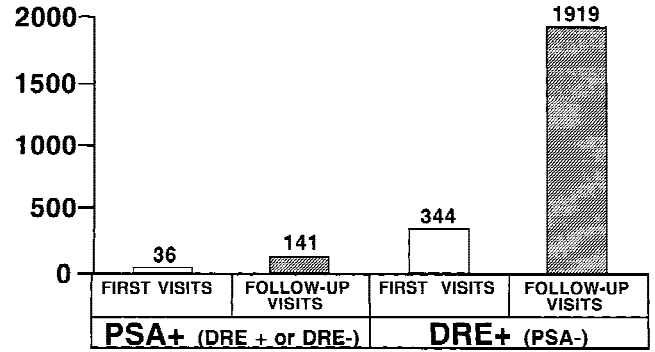


Fig. 6. Number of PSAs and DREs required to diagnose one prostate cancer at first and follow-up visits.

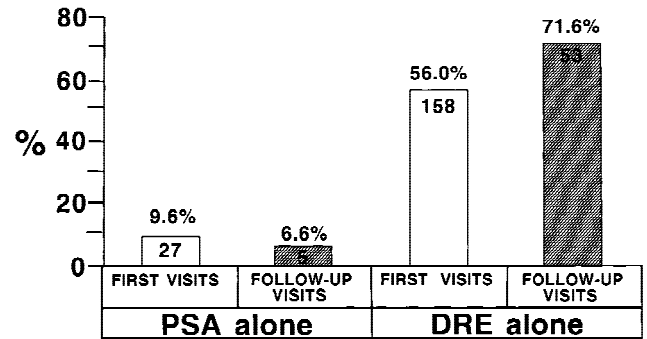


Fig. 7. Percentage of prostate cancer missed by PSA or DRE alone at first and follow-up visits.

been missed at first visit, and 53 (71.6%) at follow-up. Combining all visits, 32 cancers (9.0%) would have been missed using serum PSA alone, but 211 (59.3%) would have been missed using DRE alone for a 6.6-fold higher sensitivity of PSA compared to DRE (Fig. 8). On the other hand, when all data are combined at first visit, 90.4% (255 out of 282) of the cancers were diagnosed with PSA+ at first visit while 44.0% (124) were DRE+. At follow-up visits, 91.9% (68 of 74) of the cancers diagnosed were PSA+ while only 27.0% (20) were DRE+.

We found of interest to study a possible correlation between serum PSA and DRE at first visit and the finding of cancer at follow-up visits. As can be seen in Table III, of a total of 46,731 follow-up visits, the incidence of prostate cancer was 5.8-fold higher in men who had an abnormal PSA at first visit (0.29% compared with 1.65%) while the incidence was 2.1-fold higher in men who had DRE+ compared to DRE- at first visit (0.95% compared with 0.46%) (Fig. 9). Moreover, when PSA was normal at first visit, a positive DRE had an even lower influence in the incidence of prostate cancer at follow-up visits (0.30% vs. 0.46%) (Table III). It is also of interest to express the results as the percentage of men diagnosed with prostate cancer at follow-up visits according to PSA and DRE at first

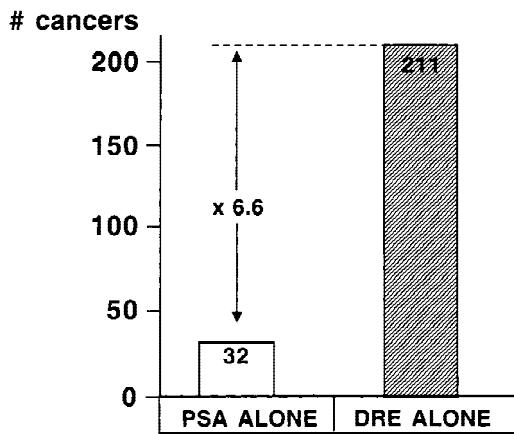


Fig. 8. Number of cancers missed by PSA alone and DRE alone (first and follow-up visits combined).

visit. With PSA⁺ and DRE⁺ at first visit, 2.78% of men were diagnosed with prostate cancer at follow-up visits compared to 1.53% with PSA⁺ DRE⁻ (Table III). On the other hand, in PSA⁻ DRE⁺ and PSA⁻ DRE⁻ subjects at first visit, prostate cancer was detected at the much lower rate of 0.46% and 0.30%, respectively.

The correlation between the concentration of serum PSA and the presence of detectable prostate cancer in invited men shows that prostate cancer was found in 36 of the 43 men (83.7%) who had serum PSA above 20.0 ng/ml (Table IA; Fig. 10A). The prevalence of prostate cancer decreased to 41.8%, 24.2%, 17.0%, 8.5%, and 6.8% in the groups with serum PSA ranges of 10.1–20 ng/ml, 7.1–10 ng/ml, 5.1–7.0 ng/ml, 4.1–5.0 ng/ml, and 3.1–4.0 ng/ml, respectively. When all subjects at first visit are considered, 41 of the 300 cancers (13.7%) diagnosed in men having a PSA at or above 3.0 ng/ml were found at PSA values between 3.1 and 4.0 ng/ml. At follow-up, the incidence showed much lower values ranging from 14.3% in those with serum PSA above 20 ng/ml compared with 83.7% for the same serum PSA value at first visit (Fig. 10B). On average, the incidence of prostate cancer for men with serum PSA above 3.0 ng/ml was 6.3-fold lower at follow-up than at initial visits (2.7% vs. 17.0% at first visit) (Fig. 2).

Because the goal of early diagnosis of prostate cancer is to find cancer at a curable stage, it is of major interest to observe that of the 206 cancers diagnosed among the invited men where clinical staging could be performed at first visit, 151 (73.3%) were at stage A/B, 42 (20.4%) were at stage C, and 13 (6.3%) were at stage D. At follow-up visits, of the 124 evaluable cancers, 110 (88.7%) were at stage B, 13 (10.5%) were at stage C and only 1 (0.8%) was at stage D. As can be seen in Table IVA, similar values were observed in noninvited men. Table IV and Figure 11 show the results obtained

when all data are pooled for a total of 337 cancers at first visit and 215 cancers at follow-up visits.

