

Screening Decreases Prostate Cancer Death: First Analysis of the 1988 Quebec Prospective Randomized Controlled Trial

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BACKGROUND. The 46,193 men aged 45 to 80 years registered in the electoral roll of Quebec City and its Metropolitan area were randomized in November 1988 between screening and no screening in a study aimed of assessing the impact of prostate cancer screening on cause-specific death.

METHODS. At first visit, screening included measurement of serum prostatic specific antigen (PSA) using 3.0 ng/ml as upper limit of normal and a digital rectal examination (DRE). Transrectal echography of the prostate (TRUS) was performed only if PSA and/or DRE was abnormal and biopsy was then done, only if PSA was above the predicted PSA value. At follow-up visits, PSA alone was used as prescreening.

RESULTS. 137 deaths due to prostate cancer occurred between 1989 and 1996, inclusively, in the 38,056 unscreened men while only 5 deaths were observed among the 8,137 screened individuals. The prostate cancer death rates during the eight-year period were 48.7 and 15 per 100,000 man-years in the unscreened and screened groups, respectively, for a 3.25 odds ratio in favor of screening and early treatment ($P < 0.01$).

CONCLUSIONS. If PSA screening is started at the age of 50 years (or 45 years in the higher risk population), annual or biannual PSA alone is highly efficient to identify the men who are at high risk of having prostate cancer. Coupled with treatment of localized disease, this approach demonstrates, for the first time, that early diagnosis and treatment permits a dramatic decrease in deaths from prostate cancer. *Prostate 38:83–91, 1999.*

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KEY WORDS: prostate cancer screening; PSA; transrectal ultrasonography; early treatment of prostate cancer; combined androgen blockade

INTRODUCTION

Prostate cancer is the second cause of cancer death in men in the Western world and its medicosocial impact is comparable to that of breast cancer in women. In fact, it is predicted that 39,200 men will die from prostate cancer in the United States in 1998 while only 11% more deaths, namely 43,500, are predicted for breast cancer during the same time period [1]. Despite progress in the treatment of advanced or metastatic prostate cancer [2–7], it is well recognized that the only possibility of a significant reduction in prostate

cancer death is treatment of localized disease. It is reasonable to assume that the recently observed decrease in deaths from prostate cancer [8] is due to earlier diagnosis with serum PSA [9–11] and transrec-

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tal echography of the prostate [12] coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy and endocrine therapy [13–19].

Proof of the potential benefits of screening and treatment of localized prostate cancer can only be obtained from prospective and randomized studies comparing 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 goals of the Laval University Prostate Cancer Screening Program (LUPCSP) started in November 1988 were the following:

1. Evaluate the efficacy of the available screening tests [10,11]
2. Optimize the use of the screening tests in the general population for detection of localized disease [11]
3. Estimate the cost of screening at first [10] and follow-up visits
4. Assess the impact of screening on prostate cancer mortality
5. Predict the life years gained by early diagnosis and treatment.

While the data pertaining to the first three objectives have already been obtained [10,11], the present report describes the most awaited results, namely the effect of screening on the incidence of prostate cancer death.

PATIENTS AND METHODS

The prospective randomized and controlled prostate cancer detection study included all the men aged from 45 to 80 years registered in the 1985 electoral rolls of the 9 constituencies of the metropolitan area of Québec City who were traceable in the Quebec provincial health registries in November 1988, at the start of the study. The 46,193 men were randomly allocated either to the group invited by letter for annual screening or to the control unscreened group at a ratio of 2:1 in favor of screening. The unequal group size was intended to compensate for the expected lower attendance rate mainly related to the lack of awareness regarding prostate cancer in the target population. The age and the constituency (i.e. the location) were used for stratification to balance possible differences in the sociodemographic factors between groups. Men in the control unscreened group were followed according to current medical practice. To minimize bias, no public announcement was made through the media. Men with a diagnosis of prostate cancer before November 15, 1988 were not eligible. Men who had previous screening and were referred to our clinic for consultation were not eligible. Death from prostate cancer

was the primary end-point. The study was approved by the Institutional review board of Laval University.

