CHAPTER 3

Impact of the European Randomized Study of Screening for Prostate Cancer on Prostate-Specific Antigen Testing Policy by Dutch General Practitioners

Van der Meer S[1,2], Kollen BJ[3], Hirdes WH[2], Steffens MG[2], Hoekstra-Weebers JEHM[4,5], Nijman JM[1], Blanker MH[3]

1. University of Groningen, University Medical Center Groningen, Department of Urology, Groningen, the Netherlands
2. Isala, Department of Urology, Zwolle, the Netherlands
3. University of Groningen, University Medical Center Groningen, Department of General Practice, Groningen, the Netherlands
4. University of Groningen, University Medical Center Groningen, Wenckebach Institute, Groningen, the Netherlands
5. Comprehensive Cancer Center Netherlands, Groningen, the Netherlands

Abstract

Introduction
PSA testing in the USA decreased slightly after publication of the European Randomized Study of Screening for Prostate Cancer (ERSPC) results in March 2009. This study wanted to determine the impact of this publication on PSA testing by Dutch general practitioners in men aged 40 years or older.

Methods
A retrospective study with databases containing PSA tests from a Dutch insurance company and a large district hospital-laboratory was performed.
The difference in primary PSA testing rate as well as follow-up testing before and after ERSPC was calculated using a chi-square test, statistical significance at p-value<0.05.

Results
A decline in PSA tests 4 months after ERSPC publication, especially for men 60 years and older was shown.
Primary testing as well as follow-up testing decreased, both for PSA <4 ng/ml as well as for PSA 4-10 ng/ml.
Referral to a urologist after a PSA result of > 4 ng/ml decreased slightly after the ERSPC publication.

Conclusion
After the ERSPC publication primary PSA testing as well as follow-up testing decreased. Follow-up testing seemed not to be adequate after an abnormal PSA result. The reasons for this remain unclear.

Introduction

Prostate cancer screening with the Prostate-Specific Antigen (PSA) test is widespread. Despite the US Preventive Services Task Force (USPSTF) recommendation against prostate cancer screening in men aged 75 years or older in 2008, PSA screening rates did not change in the USA [1]. However, Zeliadt et al showed that PSA testing in the USA decreased slightly after publication of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC) results in March 2009 [2]. But screening remained substantial (34% in men aged 40 to 54 years and 47% in men aged 55 to 74 years).
In the Netherlands most patients with questions about cancer screening will visit their general practitioner (GP). GPs can use the Dutch GP guideline Lower Urinary Tract Symptoms in older men, published in 2004, to advise these patients [3]. In this guideline, GPs are encouraged to discuss the pros and cons of PSA screening and to be reluctant to screen, as the impact of screening was unclear [3]. Much attention was given to the publication of the ERSPC in March 2009 [4]. All GPs received a Dutch version of this key article, written by the ERSPC study group. In a comment by the College of General Practitioners (NHG) send along with this article, the 20% decrease of prostate cancer mortality was weighted against the high number needed to screen and treat [5]. This resulted in a strong advice not to screen [5]. We investigated the effect of the ERSPC results on PSA testing rate by Dutch GPs in men aged 40 years or older.

Methods

We performed a retrospective study, using two separate databases. First, we used the claims database of a Dutch insurance company, Achmea, containing all PSA tests claimed for approximately 3 million insured patients from 2007 onwards. This database has not been used before for scientific research. The insurance company has its strict internal checks. We believe that the database is sound. If any irregularity would be present in the database, this would be non-specific and not related to the study outcome.
Furthermore, we analyzed a database of all PSA tests from the only laboratory in the area of a large (900 beds) district general teaching hospital from 2004 until present. This laboratory has been recognized and granted accreditation by the Coordination Committee for the improvement of Quality control for Laboratory tests in health care (CCKL, www.cckl.nl). They have a quality system which is regularly validated and independent inspections are carried out. We therefore believe that the hospital database is valid and reliable as well.

