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Screening Decreases Prostate Cancer Mortality: 11-Year Follow-Up of the 1988 Quebec Prospective Randomized Controlled Trial

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PURPOSE. This clinical trial is aimed at evaluating the impact of prostate cancer screening on cancer-specific mortality.
SUBJECTS AND METHODS. Forty-six thousand four hundred and eighty-six (46,486) men aged 45–80 years registered in the electoral roll of the Quebec city area were randomized in 1988 between screening and no screening. Screening included measurement of serum prostatic specific antigen (PSA) using 3.0 ng/ml as upper limit of normal and digital rectal examination (DRE) at first visit. At follow-up visits, serum PSA only was used.
RESULTS. Seventy-four (74) deaths from prostate cancer occurred in the 14,231 unscreened controls while 10 deaths were observed in the screened group of 7,348 men during the first 11 years following randomization. Median follow-up of screened men was 7.93 years. A Cox proportional hazards model of the age at death from prostate cancer shows a 62% reduction ($P < 0.002$, Fisher's exact test) of cause-specific mortality in the screened men ($P = 0.005$). These results are in agreement with the continuous decrease of prostate cancer mortality observed in North America. *Prostate 59: 311–318, 2004.* © 2004 Wiley-Liss, Inc.

KEY WORDS: **prostate cancer; screening; PSA; hormonal therapy**

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer and the second cause of cancer death in men in North America. It is predicted that 28,900 men would die from prostate cancer in the United States in 2003 [1]. In fact, it is estimated that one in nine men will be diagnosed with prostate cancer during his lifetime. At the present rate, prostate cancer will kill more than 2,000,000 men among the male population presently living in the United States.

Definitive proof of the benefits of screening for 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 versus a group of men receiving standard medical care. Accordingly, the Laval University Prostate Cancer Screening Program (LUPCSP) was started in November 1988 and its first analysis was published in 1999 [2]. The present publication describes the results obtained after three additional years or after a total of 11 years of follow-up.

SUBJECTS AND METHODS

Forty-six thousand four hundred and eighty-six (46,486) men were randomly allocated either to the

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group invited for annual screening or to the control group not invited for screening at a ratio of 2:1 in favor of screening. The age and residential area were used for stratification to balance possible differences in socio-demographic factors between groups. Men in the control group not invited for screening were followed according to current medical practice. Although expected to be low, the level of contamination by screening in the control group could not be assessed. Men with a diagnosis of prostate cancer before November 15, 1988 as well as 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. We do not believe that the low 24% rate of acceptance of screening introduced a bias. In fact, no shift was seen of men at greater risk of dying from prostate cancer from the screened group towards the group of men who did not accept the invitation to be screened. Accordingly, If men at greater risk would have declined the invitation for screening, the death rate would have been higher among the group of 23,785 who did not accept the invitation for screening. Accordingly, as will be described later, the incidence of prostate cancer death was the same in the group of 23,785 men who did not accept the invitation to be screened and in the true control group of 14,231 men who were not invited to be screened and were not screened at our clinic.

At first visit, all participants had measurement of serum prostatic specific antigen (PSA) and underwent digital rectal examination (DRE) [3]. 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 1,002 men who all had the three procedures, as previously described [3,4]. The study was approved by the Institutional Review Board of Laval University.

At follow-up visits, PSA alone was done as prescreening test. TRUS was performed 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 a 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 serum PSA had increased by 20% or more over the predicted PSA (prPSA) if calculated at a previous visit [5–7]. Serum samples were taken before DRE and TRUS for measurement of PSA by immunoradiometric assay (Tandem-R PSA, Hybritech Incorporated or its equivalent).

TRUS-guided biopsies were performed as previously described [3,5,8], at the judgment of the radiologist when an hypoechoic image was seen, if the measured PSA (mPSA) was above predicted PSA (prPSA) or if DRE was abnormal. In cases of negative biopsies at previous visits with measured (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 207 men with normal TRUS evaluation because of either abnormal DRE or mPSA greater than prPSA.

