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Prostate Cancer

Extent of Prostate-Specific Antigen Contamination in the Spanish Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC)

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Abstract

Objectives: The performance of tests outside prostate cancer screening trials (PSA contamination) may affect their statistical power. The present study addressed the extent of PSA contamination in the Spanish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and its impact on biopsy performance and prostate cancer detection.

Methods: Data linkage was performed to address screening-related interventions outside the study. Four databases were used: (1) Spanish ERSPC database ($n = 4278$), (2) laboratory database with all PSA determinations ($n = 31,140$), (3) database of 1608 prostate biopsies, and (4) records of all prostate cancers ($n = 819$) diagnosed at our centre. PSA contamination, biopsy performance, and cancer detection rates were calculated.

Results: Median follow-up time was 6.6 yr. A total of 2201 PSA determinations were performed for 1253 men. Cumulative PSA contamination was 29.3% (17% in the control arm during the first 4 yr). A higher proportion of men undergoing biopsies was found in the screening arm (21.3% vs. 2.9% in the control arm, $p < 0.0001$). Similarly, higher cancer detection rates were found in the screening (4.7% vs. 1.2% in the control arm, $p < 0.0001$).

Conclusions: In our experience, the PSA contamination rate has increased during the last years, but its impact on biopsy performance and cancer detection in the control arm of the trial is limited and not likely to compromise the statistical power of the ERSPC trial.

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1. Introduction

Despite the controversy surrounding prostate cancer screening with serum prostate-specific antigen (PSA) in terms of survival benefit, widespread use of this marker has been adopted in routine clinical practice. To ascertain the decrease of prostate cancer mortality due to prostate cancer screening, large randomised studies are ongoing.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) started in 1994 and includes eight participating European countries at the present time: Belgium, Finland, France, Italy, The Netherlands, Spain, Sweden, and Switzerland, with >250,000 men recruited; first conclusive results are expected by 2008. Recruited men (age, 45–75 yr) have been randomised into screening group (tests performed every 2–4 yr and therapy started when cancer is detected) and control group (no tests performed). In both arms, mortality is studied and cause of death recorded. A common analysis with another large randomised trial of similar design, the Prostate Lung Colorectal and Ovary (PLCO) cancer screening study conducted by National Cancer Institute in the United States, is planned in the future [1–4].

The ERSPC trial has been designed to demonstrate a 25% reduction in prostate cancer mortality due to screening, with a statistical power of 80–90% (1-tailed; significance level, 0.05); sample size calculation was 190,000 men in both arms of the study [5]. PSA contamination might be a potential threat for such statistical power. Contamination is defined as PSA testing (and prostate biopsy and appropriate therapy when indicated) performed to the recruited population outside the screening program (usually by general practitioners, or in routine health checks done at work centres, or even by other urologists); it has been a major point of criticism of those randomised trials [6]. PSA contamination can be especially harmful when performed in men in the control arm of the study (where no tests are expected), because it might reduce the statistical power of the study, thus creating the need for an increase of either the sample size or the follow-up period. The ERSPC has been designed to harbour up to 20% contamination rate in the control group per 4 yr of follow-up [5].

With these premises, calculation of PSA contamination as accurately as possible is of utmost importance in such studies. Efforts have been made by all ERSPC participants to calculate the extent of this phenomenon in each centre. These attempts have been done by means of telephone interviews, questionnaires mailed to participating men, or even with database linkages with laboratory records [7].

The present study addressed the extent of PSA contamination in the Spanish section of the ERSPC and studied the impact on biopsy performance and prostate cancer detection.

2. Methods

At present, 4278 men have been recruited in the Spanish section of the ERSPC (2416 in the screening arm and 1862 in the control arm). In this centre, recruitment started in February 1996 and finished in June 1999. Follow-up time for the present paper was calculated from date of randomisation to date of death or up to 31 December 2004. As stated in the study protocol, all men randomised in the screening arm underwent serum PSA determination every 4 yr, and transrectal ultrasound sextant prostate biopsy was performed when the total PSA level was ≥ 3 ng/ml.