From both databases, we collected all PSA tests requested by GPs for men aged 40 years or older.
PSA requesting rates were estimated by dividing the number of primary tests by the number of men in the target population (derived from the Central Bureau of Statistics of the Netherlands [6]) based on the postal codes from the hospital database. For the claims database, we used the number of men in each age group registered at the insurance company.
The claims database included participants from the ERSPC study region (Rotterdam). That is, these participants may have had their insurance with Achmea. The ERSPC randomized 42,376 inhabitants (response rate 40%) of Rotterdam and 12 neighboring municipalities aged 55 to 75 years between June 1994 and 2000 into a screening and control arm [7]. For the early years of the ERSPC, Otto et al showed that the opportunistic screening rate in the control arm was considerably higher than for non-participants [7]. Our claims database did not contain PSA tests performed at a four-year interval for patients in the screening arm of the ERSPC. However, it will contain PSA tests for men in the control arm as well as for nonparticipating inhabitants in this region, as these tests were requested by their GPs.

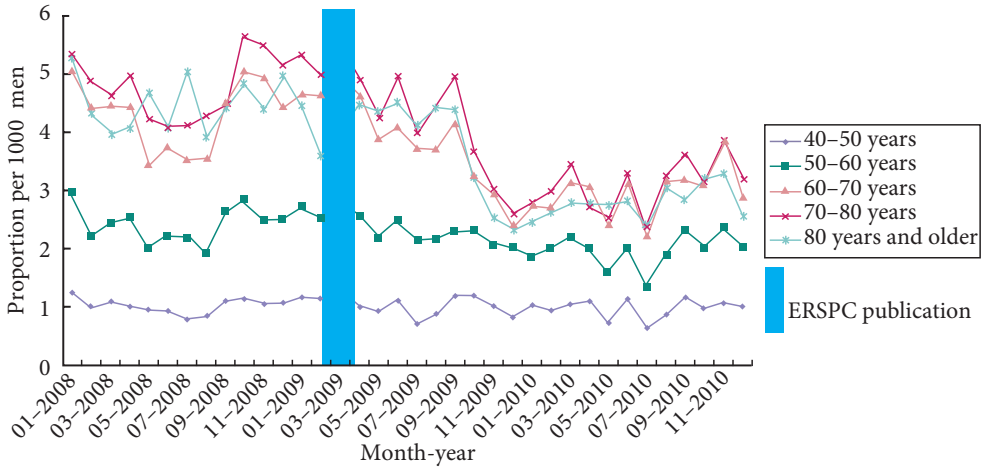
Analysis
To study the impact of the aforementioned higher opportunistic screening rate in the control arm of the ERSPC on our claims database, we performed a subgroup analysis. We selected all primary PSA tests for men living in the ERSPC-Rotterdam region, based on postal codes (information on specific region provided by Monique Roobol; personal communication). PSA requesting rates for the ERSPC-Rotterdam region were compared to the rates in men living outside this region. Notably, we were not able to select ERSPC participants from the claims database, as the insurance company did not register participation status.
To assess the influence of the ERSPC publication, we defined 12 months prior to publication as “before ERSPC” and 12 months after as “after ERSPC”. PSA tests performed in March 2009 (month of publication) were left out of the analyses.
From both databases, primary PSA tests requested by a GP were selected. We considered a PSA test to be a primary test when no earlier test was available in the databases.
For men with an increased PSA value (> 4ng/ml) without a repeat test in the hospital database, we checked the medical files to see if there had been a referral to a urologist. The proportion of men with a primary PSA test for different age groups per 1,000 men per month from January 2008 to December 2010 are presented, as derived from the claims database. We compared the

proportion of primary PSA tests (per 1,000 men) before and after publication of the ERSPC results for different age groups and regions (ERSPCRotterdam versus other regions), using a chi-square test.
From the hospital database, we compared PSA test results (categories) between the two periods, as well as the number of men with repeat testing after initial PSA tests.
For the repeat tests we used a maximum follow-up time of one year after the initial test, as for the second period (after publication of the ERSPC study) less follow-up time was available. Moreover, especially for patients with abnormal test results, a longer period of time between primary test and repeat testing was considered inadequate. Repeat tests were dichotomized as none or within one year after the initial test. Furthermore, the percentages of repeat testing for different age groups and PSA categories before and after ERSPC publication were compared, using a chi-square test. Additionally, we performed multivariable logistic regression analyses with repeat test as the dependent variable and study period, age groups, and PSA categories as the covariates (Odds Ratios are presented). Nagelkerke Rsquare was estimated to value the percentage of variance explained by the model. All analyses were performed using SPSS Version 18.0, statistical significance at p-value < 0.05.