The most important finding is thus that only 2 out of 215 (1.0%) cancers diagnosed at follow-up visits were metastatic compared with 6.7% at first visit (Table IV, Fig. 11) Stage C₂ prostate cancers, on the other hand, 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 can be seen in Tables VA and VB, the age distribution of prostate cancers discovered at first and follow-up visits was similar in invited and noninvited men. The distribution of cancers at the various age groups for all men is indicated in Tables VA and VB in Figure 12. As illustrated in this figure, the prevalence (first visits) and incidence (follow-up visits) of prostate cancer markedly increased with age although the rate of prostate cancer detection was 6.2 lower at follow-up compared to first visits. At first visit, the percentage of men diagnosed with prostate cancer goes from 0.56% (1 in every 179 men) at the age of 50–54 years to 8.6% (1 in every 11.6 men) at the age of 75–79 years. At follow-up visits, however, the rate goes from 0.2% (1 in every 500 men or visits) at the age of 50–54 to 0.92% (1 in every 109 men or visits) at the age of 75–79 years.

As part of the assessment of feasibility, cost-effectiveness, and acceptability of detection of early stage prostate cancer, it is important to consider the number of TRUS and biopsies required to detect cancer in men having serum PSA above 3.0 ng/ml and/or positive DRE. In our study, in invited men (Table IIA), TRUS was done in 19.3% of men at first visit and biopsies in 50.8% of those undergoing echography, for a percentage of positive biopsies of 31.5%. At follow-up, on the other hand, 474 TRUS were performed for 6,542 visits (7.2% of visits). Biopsies were done in 39.5% of the 474 men having TRUS, and cancer was found in 21.4% of biopsies. Of the 11,970 visits, 1,524 (12.7%) TRUS and 720 biopsies were done, and 208 cancers were detected, for an overall 28.9% of biopsies positive for prostate cancer.

The particularly large size of the population studied, the random selection of a large proportion of the subjects as well as the similarity of the results obtained in a population of subjects presenting themselves for screening, provide the basis for a valid estimate of the costs associated with the detection of early stage prostate cancer in the general population. Despite the close similarity of the results, however, the cost calculations will be made with the population of men invited for screening. It is somewhat obvious that all three tech-

TABLE III. Incidence of Prostate Cancer Diagnosed at Follow-up Visits According to First Visit PSA and DRE Results (Invited and Uninvited Men Combined)

First visit PSA	First visit DRE											
	Negative			Positive			Not done			Total		
	Visits (#)	CaP (#)	CaP (%)	Visits (#)	CaP (#)	CaP (%)	Visits (#)	CaP (#)	CaP (%)	Visits (#)	CaP (#)	CaP (%)
Negative	34,627	104	0.30	1,741	8	0.46	4,546	7	0.15	40,914	119	0.29
Positive	5,299	81	1.53	468	13	2.78	50	2	4.00	5,817	96	1.65
Total	39,926	185	0.46	2,209	21	0.95	4,596	9	0.20	46,731	215	0.46

niques presently available for detection of prostate cancer, namely PSA, DRE, and TRUS, although permitting the diagnosis of the largest number of prostate cancers, cannot be used together as a first-line approach in the general population.

As clearly suggested in our previous report [14] and well demonstrated by the present update and extension of the previous data, the most cost-effective strategy is measurement of serum PSA as a first-line approach as recently concluded by Schröder and colleagues [13] in another large-scale screening study. In fact, PSA is free of subjective assessment, is a procedure easily acceptable by the general population, and requires minimal health professional personnel. Following this strategy, the cost for finding one case of prostate cancer at first visit is estimated at \$2,418.75 (Table VI) for one case of prostate cancer discovered.

Such costs include measurement of serum PSA in 36 men for every cancer diagnosed (at \$25.00 each, for a subtotal of \$900.00), followed by TRUS at \$200.00 per man in an average of 5.5 men found to have serum PSA above 3.0 ng/ml for a second subtotal of \$1,100.00. These 5.5 men will also have DRE at \$25.00 per subject for a subtotal of \$137.50 (Table VI). Because more than 50% of men having serum PSA above 3.0 ng/ml have benign prostatic hyperplasia, which accounts for the elevated serum PSA (predicted PSA), biopsies will be performed in an average of 2.25 men having high serum PSA ($2.25 \times \$125.00 = \281.25). The total cost for finding one case of prostate cancer using this approach is thus estimated at \$2,418.75.

If, as a second cost-effective approach (Table VI), DRE is added routinely at first visit as we have done in the present study, 32 instead of 36 men will need to be examined to find one case of prostate cancer. The costs of serum PSA are thus reduced from \$900.00 to \$800.00 while the costs of DRE increase from \$137.50 to \$800.00. The number of men at risk following the addition of DRE is increased to 6.5 men. The costs of TRUS are thus increased to \$1,300.00. It is also likely that the man having DRE+, PSA- will have a biopsy,

for a total number of 3.3 biopsies, thus increasing the cost to \$412.50, for a total of \$3,312.50. On the other hand, if PSA, DRE, and TRUS are all performed at first visit, we have previously estimated the costs for finding one cancer at \$6,125.00 [16].

If follow-up visits are performed annually, 172 serum PSA measurements ($\times \$25.00$) must be performed in order to find one case of prostate cancer, for a total cost for PSA of \$4,300.00 (Table VII). Among the 28 men at high risk, 10.3 will have DRE and TRUS and biopsy will be performed in an average of 3.9 men, for a total estimated cost of \$7,105.00 to identify one case of prostate cancer. If DRE is added to PSA at each follow-up visit, 163 men will need to be examined, thus increasing the costs of DRE from \$257.50 to \$4,075.00. The number of men considered at risk will increase from 28 to 29, while increasing the number of TRUS to 11.2 and the number of biopsies to 4.4, for a total estimated cost of \$10,940.00.

DISCUSSION

With 11,811 first visits and 46,751 follow-up annual visits extending up to 11 years, the present study

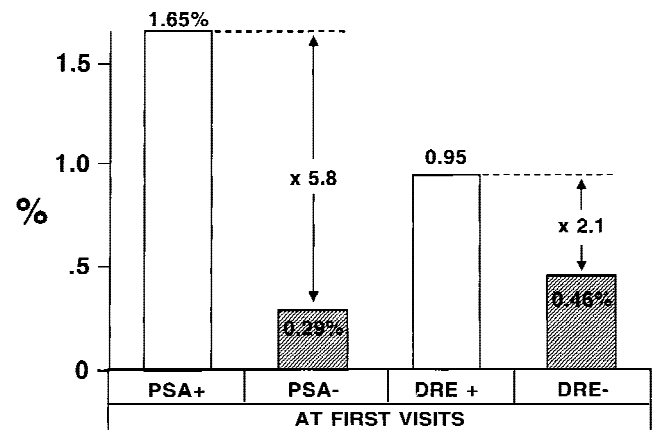


Fig. 9. Incidence of prostate cancers diagnosed at follow-up visits according to PSA and DRE at first visits.