At first visit, participants had measurement of serum prostatic specific antigen (PSA) and underwent digital rectal examination (DRE). These two tests were performed independently. Transrectal ultrasonography of the prostate (TRUS) was performed only in cases with positive PSA (> 3.0 ng/ml) and/or abnormal DRE, except for the first 1002 men who all had the three procedures, as previously described [10,11].

At follow-up visits, TRUS was done if serum PSA had increased above 3.0 ng for the first time. In cases where PSA was already above 3.0 ng/ml at previous visit, TRUS was performed only if PSA had increased by more than 20% compared with the value measured one year earlier (the interassay coefficient of variation [c.v.] being 9.6%, 10% was accepted as a possible increase attributable to the interassay [c.v.]) or if the measured PSA (mPSA) had increased by 10% or more over the predicted PSA (prPSA) calculated at a previous visit (prostate volume $\times 0.12$) [20,21]. Serum samples were taken before DRE and TRUS for measurement of PSA by immunoradiometric assay (Tandem-R PSA, Hybritech Incorporated).

TRUS-guided biopsies were performed with the automatic Biopsy system (Bard Urological, Covington, GA) and an 18-gauge needle as described [10,20,22]. TRUS-guided biopsy was performed if an hypoechoic image was seen, if the mPSA was above prPSA or if DRE was abnormal. In cases of negative biopsies at previous visits with mPSA above prPSA, the frequency of follow-up biopsies was at the judgment of the radiologist and clinician. Six sextant biopsies were performed only in 149 men with normal TRUS evaluation because of either abnormal DRE or mPSA greater than pr PSA.

Evaluation of the impact of screening is based upon comparison of the incidence rate of death from prostate cancer between the two groups. The information on cause-specific death was obtained from the Death Registry of the Health Department of the Province of Quebec. This analysis covers the period from January 1, 1989 to December 31, 1996. The annual incidence rate of cause-specific mortality is reported as the number of deaths per 100,000 person-years. For the men screened, the duration of exposure to the intervention is calculated from the date of their first visit at the screening center up to the end of 1996, regardless of their compliance to follow-up screening visits and of the treatment received if cancer was diagnosed. Analysis is thus made on an intent-to-treat basis from the time of enrollment. For those in the control unscreened group, the period of exposure is calculated from the date of initiation of the trial, i.e. November 15, 1988. Duration of exposure to screening or to cur-