Results

The claims database included approximately 715.000 insured men aged 40 years and older, of which 11% were inhabitants of the ERSPC-Rotterdam region. This database included 123,996 PSA test claims, of which 66,848 were considered primary tests requested by a GP from 2008 onwards. Of these, 9,691 tests (14.5%) were performed in the ERSPC-Rotterdam region.
A decline in the incidence of PSA tests is shown approximately 4 months after the ERSPC publication, especially for men aged 60 years and older (Figure 1).

Figure 1. Proportion of men with a primary PSA test according to age (claims data)



The age-weighted average proportion tested men per month was 33.09/1,000 men before and 27.52/1,000 men after ERSPC publication, for the total study sample (Mantel Haenszel chi-square, $p < 0.001$).

In both time periods the average proportion was significantly lower in younger men (age groups 40-50 and 50-60), compared to older men, but did not differ for older age groups (chisquare, all $p > 0.05$, except for age groups 60-69 vs. 70-79, p 0.049, Table 1). The PSA testing rate in the ERSPC-Rotterdam region was considerably higher than in the other regions (Table 1).

Table 1. Proportion of primary PSA tests (per 1,000 men) one year before and after publication of the ERSPC according to age and region, derived from claims database

	Before ERSPC	After ERSPC	p-value (chi-square)
Age group (number in group)*	(675,671)	(766,626)	
40 to 49 years	12.17	11.79	0.221
50 to 59 years	28.81	25.96	<0.001
60 to 69 years	51.63	40.97	<0.001
70 to 79 years	57.35	44.80	<0.001
80 years or older	52.08	41.32	<0.001
Within ERSPC-Rotterdam region	(78,268)	(82,365)	
40 to 49 years	14.42	12.95	0.156
50 to 59 years	40.15	33.95	<0.001
60 to 69 years	60.80	43.90	<0.001
70 to 79 years	70.30	51.02	<0.001
80 years or older	72.11	51.56	<0.001
Outside ERSPC-Rotterdam region	(597,404)	(684,261)	
40 to 49 years	8.50	8.45	0.736
50 to 59 years	26.28	24.26	<0.001
60 to 69 years	49.80	39.20	<0.001
70 to 79 years	54.51	41.70	<0.001
80 years or older	48.09	37.75	<0.001

* The number of men before and after ERSPC publication differs due to an increase in the number of insured people.

The relative risk for PSA testing varied from 1.23 in men aged 60 to 70 years to 1.70 in men aged 40 to 50 years before ERSPC publication. After the publication, these figures were 1.13 and 1.54, respectively.
The hospital database contained 30,558 PSA test results requested by GPs, of which 9,766 were considered primary tests from 2006 until 2011. In this database, PSA categories did not differ between periods (Table 2).

Table 2. PSA test results (hospital data) before and after publication of ERSPC study

PSA category	Before ERSPC	After ERSPC	p-value (chi-square)
(number of tests)	(1,098)	(1,000)	0.539
< 4 ng/ml	81.7 %	82.4 %	
4-10 ng/ml	11.0 %	11.5 %	
>10 ng/ml	7.3 %	6.1 %	

Before ERSPC publication, 38.5% of all tests were followed by a repeat test within one year. After ERSPC publication, this dropped to 26.5% (chi-square, $p < 0.001$, Table 3). For all age groups, the chance of follow-up after a normal test result (PSA < 4 ng/ml) decreased from 31.8% before to 18.8% after ERSPC publication (chi-square, $p < 0.001$, Table 3). For men with moderately increased PSA values (4-10 ng/ml) this chance also decreased from 65.3% to 52.2% (chi-square, $p = 0.028$, Table 3). However, the chance of follow-up increased for men with PSA values > 10 ng/ml from 73.8% to 82.0% (chi-square, $p = 0.171$, Table 3).