Evaluation of the impact of screening is based upon comparison of the incidence 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 of a little more than 11 years extending from November 15, 1988 to December 31, 1999. For the invited men who were screened, the duration of exposure to the intervention is calculated from the date of their first visit at the screening center up to December 31st, 1999, regardless of their compliance to follow-up screening visits and of the treatment received if cancer was diagnosed. For unscreened men not invited for screening, the period of exposure is calculated from the date of initiation of the trial, i.e., November 15, 1988. However, results are expressed in events per 100,000 man-years in order to take full account of the specific years of exposure for each man in each group (Fig. 1).

To analyze the results based on the intervention (screened vs. not screened), the time interval between the initiation of the trial and the first screening visit, in screened men, was added to the total number of man-years of unscreened exposure. Fisher's exact tests

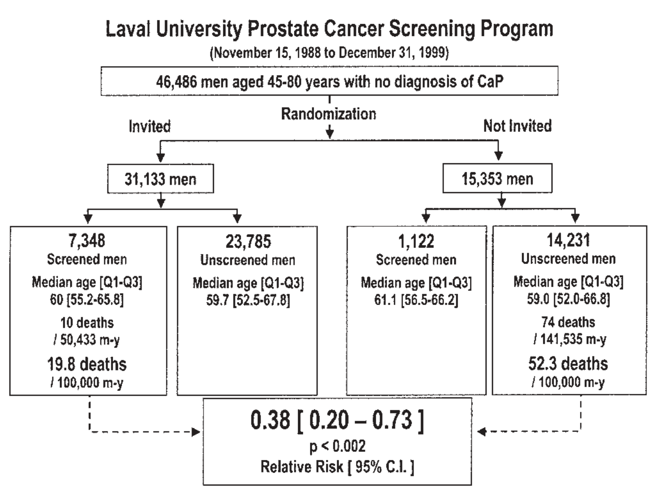

Fig. 1. Trial profile of the Laval University Prostate Cancer Screening Program (November 15, 1988 – December 31, 1999), and reduction of cancer-specific death during the first 11 years in the groups of screened versus non screened men originally invited and not invited for screening, respectively.

[9] were performed to assess the significance of an association between the outcome (prostate cancer deaths) and the intervention group (screened vs. not screened). The possible effect of age was analyzed with the Cochran–Mantel–Haenszel's test [10] applied on the data stratified by strata of 5 years of age. The homogeneity of the relative risk between the age group strata was tested by the Breslow–Day statistics [11]. The age at prostate cancer death was fitted using a Cox proportional hazards model including the following co-variables: screened versus not screened, randomization group (invited vs. non-invited), age at study initiation, and residential area of the subject at randomization. All subjects entered the risk set at the time of study initiation on November 15, 1988, regardless of compliance to the randomization. The participation to the screening program was coded by a time-dependent binary variable changed from 0 to 1 at time of the first screening visit.

RESULTS

Of the 46,486 eligible men aged between 45 and 80 years included in the study started in November 1988, 31,133 men were invited by letter to be screened for prostate cancer while 15,353 were allocated to the control group of men not invited for screening. Figure 1 shows the breakdown of the numbers according to original randomization and actual participation to screening. In the group invited for screening, 7,348 (23.6%) men were screened at our prostate clinic from November 15, 1988 through December 31, 1999. As can be seen in Figure 2, the median delay to the first screening visit in the total group of 7,348 subjects screened was 3.19 years.

