Progrès en urologie (2020) 30, 252—260

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE

Contamination in control group led to no effect of PSA-based screening on prostate cancer mortality at 9 years follow-up: Results of the French section of European Randomized Study of Screening for Prostate Cancer (ERSPC)

Absence d'effet du dépistage de cancer de la prostate par PSA à 9 ans du fait de la contamination : résultats de la section française de l'ERSPC

A. Villers[a,*], F. Bessaoud[b], B. Trétarre[b], P. Grosclaude[c], B. Malavaud[d], X. Rebillard[e], F. Iborra[f], L. Daubisse[b], S. Malavaud[g], M. Roobol[h], E.A. Heijnsdijk[i], H.J. de Koning[i], J. Hugosson[j], P. Rischmann[d], M. Soulié[d]

[a] *Department of Urology, University Lille, CHU Lille, Lille, France*
[b] *Hérault cancer registry, ICM Montpellier, Montpellier, France*
[c] *Tarn cancer registry, Albi, Toulouse, France*
[d] *Department of Urology, University Toulouse, CHU Toulouse, Toulouse, France*
[e] *Department of Urology, Clinique Beau Soleil, Montpellier, France*
[f] *Department of Urology, University Montpellier, CHU Montpellier, Montpellier, France*
[g] *Department of Public Health, University Toulouse, CHU Toulouse, Toulouse, France*
[h] *Department of Urology, Erasmus University Medical center, Rotterdam, The Netherlands*
[i] *Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands*
[j] *Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden*

Received 20 January 2020; received in revised form 16 February 2020; accepted 18 February 2020
Available online 18 March 2020

* Corresponding author.
E-mail address: arnauld.villers@wanadoo.fr (A. Villers).

https://doi.org/10.1016/j.purol.2020.02.011

KEYWORDS
Prostate cancer;
Screening;
PSA;
Incidence;
Mortality

Summary
Introduction. — European Randomized Study of Screening for Prostate Cancer (ERSPC) mortality results were reported for 7 European countries (excluding France) and showed a significant reduction in Prostate cancer (PCa) mortality. As those results have not been part of the global ERSPC results, it is of interest to report PCa mortality at a median follow-up of 9 years for French section of ERSPC.
Material and methods. — Two administrative departments were involved in the study. Only men after randomization in the screening group were invited by mail to be screened by PSA testing with two rounds at 4—6 year intervals. Biopsy was recommended if PSA > = 3.0 ng/mL. No information other that the French Association of Urology recommandations on the use of PSA was offered to the control group (own decision of physicians and patients). Follow up was based on cancer registry database. Contamination defined as the receipt of PSA testing in control arm was measured. Poisson regression models were used to estimate the Rate Ratio (RR) of PCa mortality and incidence in the screening *vs*. control arm.
Results. — Starting from 2003, 80,696 men aged 55—69 years were included. The percentage of men in the screening arm with at least one PSA test (compliance) was 31%. Compared to the control arm, PCa incidence increased by 10% in the screening arm (RR = 1.10; 95% CI = [1.04—1.16], $P = 0.001$), but PCa mortality did not differ (0.222 and 0.215 deaths/1000 person-years; RR = 1.03[0.75—1.42], $P = 0.9$).
Discussion. — Limitations include low participation rate. PSA testing in the control arm was observed in 32% of men (contamination).
Conclusions. — Contamination in control group led to no effect of PSA-based screening on prostate cancer mortality at 9 years follow-up.
Level of evidence. — 3.

MOTS CLÉS
Prostate cancer ;
Dépistage ;
PSA ;
Incidence ;
Mortalité.

Résumé
Introduction. — Les résultats de l'étude européenne randomisée sur le dépistage du cancer de la prostate (ERSPC) ont été publiés pour 7 pays européens (hors France) et ont montré une réduction significative de la mortalité par cancer de la prostate (PCa). Ces résultats ne faisant pas partie des résultats globaux de l'ERSPC, il d'intérêt de publier la mortalité par PCa à un suivi médian de 9 ans pour la section française de l'ERSPC.
Matériel et méthodes. — Deux départements administratifs ont été impliqués dans l'étude. Seuls les hommes après randomisation dans le groupe de dépistage ont été invités par courrier à un test de dépistage par PSA (deux cycles à des intervalles de 4 à 6 ans). Une biopsie était recommandée si PSA > = 3,0 ng/mL. Aucune information autre que les recommandations de l'Association Française d'Urologie sur l'utilisation du PSA n'a été proposée au groupe témoin (décision propre des médecins et des patients). Le suivi était basé sur la base de données du registre du cancer. La contamination était définie comme la pratique de tests PSA dans le bras de contrôle. Des modèles de régression de Poisson ont été utilisés pour estimer le risque/ratio (RR) de mortalité et d'incidence du PCa dans le bras dépistage vs contrôle.
Résultats. — À partir de 2003, 80 696 hommes âgés de 55 à 69 ans ont été inclus. Le pourcentage d'hommes dans le bras de dépistage avec au moins un test PSA (conformité) était de 31 %. Par rapport au bras témoin, l'incidence de PCa a augmenté de 10 % dans le bras de dépistage (RR = 1,10; IC à 95 % = [1,04—1,16], $p = 0,001$), mais la mortalité par PCa n'était pas différente (0,222 et 0,215 décès/1000 personnes/an; RR = 1,03 [0,75—1,42], $p = 0,9$).
Discussion. — Les limites incluent un faible taux de participation. La pratique de test de PSA dans le bras témoin a été observée chez 32 % des hommes (contamination).
Conclusion. — La contamination dans le groupe témoin n'a entraîné aucun effet du dépistage par dosage du PSA sur la mortalité par cancer de la prostate après un délai de 9 ans de suivi.
Niveau de preuve.— 3.