Data linkage was performed address screening-related interventions performed outside the study (PSA sampling, prostate biopsies, and prostate cancer detection). For such data linkage, four databases were used:

1. Database of men recruited in the Spanish arm of ERSPC ($n = 4278$). Fields included were first name, second name (when applicable), first and second surnames, date of birth, date of randomisation, arm of study (screening or control), and dates of attendance (PSA testing), biopsy, and prostate cancer detection.
2. Laboratory database with all PSA determinations carried at Getafe Hospital ($n = 31,140$) from February 1996 to 31 December 2004. The study population in the Spanish centre comprises men recruited from two cities (Getafe and Parla) located at the 10th Health Area from Comunidad de Madrid. It should be emphasised that most of medical care in this area is supported by the public health services, and all PSA determinations performed in the study area in the public setting have been processed at the biochemistry laboratory of Getafe Hospital. Only PSA draws done in private practice or in the medical services of work centres “escaped” from the control of PSA contamination calculations (supposed to be a small proportion of PSA testing in our setting). For the linkage process, fields available were also first and second names, first and second surnames, date of birth, and date of blood sampling. These fields were fully matched (all characters) with the ERSPC database to identify samples performed within ERSPC study. When processing records with missing date of birth, common surnames were manually excluded from the matching process to guarantee the correct identity of each record.
3. Database of 1608 transrectal ultrasound-guided sextant prostate biopsies performed at our centre from February 1996 to 31 December 2004. Fields included for matching were first and second names and surnames, date of birth, and hospital record number. Again, all biopsies performed in the public setting in our health area are included in this database.
4. Database of all prostate cancers ($n = 819$) diagnosed at our centre. Fields included were also first and second names and surnames, date of birth, and hospital record number.

This database includes all cancers diagnosed in the public setting in our health area.

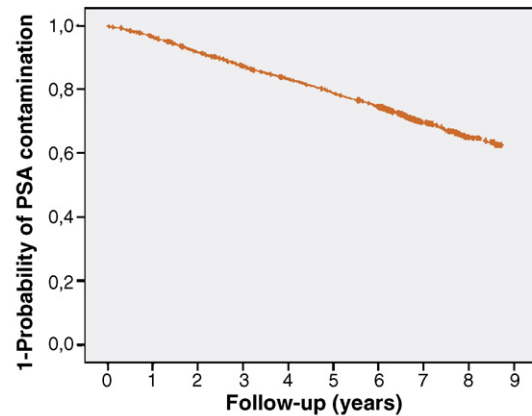
PSA contamination rates were calculated for the population included and also rates for opportunistic biopsy performance and cancer detection. Survival analysis (Kaplan-Meier curves) was used to report contamination rates at each point during the period of the study.

All databases were included in a Microsoft Access (Microsoft, Chicago, IL) database to carry out all matching processes. Statistical processing was done with the SPSS package (SPSS, Chicago, IL). The significance level for all comparisons was set to 0.05.

3. Results

The age of the 4278 studied men ranged from 46 to 71 yr, with a mean of 57.8 yr (standard error [SE] 0.09) and a median of 57 yr. Follow-up time was 0.03–8.90 yr (mean, 6.8 ± 0.016; median, 6.6 yr).

From the 31,140 PSA determinations available, 2201 were performed on 1253 men recruited in the Spanish section of ERSPC outside the study protocol (PSA contamination). Therefore, the contamination rate during the full follow-up period of the study was 29.3% (1253 of 4278). This rate was 16.7% when only the first 4 yr were considered (17% in the control arm). Mean estimated actuarial time to PSA contamination was 7.1 yr (SE, 0.04), with median time calculation not feasible. In Table 1, PSA contamination is detailed with regard to both arms of the study (screening and control). In Figs. 1 and 2, PSA contamination with regard to follow-up time is



| | Starting of interval (year) | | | | | | | | |
|---|-----------------------------|------|------|------|------|------|------|------|------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Men starting interval | 4278 | 4118 | 3878 | 3672 | 3479 | 3287 | 2966 | 934 | 193 |
| Events | 149 | 211 | 182 | 172 | 181 | 173 | 135 | 45 | 5 |
| Probability of being free of contamination at end of interval | .965 | .915 | .872 | .831 | .788 | .745 | .695 | .642 | .609 |

Fig. 1 – Kaplan-Meier curve showing the probability of being PSA contamination free over time during the follow-up period. The whole population enrolled in the Spanish section of ERSPC (n = 4278) is represented. Note the steady, constant trend for contamination with time elapsed.

represented. In Fig. 3, hazard function of PSA contamination is shown.