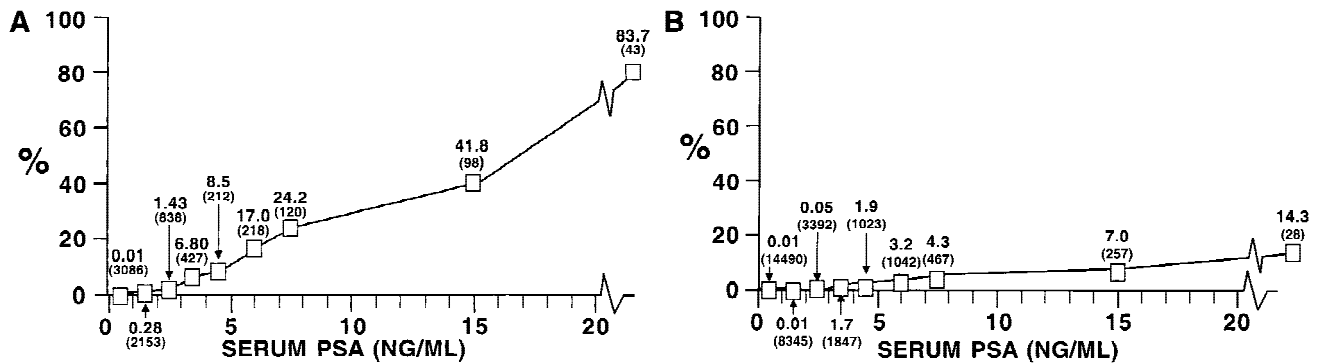


Fig. 10. Prevalence of prostate cancers diagnosed at first visits (A) and incidence of prostate cancer at follow-up visits (B) according to serum PSA.

TABLE IV. Correlation Between Positivity of Serum PSA and/or DRE and the Clinical Stage of Prostate Cancer Discovered at First and Follow-Up Visits

Clinical stage	First visit						Follow-up visits					
	Uninvited men		Invited men		Total		Uninvited men		Invited men		Total	
	(#)	(%)	(#)	(%)	(#)	(%)	(#)	(%)	(#)	(%)	(#)	(%)
A2			1	0.49	1	0.31	1	1.22			1	0.49
A3			2	0.97	2	0.61						
B0	5	4.13	15	7.28	20	6.12	17	20.73	21	16.94	38	18.45
B1	42	34.71	74	35.92	116	35.47	40	48.78	67	54.03	107	51.94
B2	36	29.75	59	28.64	95	29.05	16	19.51	22	17.74	38	18.45
C1	11	9.09	25	12.14	36	11.01	6	7.32	9	7.26	15	7.28
C2	18	14.88	17	8.25	35	10.70	1	1.22	4	3.23	5	2.43
D1	4	3.31	4	1.94	8	2.45						
D2	5	4.13	9	4.37	14	4.28	1	1.22	1	0.81	2	0.97
Not Staged	5		5		10		5		4		9	
Total	126		211		337		87		128		215	

clearly demonstrates the high level of efficacy of a low-cost strategy which can be easily, efficiently, and successfully applied in the general population for screening and diagnosis of prostate cancer at a localized and curable stage. In fact, as demonstrated before, and confirmed by the present study, the diagnosis of metastatic prostate cancer can practically be eliminated by population screening [17 and the present data], thus offering a unique opportunity to use curative therapies and successfully decrease death from prostate cancer. If every man simply follows the recommendations of the American Cancer Society [18] and of the American Urological Association [19], namely annual screening starting at the age of 50 years in the general population and at 40 years for men at high risk, the proportion of localized or potentially curable prostate cancer can be increased from approximately 40% in the absence of screening [20,21] to close to 100% [17 and present data]. As shown in this study,

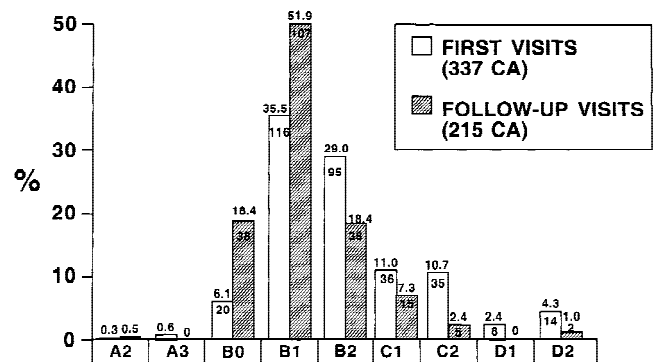


Fig. 11. Distribution of clinical stages of 337 and 215 (327 and 206 staged) prostate cancers diagnosed at first and follow-up screening visits, respectively. Data are expressed as percentage of total number of staged cancers in each group to facilitate comparison.

TABLE V. Age Distribution Versus Prevalence and Incidence of Prostate Cancers at First (A) and Follow-up (B) Visits

(A) First visit												
Age (years)	Not invited				Invited				Total			
	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)
45-49	734	15.90	0	0.00	230	3.20	0	0.00	964	8.16	0	0.00
50-54	934	20.23	6	0.64	1,370	19.04	7	0.51	2,304	19.51	13	0.56
55-59	834	18.07	17	2.04	1,923	26.73	31	1.61	2,757	23.34	48	1.74
60-64	875	18.96	32	3.66	1,572	21.85	46	2.93	2,447	20.72	78	3.19
65-69	707	15.32	32	4.53	1,247	17.33	67	5.37	1,954	16.54	99	5.07
70-74	378	8.19	24	6.35	618	8.59	40	6.47	996	8.43	64	6.43
75-79	145	3.14	14	9.66	214	2.97	17	7.94	359	3.04	31	8.64
80-84	9	0.19	1	11.11	21	0.29	3	14.29	30	0.25	4	13.33
Total	4,616	100.0	126	2.73	7,195	100.0	211	2.93	11,811	100.0	337	2.85

(B) Follow-up visits												
Age (years)	Not invited				Invited				Total			
	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)	Visits (#)	Total (%)	CaP (#)	CaP (%)
45-49	874	5.51	1	0.11	171	0.55	0	0.00	1,045	2.24	1	0.10
50-54	2,970	18.73	6	0.20	2,639	8.54	5	0.19	5,609	12.00	11	0.20
55-59	3,117	19.65	6	0.19	7,899	25.57	16	0.20	11,016	23.56	22	0.20
60-64	3,112	19.62	18	0.58	7,897	25.56	26	0.33	11,009	23.55	44	0.40
65-69	2,907	18.33	24	0.83	6,322	20.47	36	0.57	9,229	19.74	60	0.65
70-74	1,885	11.89	19	1.01	3,877	12.55	28	0.72	5,762	12.32	47	0.82
75-79	781	4.92	9	1.15	1,723	5.58	14	0.81	2,504	5.36	23	0.92
80-84	205	1.29	4	1.95	349	1.13	3	0.86	554	1.19	7	1.26
85-89	9	0.06	0	0.00	14	0.05	0	0.00	23	0.05	0	0.00
Total	15,860	100.0	87	0.55	30,891	100.0	128	0.41	46,751	100.0	215	0.46