Introduction

Prostate cancer (PCa) is the most common male cancer, and screening remains a major public health issue. The European Randomised study of Screening for Prostate Cancer (ERSPC) began in 1993 in 8 countries, with the aim of investigating the effect of prostate-specific antigen (PSA) screening on PCa mortality. Recruitment started in Belgium and the Netherlands in 1993, and the last country to join was France, in 2003. Due to the late start of France's participation, only reaching a median follow-up of 9 years at the end of 2013, and due to a failure to comply with the primary criteria (screening participation > 50% and low PSA testing for PCa in control arm, i.e. low contamination)[1], French incidence and mortality data were excluded from the four ERSPC analyses, and the findings were analysed and reported as pre-specified in the protocol [2—5] based on data from the other 7 participating European countries. A total of 182,160 men were randomised, of whom 162,388 were part of the pre-defined core age-group of 55—69 years. Cumulative PCa-specific incidence at 16 years was 1.4-fold higher in the screening arm vs. control arm. The relative risk reduction in PCa mortality remained roughly unchanged, at about 20% since the initial report. In contrast, the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) trial [6,7] results reported at 15 years of follow-up, and the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) [8] results at 10 years of follow-up showed no reduction in PCa mortality.

As those results have not been part of the global ERSPC results, it is of interest to have incidence and mortality data for France. The primary analysis is an intention-to-screen comparison of PCa mortality rates between arms at a median follow-up of 9 years. Secondary analysis compares PCa-specific incidence rates.

Material and methods

Study population and design

The ERSPC was designed to determine the effect of PSA screening on mortality from PCa. The study design has previously been described elsewhere [2,9]. The French contribution to ERSPC took place in two administrative areas, namely the Tarn and Hérault Departments in the south of France. Both areas have a population-based cancer registry based on medical records. Men living in the Tarn and Hérault areas were identified through health insurance databases. Men aged 55 to 69 years at the time of randomisation were eligible. Pre-consent randomisation was performed, and within each area, men were randomly assigned in a 1:1 ratio to the screening arm (intervention group) or control arm. Participation in the trial started in 2000 with a feasibility study which included 9% of the Tarn population. To increase compliance in the Tarn area during the feasibility study, non-responders to PSA testing and/or biopsy invitations were contacted by mail and telephone. The remaining population of Tarn, and the whole population of Hérault were subsequently invited and included after ERSPC approval. The first round occurred over the period 2003—2005 and included 80,696 men. The second screening round took place over the period 2009—2011. Contamination, defined as PSA testing in the control arm, was assessed by interviews (telephone and mail, in 2001—2002) in a random sample of 243 men in the control arm [10]. PSA testing was assessed in 229 non-responders in the screening arm. Compliance with interviews in the screening arm non-responders, and in the control arm was 42% and 67% respectively (Supplementary table* S1.A). In addition, in the screening arm, at the time of invitation and consent (in Tarn only), men were asked about their previous PSA practices by mean of a self-administered questionnaire (Supplementary table* S1.B).

This study was registered with Current Controlled Trials under the number ISRCTN49127736. Ethical approval was obtained from the French Consultative Committee on Data Processing for Medical Research and the National Commission on Data Processing and Rights (900075). The study design has previously been described [9]. Briefly, measurement of serum PSA was centralised, and a cutoff of 3.0 ng/mL or higher was an indication for biopsy. Sextant biopsy was initially recommended for screen-positive men, in line with recommendations during the ERSPC trial. The number of biopsy cores sampled varied over time. Starting in 2005, most urologists moved from 6 sextant biopsy to a 10—12 core systematic biopsy scheme according to the EAU guidelines. Screening was discontinued after the second round, which occurred after a 4—6 year interval.