Also, effective PSA contamination (PSA sampling that prompts biopsy indication and performance) was studied. Comparisons with regard to biopsy performance and cancer detection between screening and control arms are shown in Table 2 and Fig. 4. When we considered individuals with at least one prostate biopsy available, a significant difference

Table 1 – PSA contamination (only outside protocol sampling) related indexes in screening and control arms of the trial

| | Screening | Control |
|---|---|--|
| Recruited men | 2416 | 1862 |
| Individuals with at least one PSA performed outside ERSPC protocol (PSA contamination, cumulative percentage) | 735 of 2416 (30.4%) full period 399 of 2416 (16.5%) first 4 yr | 518 of 1862 (27.8%) full period 316 of 1862 (17.0%) first 4 yr |
| No. of PSA draws (outside protocol) | 1 sample 456 of 735 (62.0%) ≥3 samples 130 of 735 (17.7%) range 1–10 mean 1.76 median 1 | 1 sample 300/518 (57.9%) ≥ 3 samples 85 of 518 (16.4%) range 1–11 mean 1.75 median 1 |
| No. of PSA/yr (outside protocol) | range 0.11–2.03 mean 0.26 median 0.16 | range 0.11–4.74 mean 0.29 median 0.16 |
| Period of study (y) | range 0.49–8.90 mean 6.97 median 6.91 | range 0.21–8.72 mean 6.66 median 6.67 |

Median follow-up time is 6.6 yr.

Table 2 – Comparisons in terms of biopsy performance and cancer detection between both arms of the study, including biopsies performed and cancers detected (inside or outside the study protocol) for men recruited in the Spanish section of ERSPC

| | | Screening | Control | p |
|--|--|---------------------|-------------------|---------|
| All men recruited in the study, any PSA value | No. | 2416 | 1862 | |
| | Individuals at least with 1 biopsy performed during the period of study | 514 of 2416 (21.3%) | 55 of 1862 (2.9%) | <0.0001 |
| | Cancer detection (only biopsied) | 114 of 514 (22.2%) | 22 of 55 (40%) | 0.0033 |
| | Cancer detection (overall) | 114 of 2416 (4.7%) | 22 of 1862 (1.2%) | <0.0001 |
| Men recruited with at least 1 PSA ≥3 ng/ml at anytime during the period of study | No. | 493 | 131 | |
| | Individuals at least with 1 biopsy performed during the period of study (cumulative biopsy referral) | 326 of 493 (66.1%) | 46 of 131 (35.1%) | <0.001 |
| | Cancer detection (only biopsied) | 85 of 326 (26.1%) | 18 of 46 (39.1%) | 0.086 |
| | Cancer detection (overall) | 85 of 493 (17.2%) | 18 of 131(13.7%) | 0.311 |

was noted when we compared both arms of the study: 514 of 2416 (21.3%) in the screening arm versus 55 of 1862 (2.9%; $p < 0.0001$) in the control arm.

A total of 114 cancers were detected in the screening arm (17 of them outside the screening protocol, due to PSA contamination), and 22 in the control arm of the trial (all from contamination attendances). Again, higher overall detection rates were found in the screening arm when compared to the control arm, 114 of 2416 (4.7%) versus 22 of 1862 (1.2%; $p < 0.0001$), respectively. Such differences (in terms of overall cancer detection) were not shown when only men with serum PSA levels of ≥ 3 ng/ml at any time during the study were considered ($p = 0.311$).

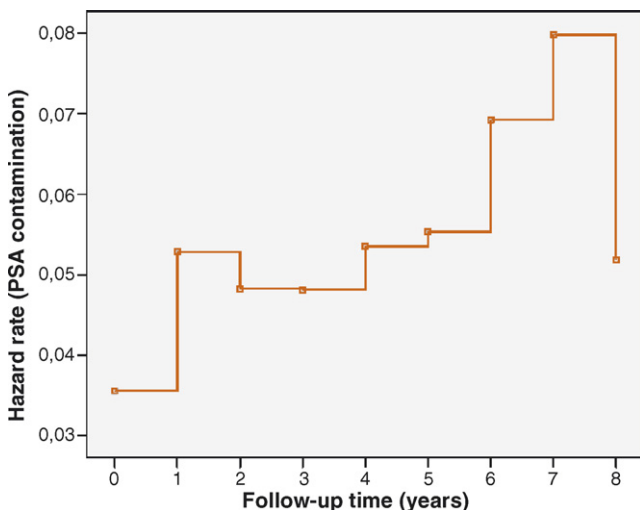


Fig. 2 – Hazard function of PSA contamination in the studied population. Hazard at a given interval means the risk of PSA contamination for a man with no previous contamination in the preceding intervals.