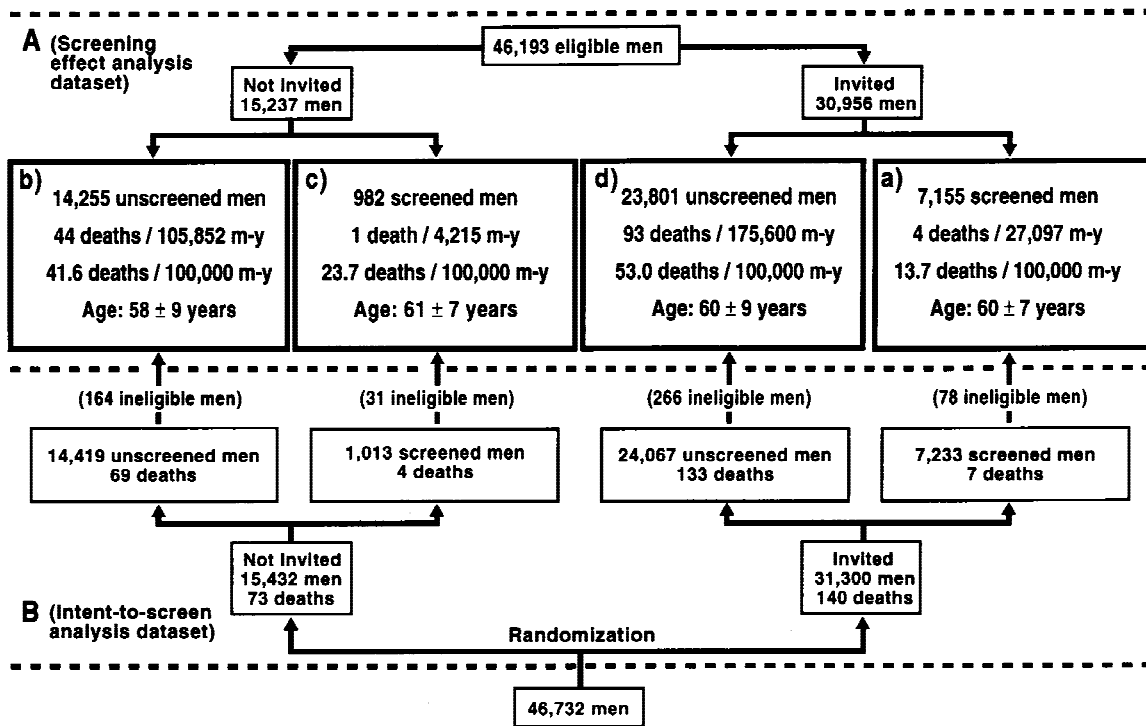


Fig. 1. Trial profile of the Laval University Prostate Cancer Screening Program (November 15, 1988 to December 31, 1996). m-y, man-years; age, mean ± standard deviation.

rent medical practice is thus normalized by dividing the number of cause-specific deaths by the number of person-years. The number of years of exposure in both groups was also adjusted for all other causes of death according to the life table of the Province of Quebec [23] and age distribution in each group. Prostate cancer diagnosed prior to November 15, 1988 was an exclusion criteria that was assessed using the Quebec Tumor registry (Health Department of the Province of Quebec).

Comparisons of the annual incidences of death were performed using two-sided Fisher's exact [24] and Barnard's [25,26] tests. All results obtained with Barnard's test agree with the conclusions of the Fisher's exact test. Another test evaluated if compliance to the randomization had an impact on the outcome. Two 2 × 2 tables were thus constructed, the first 2 × 2 table including only the invited and screened men vs. the unscreened non-invited controls, while the second one included the non-invited men who were screened vs. the invited men who did not respond and were thus not screened. The two tables were tested for the homogeneity of the odds-ratios according to Breslow and Day [27].

Intent-to-screen analysis was also performed to estimate the relative risk of prostate cancer death between the invited and non-invited men, according exclusively to the initial groups randomized. Since this

type of assessment includes all men according to the initial randomization, no men were excluded, irrespective of compliance to randomization, prior diagnosis of prostate cancer, or referral for suspicion of prostate cancer. In other words, all men who were invited for screening were analyzed in the screened group even if only 23.1% of them were, in fact, screened. The unscreened group, on the other hand, included all men originally randomized to this group of which 6.5% were screened. The impact of early screening and treatment on cause-specific death was estimated following adjustment of the relative risk for non-compliance and contamination [28].

Statistical significance was declared for type one error rate below 5%.

RESULTS

Of the 46,193 eligible men aged between 45 and 80 years included in the study started in 1988, 30,956 were invited by letter to be screened for prostate cancer while 15,237 were allocated to the control unscreened group. Figure 1A shows the breakdown of these numbers according to original randomization and participation to screening. In the invited group, 7,155 (23.1%) eligible men were screened at our prostate clinic from November 15, 1988 through December 31, 1996. On the other hand, 982 men (or 6.5% of the

initial control group of 15,237) presented at the clinic for screening, despite being not invited by letter, and had to be withdrawn from the original control group. The age at entry into the study within the 4 different subgroups is comparable with a slightly younger mean age in the not invited/not screened group.

Four out of the 7,155 men who responded to the invitation for screening died from prostate cancer, while 44 of the 14,255 unscreened men died. The exposures in the screened and unscreened control groups are 29,097 and 105,852 man-years, respectively. Thus, over the 8-year period, the annual cause-specific death rate incidences are 13.7 and 41.6 per 100,000 man-years in the screened and control unscreened groups, respectively ($P = 0.02$). The prostate cancer death rate incidence is thus 67.1% lower in men of the screened group.