Incidence and mortality measurements

Incidence of PCa was updated by crosschecking ERSPC data with data from the Tarn and Hérault population-based cancer. Tumour characteristics and treatment modalities were recorded. Tumours were classified into risk groups according to the ERSPC study code-book (Supplementary table* S2: category 1 [T1-2/unknown and not N1/M1 and Gleason score ≤ 6 and PSA < 10 ng/ml], category 2 [T1-2/unknown and not N1/M1 and (Gleason score ≤ 6 and $10 \leq$ PSA < 20 ng/ml or Gleason score = 7 and PSA < 20 ng/ml)], category 3 [T1-2/unknown and not N1/M1 and (Gleason score ≤ 7/unknown and PSA ≥ 20 ng/ml or $7 \leq$ Gleason score ≤ 10) or T3 and not N1/M1], category 4 [T4 or N1/M1 or PSA > 100 ng/ml].

Information on vital status was obtained from French National Institute of Statistics and Economic Studies (INSEE) and the National Directory for the Identification of Individuals (RNIPP). Cause of death was obtained from the cancer registries and from the French National Epidemiological Center for the Medical Causes of Death (CépiDc).

Statistical analysis

The primary analysis is an intention-to-screen comparison of PCa mortality rates between the two arms. Secondary analyses compared PCa incidence rates. Event rates were defined as the ratio of the number of events (death or diagnosis) divided by the person-years at risk for the event. Poisson regression models were used to estimate the Rate Ratio (RR) and associated 95% confidence interval (CI) of PCa mortality and incidence in the screening *vs.* control arm. Cumulative PCa mortality and cancer incidence by arm was calculated with the Nelson-Aalen method. Continuous variables were compared using the Student t test (if

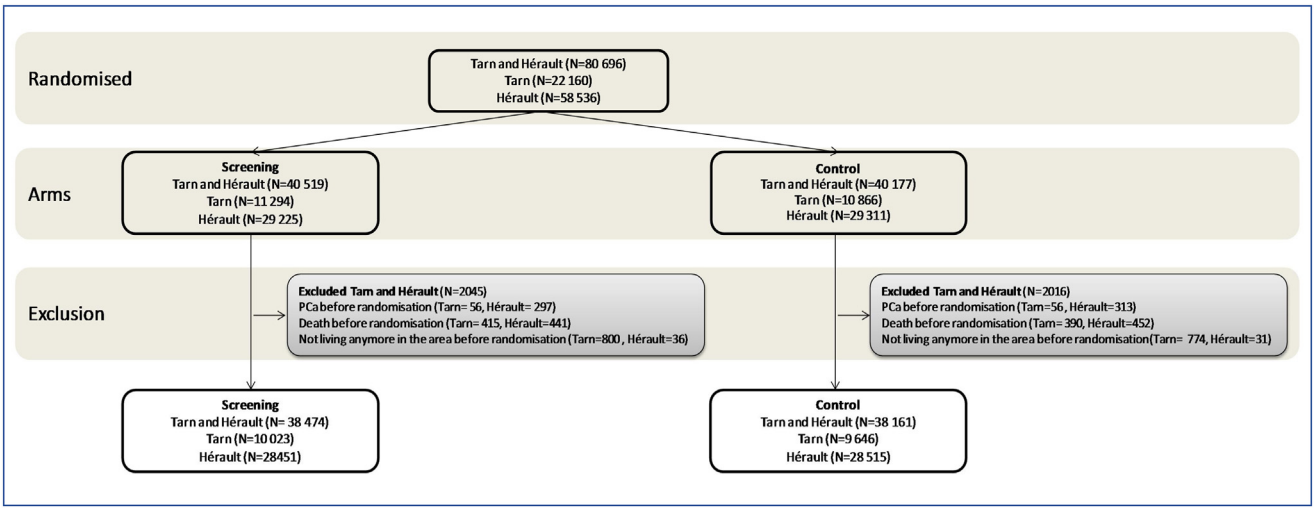

Figure 1. Enrollment of men aged 55—69 years - France section of ERSPC (Tarn and Hérault centers).

normally distributed) or otherwise, using the Mann—Whitney test. Categorical variables were compared using the Chi^2 or Fisher's exact test. All *P*-values are two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed with the R software package.

Results

Characteristics of the study population

A total of 80,696 men were included, 40,519 were randomly assigned to the screening arm. We excluded 4,061 men due to PCa diagnosis ($n = 722$) or death ($n = 1{,}698$) before randomisation or because they did not live in the area ($n = 1{,}641$), leaving a total of 76,635 men for the final analysis (Fig. 1). Median age at randomisation in the screening arm (61—IQR: 58—65) was similar to that of the control arm (61—IQR: 58—65). Median follow-up was 9.5 years (IQR: 8.9—9.8) in both arms.

