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EDITORIAL

Nothing like data showing significant death reduction can better support prostate cancer screening

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Abstract

At 13 years of follow-up, the European Randomized Study of Screening for Prostate Cancer shows a 21% decrease in prostate cancer deaths in the prostate-specific antigen-screened group compared to control. This difference increases to 27% when non compliance is taken into account. The benefits of screening compared to control are higher at 28% (compared to 21%) when duration of follow-up ranges between 8 and 12 years. Such data obtained following an average rate of one screening performed once every 5.7 years in quite impressive and strongly supports the use of screening for a successful fight against a cancer which grows to an advanced and non curable stage without any specific sign or symptom.

Key words: Prostate cancer; Screening; Prostate-specific antigen; Early diagnosis; Early treatment

Core tip: The wide use of prostate-specific antigen for screening of prostate cancer is a major issue preventing the recruitment of true unscreened controls in studies on prostate cancer screening. This is why only studies performed some time ago can meet this requirement of a small contamination of the control group. The European Randomized Study on Screening for Prostate Cancer had a contamination of 23%-40%, thus permitting to see, at 13 years of follow-up, a 21% decrease in prostate cancer deaths in the screened group compared to no screening. The earlier Quebec trial had a contamination of only 7% with a 62% decrease in death from prostate cancer at a median follow-up of 7.9 years. A contamination of 85% of the control group prevented the United States PLCO trial from providing reliable data. The data obtained in the European and Quebec trials are strong arguments for a major positive impact of early diagnosis which needs screening for a successful fight against prostate cancer.

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INTRODUCTION

The significant decrease in prostate cancer deaths

Table 1 Comparative characteristics of the randomized European Randomized Study of Screening for Prostate Cancer and Quebec studies

Study	No. in study	Date of start/ end enrolment	Contamination of control group	PSA cut off (ng/mL)	Screening frequency	Median follow-up	Planned screening interval	Controlled treatment	Effect on prostate cancer deaths
ERSPC[4]	162388 55-69 yr	1993-2003	23%-40%	3	1/5.7 yr	13 yr	4 yr	No	21% reduction (P = 0.001) 27% after adjustment for non-compliance
Quebec[6]	46486 45-80 yr	1988-1999	7.30% (no prestudy screening)	3	1/yr	7.9 yr	1 yr	Yes	62% reduction (P < 0.002)

PSA: Prostate-specific antigen; ERSPC: European Randomized Study of Screening for Prostate Cancer.

during the last two decades is mostly attributed to early diagnosis and improved treatments[1]. Prostate cancer, however, remains the second cause of cancer death with 27740 (76/d) deaths predicted to occur in the United States alone in 2015[2]. Two facts about prostate cancer screening deserve special consideration: (1) prostate cancer progresses insidiously to the advanced or metastatic and non-curable stage without any cancer-specific symptom or sign and; and (2) consequently, without screening, almost all men would be diagnosed with prostate cancer only at the advanced stage after loosing the possibility of a cure, a situation superimposable to that of 50 years ago when late diagnosis was equivalent to the prognosis of a painful death from the disease within 2 to 3 years.

FIRST SCREENING STUDIES

While the follow-up of the European Randomized Study of Screening for Prostate Cancer (ERSPC) has already shown reduction in prostate cancer mortality after 9 and 11 years of follow-up[3], even better results have been observed at 13 years of follow-up[4]. The ERSPC is a multicentre and randomized trial performed in eight European countries with some variations in the protocol(s) used not but somewhat similar to the earlier Quebec clinical trial[5] (Table 1).

At a follow-up through 2010 (13 years), the rate ratio of prostate cancer mortality was 0.79 (95%CI: 0.69-0.91) (-21%) decreasing to 0.73 (-27%) (95%CI: 0.61-0.88) after adjustment for non-participation[4]. There were 355 deaths from prostate cancer in the screened group *vs* 545 in the control group for a 0.79 (-21%) rate ratio (P = 0.001). Men, on average, were screened 2.3 times during the 13 years of follow-up for an average of one screening every 5.7 years (Table 1).

Although expected from the long-term follow-up needed to assess the development of early stage prostate cancer, it is quite interesting to see that the benefits of screening increase with the duration of follow-up with relative ratios of death of 0.88 for years 0-4 (-12%), 0.82 at years 4-8 (-18%) and a further decrease to 0.72 (95%CI: 0.59-0.88) (-28%) at years 8-12. These ERSPC benefits, despite being of some lower magnitude, are in agreement with the previous data of the Quebec Prostate Cancer Screening (QPCS) Trial (Table 1)[5,6]. One partial explanation for the difference could be the absence of standardized optimal treatment in the ERSPC study[4] since an optimal/ standardized treatment should offer advantages. A second difference of importance in the two trials is the screening rate observed in the "control group" (contamination) estimated at 23%-40%[4] in the ERSPC study compared to only 7% in the QPCS trial (Table 1)[6]. A third difference is that screening was performed once a year in the QPCS study compared to only once every 5.7 years on average in the ERSPC trial, thus delaying the diagnosis up to an average of 4.7 years in the ERSPC study.

Despite these data showing that a significant number of lives are saved[4,6] in the screened group and the knowledge that quality-of-life adjusted life-years is significantly improved despite the reported overdiagnosis[7], screening remains controversial despite the fact that a large number of well-informed men decide to be screened. It seems preferable for a man to know that he has early stage prostate cancer discovered at screening and be in a position to be able to decide about treatment instead of being a non-screened person who learns later that he has only 2 to 3 years to live under the very difficult/painful conditions of advanced prostate cancer. A major source of controversy about prostate-specific antigen (PSA) screening apparently comes from the United States Prostate, Lung Colorectal and Ovarian Cancer (PLCO) study where the results obtained should never have been considered since 85% of men in the control group had been screened. In other words, both groups of men were highly screened, thus making impossible to detect a statistically significant effect on prostate cancer deaths. In short, the PLCO trial did not have a true control group, thus resulting in insufficient statistical power to reach any valid conclusion (for review see Labrie 2013)[1].

TREATMENT DECISION INVOLVING PATIENT

The main argument for those who do not support

screening or show a hesitant position[4] despite the convincing data of well performed studies (Table 1) concerns overdiagnosis. The facts, however, are that overdiagnosis has been estimated to occur in about 40% of cases detected by screening[8,9] while a comparable 27%-62% decrease in deaths from prostate cancer can be achieved with screening[4,6]. It would seem that avoiding death from prostate cancer is much preferable to "overdiagnosis" which, it must be recognized, includes the strong possibility of a cure or long-term life and is most likely to avoid death from prostate cancer.

It is clear that future research should attempt to differentiate between aggressive cancers and those which could be considered "indolent". The reality, however, is that cancers are usually multifocal, thus seriously complicating any reliable prognostic attempt. In any case, until reliable prognostic tools become available, screening accompanied by a well informed decision about treatment shared between the patient and the physican(s) appears to be the best choice if one wants to have a high probability of avoiding death from prostate cancer.

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