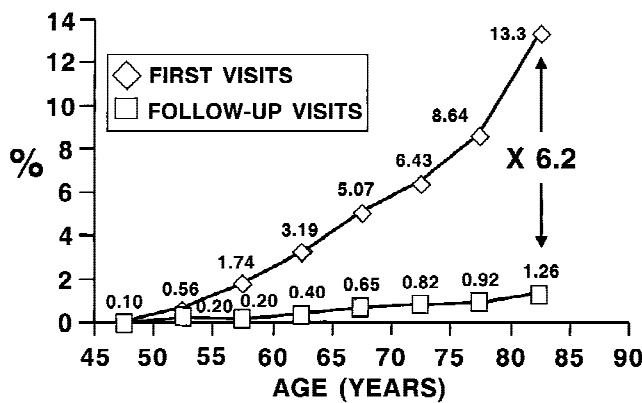


Fig. 12. Effect of age on the prevalence (first visits) and incidence (follow-up visits) of prostate cancer in 45- to 80-year-old men.

only 2 out of 215 cancers (1%) diagnosed at follow-up visits were metastatic, thus permitting up to 99% of patients being diagnosed at a localized stage and thus be candidates for curative therapy (C1 to D2). It is thus reasonable to suggest that if one starts screening at the age of 50 years, all subsequent visits should be equivalent to the follow-up visits of the present study, thus practically eliminating the diagnosis of metastatic prostate cancer.

Screening for prostate cancer is accepted as a health care policy by prestigious organizations, though others disagree [18,19,22]. Nobody can argue, however, that the high mortality and morbidity rates associated with prostate cancer very strongly support the need for screening [23-25]. Knowing that the possibility of a cure cannot be offered to patients diagnosed at the metastatic stage [2-4,26-28], it is logical that many recent studies have focused on the detection of prostate cancer confined to the prostate and still potentially

TABLE VI. Estimated Costs for Finding One Case of Prostate Cancer in a Randomly Selected Population of Men Aged Between 45 to 80 Years Using PSA Alone, PSA + DRE, or PSA + DRE + TRUS as First Approach at First Visit*

Strategy	No. of men	At high risk		Costs				Total
		No. of men	%	PSA (\$25.00)	DRE (\$25.00)	TRUS (\$200.00)	Biopsy-histopathology (\$125.00)	
A) PSA alone followed by DRE and TRUS	36	5.5	15.2	\$900.00	\$137.50	\$1,100.00	\$281.25	\$2,418.75
B) PSA + DRE followed by TRUS	32	6.5	20.2	\$800.00	\$800.00	\$1,300.00	\$412.50	\$3,312.50

*PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal ultrasonography.

TABLE VII. Estimated Costs for Finding One Prostate Cancer at Follow-up Annual Visits in a Randomly Selected Population of Men Aged 45 to 80 Years Using PSA Alone or PSA + DRE as First Approach at Follow-up*

Strategy	No. of men	At high risk		Costs				Total
		No. of men	%	PSA (\$25.00)	DRE (\$25.00)	TRUS (\$200.00)	Biopsy-histopathology (\$125.00)	
A) PSA alone followed by DRE and TRUS	172	28	16.1	\$4,300.00	\$257.50	\$2,060.00	\$487.50	\$7,105.00
B) PSA + DRE followed by TRUS	163	29	17.8	\$4,075.00	\$4,075.00	\$2,240.00	\$550.00	\$10,940.00

*PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal ultrasonography.

curable. A main issue in deciding the best screening strategy is the relative value of PSA and DRE.

In terms of feasibility and acceptability of screening in a general population of men aged 45 to 80 years and not screened before, an important finding of the present study is that 90.5% of the cancers detected at first visit were PSA positive (> 3.0 ng/ml) and could thus be detected by PSA alone while at follow-up visits, as many as 95% of the cancers detected were PSA positive and could thus be detected by PSA alone. At first visit in men who start screening after the age of 50 years, we still recommend DRE, since it can detect 9.6% of cancers in the presence of normal serum PSA. At follow-up visits, however, or if screening is started at the age of 50 years or before, serum PSA alone is recommended since DRE adds only 6.8% of cancers and a disproportionately large increase in costs. In fact, at follow-up visits, approximately 2,000 DREs are required to find one case of prostate cancer when PSA is normal. As done in the present study, transrectal echography of the prostate (TRUS) should be limited to patients having serum PSA above 3.0 ng/ml and/or with positive DRE [14,16] or showing an annual PSA increase greater than 20% when PSA was already above 3.0 ng at previous visit. In a screening study performed in 2,576 men, it was concluded that neither DRE nor TRUS are necessary in patients with PSA < 4

ng/ml [29]. Obviously, cancer is present in a significant proportion of men having a serum PSA at or below 3 ng/ml. The present data show, however, that with the strategy of screening used, these cancers are diagnosed when still being at a clinically localized stage and potentially curable.

PSA was first purified in 1979 [30] and identified in the blood in 1980 [31]. PSA measurement in blood [32] was then rapidly used to monitor prostate cancer [33]. In today's practice, the majority of prostate cancers are diagnosed by abnormal PSA in the presence of normal DRE [34,35]. However, while diagnosis with PSA permits to diagnose prostate cancer earlier [24], only 60% of the cancers detectable by PSA are organ-confined at radical prostatectomy [36]. When DRE is added to PSA, only 60% of the newly diagnosed tumors are clinically localized [34,35,37], thus indicating that the addition of DRE to PSA does not improve the stage of the cancers diagnosed. Such data presented in the recent review on PSA by Polascik and colleagues [34] indicate, as expected, that although DRE added to PSA can increase the number of prostate cancers detected compared to PSA alone, the percentage of cancers organ-confined or curable by surgery is lower by adding DRE, thus confirming the lower sensitivity of DRE to diagnose organ-confined prostate cancer.