Several other tests were performed on the basis of the eligible cases in order to assess any possible lack of homogeneity that might be related to the lack of compliance to initial randomization. The men who were invited but did not come to our clinic for screening were first compared to the unscreened controls (Fig. 1Ad vs. 1Ab). Ninety-three prostate cancer deaths were recorded in the 23,801 men who did not respond to the invitation, for a total number 175,600 man-years. This translates into an annual death rate of 53.0/100,000 man-years compared to 41.6/100,000 man-years in the unscreened men who were not invited ($P = 0.22$). Thus, among men who were not screened, no difference in prostate cancer death can be detected between the group of men who were not invited for screening (original control group) and were not screened and the group of men who were invited for screening but were not screened. On the other hand, among the originally invited men, comparison of the incidence rates of death between the screened (Fig. 1Aa) and the unscreened (Fig. 1Ad) men reveals a highly significant effect of screening (odds ratio = 3.85, $P < 0.01$). Finally, the odds ratio of the two 2×2 tables of men who complied with initial randomization (Fig. 1Aa and 1Ab) and those who did not (Fig. 1Ac and 1Ad) are not statistically different ($P = 0.57$). It can thus be concluded that there is no significant relationship between the randomly assigned invitation and the observed incidence rates of death from prostate cancer, screening being the only significant determinant factor of the outcome.

According to the results of the above-described analyses, the subpopulations of screened (Fig. 1Aa and 1Ac) and unscreened (Fig. 1Ab and 1Ad) men can be pooled, regardless of the initial treatment allocation. Among the 38,056 men who were not screened, 137 deaths from prostate cancer occurred for an annual death rate of 48.7/100,000 man-years while only

5 deaths were found in the 8,137 men enrolled in the screening program for an annual incidence rate of 15.0/100,000 man-years. The death rate is thus 3.25-fold or 69.2% lower in the screened men ($P < 0.01$).

Since a limitation of screening studies is the high percentage of men who do not respond to the invitation to be screened, it is also of interest to analyze the data on an intent-to-screen basis (Fig. 1B), without consideration to the fact that 76.9% of the men in the group originally randomized for screening were not screened. Of the 46,732 men aged between 45 and 80 years, 73 and 140 deaths due to prostate cancer occurred in the 15,432 and 31,300 men that were originally randomly assigned to the non-screened (i.e., not invited) and screened (i.e., invited) group, respectively. Figure 1 provides the breakdown of the initial allocation of the subjects into the compliant, non-compliant and contamination subgroups along with the corresponding numbers of deaths from prostate cancer and the ineligible men in each of the 4 subgroups. It can be seen in Figure 1 that 1.08% and 1.14% of men were ineligible (prior prostate cancer diagnosis or referral to our clinic for suspicion of prostate cancer) in the invited screened men (Fig. 1Aa) and uninvited unscreened control (Fig. 1Ab) men, respectively. Such data indicate the similarity of the two groups. When all men actually screened and unscreened are pooled, 1.32% and 1.12% of men were ineligible, respectively. The somewhat higher rate of ineligibility in the total screened group can be explained by the non invited men who came to the clinic following diagnosis of prostate cancer or had suspicion of the disease. This leads to a contamination effect of the screenees, an effect which is analyzed below according to Cuzick et al. [28].

The intent-to-screen analysis with 23.1% of men actually screened shows a 6% decrease of the prostate cancer death rate in favor of the group of men who were initially invited to be screened. This 6% difference is obtained despite a non compliance of 76.9% and a contamination of the uninvited men of 6.6%. When the difference observed between the randomization groups is adjusted for such non compliance and contamination, the effect of screening is estimated to reduce death from prostate cancer by 54 and 100%, respectively. The analysis, presented above, of a 69% benefit associated with screening is thus well supported by the results of the intent-to-screen analysis.

The prevalence of prostate cancer at first visit was 3.00% and the average annual incidence was 0.52% over the 8 years of follow-up (Table 1). As can also be seen in Table 1, 8.4% of cancers were at the metastatic stage at first visit. Most interestingly, none of the 123 prostate cancers diagnosed during the 23,423 follow-up visits was clinically metastatic, thus confirming

TABLE I. Prostate Cancer Diagnosis in the Screened Cohort Between November 15, 1988 and December 31, 1996

Clinical stage	Visit			
	1 st		Follow-up	
	n	(%)	n	(%)
A2	1	(0.4)		
A3	2	(0.8)		
B0	15	(6.4)	21	(17.9)
B1	86	(36.4)	63	(53.9)
B2	69	(29.2)	22	(18.8)
C1	28	(11.9)	10	(8.5)
C2	20	(8.5)	1	(0.8)
D1	3	(1.3)		
D2	12	(5.1)		
N/A	8	—	6	—
Total	244		123	
# Visits	8137		23423	
Ratio				
Diagnosis/Visit	3.00%		0.52%	

that the diagnostic procedures used practically eliminate the diagnosis of metastatic prostate cancer [11].