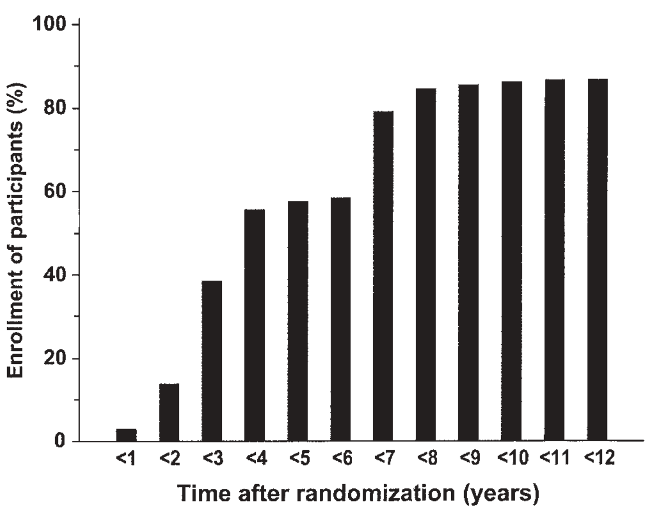

Fig. 2. Time course of enrollment of participants in the Laval University Prostate Cancer Screening Program.

Ten out of the 7,348 screened men of the invited group died from prostate cancer, while 74 of the 14,231 men not invited for screening died from the disease. The exposures in the invited screened and the control unscreened groups are 50,433 and 141,535 man-years, respectively. Thus, over the 11-year period, the annual cause-specific death rate incidences are 19.8 and 52.3 per 100,000 man-years in the invited screened and the control unscreened groups, respectively (two sided P value < 0.002, Fisher's exact test) (Fig. 1). The prostate cancer death rate incidence is thus 62% lower in the group of men screened for prostate cancer compared with the men of the control group who followed standard medical practice (Fig. 3).

To assess a possible effect of the difference of length of follow-up between screened and unscreened men, the duration of exposure of unscreened men was adjusted to limit their follow-up to a maximum of 7.93 years and therefore match the median follow-up duration of screened men. Using the adjusted dataset, the comparison of all screened men versus all unscreened men shows a relative risk of 0.49 (0.25–0.99, 95% confidence interval (CI), $P = 0.047$) in favor of screening. The 95% CI of the relative risk estimates agrees well with those presented in Figure 1.

Among the 15,353 men not invited for screening, 1,122 (7,3%) came on their own to the clinic for screening, despite not being invited for screening by letter (Fig. 4). Among these men, one died from prostate cancer, thus resulting in an exposure of 7,317 man-years in this group of not invited men who were

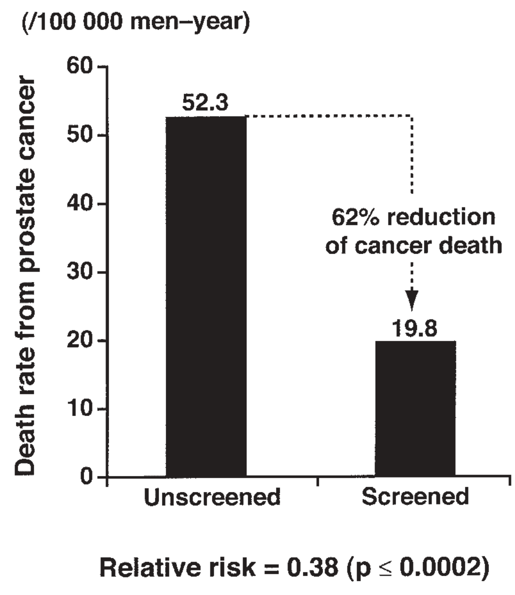

Fig. 3. Comparison of the incidence of death from prostate cancer in the men screened compared to the men unscreened for prostate cancer during the first 11 years of the study (same data as Fig. 1).