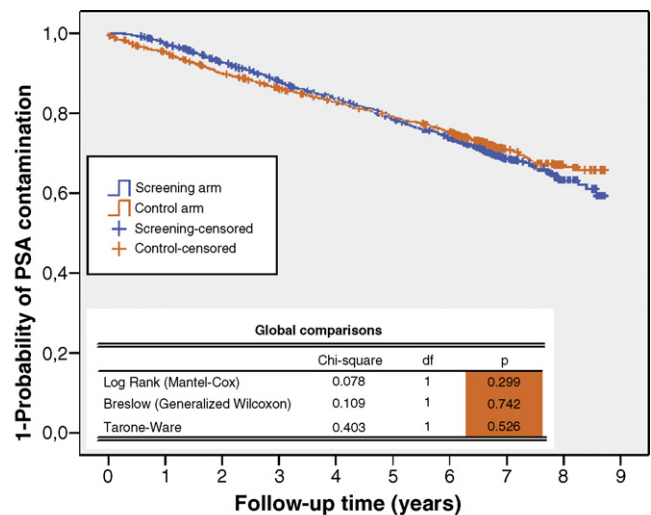


Fig. 3 – Probability of being contamination free with regard to the screening and control arms of the study. Note that the probability of being tested for PSA elsewhere outside the study is the same in both arms.

4. Discussion

In the present paper, PSA contamination in the Spanish section of ERSPC has been calculated. With a median time of 6.6 yr, we found a 27.8% cumulative PSA contamination rate in the control group during the whole follow-up period, and 17% in the first 4 yr, higher than the previously reported 6.7% in the period 1998–2001 [7,8]. Despite the increase in contamination rate, it is still below the limit supported by the ERSPC (20% in 4 yr in both arms of the trial) [5]. If we also consider that sample size in the whole trial has increased (190,000 at initial calculations to 250,000 at the present time), we do not believe this will jeopardise the statistical power of the study if PSA contamination stays at moderate levels in other participating centres of the ERSPC.

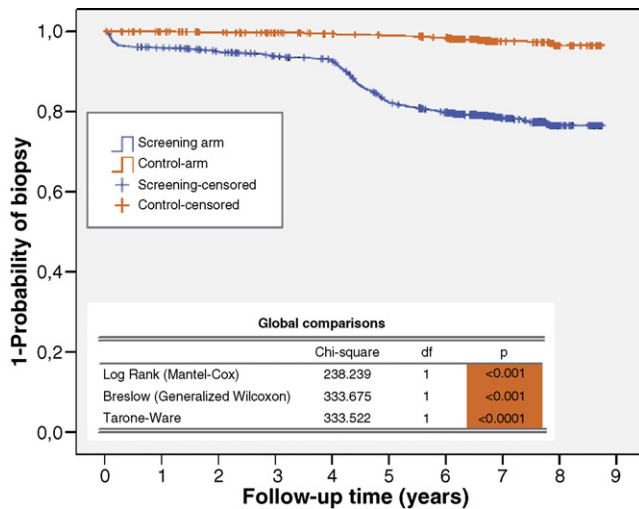


Fig. 4 – Probability of being free from prostate biopsy (inside or outside the study protocol). The probability stays closer to 100% in the control group throughout the period of study.

Moreover, if we consider *effective* PSA contamination (defined as the proportion of men in whom prostate biopsy is indicated and performed, the only fact that ultimately might have a deleterious effect on the trial), only 2.9% of men in our control group have undergone biopsy throughout the whole period of the study reported in this paper. Another ERSPC participant, The Netherlands, has reported PSA contamination rates also by means of database linkage [9]. Although a 20% rate of PSA testing in the control group was found in a period of almost 3 yr, effective PSA contamination was <8%, and cancer detection was only 3%.

In our experience, an important gap exists between the rate of men tested for PSA in the control group and the small proportion of men who finally undergo biopsy: only 35% of men with at least one PSA determination ≥ 3 ng/ml are biopsied. It must be remarked that such low biopsy referral (outside the study) cannot be explained by aging (oldest man is 71 yr old) nor by comorbidity status (according to study protocol, men with life expectancy <10 yr were not included at the time of randomisation). We suspect that there is a considerable lack of protocol-based decisions with regard to biopsy indication in the regular clinical practice in our setting. In other words, opportunistic screening with PSA is performed, but in many cases biopsy is not indicated (even with PSA level above the usual threshold value).