The present study shows that in a previously un-

screened population, 90.4% of the cancers could be identified at first visit by measurement of serum PSA alone, whereas only 44% of cancers could be identified by DRE alone. In fact, of the 282 cancers found at first visits in men with serum PSA above 3.0 ng/ml, only 124 were DRE⁺. On the other hand, adding DRE to serum PSA at first visit improved detection by adding 27 cancers (9.6%), while the addition of serum PSA to DRE could add 158 cancers (56.0%) at first visit. In summary, 105% more cancers could be identified by serum PSA than with DRE at first visit. In a study of 6,630 men invited for screening aged 50 years or more [38], 45% of the cancers were detected by PSA and not by DRE while 18% were detected by DRE and not by PSA, taking 4.0 ng/ml as upper limit of normal. The addition of PSA to DRE alone increased by 81% the number of cancers detected.

Previous studies reached similar conclusions about the relatively low sensitivity of DRE [39–41]. In the American Cancer Society-National Prostate Cancer Detection Project (ACS-NPCDP) study, the sensitivity of DRE was 41.1% [42], compared to 44% in the present study. Using DRE alone for screening, only one-third of patients are diagnosed with organ-confined disease [43–46]. In fact, as mentioned above, screening with DRE alone has not been shown to improve the proportion of organ-confined disease at diagnosis [44,45,47,48] or to increase the percentage of localized stages compared to nonscreened population [49,50].

The advantages of PSA over DRE become even more striking at follow-up annual visits when, most importantly, only 5 of the 74 cancers diagnosed at follow-up visits were detected by adding DRE to PSA, thus indicating the particularly low sensitivity of DRE at follow-up visits. Abnormal DRE at first visit, on the other hand, had no influence on prostate cancer diagnosis at follow-up visits in men with normal PSA. In the Rotterdam section of the ERSPC screening study, 17.3% of cancers would have been missed by PSA alone using a cut-off value of 4.0 ng/ml [13]. Since 35 cancers were detected at a PSA value of 3.0 to 3.9 ng/ml, only 47 cancers (9.9%) would have been missed if DRE had not been used at first visit using 3.0 instead of 4.0 ng/ml PSA as upper limit of normal. Such data are thus almost superimposable to our study. In the Swedish screening study, similar conclusions were reached before the start of the study and only PSA was used for first-line screening [51]. The ERSPC has decided that the yield of cancer was too low to justify DRE, which was eliminated from the screening procedure in 1997. In the less than 3.0 ng/ml PSA range, at first visit, Schröder and colleagues [13] have found that 135 DREs are required to find one cancer. As concluded also in the European study, “detection rates are dramatically lower with DRE alone

and strongly depend on PSA levels” [13]. In the Swedish study, men having PSA < 3.0 ng/ml at first visit were not further evaluated [52].

In agreement with the present data showing a lead time of 6.2 years, it has been estimated in other studies that screening with PSA provides a lead time of about 5–6 years [17,53]. Using an efficient strategy of screening with PSA, such a window of a few years permits detection of prostate cancer before it migrates to the bones and becomes noncurable.

A recent study offers very important support for the unique role of PSA in prostate cancer diagnosis: 75% of prostate cancers that were diagnosed during the four years following first PSA measurement had abnormal PSA at start of study [53]. Most important, men having a serum PSA between 3.01 and 4.0 ng/ml had a 8.6-fold increased risk of being diagnosed with prostate cancer, while men having a serum PSA between 4.01 and 10.0 ng/ml had a 22.2-fold increased risk compared to those having serum PSA below 1.0 ng/ml. These risk values are much higher than any other risk factor so far described for prostate cancer [54] or any other type of cancer. In agreement with those data, the present study shows that men who had an abnormal PSA (3.0 ng/ml) and were not diagnosed with prostate cancer at first visit had a 6-fold higher risk of being diagnosed with prostate cancer at follow-up visits than those with normal PSA at first visit.

It is also important to note that the present study confirms that screening does not detect an important proportion of small cancers [16,55]. Following surgical staging, Catalona and colleagues [24] found microscopically focal and well-differentiated cancer in 2.5% (1/40) of patients referred to the clinic, 2.9% of men screened for the first time and 7.8% of men at follow-up screening. It is important to mention that all cancers detected by the present approach have an average diameter larger than 0.7 cm (0.33 cm³) [56] and thus cannot be considered cancers of no significance to the future health and life of the patients, unlike tumors with an average diameter less than 0.7 cm, which could be regarded as less aggressive [57]. Of the autopsy cancers and those diagnosed in a series of cystoprostatectomies for pathological conditions of the bladder [58–60], only 3% had extracapsular extension and nondemonstrated positive surgical margins, seminal vesicle invasion, or positive lymph nodes [reviewed in 61].

Clearly, the three techniques presently available for the diagnosis of prostate cancer are simply not sensitive enough to discover small cancers such as stage A₁ that are incidental findings at transurethral resection of the prostate that primarily samples the transition zone, where only 20% of the cancers originate [62–64]. The lower limit of 0.3 cc in the volume of the cancers

identifiable by the present detection or screening techniques results in the diagnosis of relatively large cancers [57], thus eliminating the argument that detection or screening discovers cancers of no significance to the health or even the life of a patient having at least a 5- to 10-year life expectancy. A strong argument supporting these findings is provided by the observation that 75% of men who developed prostate cancer with an elevated PSA died from this cancer [53].

In the Rotterdam arm of the ERSPC, 9,776 men aged 55 to 76 years of age had PSA, DRE and TRUS, 2,262 men had biopsies, and 474 prostate cancers were found for an incidence of prostate cancer of 4.8% [61]. The rate of positive biopsies was 21.0%. In the present study, the percentage of positive biopsies was 31.5% and 21.5% at first and follow-up visits, respectively. The overall sensitivity and specificity of the proposed strategy compares favorably with screening for breast, colon, uterine, and lung cancer [65]. The positive predictive value of the simple PSA procedure is higher or at least comparable to that reported for mammography used for detection of breast cancer estimated at 10–25% [66,67]. Prostate cancer can be diagnosed by the present approach at an estimated cost of \$2,420.00 (CDN) per cancer at first visit [16], a value well below the costs estimated at \$10,000 and \$30,000 for one case of cervical and breast cancer, respectively.

Prostate cancer has resulted in high individual and social costs [68–70]. The positive economic impact of such an approach on health care costs has been previously discussed [16,71–73]. The calculations then performed leave little doubt that this strategy based on efficient screening could play a key role in a successful fight against prostate cancer while decreasing the costs for the health care system and society [74,75].