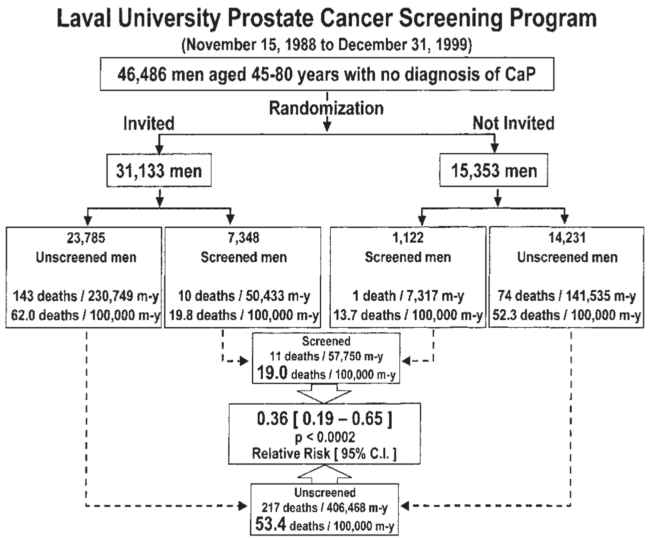

Fig. 4. Cancer-specific mortality reduction observed during the first 11 years of the screening program. Since there was no influence of the fact of being invited or not invited for screening, all screened men were compared to all unscreened men irrespective of the original randomization group.

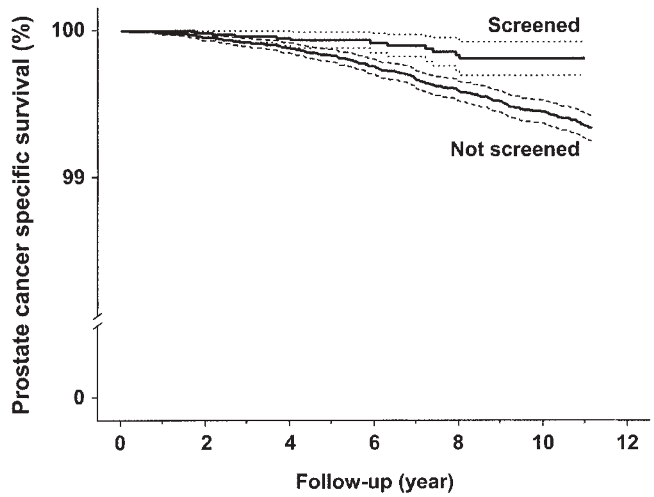

Fig. 5. Kaplan–Meier estimates with 95% confidence intervals of prostate cancer cause specific survival in screened and unscreened men.

screened. On the other hand, as mentioned above, in the group of men invited for screening, 23,785 did not respond to the invitation, Thus, when analyzing the data with respect to the intervention (screened and not screened) rather than the original group of randomization (Fig. 4), there were 11 deaths in the 8,470 men who were actually screened with an exposure of 57,750 man-years. On the other hand, 217 men died from prostate cancer during the 406,468 man-years of exposure in the group of men who were not screened. These data result in a 64% reduction in prostate cancer mortality ($P < 0.0002$) or a relative risk of 0.36 (95% CI = 0.19–0.65) (Fig. 4).

The results presented in Figure 1 were analyzed by age-group strata (5 years per strata) using the Cochran–Mantel–Haenszel test. This analysis shows that the effect of screening is consistently significant within each age strata ($P = 0.004$) with a common estimate for the relative risk of 0.38 (0.20–0.73, 95% CI) in favor of screening. Moreover, a Breslow–Day test rejected the hypothesis of heterogeneity of the screening effect across age strata ($P = 0.90$). It is therefore legitimate to pool all age groups together and perform Fisher exact tests as presented in Figures 1 and 4.

The Kaplan–Meier estimate of prostate cancer specific survival is presented in Figure 5 and shows that the 95% CI of the two curves separates after 5 years of follow-up.

A comparable effect of screening was obtained with the Cox proportional hazards model (best fitted model) presented in Table I which shows that screening is associated with a highly significant 61.5% ($P = 0.0025$) reduction in prostate cancer mortality, or a relative risk of 0.385 (95% CI = 0.207–0.719). It can also be seen in this table that the same advantage of screening was observed in the group of screened men originally invited for screening by letter and those who were screened despite being randomized in the group of men who were not invited. These men decided on their own to be screened. On the other hand, the location of men in the various areas of Quebec city had no influence on the results while age had a small (6%), but highly significant effect ($P = 0.0054$). The Cox proportional hazards model presented in Table I includes the age of the subjects in the list of significant explanatory variables. This allows to estimate the impact of screening on the time to prostate cancer specific death, not confounding the age effect.

