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Change of tumour characteristics and treatment over time in both arms of the European Randomized study of Screening for Prostate Cancer

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ABSTRACT

Objective: To evaluate a change in tumour characteristics and applied treatments over time in the control arm of all centres of the European Randomized study of Screening for Prostate Cancer (ERSPC) and to compare this with similar data of the screening arm.
Methods: Between 1993 and 2003, 182,160 men, aged 50–74 years, were randomised to the screening arm (N = 82,816) and the control arm (N = 99,184). Men in the screening arm were offered Prostate Specific Antigen (PSA) testing every 4 years whilst men in the control arm received usual care. Tumour characteristics and treatment were evaluated in all men diagnosed with prostate cancer up to December 2006 or the third screening round. Data on the control arm were divided into 3 periods: 1994–1998, 1999–2002 and 2003–2006.
Results: Tumour characteristics were more favourable over time in both the control and the screening arm, with especially increasing proportions of T1C tumours with 29% in 1994–1998 versus 50% in 2003–2006 and 48% at the initial screening round versus 75% at the third screening round, respectively. Tumour characteristics observed in the last period of the control arm were comparable to tumour characteristics in the initial screening round. In the control arm, treatment changed over time with surgery as the most common treatment in the entire observed period, but almost doubling of expectant management and the combination of hormone therapy and radiotherapy over time. In the initial screening round, surgery was the most common treatment (42%), changing over time to expectant management as the most frequently applied treatment in the third screening round (33%).
Conclusion: Tumour characteristics in the control arm became more favourable over time and show similarity with prostate cancer cases detected at the initial screening round. The most prominent change in treatment over time was an increase of application of

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expectant management in both arms of the ERSPC. These observations reflect an increasing rate of opportunistic testing over time in men randomised to the control arm.

1. Introduction

The European Randomized study of Screening for Prostate Cancer (ERSPC) was initiated in 1994 to assess whether screening for prostate cancer is effective in decreasing prostate cancer mortality at an acceptable cost, both in terms of quality of life and finance.[1]

After a mean follow-up of 9 years the third interim intention to screen analysis resulted in a significant 20% reduction in prostate cancer mortality in favour of screening.[2] This reduction was 30% when corrected for non-compliance and contamination.[3] The study is still ongoing, continued follow-up will provide further information needed for the decision on whether prostate cancer screening should become a population-based programme.

Next to the main end-point, disease specific mortality, studies on the so-called secondary end-points (i.e. stage and grade shift of tumours detected in both intervention and control arm) are of great value. Earlier studies comparing the tumour characteristics between the screening and the control arm showed that prostate cancer patients in the control arm had significantly higher PSA levels at diagnosis and had more advanced clinical stage as compared to prostate cancer patients in the screening arm. The distribution of Gleason score of the sextant prostate biopsies showed a similar pattern, the prostate cancers detected in men in the control arm had a significantly higher proportion of cancers with Gleason >7. All data point towards a shift towards more favourable tumour characteristics at diagnosis in the screening arm.[4–6] This was also confirmed when comparing tumour characteristics between two subsequent screening rounds.[5–8]

Therapy choices reflect stage and grade distribution at diagnosis and hence were different between the screening arm and the control arm. Men in the screening arm were offered curative therapy more often, whilst men in the control arm received endocrine therapy more often.[4] A similar pattern was seen between prostate cancers detected at initial and repeat screening. The proportion of men managed by active surveillance increased drastically and more than doubled, reflecting the more favourable tumour characteristics at diagnosis.[8] It must be noted however, that within ERSPC there was no imbalance in treatments applied between the two study arms after correcting for differences in tumour characteristics at diagnosis.[9]

Meanwhile, PSA testing in asymptomatic men occurs in the control arm, and if the contamination is effective: i.e. opportunistic PSA testing followed by a prostate biopsy and early diagnosis it may have an effect on the characteristics of the prostate cancers detected and thus therapy. This so-called opportunistic PSA testing or contamination testing occurs also in men randomised to the screening arm but to a lesser extent.[10]

The aim of the study presented here was to inventory the tumour characteristics and applied treatments over time in the control arm of the different ERSPC centres and to compare this with similar data from the screening arm in order to (a) assess the effect of contamination (i.e. opportunistic screening) in the control arm over time and (b) to further explore the earlier reported favourable grade and stage shift and subsequent treatment changes as a result of PSA based screening.