As mentioned above, no curative therapy exists for advanced prostate cancer. Unfortunately, such a cure is unlikely to be available in the foreseeable future, thus illustrating the absolute requirement to diagnose and treat prostate cancer at a localized stage. Reports from cancer registries in all the states followed by the SEER program of the NCI indicate that prostate cancer incidence rates have begun to fall [76]. In Olmsted County, a 22% decline in prostate cancer death has been observed between 1980 and 1997 after PSA screening was introduced [77]. Part of the success could be attributed to the early treatment applied at the Mayo Clinic, a major treatment site in Olmsted County. This finding parallels a 6.3% decrease in prostate cancer death nationwide in the United States [78]. In Canada, the death rate from prostate cancer has decreased by 9.6% between 1992 and 1996, while in the province of Quebec, prostate cancer death has decreased by 23% [79]. It is reasonable to assume that the recently observed decrease in deaths from prostate

cancer is due to earlier diagnosis with serum PSA [14,17,80] and transrectal echography of the prostate [81] coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy, and endocrine therapy [8,56,82–86].

Although screening of prostate cancer is a controversial issue, it remains that the diagnosis of prostate cancer at a localized stage is the only foreseeable possibility for reducing the high death rate from this disease. In fact, the significant progress recently achieved in the screening procedures [14,16,50,83,87,88] has made detection of localized prostate cancer a realistic objective. Moreover, recent data provide extremely convincing evidence for the need to detect and treat prostate cancer at a localized stage [8–10,53,77,89–94]. It seems reasonable to suggest that the use of the presently available technology for diagnostic and treatment of localized prostate cancer could lead to a significant decrease in the death rate from prostate cancer. In fact, the data of our randomized screening study have shown a 69% decrease in prostate cancer death in the period 1988–1996 in the group of men screened compared to a randomized control group of men followed by standard medical practice [94].

REFERENCES

1. Labrie F, Dupont A, Bélanger A. Complete androgen blockade for the treatment of prostate cancer. In: de Vita VT, Hellman S, Rosenberg SA, editors. *Important advances in oncology*. Philadelphia: J.B. Lippincott; 1985. p 193–217.
2. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, Blumenstein DA, Davis MA, Goodman PJ. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989;321:419–424.
3. Denis L, Carmelro de Moura J, Bono A, Sylvester R, Whelan P, Newling D, Depauw M. Goserelin acetate and flutamide vs bilateral orchiectomy: a phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. *Urology* 1993;42:119–129.
4. Dijkman GA, Janknegt RA, Dereijke TM, Debryne FMJ. Long-term efficacy and safety of nilutamide plus castration in advanced prostate-cancer, and the significance of early prostate-specific antigen normalization. *J Urol* 1997;158:160–163.
5. Caubet JF, Tosteson TD, Dong EW, Naylon EM, Whiting GW, Ernstoff MS, Ross SD. Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens. *Urology* 1997;49:71–78.
6. Bennett CL, Tosteson TD, Schmitt B, Weinberg PD, Ernstoff MS, Ross SD. Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: a meta-analysis of nine published randomized controlled trials and 4,128 patients using Flutamide. *Prostate Cancer Prostatic Dis* 1999;2:4–8.
7. Landis SH, Murray T, Bolden S, Wingo PA. *Cancer Statistics, 1999*. *CA Cancer J Clin* 1999;49:8–31.
8. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.

9. Pilepich MV, Caplan R, Byhardt RW, Lawton CA, Gallagher MJ, Mesic JB, Hanks GE, Coughlin CT, Porter A, Shipley WU, Grignon D. Phase III trial of androgen suppression using Goserelin in unfavorable prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group protocol 85-31. *J Clin Oncol* 1997;15:1013-1021.
10. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Br J Urol* 1997;79:235-246.
11. Labrie F. Prostate cancer: a disease controlled by androgens. In: Pinchera A, Bertega X, Binder C, Fischer J, Braverman L, editors. *Textbook of clinical endocrinology*. Milan: McGraw-Hill Libreria Italia Srl; 1999, in press.
12. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *New J Engl Med* 1999;341:1781-1788.
13. Schröder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemaeker R, Rietbergen J, Kranse R. Evaluation of the digital rectal examination as a screening test for prostate cancer. *J Natl Cancer Inst* 1998;90:1817-1823.
14. Labrie F, Dupont A, Suburu R, Cusan L, Tremblay M, Gomez J, Lemond J. Serum prostatic specific antigen (PSA) as prescreening test for prostate cancer. *J Urol* 1992;147:846-851.
15. Lee F, Littrup PJ, Loft-Christensen L, Kelly Jr BS, McHugh TA, Siders DB, Mitchell AE, Newby JE. Predicted prostate specific antigen results using transrectal ultrasound gland volume. Differentiation of benign prostatic hyperplasia and prostate cancer. *Cancer* 1992;70 (suppl.):211-220.
16. Labrie F, Dupont A, Suburu R, Cusan L, Gomez JL, Koutsilieris M, Diamond P, Emond J, Lemay M, Têtu B. Optimized strategy for detection of early stage, curable prostate cancer: role of prescreening with prostatic-specific antigen. *Clin Invest Med* 1993;16:425-439.
17. Labrie F, Candas B, Cusan L, Gomez JL, Diamond P, Suburu R, Lemay M. Diagnosis of advanced or noncurable prostate cancer can be practically eliminated by prostate-specific antigen. *Urology* 1996;47:212-217.
18. American Cancer Society. *Guidelines for the cancer-related checkup: an update*. Atlanta (GA): American Cancer Society 1993;
19. American Urological Association. *Executive Committee report*. Baltimore (MD): American Urological Association 1992;January.
20. Murphy GP, Natarajan N, Pontes JE, Schmitz RL, Smart CR, Schmidt JD, Mettlin C. The national survey of prostate cancer in the United States by the American College of Surgeons. *J Urol* 1982;127:928-934.
21. Schmidt JD, Mettlin CJ, Natarajan N, Peace BB, Beart Jr RW, Winchester DP, Murphy GP. Trends in patterns of care for prostatic cancer, 1974-1983: results of surveys by the American College of Surgeons. *J Urol* 1986;136:416-421.
22. Adami HO, Baron JA, Rothman KJ. Ethics of a prostate cancer screening trial. *Lancet* 1994;343:958-960.
23. Andriole GL, Catalona WJ. Using PSA to screen for prostate cancer. *Urol Clinics North Amer* 1993;20:647-651.
24. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. *JAMA* 1993;270:948-954.
25. Slawin KM, Ohori M, Dilliogluligil O, Scardino PT. Screening for prostate cancer: an analysis of the early experience. *CA Cancer J Clin* 1995;45:134-147.
26. Labrie F, Dupont A, Bélanger A, Cusan L, Lacourcière Y, Monfette G, Laberge JG, Emond J, Fazekas AT, Raynaud JP, Husson JM. New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. *Clin Invest Med* 1982;5:267-275.
27. Labrie F. Endocrine therapy for prostate cancer. *Endocrinol Metab Clin North Am* 1991;20:845-872.
28. Janknegt RA, Abbou CC, Bartoletti R, Bernstein-Hahn L, Bracken B, Brisset JM, Da Silva FC, Chisholm G, Crawford ED, Debruyne FM, et al. Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 1993;149:77-83.
29. Martin E, Lujan M, Sanchez E, Herrero A, Paez A, Berenguer A. Final results of a screening campaign for prostate cancer. *Eur Urol* 1999;35:26-31.
30. Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of human prostate specific antigen. *Invest Urol* 1979;17:159-163.
31. Papsidero LD, Wang MC, Valenzuela LA, Murphy GP, Chu TM. A prostate antigen in sera of prostatic cancer patients. *Cancer Res* 1980;40:2428-32.
32. Kuriyama M, Wang MC, Papsidero LD, Killian CS, Chu TM. Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. *Cancer Res* 1980;40:4658-4662.
33. Kuriyama M, Wang MC, Lee CL, Papsidero LD, Killian CS, Inaji H, Nishiura T, Murphy GP, Chu TM. Use of human prostate-specific antigen in monitoring prostate cancer. *Cancer Res* 1981;41:3874-3876.
34. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery—what we have learned and where we are going [In Process Citation]. *J Urol* 1999;162:293-306.
35. Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. *Urol Clin North Am* 1997;24:395-406.
36. Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, Scardino PT, Pearson JD. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update [see comments] [published erratum appears in *JAMA* 1997;278(2):118] *JAMA* 1997;277:1445-1451.
37. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996 [see comments]. *CA Cancer J Clin* 1996;46:5-27.
38. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151:1283-1290.
39. Lee F, Littrup PJ, Torp-Pedersen ST, Mettlin C, McHugh TA, Gray JM, Kumasaka GH, McLeary RD. Prostate cancer: comparison of transrectal US and digital rectal examination for screening. *Radiology* 1988;168:389-394.
40. Hodge KK, McNeal JE, Terris MF, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J Urol* 1989;142:71-75.
41. Nesbitt JA, Drago JR, Badalament RA. Transrectal ultrasonography. Early experience with use as prostate cancer detection tool. *Urology* 1989;34:120-122.
42. Mettlin C, Murphy GP, Ray P, Shanberg A, Toi A, Chesley A, Babaian R, Badalament R, Kane RA, Lee F. American Cancer Society National Prostate Cancer Detection Project: results from multiple examinations by transrectal ultrasound, digital rectal examination and prostate-specific antigen. *Cancer* 1993;71 (Suppl):891-898.
43. Thompson IM, Ernst JJ, Gangai MP, Spence CR. Adenocarci-