Compliance

The compliance rate (i.e. men in the screening arm who had at least one PSA test) was 31% (39% for Tarn, 29% for Hérault) and differed by age ($P < 0.001$). Among the men who had at least one test, 19% had a positive PSA result (Table 1). Among those with positive PSA test result, 35% underwent prostate biopsy within 1 year (46% for Tarn, 30% for Hérault).

Contamination

Interviews showed that 32% of men in the control arm had had a PSA test in the previous 2 years (Supplementary table* S1.A), while corresponding rate was 56% in the non-responders in the screening arm. Analysis of the self-administered questionnaires sent to men in the screening arm showed that 42% had had a PSA test in the previous 2 years (Table S1.B).

Prostate Cancer incidence

In the screening arm, a total of 2,479 PCa were diagnosed vs. 2,240 in the control arm (Table 2 and Fig. 2A). Among the 2,479 PCa detected in the screening arm, 14% were diagnosed within 1 year of PSA testing (screen detected). PCa incidence increased by 10% in the screening arm as compared to the control arm (RR = 1.10; 95%CI = [1.04—1.16], $P = 0.001$). The risk classification at time of diagnosis is described in Table 3, and shows similar percentages of each risk category in men randomised to the screening (attenders and non-attenders) and control arms ($P = 0.1$).

Prostate Cancer mortality

Among 153 deaths due to PCa, 78 occurred in the screening arm (Table 4). Nelson-Aalen curves of the cumulative risk of PCa death are shown (Fig. 2B). Mortality from PCa did not differ between arms (RR = 1.03 [0.75—1.42], $P = 0.9$). The absolute difference in PCa deaths between the screening and control arms was 0.06 deaths per man randomised. All-cause mortality did not differ between the 2 arms (RR = 1.03 [0.99—1.08], $P = 0.1$) (Table 5).

Discussion

Based on a median follow-up of 9 years and including men aged 55—69 years at the time of randomisation, our results show a relative increase of 10% in the rate of PCa incidence in the screening arm, compared to the control arm. While results from the ERSPC trial (excluding France) continue to show a 20% reduction in PCa mortality with screening [2—5], our results found no difference in PCa mortality between the screening and control arms. Unfortunately, an increased 10% in PCa diagnosis is reported in the screening group but distribution of PCa aggressivity showed no difference with a number of uncompliant people in this group. However, as mentioned, unfavourable results are probably due to a

Table 1 number of men and results of pca screening according to age.

Screening arm	Tarn	Hérault	Tarn + Hérault
Follow-up, years, median (IQR)	10.5 (9.6—10.5)	9.4 (8.8—9.6)	9.5 (8.9—9.8)
Age, *N* (%[a])			
All	10023 (100%)	28451 (100%)	38474 (100%)
55—59	3812 (38%)	9878 (35%)	13690 (36%)
60—64	3000 (30%)	9910 (35%)	12910 (34%)
65—69	3211 (32%)	8663 (30%)	11874 (31%)
Screening arm			
Screened at least once (Compliant), *N* (%[a])			
All	3911 (39%)	8119 (29%)	12030 (31%)
55—59	1687 (44%)	3085 (31%)	4772 (35%)
60—64	1191 (40%)	2928 (30%)	4119 (32%)
65—69	1033 (32%)	2106 (24%)	3139 (26%)
Men with positive test, *N* (%[b])			
All age	714 (18%)	1560 (19%)	2274 (19%)
55—59	244 (14%)	513 (17%)	757 (16%)
60—64	250 (21%)	611 (21%)	861 (21%)
65—69	220 (21%)	436 (21%)	656 (21%)
Men with at least one biopsy, *N* (% [c])			
All age	325 (46%)	469 (30%)	794 (35%)
55—59	105 (43%)	158 (31%)	263 (35%)
60—64	103 (41%)	178 (29%)	281 (33%)
5—69	117 (53%)	133 (31%)	250 (38%)
Prostate cancer			
All, N	763	1716	2479
Screen-detected cancers	112	232	344
Positive predictive value of screening[d]	15.7%	14.9%	15.1%
Control arm			
Follow-up, years, median (IQR)	10.5 (9.6—10.5)	9.4 (8.8—9.6)	9.5 (8.9—9.8)
Age, N (% a)			
All	9646 (100%)	28515 (100%)	38161 (100%)
55—59	3896 (40%)	9819 (34%)	13715 (36%)
60—64	2818 (29%)	9968 (35%)	12786 (34%)
65—69	2932 (30%)	8727 (31%)	11659 (31%)
Prostate cancer			
All	700 (7%)	1540 (5%)	2240 (6%)

[a] Percentage calculated in each age group of screening arm and control arm respectively.
[b] Percentage calculated in each age group of compliant men.
[c] Percentage calculated in each age group of men with positive test.
[d] Positive predictive value of screening corresponds to the number of screen detected cancers divided by the number of men with positive tests.

Table 2 Prostate cancer incidence.