2. Materials and methods

2.1. Study population

Between 1993 and 2003, a total of 182,160 men, aged 50–74 years, were included in the screen and control arm of the ERSPC. Participating centres were located in Finland, The Netherlands, Sweden, Belgium, Italy, Switzerland and Spain. Men who were randomised to the intervention arm ($N = 82,816$) received systematic screening every 2 or 4 years and men who were randomised to the control arm ($N = 99,184$) received usual care.[11] Follow-up for mortality analyses began at randomization and ended at death, emigration or a uniform censoring date (December 31, 2006) with identical follow-up in the two study arms.[2] The mean follow-up for both arms is 9 years. In the current study, all men diagnosed with prostate cancer in the control arm between January 1994 and December 2006 and all men diagnosed with prostate cancer in the intervention arm from the initial screening round up to the third screening round are included (for Sweden, men are included up to the 6th screening round because of a 2-year screening interval). Cancers diagnosed in men who did never attend screening, and cancers diagnosed between the two screening intervals clinical or due to opportunistic screening, transurethral resection of the prostate (TURP) for benign disease, and cystoprostatectomy specimens, were considered as well and defined as interval cancers.

Men with prostate cancer in the control group were identified through a linkage with national cancer registries. These men received standard medical care consisting of symptom evaluation as well as prostate cancer diagnosing and treatment by a general practitioner and a local urologist. Screening methodology was reviewed for all centres by Schröder et al. In most centres a PSA cut-off value of 3.0 ng/ml was used as an indication for prostate biopsy. In Finland a PSA value of $\geqslant$4.0 ng/ml was defined as a biopsy indication. Men with a PSA value of 3.0–3.9 ng/ml underwent an ancillary test. Up to 1998 this meant that men underwent a digital rectal examination (DRE). In 1999 the Finnish centre started to calculate the ratio of the free PSA value to the total PSA value. If the ancillary test was positive, men were referred for biopsy. In Italy, men with a PSA value of 2.5–3.9 ng/ml underwent ancillary tests (i.e. DRE and transrectal ultrasonography (TRUS)). A PSA of $\geqslant$4.0 ng/ml was defined positive to refer men for prostate biopsy. In both the Dutch and the Belgium centres, a

combination of DRE, TRUS and PSA testing with a cut-off value of 4.0 ng/ml was used for screening up to February 1997. After February 1997 this combination was replaced by PSA testing only with the cut-off value of 3.0 ng/ml. In Belgium, they initially used a PSA cut-off value of 10 ng/ml since the results of a pilot study were included in the data set. Most centres used sextant biopsies guided by TRUS. From June 1996 on, lateralised sextant biopsies were recommended. In Italy they have used transperineal sextant biopsies, whilst in Finland a biopsy procedure with 10–12 biopsy cores was adopted as the general policy in 2002. Most centres adopted a screening interval of 4 years; whilst Sweden used a 2-year interval.[2,11]

Screening rounds 1 and 2, 3 and 4 and 5 and 6 in Sweden were added to screening rounds 1, 2 and 3 of the centres with a 4-year interval, respectively.

Cancers were classified according to the 1992 TNM classification. Grading of the cancers was done using the Gleason grading system. Organ confined disease was considered as T1 and T2 disease, advanced disease as T3 and T4 disease and metastatic disease as N1, N2, N3 and M1. Incidence data of the control arm were subdivided according to year of diagnosis. The periods were: 1994–1998, 1999–2002 and 2003–2006 and compared to the initial, repeat and third screening round. Prostate cancers diagnosed before randomisation were excluded, both in the control and the screening arm. Missing data on stage and grade were filled in taking into account the stage and grade distribution in the available data, assuming that there is no bias in this respect in obtaining follow-up data.

2.2. Statistical analysis

The statistics are mainly descriptive. Cumulative incidence was calculated for tumour characteristics per 10,000 men at risk. We used the men at risk at the start of the predefined periods of the control arm for both arms. Tumour characteristics, i.e. stage and grade, and treatment were compared amongst the predefined successive periods. Furthermore, we compared the change in tumour characteristics over time in the control arm with the tumour characteristics in subsequent screening rounds of the screening arm. The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0, software was used. *T*-test for independent samples and the Mann–Whitney-*U* test were used to compare between groups.

ERSPC is registered under the Current Controlled Trials number ISRCTN49127736.

3. Results

3.1. Patient characteristics and incidence data

A total of 4782 prostate cancers (4.8%) were diagnosed between January 1994 and December 2006 in the control arm ($N = 99{,}184$). In the screening arm ($N = 82{,}816$) a total of 6,567 prostate cancers (7.9%) were detected in subsequent screening rounds.