- noma of the prostate: results of routine urological screening. *J Urol* 1984;132:690–692.
44. Thompson IM, Rounder JB, Teague JL, Peek M, Spence CR. Impact of routine screening for adenocarcinoma of the prostate on stage distribution. *J Urol* 1987;137:424–426.
 45. Catalona WJ, Bigg SW. Nerve-sparing radical prostatectomy: evaluation of results after 250 patients. *J Urol* 1987;143:538–544.
 46. Babaian RJ, Mettlin C, Kane R, Murphy GP, Lee F, Drago JR, Chesley A. The relationship of prostate-specific antigen to digital rectal examination and transrectal ultrasonography. Findings of the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1992;69:1195–2000.
 47. Catalona WJ. Re: Serum prostate specific antigen as prescreening test for prostate cancer [letter; comment]. *J Urol* 1993;149:1149–1150.
 48. Gerber GS, Thompson IM, Thisted R, Chodak GW. Disease-specific survival following routine prostate cancer screening by digital rectal examination. *JAMA* 1993;269:61–64.
 49. Chodak GW, Schoenberg HW. Early detection of prostate cancer by routine screening. *JAMA* 1984;252:3261–3264.
 50. Mettlin C. Early detection of prostate cancer following repeated examinations by multiple modalities: results of the American Cancer Society National Prostate Cancer Detection Project. *Clin Invest Med* 1993;16:440–447.
 51. Lodding P, Aus G, Bergdahl S, Frosing R, Lilja H, Pihl CG, Hugosson J. Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng./ml. Prostate specific antigen [see comments]. *J Urol* 1998;159:899–903.
 52. Hugosson J. What is the optimal strategy for early detection of prostate cancer? In: Kurth K, Mickisch G, Schröder F, editors. *Renal, bladder and prostate cancer: an update*. New York and London: Parthenon Publishing; 1998. p 103–107.
 53. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995;273:289–294.
 54. Narod S, Dupont A, Cusan L, Diamond P, Gomez JL, Suburu RE, Labrie F. The impact of family history on early detection of prostate cancer. *Nat Med* 1995;1:99–101.
 55. Catalona WJ. Management of cancer of the prostate. *N Engl J Med* 1994;331:996–1004.
 56. Labrie F, Cusan L, Gomez JL, Diamond P, Suburu R, Lemay M, Tetu B, Fradet Y, Candas B. Down-staging of early stage prostate cancer before radical prostatectomy: the first randomized trial of neoadjuvant combination therapy with flutamide and a luteinizing hormone-releasing hormone agonist. *Urology* 1994;44:29–37.
 57. Bostwick DG. Anatomy of the prostate: histopathology of cancer and BPH. Seventh International Symposium: transrectal ultrasound in the diagnosis and management of BPH and prostate cancer. Chicago: American Institute of Ultrasound and Medicine, 1992. p 1–13.
 58. Franks LM. Latent carcinoma of the prostate. *J Pathol Bacteriol* 1954;68:603–616.
 59. Montie JE, Wood Jr DP, Pontes JE, Boyett JM, Levin HS. Adenocarcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. *Cancer* 1989;63:381–385.
 60. Kabalin JN, McNeal JE, Price HM, Freiha FS, Stamey TA. Unsuspected adenocarcinoma of the prostate in patients undergoing cystoprostatectomy for other causes: incidence, histology and morphometric observations. *J Urol* 1989;141:1091–1094.
 61. Reitbergen JB, Hoedemaeker RF, Kruger AE, Kirkels WJ, Schroder FH. The changing pattern of prostate cancer at the time of diagnosis: characteristics of screen detected prostate cancer in a population-based screening study. *J Urol* 1999;161:1192–1198.
 62. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909–916.
 63. McNeal JE, Bostwick DG, Kindrachuk RA, Redwine EA, Freiha FS, Stamey TA. Patterns of progression in prostate cancer. *Lancet* 1986;1:60–63.
 64. McNeal JE. Normal histology of the prostate. *Am J Surg Pathol* 1988;12:896–897.
 65. Hulka BS. Cancer screening: degrees of proof and practical application. *Cancer* 1988;62:776–780.
 66. Moskowitz M. Cost-benefit determinations in screening mammography. *Cancer* 1987;60 Suppl.:1680–1683.
 67. Kinne DW, Kopans DB. Physical examination and mammography in the diagnosis of breast disease. In: Harris JR, editor. *Breast disease*. Philadelphia: J.B. Lippincott; 1987. p 54–86.
 68. Ellison LF, Stokes J, Gibbons L, Lindsay J, Levy I, Morrison H. Monograph series on aging-related diseases. X. Prostate cancer. *Chronic Dis Can* 1998;19:1–18.
 69. Litwin MS, Pasta DJ, Stoddard ML, Henning JM, Carroll PR. Epidemiological trends and financial outcomes in radical prostatectomy among Medicare beneficiaries, 1991 to 1993 [published erratum appears in *J Urol* 1998;160(6 Pt 1):2164]. *J Urol* 1998;160:445–448.
 70. Borre M, Nerstrom B, Overgaard J. The dilemma of prostate cancer—a growing human and economic burden irrespective of treatment strategies. *Acta Oncol* 1997;36:681–687.
 71. Labrie F, Dupont A, Cusan L, Gomez JL, Diamond P, Koutsilieris M, Suburu R, Fradet Y, Lemay M, Têtu B, Emond J, Candas B. Downstaging of localized prostate cancer by neoadjuvant therapy with flutamide and lupon: the first controlled and randomized trial. *Clin Invest Med* 1993;16:499–509.
 72. Littrup PJ, Kane RA, Mettlin CJ, Murphy GP, Lee F, Toi A, Badalament R, Babaian R. Cost-effective prostate-cancer detection: reduction of low-field biopsies. *Cancer* 1994;74:3146–3158.
 73. Aus G, Hugosson J, Norlén L. Long-term survival and mortality in prostate cancer treated with noncurative intent. *J Urol* 1995;154:460–465.
 74. Labrie F. Intracrinology and cancer therapy. *Science Watch* 1994;5:3–8.
 75. Labrie F, Cusan L, Gomez JL, Diamond P, Candas B. Combination of screening and preoperative endocrine therapy: the potential for an important decrease in prostate cancer mortality. *J Clin Endocrinol Metab* 1995;80:2002–2013.
 76. Merrill RM, Potosky AL, Feuer EJ. Changing trends in U.S. prostate cancer incidence rates. *J Natl Cancer Inst* 1996;88:1683–1685.
 77. Roberts RO, Bergstralh EJ, Katusic SK, Lieber MM, Jacobsen SJ. Decline in prostate cancer mortality from 1980 to 1997, and an update on incidence trends in Olmsted County, Minnesota. *J Urol* 1999;161:529–533.
 78. Hoeksema MJ, Law C. Cancer mortality rates fall: a turning point for the nation. *J Natl Cancer Inst* 1996;88:1706–1707.
 79. Meyer F, Moore L, Bairati I, Fradet Y. Downward trend in prostate cancer mortality in Quebec and Canada. *J Urol* 1999;161:1189–1191.
 80. Killian CS, Emrich LJ, Vargas FP, Yang N, Wang MC, Priore RL, Murphy GP, Chu TM. Relative reliability of five serially measured markers for prognosis of progression in prostate cancer. *J Natl Cancer Inst* 1986;76:179–185.
 81. Lee F, Torp-Pedersen ST, Siders DB, Littrup PJ, McLeary RD. Transrectal ultrasound in the diagnosis and staging of prostatic carcinoma. *Radiology* 1989;170:609–615.
 82. Hanks GE, Asbell SO, Krall JM, Perez CA, Doggett S, Rubin P, Sause WT, Pilepich MV. Outcome for lymph node dissection negative T-1b, T-2 (A-2,B) prostate cancer treated with external beam radiation therapy in RTOG 77-06. *Int J Radiat Oncol Biol Phys* 1991;21:1099–1103.