Four out of the five deaths in the screened group were in men diagnosed at their first visit. The fifth man who died from prostate cancer was not seen at our clinic after his first follow-up visit and was diagnosed in another institution. Of these five deaths in the screened group, one was diagnosed at clinical stage D2, one at stage C2 who was later identified as a D1 after radical prostatectomy while a third one was diagnosed at stage C2 and failed radiation therapy, with a nadir PSA at 29 ng/ml. The two other patients were staged elsewhere.

As illustrated in Table 2, the distribution of prostate cancer deaths in our unscreened population is similar to that of the general population of men within the same ranges of ages in the total population of the province of Québec. In fact, while 237.5 deaths were expected during the study period in the control unscreened cohort, 202 deaths did in fact occur when including 65 deaths from patients who were diagnosed with prostate cancer before November 15, 1988 and died during the study period ending on December 31, 1996. Such data eliminate the hypothesis of a particularly high death rate from prostate cancer in the control group.

If the screened cohort had behaved as the unscreened group, a total of 171 expected remaining years of life would have been lost as compared to an

actual 53 years, thus leading to a 3.2 fold reduction in the prostate cancer-specific loss of years of life during the duration of the study (Table 3).

Among the 367 patients diagnosed with prostate cancer, 339 (92%) were followed at our clinic, at least for their initial treatment (Table 4). Radical prostatectomy or radiation therapy was performed in 155 (46%) and 109 (32%) men, respectively, either alone or in association with combined androgen blockade. Hormonal therapy alone has been received by 50 (15%) patients. Altogether, 70.5% of all patients received combined androgen blockade during their initial treatment.

DISCUSSION

This first randomized and prospective study on prostate cancer screening shows a 69% decrease in the incidence of deaths due to prostate cancer in the screened compared to the unscreened populations. Ten years after the start of this screening study, the present data clearly demonstrate the efficacy, reliability, feasibility, and acceptability of diagnosis and treatment of localized prostate cancer in the general population. The data obtained in this study permit, for the first time, to inform men of the estimated risk of death from prostate cancer if not screened and not treated early. Knowing the medical benefits of a screening program, it is now a matter of medical policy and ethics to create the appropriate conditions which will allow the general population of men to benefit from this new information. It thus seems appropriate to briefly comment the algorithm of prostate cancer screening recommended for the general population.

We would like to insist that the upper limit of normal of serum PSA should be 3.0 ng/ml and not 4.0 ng/ml (as measured by the Hybritech assay or its equivalent). It should be remembered that the cut-off value of 3.0 ng/ml is the only value scientifically demonstrated to provide optimal sensitivity and specificity to the PSA test [10,29]. In fact, the still commonly used value of 4.0 ng/ml suggested by the manufacturer is empirical and not scientifically based. It should be known that 11% and 18% of the smaller and potentially most curable prostate cancers are missed when a cut-off value of 4.0 ng/ml is used instead of 3.0 ng/ml at first and follow-up visits, respectively [11].

Another observation of practical importance is the relative value of digital rectal examination (DRE) and PSA measurement for the diagnosis of prostate cancer. At first visit, where both PSA and DRE were used, 14% of cancers were found by DRE in men having normal PSA, thus indicating that men at first visit should have both serum PSA measurement and DRE [10,11] in order to avoid missing 14% of detectable

TABLE II. Prostate Cancer Death Incidence in the Province of Québec and in the Unscreened Control Cohort Between 1989 and 1996*

Age (yr)	Province of Québec		Unscreened control cohort		
	Number of deaths	Number of men	Actual number of deaths	Expected number of deaths	Number of men
45-49	41	209,100	1	1.1	5,439
50-54	113	166,300	13	4.6	6,830
55-59	292	161,300	8	12.2	6,748
60-64	649	144,000	28	28.6	6,342
65-69	989	115,800	44	45.2	5,259
70-74	1,192	79,700	45	61.8	4,124
75+	1,519	61,500	63	84.0	3,611
Total	4,795	937,700	202	237.5	38,353

*Ages were calculated on July 1, 1989 to comply with the standard methods of Canadian population registries. For the purpose of comparison with the general population, all unscreened individuals of the original cohort are accounted for in this table, including those with a known diagnosis of prostate cancer before the initiation of the study (November 15, 1988). The expected number of deaths is estimated using the age-specific death rates from prostate cancer between 1989 and 1996 in the Québec overall population.