	Screening			Control			Rate Ratio, 95%CI	*P*-value
	Cases	Person-years (PY)	Rate per 1000 PY	Cases	Person-years (PY)	Rate per 1000 PY		
All	2479	338482	7.3	2240	337262	6.6	1.10[1.04—1.16]	*P* = 0.001
55—59 y	676	124509	5.4	580	125319	4.6	1.17 [1.05;1.31]	
60—64 y	883	113498	7.8	766	112927	6.8	1.15 [1.04—1.26]	
65—69 y	920	100475	9.2	894	99016	9.0	1.01 [0.92—1.11]	

Test for homogeneity of OR: $\chi 2 = 15.6$, df = 2, *P* = 0.004. Y: years; CI: confidence interval.

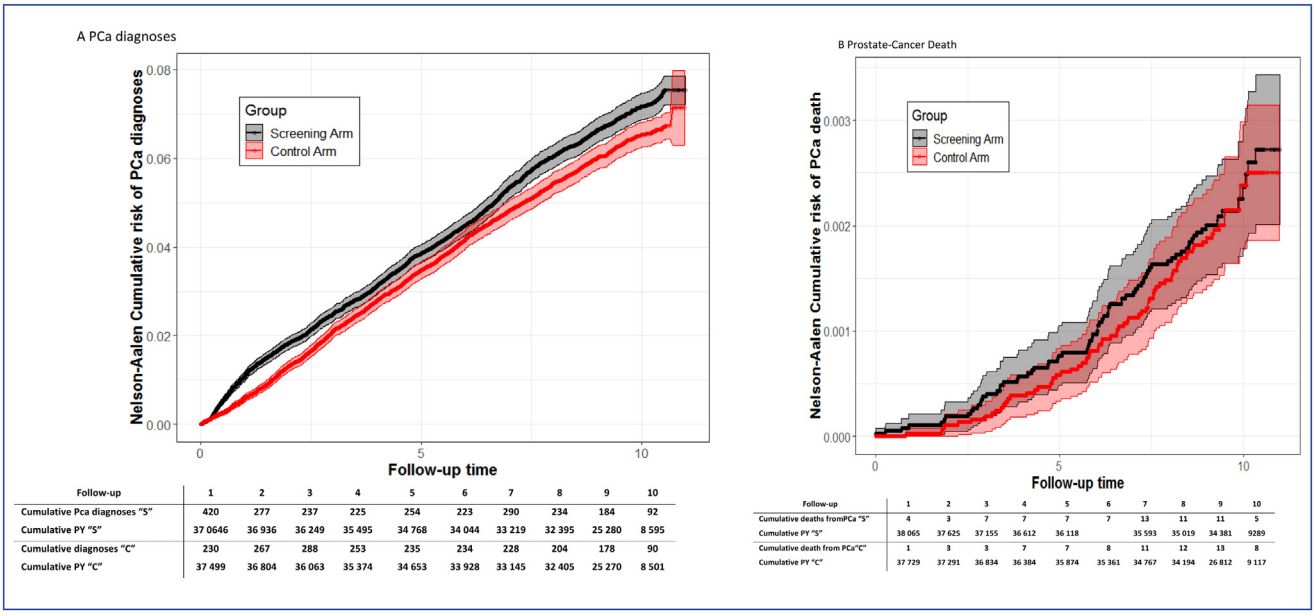

Figure 2. Cumulative risk of PCa diagnoses (A) and cumulative risk of PCa death (B) for both Tarn and Hérault centers at a median of 9 years of follow-up.
''S'': Screening arm; ''C'': Control arm; PY: person-years.

Table 3 Distribution of PCa risk classification among screening (stratified by attenders and non-attenders) and control arms.

	Screening arm		Control arm
Risk classification*	Attenders (%)	Non-attenders (%)	
1	400 (43%)	485 (32%)	741 (33%)
2	328 (35%)	590 (38%)	891 (40%)
3	115 (12%)	237 (15%)	327 (15%)
4	32 (3%)	111 (7%)	148 (7%)
Unknown	63 (7%)	118 (8%)	133 (6%)
All	938 (19%)	1541 (33%)	2240 (47%)

* Risk classification: category 1 [T1-2/unknown and not N1/M1 and Gleason score $\leq$ 6 and PSA < 10 ng/ml], category 2 [T1-2/unknown and not N1/M1 and (Gleason score $\leq$ 6 and 10 $\leq$ PSA < 20 ng/ml or Gleason score = 7 and PSA < 20 ng/ml)], category 3 [T1-2/unknown and not N1/M1 and (Gleason score $\leq$ 7/unknown and PSA $\geq$ 20 ng/ml or 7 $\leq$ Gleason score $\leq$ 10) or T3 and not N1/M1], category 4 [T4 or N1/M1 or PSA > 100 ng/ml], unknown [not meeting the criteria of categories 1 to 4].