The characteristics at diagnosis and the treatment received by the eleven men who were screened and died from prostate cancer are shown in Table II. It is of interest to mention that seven out of the eleven deaths were in men diagnosed at their first visit. Three other men who died from prostate cancer did not follow the annual visits at our clinic and were thus diagnosed and/or received unknown treatment in other institutions, including one who interrupted androgen blockade early after radical prostatectomy, despite having been upgraded from stage B2 to D1 and responding well to combined androgen blockade with undetectable PSA. The last man who died from prostate cancer did not accept immediate treatment and his follow-up is unknown.

Three patients had locally advanced disease and one had bone metastases at diagnosis. In fact, of the eleven

TABLE I. Analysis of the Effect of Screening, Group at Randomisation, Age and Area of Residency on Prostate Cancer Death Using the Cox Proportional Hazards Models

	Intervention model		
	Relative risk	95% CI	*P*-value
Screened versus unscreened	0.385	(0.207–0.714)	0.0025**
Invited versus not invited	1.085	(0.822–1.433)	0.5637
Age (on Nov. 15, 1988)	0.938	(0.897–0.981)	0.0054**
Residential area			
Dummy variables			
C1	1.088	(0.833–1.421)	0.5341
C2	0.926	(0.711–1.206)	0.5697
C3	0.964	(0.741–1.254)	0.7831

CI, confidence interval.
**, statiscally significant

deaths from prostate cancer among the screened men for whom staging is known, one was diagnosed at clinical stage D2, three at stage C2, three at stage B2, and one at stage B1. Staging is unknown for two patients (Table II). One stage C2 and one stage B2 patients at diagnosis were later upstaged to D1 at radical prostatectomy while one stage B2 patient was upstaged to C1 at surgery. A C2 patient failed radiation therapy, with a nadir PSA at 29 ng/ml, thus indicating advanced disease at diagnosis at first visit. It is important to mention that only four patients who died from prostate cancer were diagnosed at follow-up visits. One of these patients, as mentioned above, was upstaged from B2 to D1 at surgery. In order to regain libido and sexual activity, this patient stopped combined androgen blockade after only 18 months. At the time he decided to stop androgen blockade, and adopt intermittent therapy, this patient was responding well to treatment with an undetectable PSA. Unfortunately, the re-initiation of androgen blockade was markedly delayed until serum PSA reached 189 ng/ml. The second patient diagnosed at a follow-up visit and who died from prostate cancer decided to defer treatment and the treatment used, if any, is unknown. For two other patients, the diagnosis was made at another institution and the treatment is unknown from us.

DISCUSSION

An argument frequently cited against screening is that screening could detect insignificant cancers. It is known that one third of men older than 50 years have incidental prostate cancer found at autopsy while, on the other hand, only 10% of men develop clinical prostate cancer during their lifetime [12]. This apparent paradox has been used to suggest that screening could detect the small and still insignificant cancers which are found at autopsy or by transurethral resection of the prostate for treatment of benign prostatic hyperplasia, thus potentially leading to unnecessary treatment. The data obtained, however, do not support this hypothesis. On the contrary, it is well recognized that the available screening techniques, namely, PSA, DRE, and TRUS do not detect such small autopsy cancers [13,14]. In fact, when random or sextant biopsies are performed only in patients having a serum PSA above the predicted PSA and/or a positive DRE in the absence of hypoechoic area at TRUS [13,14], screening detects only cancers having a diameter greater than 0.75 cm. Moreover, more than 90% [15,16] of PSA-detected cancers have features typical of potentially aggressive cancers. The evidence obtained clearly shows that only approximately 7% of cancers detected by screening are microfocal and low grade [15,17,18] and are not an immediate threat for the life of the patient.