Median PSA at diagnosis decreased in the successive periods in the control arm; 12.7 ng/ml (1994–1998), 10.9 ng/ml (1999–2002) and 9.4 ng/ml in the period 2003–2006. Median PSA at diagnosis in subsequent screening rounds was quite stable; 5.3 ng/ml (initial screening), 4.7 ng/ml (repeat screening) and 5.4 ng/ml at the third screening round (4 year interval). Men diagnosed with prostate cancer in the control arm had significantly ($P < 0.01$) higher PSA levels at diagnosis as compared to men in the screening arm. Mean age at diagnosis was 67.72 years in the control arm and 66.21 in the screening arm and differed significantly ($P < 0.001$).

3.2. Tumour characteristics

3.2.1. Clinical TNM classification

The clinical T stage distribution showed a favourable shift over time, in both the control arm and the screening arm (Table 1). The proportion of T1C tumours in the control arm increased from 29% [95% confidence interval (CI): 28.2–28.8] in 1994–1998 to 37% [36.7–37.3] in 1999–2002 and to 50% [49.7–50.3] in 2003–2006. The percentage of screen detected T1C prostate cancers increased from 48% [47.4–48.2] in the initial screening round, 65% [64.8–65.4] in the repeat screening round to 75% [74.6–75.2] in the third screening round. The opposite was seen in T3 prostate cancers. In the control arm T3 tumours decreased from 23% in 1994–1998 to 13% in 2003–2006. At the initial screening round T3 tumours accounted for 14% of all tumours detected. This proportion decreased to 4% in the third screening round. This positive effect was also reflected by cumulative incidence in the screening arm, particularly between the initial screening round and the second screening round where advanced disease decreased (61.6 to 14.8 per 10,000 men at risk) and T1C cancers increased (204.9 to 214.1 per 10,000 men at risk).

Prostate cancers in the control arm showed in the last period (2003–2006) a similar clinical T stage distribution as compared to prostate cancers detected at the initial screening round. In 2003–2006 in the control arm, T1C and T3 accounted for 50% and 13% of the tumours, respectively. At the initial screening round T1C and T3 tumours had similar proportions of 48% and 14%, respectively.

A favourable shift over time was seen in metastasis status in the control arm (3.2 to 1.6% in lymph node metastasis and 10 to 4% in distant metastasis), whilst in the screening arm the proportion of lymph node metastasis was slightly decreasing (1.3 to 0.9%) and distant metastasis were quite stable over time (2%).

3.2.2. Gleason score

Gleason score distribution showed no explicit shift over time in both trial arms (Table 1). Only low-grade tumours, i.e. Gleason scores 2–6, decreased over time (58 to 51%) and moderate Gleason grade tumours (Gleason score 7) increased over time (21 to 32%) in the control arm. A decreasing trend was however seen in high Gleason grade tumours (Gleason 8–10) in the control arm. In the first study period the proportion was 21% [21.0–21.6], decreasing to 17% [16.6–17.0] in the last study period. In the screening arm these proportions were: 7.9% [7.7–8.1], 7.0% [6.8–7.2] and 9.2% [9.0–9.4] at 1st, 2nd and 3rd screening, respectively.

The comparison of Gleason score distributions between the control arm and the screening arm showed that in the control arm only Gleason scores 8–10 reached a comparable

Table 1 – Tumour characteristics in the control and screening arm of ERSPC.

	Control arm				Screening arm			
	1994–1998 Cum. Inc.* (%)	1999–2002 Cum. Inc. (%)	2003–2006 Cum. Inc. (%)	Total No.	Initial round Cum. Inc. (%)	2nd round Cum. Inc. (%)	3rd round Cum. Inc. (%)	Total No.
Clinical T stage								
T1A–T1B	4.8 (6.2)	11.5 (6.2)	20.6 (7.2)	322	5.8 (1.3)	11.6 (3.5)	7.7 (3.7)	178
T1C	21.9 (28.5)	68.3 (37.0)	142.9 (50.0)	2044	204.9 (47.8)	214.1 (65.1)	155.0 (74.9)	3968
T2	29.5 (38.4)	63.3 (34.3)	75.7 (26.5)	1468	156.5 (36.5)	88.0 (26.8)	34.7 (16.7)	1867
T3	17.5 (22.8)	34.9 (18.9)	37.7 (13.2)	783	59.8 (13.9)	13.6 (4.1)	9.0 (4.4)	530
T4	3.2 (4.1)	6.6 (3.6)	9.2 (3.2)	165	1.8 (0.4)	1.2 (0.4)	0.6 (0.3)	24
Total	76.9 (100)	184.6 (100)	286.2 (100)	4782	428.8 (100)	328.4 (100)	207.0 (100)	6567
Metastasis								
Lymph node	2.5 (3.2)	4.9 (2.6)	4.7 (1.6)	105	5.6 (1.3)	3.3 (1.0)	1.9 (0.9)	72
Distant	8.0 (10.4)	13.0 (7.0)	12.4 (4.3)	288	9.6 (2.2)	8.0 (2.4)	4.3 (2.1)	149
Biopsy Gleason score								
Gleason 2–6	44.5 (57.9)	105.7 (57.2)	145.6 (50.9)	2583	300.9 (70.2)	249.3 (75.9)	141.4 (68.3)	4726
Gleason 7	16.0 (20.8)	51.3 (27.8)	92.6 (32.4)	1404	93.9 (21.9)	56.1 (17.1)	46.7 (22.6)	1326
Gleason 8–10	16.4 (21.3)	27.5 (14.9)	48.0 (16.8)	795	33.9 (7.9)	23.1 (7.0)	18.9 (9.2)	515
Total	76.9 (100)	184.6 (100)	286.2 (100)	4782	428.8 (100)	328.4 (100)	207.0 (100)	6567
Men at risk	72,549	94,094	86,894		60,711	76,698	69,796	