Table 4 PCa mortality.

	Screening			Control			Rate Ratio, 95% CI	*P*-value
	Cases	Person-years (PY)	Rate per 1000 PY	Cases	Person-years (PY)	Rate per 1000 PY		
all	78	351090	0.22	75	348291	0.22	1.03 [0.75,1.42]	$P = 0.9$
55—59 y	15	127785	0.12	14	128170	0.11	1.07 [0.52;2.25]	
60—64 y	31	117844	0.26	22	116567	0.19	1.39 [0.81;2.44]	
65—69 y	32	105460	0.30	39	103555	0.38	0.81 [0.5;1.28]	

Test for homogeneity of OR: $\chi^2 = 2.3$, df = 2, $P = 0.3$. Y: years; CI: confidence interval.

Table 5 All-Cause Mortality.

	Screening			Control			Rate Ratio, 95% CI	*P*-value
	Cases	Person-years (PY)	Rate per 1000 PY	Cases	Person-years (PY)	Rate per 1000 PY		
All	5249	351090	14.9	5028	348291	14.4	1.03 [0.99,1.08]	$P = 0.1$
55—59 y	1383	127785	10.8	1318	128170	10.3	1.05 [0.98;1.13]	
60—64 y	1625	117844	13.8	1589	116567	13.6	1.01 [0.94;1.08]	
65—69 y	2241	105460	21.2	2121	103555	20.5	1.04 [0.98;1.10]	

Test for homogeneity of OR: $\chi 2 = 0.6$ df = 2, $P = 0.7$. Y: years; CI: confidence interval.

contamination and a low compliance in both groups and probably in regard of the methodology.

One possible explanation for the difference in the main outcome between the ERSPC and PLCO trials is the low rate of biopsy compliance after a positive test in the screening arm (35% in PLCO vs. 86% in ERSPC), as well as a high rate of contamination in the control arm of PLCO. It was shown that, when corrected for differences in contamination and compliance the effects of trials did not differ [11]. The compliance rate in the CAP study was comparable to the rate we report here, i.e. 31%. Accordingly, the absence of any reduction in PCa mortality in our study could possibly also be explained by low compliance (PSA testing and/or biopsy) and contamination. Furthermore, we cannot rule out the possibility that our results, as well as others (PLCO and CAP), simply reflect the fact that PSA testing does not reduce PCa mortality.

The assessment of contamination in patients from Tarn in our study shows that the individual PSA testing rate was 32% in the control arm [10]. The national screening policy in France, favoring individual PCa screening during the ERSPC trial, is a possible explanation for this high level of contamination and subsequent lack of reduction in PCa mortality. In 2003, the French Urology Association published guidelines for PCa screening (screening on the basis of an annual PSA test and DRE was recommended for men aged 50—75 years) and the guidelines advised that information about the risk and benefit of screening be given before testing [12].

French national epidemiological data [13] showed an increase in PCa incidence over the period 1990—2005, which was strongly related to the introduction of PSA as a means of cancer detection (Fig. 3). This increase in incidence, with a peak in 2005, was followed, as observed in other countries, by a decline [14]. This decrease in incidence can be explained by the reduction of the reservoir of undiagnosed PCa cases, and by the growing awareness of the risk of overdiagnosis. Mortality has declined steadily since 1990, but this cannot be explained by the introduction of PSA testing alone. Indeed, in ProtecT, the introduction of PSA screening failed to have any mortality impact over at least the first 10 years [15]. ProtecT was not showing an effect because of lead time of these low/intermediate risk PCa cases that were included in the trial. ERSPC showing an effect after median of 9 years is due to the cancers detected at an advanced stage. Hence, data from ERSPC, excluding France, reported decreases in mortality observable less than 10 years after introduction of PSA screening [2]. Therefore, PSA testing cannot wholly account for the mortality decline that occurred before 2000 in France. There are likely other additional contributors, such as improvements in the treatment of PCa.

Among the ERSPC countries (excluding France), contamination by opportunistic PSA testing ranged from 7% to 37% [10]. This wide range can be partly explained by differences between countries in the methods of assessing contamination, based on estimates of PSA use (ever) or within the previous 12 months. Some countries assessed contamination by database linkage, others by interviews. The Finnish and Dutch sections of the ERSPC, with contamination rates of 10% and 13% respectively, showed reductions in the relative risk of PCa mortality of 15% and 20% respectively at 12 years [16,17]. However, only results from the Dutch centers were statistically significant.

PSA testing and biopsy compliance were lower in the French ERSPC data than in the other ERSPC centers [2—4]. In our study, compliance with PSA testing was 30%, whereas results for the other European centers were in the range of 70—100%. These high compliance rates were likely due to the post-consent randomization [18]. The biopsy compliance rate (35%) was also low in our study, and lower than in the other ERSPC centers, with the highest rates of biopsy observed in Finnish and Dutch centers.