TABLE III. Prostate Cancer Death Incidence Rates in the Unscreened and the Screened Cohorts Between 1989 and 1996

Age at initiation of study (Nov. 15, 1988)	Unscreened control cohort				Screened cohort				
	Actual # deaths	# men	# man-years	Death incidence rate ^a	Actual # deaths (years of life lost)	# men	# man-years	Death incidence rate ^a	Expected ^b # deaths (Lost expected years of life)
45-49	2	6,374	50,800	3.9	0	1,656	6,245	0.0	0.05 (1.3)
50-54	12	6,743	53,083	22.6	0	1,929	7,645	0.0	1.91 (42.5)
55-59	7	6,691	51,548	13.6	0	1,897	8,062	0.0	0.76 (13.1)
60-64	23	6,229	46,439	49.5	0	1,440	6,152	0.0	3.07 (44.5)
65-69	29	4,982	35,366	82.0	3 (34.8)	835	3,622	82.8	3.67 (45.1)
70-74	25	3,940	26,020	96.1	2 (18.6)	348	1,425	140.4	1.90 (17.6)
75+	39	3,097	18,197	214.3	0	32	162	0.0	0.97 (7.0)
Total	137	38,056	281,452	48.7	5 (53.4)	8,137	33,312	15.0	12.3 (171.1)

^aDeaths/100,000 man-years.

^bThe expected number of deaths is estimated using the age-specific death rates of the unscreened control cohort applied to the screened cohort.

cancers. At follow-up visits, however, only 3% of cancers were found by DRE in men having normal PSA [11]. Accordingly, approximately 5,000 DREs were required to diagnose one case of prostate cancer, thus strongly arguing against the routine use of DRE at follow-up visits. It thus seems reasonable to suggest that PSA measurement alone, performed once a year or once every second year should be used at follow-up visits in the general population. Screening once every second year or biannually should be for men having serum PSA \leq 2.0 ng/ml, a recommendation which applies to 70% of the population of men aged 50 years

or more (11) while men having a serum PSA of 2.0 ng/ml or above should have their serum PSA measured annually (Fig. 2).

The approach used in the present study, while being highly efficient in detecting prostate cancer at the clinically localized stage in practically 100% of cases [11] (Table 1), does minimize the number of TRUS and biopsies. In fact, 34.3% and 25.5% of biopsies at first and follow-up visits were positive for cancer [11]. The overall sensitivity and specificity of the proposed strategy compares favorably with screening for breast, colon, uterine, and lung cancer [30]. Prostate cancer

TABLE IV. Treatment Received by 339 Patients (92%) out of the 367 Men Diagnosed With Prostate Cancer Between November 15, 1988 and December 31, 1996*

	Radical prostatectomy	Radiotherapy	Hormonal treatment	Total
No CAB	49	25	25 (delayed)	99 (29.2%)
Hormonal monotherapy	—	1	—	1 (0.3%)
CAB	106	83	50	239 (70.5%)
Total	155	109	75	339

*Others were treated elsewhere.