The low impact of opportunistic PSA testing on biopsy performance is also shown with regard to cancer detection. The cumulative detection rate in the screening arm was 4.7% during the whole

follow-up period versus only 1.2% in the control arm ($p < 0.0001$). Thus, at least in the Spanish section of the ERSPC trial, it seems unlikely that PSA contamination will alter the expected results of the study.

Other issues are to be considered. First, because of the study design (invitation to participate in a prostate cancer screening trial), most men who accept the invitation are probably interested in PSA screening. Therefore, it is not surprising that men not randomised in the screening arm would seek to be screened somewhere else, thus explaining the increasing contamination rate in the control arm. Second, given the fact that many recommend annual PSA testing, the long retesting interval chosen in the study (4 yr) may have an impact on the increasing contamination rate and probably a shorter screening interval would decrease the “need” for opportunistic PSA testing in the recruited population. Third, the steadily increasing risk of being PSA contaminated over time as shown in Figs. 1 and 2 and the equal contamination rates in both screening and control arms (Fig. 3) are facts that should be discussed. They may reflect not only the attitude of the patient towards prostate cancer screening, but a periodic and fixed sampling process performed by general practitioners or other medical professionals (although biopsy referral seems to be surprisingly low). It seems that many medical professionals perform routine health checks unaware of the fact that some men have been previously screened (as participants in the ERSPC study) [6].

A known limitation of our study is that only PSA determinations performed in the public setting of our health area have been included and therefore the proportion of men screened in private practice is unknown, but supposed to be relatively small. The estimation of private practice in Spain is 20–25% in big cities, such as Madrid and Barcelona, and an overall 8.9% in the whole Spanish territory [10]. It should be noted that these percentages would not reflect the proportion of men that “escaped” from our database control. In fact, private practice in Spain is complimentary to public system. In other words, a proportion of the population is voluntarily covered with private health insurance plans and simultaneously covered by the public system. Therefore, many men with private coverage may still have had their PSA and biopsy performed within the public system (and then collected in the databases used in the present study).

Another limitation is the lack of a centralised cancer registry with all cancer cases diagnosed in our area. Fortunately, all cancers diagnosed in the

public setting in our area are collected in the databases used in this study and, as mentioned, the proportion of cancers diagnosed in the private setting is supposed to be too low to change in an important manner the results of the present study.

5. Conclusions

Although the PSA contamination rate in the Spanish arm of the ERSPC has increased importantly during the last years, its impact on biopsy performance and cancer detection in the control arm seems to be limited and not likely to compromise the statistical power of ERSPC trial.

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Editorial Comment

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The paper by Luján and colleagues confirms previous reports of increasing opportunistic PSA use in European countries [1]. This evidence is somehow “mitigated” by the relatively lower frequency of prostate biopsies, suggesting that opportunistic screening is less “effective” than organized screening. This may be reassuring as to the contamination bias within the ERSPC study, but confirms that substantial opportunistic screening is ongoing in the general population. The evident trend of increasing prostate cancer incidence in developed countries, particularly in the USA, demonstrates that, although less effective, opportunistic screening is obtaining substantial diagnostic anticipation.

Unfortunately, the diffusion of screening by PSA is not supported by any convincing evidence of its

efficacy. Preliminary findings are unreliable, either for major flaws in study design [2], or being not confirmed at proper follow-up [3]. Two randomised clinical trials (PLCO in the USA, ERSPC in Europe) are ongoing and have not provided evidence of screening efficacy, thus far. On the contrary, strong evidence is available of a major negative effect of PSA screening, overdiagnosis (and overtreatment), which has been consistently estimated to be at least 50% [4,5], and is confirmed by excess incidence, observed and persisting over time on a population basis. PSA screening represents probably the most convincing and also most frightening example of how early cancer detection through screening may be harmful. Whether it is also beneficial, and to what extent, we still do not know. A major question should be addressed to those who recommend and/or perform screening as a current policy: is PSA screening ethical, when the only available evidence deals with its major negative effects, and before ongoing randomised trials could give an answer as to its efficacy?

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