In the French study, biopsy was recommended when PSA was ≥ 3 ng/mL. In that case, a letter was sent to the patient's family doctor with the PSA result, asking him/her to refer the patient to an urologist for a biopsy. Biopsies were not centralized. The decision to biopsy was left to the family doctor, patient and urologist. Many reasons could explain the fact that only 35% of patients actually had a biopsy. Some reasons were mentioned during interviews but not in detail, such as patient refusal, normal DRE, PSA testing redone with a different test and a different threshold value and found to be non-suspicious, or TRUS performed and found to be non-suspicious. Interviews were intended to tell the patient to see a urologist for a biopsy, but not to discuss the causes of refusal.

Several studies [8,19,20] have shown that PCa in the screening arm are detected at an earlier stage than cancers detected in the control arm, contributing to mortality reduction. In our study, PCa diagnosed in attenders from the intervention arm was diagnosed at an earlier stage than that in non-attenders in the intervention arm or than PCa detected in men in the control arm. However, these results were not associated with reduced mortality.

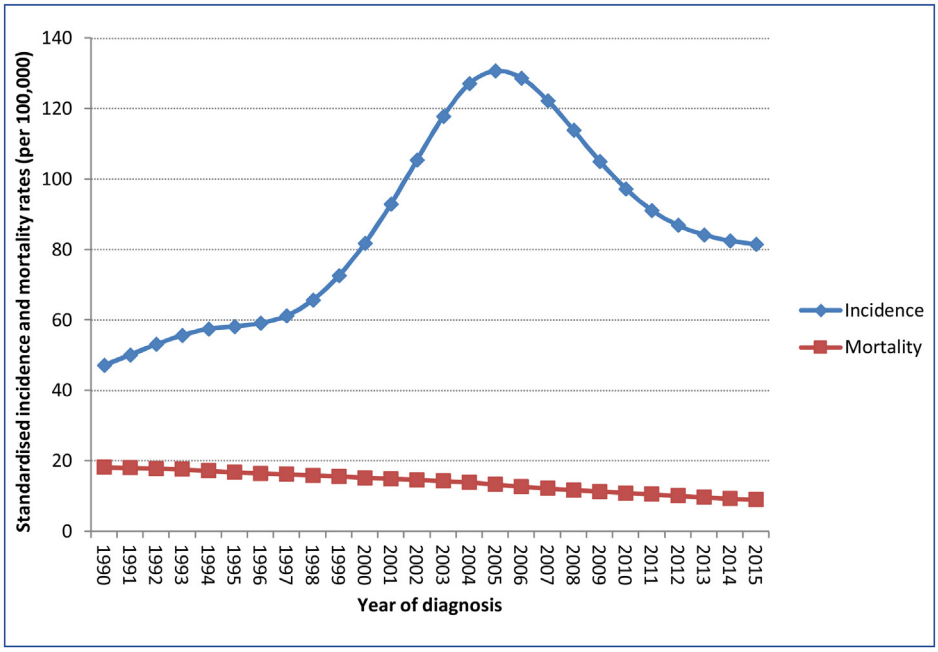

Figure 3. World standardized incidence and mortality rates in France between 1990 and 2015. The ERSPC trial started in France in 2003 after a feasibility study.

Our study has several limitations. The sample size and power calculations for the ERSPC study indicated that 20,000 men randomized in each arm would be required to show a 25% reduction in PCa mortality with 80% power at 10 years of follow up, without taking account of potential non-compliance or contamination [21]. Although our sample size at the outset met this criterion, the statistical power of our study is limited by the low compliance and high contamination rates. Another limitation was the scarce information regarding the contamination level in the control arm and the reason(s) for non-compliance in the screening arm. Adjustment for contamination and non-participation according the Cuzick method [22] was not possible and it remains unknown how these factors may have affected our mortality results. Nevertheless, our results are in line with those of the PLCO trial, which had similar rates of PSA contamination and biopsy compliance.

Conclusion

The French ERSPC data had almost equal amounts of screening in both arms of the trial due to low compliance in the screening arm, and contamination in control arm, and did not show a reduction in PCa mortality at 9 years of follow-up.

Financial disclosures

Grants received for French centers investigation. French regional Health insurance (Midi-Pyrénées and Languedoc Roussillon). French Association of Urology. Institut National du Cancer convention 12-2008 Convention: 07/3D1616/SPC-111-13/NG-NC. Ligue Nationale Contre le cancer PROJET N° PRE08/AV—CONV. DRC 2009/119. Ligue Nationale Contre le cancer PROJET N°: EPDCD14646—DRC n° 2014/620- N° PRE2014.LNCC/AV. Grants received for International coordination: European Union Grants SOC 95 35109, SOC 96 201869 05F022, SOC 97 201329, SOC 98 32241, the 6th Framework Program of the EU: PMark:LSHC-CT-2004-503011; Unrestricted educational grants from Beckman-Coulter-Hybritech Inc.