Table 3. Percentage of repeat PSA tests within 1 year after initial test, according to initial PSA value and age groups derived from hospital database

	Before ERSPC	After ERSPC	p-value
(number)	(1,098)	(1,000)	
Total study population	38.5 %	26.5 %	<0.001
PSA values			
	(897)	(824)	
< 4 ng/ml	31.8%	18.8 %	<0.001
	(121)	(115)	
4-10 ng/ml	65.3 %	52.2 %	0.028
	(107)	(83)	
> 10 ng/ml	73.8 %	82.0%	0.171
Age groups			
	(125)	(134)	
40 to 50 years	23.2 %	11.9 %	0.017
	(332)	(279)	
50 to 60 year	39.5 %	21.1 %	< 0.001
	(348)	(328)	
60 to 70 years	46.0 %	34.8 %	0.002
	(209)	(166)	
70 to 80 years	35.9 %	33.7 %	0.373
	(84)	(93)	
80 years and older	33.3 %	21.5 %	0.055

The medical files of the 190 men with PSA > 4 ng/ml without a repeat test were searched. Of these men 28.3% before and 23.5% after ERSPC publication did receive follow-up by a urologist, but the urologist decided not to repeat the PSA test (Mantel Haenszel chi-square p = 0.044). We did not look for the reason for referral, nor for outcome of the analyses performed by the urologist as this was beyond the scope of this study.
Repeat testing decreased for all age groups after ERSPC publication (Table 3), with the largest difference for men 40-50 and 50-60 years (Relative Risk Reduction of 48.7% and 46.6%, respectively) and smallest difference for men

40-50 and 50-60 years (Relative Risk Reduction of 48.7% and 46.6%, respectively) and smallest difference for men aged 70-80 years (6.1% reduction).
Multivariable logistic regression analyses showed that age, initial PSA value and study period were all associated with the chance of repeat testing (Table 4). Nagelkerke R-square for this model was 0.20.

Table 4. Multivariable logistic regression analyses on repeat testing according to age, PSA group and study period

	OR	CI 95%	p-value
Study period			
before ERSPC (reference)	-		<0.001
after ERSPC	0.55	0.45 - 0.67	
PSA categories			
< 4 ng/ml (reference)	-		< 0.001
4-10 ng/ml	4.79	3.54 - 6.49	
>10 ng/ml	13.63	8.73 - 21.27	
Age groups (years)			
40-50 (reference) -			<0.001
50-60	1.95	1.34 - 2.84	
60-70	2.66	1.84 - 3.86	
70-80	1.37	0.90 - 2.07	
80 or older	0.72	0.42 - 1.22	

OR odds ratio, CI 95% confidence interval

Discussion

This study shows a considerable decline in primary PSA testing as well as in follow-up testing after the ERSPC publication. Although this study was not designed to establish a causal relationship, we believe this decrease in PSA testing can be mainly explained by the impact of the ERSPC publication on GPs' testing rates as no other factors could be identified.
Insurance companies in the Netherlands completely reimburse PSA testing costs. Therefore, this could not account for the reduction in PSA testing. Furthermore, GPs in the Netherlands are advised to follow their guideline, which has not been changed during our study period. International guidelines are not commonly well-known by Dutch GPs. We assume that any influence by other guidelines is unlikely.
Furthermore, we do not think that follow-up for prostate cancer played a role in PSA testing in our study. As we focussed on primary tests and follow-up tests requested by GPs only, the chance of these being performed for malignant disease is rather small. In the Netherlands, as in most countries, follow-up for prostate cancer is part of specialized care, provided by urologists and oncologists, and not by GPs. Although we cannot rule out that some of the tests were indeed for malignant disease, the impact on this study would be neglectable. The area of the insurance company (claims database) included the ERSPC-Rotterdam region. We showed that the PSA testing rate in this region was considerably higher. This is in line with the figures shown by Otto et al, who described the opportunistic screening rates for ERSPC participants in the early years of that study [7]. Approximately 40% of all men in this region were randomized. We believe that the higher primary testing rate in this region cannot be the result of study participation only. It may reflect a higher awareness of non-participants as well. Moreover, based on the experience with a higher number of prostate cancer cases, GPs in this region may be more acquainted with PSA tests and might be less reluctant. Because no information on the background of these tests was available from this database, these can only be theoretical explanations.
As 11% of the men included in the claims database lived in the ERSPC-region, in our database 2.2% of the men participated in the screening arm, and 2.2% participated in the control arm. We assume that these small percentages did not influence the main results of our study. We therefore believe, that the screening rates shown and the alterations after the ERSPC publication represent the screening patterns of all Dutch GPs.
We confirmed the age-specific effect of the ERSPC (and PLCO) publication on PSA testing described by Zeliadt et al, but we observed a considerably larger