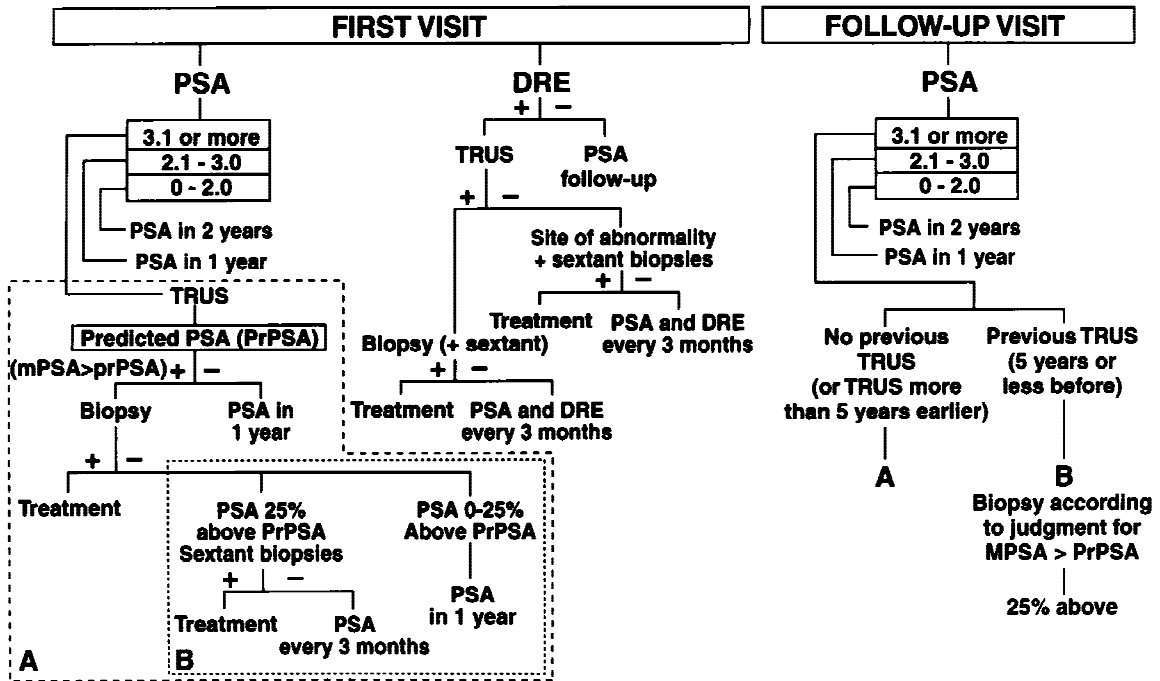


Fig. 2. Algorithm of prostate cancer screening.

can be diagnosed by the present approach at an estimated cost of \$2,665 per cancer at first visit [31], a value well below the costs estimated at \$10,000 and \$30,000 per case of cervical and breast cancer diagnosed by screening, respectively. In agreement with the recommendation of the American Cancer Society, the present data indicate that screening should be started at the age of 50 years except in men of African-American descent and those having a history of prostate cancer [32,33] where screening should be started at the age of 40 years.

A major source of controversy concerning early diagnosis and treatment of prostate cancer is that until recently, no prospective and randomized trial had shown statistically significant benefits of treatment of localized prostate cancer on survival [34]. The absence

of data from well-designed clinical trials was erroneously interpreted as negative data. Most fortunately, two prospective randomized trials have recently demonstrated for the first time that not only quality of life but, most importantly, prolongation of life could be achieved in localized prostate cancer patients treated with androgen blockade. In the EORTC trial performed in stage T₃ patients, survival at 5 years was increased from 62% in the group of patients who received radiation therapy alone to 79% (45% difference) in those who received androgen blockade using an LHRH agonist for 3 years and an antiandrogen for one month in association with radiotherapy [18]. A similar observation has been made in RTOG trial 08351 in the subgroup of high Gleason score patients [35].

Consequently, no valid reason remains to doubt

that treatment of clinically localized prostate cancer can prolong survival. In fact, the major benefits observed in the present study in the screened group can only be due to the treatments used. In fact, the patients diagnosed with localized prostate cancer in the present study were usually enrolled in our randomized trials associating neoadjuvant and/or adjuvant combined androgen blockade with surgery [15], radiotherapy [16] or endocrine therapy alone [36].

Two other randomized screening trials for prostate cancer are ongoing, namely the prostate, lung, colon, and ovarian (PLCO)-trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC). The objective is to recruit 70,000 and 50,000 men, respectively, in those trials. Results from those trials are not expected before year 2005. Moreover, their relatively late start carries the high risk that the popular knowledge about PSA has already led to screening of a significant proportion of men, thus increasing contamination by screening in the control group.