Funding All centers funding: ERSPC was supported by Hybritech Inc, but this sponsor had no access to data, no influence on data analysis or drafting of the manuscript. The maintenance of the Central database is sponsored by European Association of Urology.

Acknowledgement

We would like to thank all those who contributed to this work, especially the men who participated in our research. We also would like to thank Fiona Ecarnot, PhD (EA3920, University of Franche-Comté, Besancon, France) for her valuable contribution in editing the final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.purol.2020.02.011.

References

[1] de Koning HJ, Liem MK, Baan CA, Boer R, Schröder FH, Alexander FE, et al. Prostate cancer mortality reduction by screening: power and time frame with complete enrollment in the European Randomised Screening for Prostate Cancer (ERSPC) trial. Int J Cancer 2002;98:268—73.

[2] Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320—8, http://dx.doi.org/10.1056/NEJMoa0810084.

[3] Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981—90, http://dx.doi.org/10.1056/NEJMoa1113135.

[4] Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Zappa M, Nelen V, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027—35, http://dx.doi.org/10.1016/S0140-6736(14)60525-0.

[5] Hugosson J, Robol MJ, Manson M, Tammela TLJ, et al. A 16-year Follow-up of the ERSPC trial. Eur Urol 2019.

[6] Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310—9, http://dx.doi.org/10.1056/NEJMoa0810696.

[7] Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR, et al. Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125—32, http://dx.doi.org/10.1093/jnci/djr500.

[8] Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, et al. Effect of a low-intensity psa-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA 2018;319:883—95, http://dx.doi.org/10.1001/jama.2018.0154.

[9] Villers A, Malavaud B, Rebillard X, Bataille V, Iborra F. ERSPC: features and preliminary results of France. BJU Int 2003;92(Suppl 2):27—9.

[10] Ciatto S, Zappa M, Villers A, Paez A, Otto SJ, Auvinen A. Contamination by opportunistic screening in the European Randomized Study of Prostate Cancer Screening. BJU Int 2003;92(Suppl 2):97—100.

[11] de Koning HJ, Gulati R, Moss SM, Hugosson J, Pinsky PF, Berg CD, et al. The efficacy of prostate-specific antigen screening: Impact of key components in the ERSPC and PLCO trials. Cancer 2018;124:1197—206, http://dx.doi.org/10.1002/cncr.31178.

[12] Villers A, Rébillard X, Soulié M, Davin J-L, Coloby P, Moreau J-L, et al. [Prostate cancer screening]. Prog Urol 2003;13:209—14.

[13] Binder-Foucard F, Bossard N, Delafosse P, Belot A, Woronoff A-S, Remontet L, et al. Cancer incidence and mortality in France over the 1980-2012 period: solid tumors. Rev Epidemiol Sante Publique 2014;62:95—108, http://dx.doi.org/10.1016/j.respe.2013.11.073.

[14] Bray F, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer 2010;46:3040—52, http://dx.doi.org/10.1016/j.ejca.2010.09.013.

[15] Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P. 10-year outcomes after monitoring-surgery, or radiotherapy for localized prostate cancer. New England Journal of Medicine 2016;375:1415—24, http://dx.doi.org/10.1056/NEJMoa1606220.

[16] Roobol MJ, Kranse R, Bangma CH, van Leenders AGJLH, Blijenberg BG, van Schaik RHN, et al. Screening for prostate cancer: results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013;64:530—9, http://dx.doi.org/10.1016/j.eururo.2013.05.030.

[17] Kilpeläinen TP, Tammela TL, Malila N, Hakama M, Santti H, Määttänen L, et al. Prostate cancer mortality in the Finnish randomized screening trial. J Natl Cancer Inst 2013;105:719—25, http://dx.doi.org/10.1093/jnci/djt038.

[18] Schröder FH, Denis LJ, Roobol M, Nelen V, Auvinen A, Tammela T, et al. The story of the European Randomized Study of Screening for Prostate Cancer. BJU Int 2003;92(Suppl 2):1—13.

[19] Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725—32, http://dx.doi.org/10.1016/S1470-2045(10)70146-7.

[20] Pinsky PF, Miller E, Prorok P, Grubb R, Crawford ED, Andriole G. Extended follow-up for prostate cancer incidence and mortality among participants in the prostate, lung, colorectal and ovarian randomized cancer screening trial. BJU Int 2018, http://dx.doi.org/10.1111/bju.14580.

[21] Publications related to ERSPC. European Randomized Study for Screening of Prostate Cancer Web site. www.erspc.org/publist.php. n.d.

[22] Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997;16:1017—29.