83. Cooner WH, Mosley BR, Rutherford Jr CL, Beard JH, Pond HS, Terry WJ, Igel TC, Kidd DD. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate-specific antigen. *Urology* 1990;143:1146-1154.
84. Laverdiere J, Gomez JL, Cusan L, Suburu R, Diamond P, Lemay M, Candas B, Fortin A, Labrie F. Beneficial effect of combination therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;37:247-252.
85. Pilepich MV, Krall JM, Al-Saffaf M, John MJ, Dogget RL, Sause WT, Lawton CA, Abrams RA, Rotman M, Rubin P, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. *Urology* 1995;45:616-623.
86. Blasko JC, Ragde H, Luse RW, Sylvester JE, Cavanagh W, Grimm PD. Should brachytherapy be considered a therapeutic option in localized prostate cancer? *Urol Clin North Am* 1996;23:633-649.
87. Lee F, Torp-Pedersen ST, Siders DB. Use of transrectal ultrasound in diagnosis, guided biopsy, staging, and screening of prostate cancer. *Urology* 1989;33 (suppl):7-12.
88. Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, Petros JA, Andriole GL. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *New Engl J Med* 1991;324:1156-1161.
89. Aus G, Bergdahl S, Hugosson J, Lodding P, Norlén L. Influence of benign prostatic hyperplasia, testosterone and age on serum levels of prostate-specific antigen. *Scand J Urol Nephrol* 1994;28:379-384.
90. Hugosson J, Aus G, Bergdahl C, Bergdahl S. Prostate cancer mortality in patients surviving more than 10 years after diagnosis. *J Urol* 1995;154:2115-2117.
91. Krongrad A, Lai H, Lamm SH, Lai S. Mortality in prostate cancer. *J Urol* 1996;156:1084-1091.
92. Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet* 1997;349:906-910.
93. Brasso K, Friis S, Juel K, Jorgensen T, Iversen P. Mortality of patients with clinically localized prostate cancer treated with observation for 10 years or longer: a population based registry study. *J Urol* 1999;161:524-528.
94. Labrie F, Candas B, Dupont A, Cusan L, Gomez JL, Suburu RE, Lévesque J, Diamond P, Bélanger A. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate* 1999;38:83-91.