In addition to the major impact on prostate cancer deaths, the economic savings on health care costs has been previously discussed [31,37–39]. The calculations performed leave little doubt that the present strategy based upon efficient screening and treatment, namely androgen blockade, surgery, radiotherapy or brachytherapy alone or in combination with androgen blockade should play a key role in the successful fight against prostate cancer while decreasing the costs for the health care system and society [40,41].

REFERENCES

- Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998;48:6–30.
- 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.
- 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.
- Denis L, Carnelro de Moura JL, Bono A, Sylvester R, Whelan R, Newling D, De Pauw 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.
- Janknegt RA, Abbou CC, Bartoletti R, Bernstein-Hahn L, Bracken B, Brisset JM, Da Silva FC, Chisholm G, Crawford ED, Debruyne FM, Dijkman GD, Frick J, Goedhals L, Knönagel H, Venner PM. Orchiectomy and Nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 1993;149:77–83.
- Caubet JF, Tosteson TD, Dong EW, Naylor 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.
- Dijkman GA, Janknegt RA, Dereijke TM, Debruyne 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.
- Hoeksema MJ, Law C. Cancer mortality rates fall: a turning point for the nation. *J Natl Cancer Inst* 1996;88:1706–1707.
- 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.
- Labrie F, Dupont A, Suburu R, Cusan L, Tremblay M, Gomez JL, Emond J. Serum prostatic specific antigen (PSA) as prescreening test for prostate cancer. *J Urol* 1992;147:846–851.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Pilepich MV, Krall JM, Al-Saffaf M, John MJ, Dogget RL, Sause WT, Lawton CA, Abrams RA, Rotman M, Rubin P, Shipley WU, Grignon D, Caplan R, Cox JD. 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.
- 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.
- Blasko J, Ragde H, Luse R, 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.
- 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.
- Littrup PJ, Williams CR, Egglin TK, Kane RA. Determination of prostate volume by transrectal US for cancer screening. Part II. Clinical utility of transrectal accuracy of in vivo and in vitro techniques. *Radiology* 1991;179:45–53.

22. 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.
23. Statistics Canada, Health Statistics Division: Life Tables, Canada and Provinces, 1990-1992. Statistics Canada: Ottawa, 1995.
24. Agresti A. Categorical data analysis. In: Wiley Series in Probability and Mathematical Statistics. Applied Probability and Statistics, 0271-6356. New York: John Wiley & Sons, 1990, 558 pp.
25. Barnard GA. A new test for 2×2 tables. *Nature* 1945;156:177.
26. Suissa S, Shuster J. Exact unconditional sample sizes for the 2×2 binomial trial. *J R Statist Soc Ser A* 1985;138:317-327.
27. Breslow NE, Day NE. Statistical methods in cancer research. Volume I—The analysis of case-control studies. IARC Scientific Publications 1980;32:5-338.
28. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med* 1997; 16:1017-1029.
29. Littrup PJ, Goodman AC, Mettlin CJ. The benefit and cost of prostate cancer early detection. The Investigators of the American Cancer Society-National Prostate Cancer Detection Project. *CA Cancer J Clin* 1993; 43: 143-149.
30. Hulka BS. Cancer screening. Degrees of proof and practical application. *Cancer* 1988;62:776-780.
31. 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 pre-screening with prostatic-specific antigen. *Clin Invest Med* 1993; 16:425-439.
32. 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.
33. Sun S, Narod S, Aprikian A, Ghadirian P, Labrie F. Androgen receptor and familial prostate cancer. *Nature Medicine* 1995;1: 848-849.
34. Kolata G. Prostate cancer consensus hampered by lack of data. *Science* 1987;236:1626-1627.
35. 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.
36. Labrie F, Cusan L, Gomez JL, Diamond P, Bélanger A. Long-term neoadjuvant and adjuvant combined androgen blockade is needed for efficacy of treatment in localized prostate cancer. *Mol Urol* 1997;1:253-263.
37. 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 luproin: the first controlled and randomized trial. *Clin Invest Med* 1993;16:499-509.
38. 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.
39. Aus G, Hugosson J, Norlén L. Long-term survival and mortality in prostate cancer treated with noncurative intent. *J Urol* 1995; 154:460-465.
40. Labrie F. Intracrinology and cancer therapy. *Science Watch* 1994;5:3-8.
41. 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.