decrease in testing rates. Zeliadt et al excluded the first 4 months after publication of the ERSPC and PLCO, while we only excluded the month of publication [2]. Excluding the first 4 months, would make the decrease in PSA testing in our study even more apparent. The smaller impact in the USA as shown by Zeliadt et al may reflect differences in prostate cancer screening as a whole; the prevalence of PSA testing is much higher in the USA compared to the Netherlands as screening was never advocated in the Netherlands.
Furthermore, Zeliadt et al also evaluated the effect of an update of the USPSTF (suggesting an upper age limit of 75 years for PSA screening) published in August 2008 [2]. Following this publication, a decrease in PSA testing in men aged ≥ 75 years was shown, as well as an increase in men aged 40-54 and 55-74 years. This might be explained by the publicity regarding PSA testing at the time of the USPSTF publication. After publication of the ERSPC and the PLCO results they described that the subsequent decrease in PSA testing was statistically significant in all age groups compared to the period after the USPSTF publication. But when comparing the study period after the ERSPC and PLCO with all the previous study periods (before and after USPSTF) the decrease was only statistically significant in younger (40-54 years) and older men (≥ 75 years) [2]. This may in part be explained by the earlier increase in PSA testing after the USPSTF publication and by the varying PSA testing practice found among their studied practice groups [2].
Although the ERSPC analyzed a core age group, it is well known that PSA tests are ordered for both younger and (much) older men. Although this may be incorrect, in daily practice, physicians may regard the ERSPC results as "evidence for the effect of PSA screening in general". This is comparable to the implementation of, for example, drug treatments, which are in general tested in defined groups, but used in non-defined groups later on. Therefore, we were interested in all age groups and we have used age group comparisons.
After the ERSPC publication, primary testing as well as follow-up testing decreased, both for normal PSA results (<4 ng/ml) as well as for moderately elevated PSA results (4-10 ng/ml). GPs might regard the latter as less relevant since the ERSPC publication. Follow-up testing after an elevated PSA result of >10 ng/ml increased moderately after the ERSPC, but referral rates for this group decreased slightly. This suggests, that follow-up testing was not adequate after an abnormal PSA result (>4 ng/ml) and even less adequate after ERSPC publication. We presume that patients wanted to be informed on their likelihood to develop prostate cancer and as a consequence were counselled before testing. As abnormal PSA values coincide with an increased chance of prostate cancer, it was surprising to see that GPs refrained from repeating such a test.

The reasons for this remain unclear, but the NHG advice on restrained PSA use could be of influence. The validated prostate cancer risk calculator (www.prostatecancer-riskcalculator.com) of the Prostate Cancer Research Foundation (SWOP) could help GPs in determining their policy for follow-up testing, especially for men with elevated PSA values [8].

Conclusion

After the ERSPC publication primary PSA testing as well as follow-up testing decreased. Follow-up testing seemed not to be adequate after an abnormal PSA result. The reasons for this remain unclear.

References

1. Prasad SM, Drazer MW, Hou D, Hu JC, Eggener SE. 2008 US Preventive Services Task Force recommendations and prostate cancer screening rates. JAMA 2012;307(16):1692- 4.
2. Zeliadt SB, Hoffman RM, Etzioni R, et al. Influence of publications of US and European prostate cancer screening trials on PSA testing practices. J Natl Cancer Inst 2011;103(6):520-3.
3. Wolters RJ, Spigt MG, Van Reedt Dorland PFH, Gercema AJ, Klomp MLF. NHGStandard “Difficult voiding in older men” (second revision). Huisarts Wet 2004;47:571-86.
4. Schröder FH, Hugosson J, Roobol MJ et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
5. Van Weert H, Wiersma TJ. Prostate cancer screening? Not yet! Huisarts Wet 2009;7:350-1.
6. www.cbs.nl from Statistics Netherlands.
7. Otto SJ, van der Cruijsen IW, Liem MK, Korfage IJ, Lous JJ, Schröder FH, de Koning HJ. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Int J Cancer 2003;105(3):394-9.
8. Roobol MJ, van Vugt HA, Loeb S, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol 2012;61(3):577-83.