In the present study, only 1 out of 159 cancers (0.6%) diagnosed at follow-up visits was metastatic, thus permitting 99.4% of patients to be diagnosed at a localized stage [19]. Similarly, in the screening program of the American Cancer Society National Prostate Cancer Detection Program (ACS-NPCDP), only one of a total of 51 cancers diagnosed at follow-up visits was at a clinically advanced (C2) stage [20]. Hugosson et al. [21] have found that 97% of the cancers detected by screening were clinically localized. It is thus reasonable to suggest that if one follows the recommendations of the American Cancer Society [22] and of the American Urological Association [23], namely annual screening starting at the age of 50 years for the general population at no special risk, all subsequent visits should be equivalent to the follow-up visits of the present study, thus practically eliminating the diagnosis of metastatic prostate cancer [4].

Reports from cancer registries in all the states followed by the SEER program indicate that prostate cancer incidence rates have begun to fall [24]. In

TABLE II. Characteristics at Diagnosis and Treatment Received by the 11 Men Who Died From Prostate Cancer Among the Screened Men

	1st visit		Diagnosis				Death from PCa	
Identification	PSA (ng/ml)	Age (years)	Visit	Age (years)	Clinical stage	Initial treatment	Years after diagnosis	Age (years)
1	25.9	75	1st visit	75	C2	EBRT[b]; failure with nadir PSA at 29 ng/ml	2.2	77
2	87.0	65	1st visit	65	D2	CAB[a]	2.7	68
3	4.6	66	1st visit	66	C2	Radical prostatectomy; castration upstaged to D1 at surgery	4.0	70
4	3.9	66	1st visit	66	B2	Radical prostatectomy with neoadjuvant CAB[a]	6.3	73
5	15.7	60	1st visit	60	C2	EBRT[b] with neoadjuvant + adjuvant CAB[a]	7.2	67
6	2.1	58	3rd visit (PSA = 5.8)	61	B2	Radical prostatectomy; upstaged to D1 at surgery; neoadjuvant and 1 year of adjuvant CAB[a] before stopping treatment	4.5	65
7	3.2	69	External follow-up	Unknown		Unknown		75
8	23.0	60	1st visit	60	B2	Neoadjuvant + adjuvant CAB[a]; radical prostatectomy; upstaged to C1 at surgery	7.9	68
9	6.5	74	3rd visit (PSA = 10.4)	77	B1	Deferred unknown treatment	8.0	82
10	5.4	56	External follow-up	Unknown		Unknown		60
11 (not invited)	33.8	72	1st visit	72	Unknown	Unknown	1.8	74

[a]Combined androgen blockade.
[b]External beam radiotherapy.

Olmsted County, a 22% decline in prostate cancer death has been observed between 1980 and 1997 after PSA screening was introduced [25]. 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 USA [26].

It is reasonable to suggest that the recently observed decrease in deaths from prostate cancer mentioned above [25–28] is due to earlier diagnosis with serum PSA [4] and transrectal echography of the prostate [29] coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy, and endocrine therapy [30–39].

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

In the United States, it has been estimated that the health care costs for the treatment of prostate cancer are $4.5 billion annually [40]. These costs are largely related to the treatment of advanced disease. The calculations performed leave little doubt that the strategy based upon efficient screening and early 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 [14,41–47].

As strong support for the crucial role of early diagnosis and treatment, this first prospective and randomized prostate cancer screening study, shows that early diagnosis combined with treatment of localized disease decreased death from prostate cancer by 62%. The present data are also in agreement with the 42% decrease observed in 1998 in the prostate cancer death rate in the Tyrol area where PSA screening was made available since 1993 compared to the rest of Austria where PSA screening was not offered [48]. Since about two thirds of men were screened in Tyrol during that period, the 42% decreased death rate observed is similar to the 62% value measured in our study among the men who were all screened (Figs. 1–4).

Clearly, the rational use of the presently available diagnostic and therapeutic approaches could decrease prostate cancer death by at least 50% [2,4]. As an example, between 1991 and 1999, the death rate from prostate cancer has decreased by 38% in the whole population of Québec City and its metropolitan area [49] while the death rate has decreased by 62% in the group of men who have been screened.

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