* Cum. Inc. = cumulative incidence per 10,000 men at risk.

proportion with that of the initial screening round in 2003–2006 (17% versus 8%, respectively). A substantial difference remained in Gleason scores 2–6 (51% in 2003–2006 versus >70% in the initial screening round).

3.3. *Treatment*

Table 2 shows the distribution of initial treatment over time in both the control and the screening arm. The category "Other treatments" consists of therapies rarely applied in at most 9 prostate cancer cases per arm and comprised surgery with gene therapy, surgery with radiotherapy and hormone therapy, expectant management followed by surgery, expectant management followed by radiotherapy and expectant management followed by hormone therapy.

In the control arm surgery was the most frequently applied treatment in 1994–1998, in 31% of the patients. This was followed by hormone therapy and radiotherapy, accounting for 24% and 21% of treatments, respectively. At the initial screening round surgery was the most frequently applied treatment in 42% of the cases, followed by radiotherapy, applied in 29% of the cases.

In the last period of the control arm surgery was still the most common treatment, but had decreased to 25% of all treatments applied. Surgery was now closely followed by hormone therapy (22%) and the increased proportion of expectant management (19%). In the screening arm, at the third screening round, expectant management was most commonly applied (33%) and followed by surgery (30%) and radiotherapy (16%).

The comparison of treatments applied between the control and the screening arm showed that the changes over time regarding expectant management (increasing) and the combination of hormone therapy and radiotherapy (increasing) and the decreasing proportion of surgery and radiotherapy were similar. A difference was seen in the frequency of the combination of hormone and radiotherapy and hormone therapy. These therapies are being more frequently applied in the control arm during the study period. The proportion of men treated with hormone therapy was on average 22% in the control arm versus 8% in the screening arm. The combination of hormone therapy and radiotherapy was chosen in 17% of cases in the control arm versus 7% of cases in the screening arm on average.

Tables 2a and 2b show treatment broken down by stage for the screening arm and the control arm, respectively. Both trial arms showed an increase over time of expectant management and the combination of hormone therapy and radiotherapy in both organ confined and advanced disease.

First, surgery was the most applied treatment in organ confined disease for both trial arms. Surgery remained the most applied treatment for the control arm, but changed into expectant management for the screening arm in the third screening round.

In advanced disease radiotherapy was the most common treatment at initial screening and the combination of hormone therapy and radiotherapy in the third screening round. In the control arm hormone therapy was the most applied treatment during the whole observation period.

Hormone therapy was the most common applied treatment in metastatic disease during the whole observation period in both trial arms.

4. Discussion

In this report based on data of the ERSPC, tumour characteristics (stage and grade) at diagnosis and applied treatments of prostate cancers detected in men randomised to the screening or control arm were inventoried over a period covering the years 1994–2006.

During the study period especially the clinical T stage of prostate cancers detected in the control arm showed a more

Table 2 – Treatment in the screening and control arm of the ERSPC.

Treatment	Control arm				Screening arm			
	1994–1998 % (No.)	1999–2002 % (No.)	2003–2006 % (No.)	Total% (No.)	Initial round % (No.)	2nd round % (No.)	3rd round % (No.)	Total % (No.)
Hormone and radiotherapy	9.0 (50)	17.9 (310)	18.3 (455)	16.7 (815)	4.0 (104)	8.6 (218)	11.2 (162)	7.2 (484)
Hormone therapy alone	23.9 (133)	20.3 (353)	21.8 (542)	21.5 (1028)	7.4 (192)	8.0 (201)	8.7 (126)	7.9 (519)
Radiotherapy alone	21.1 (118)	18.4 (319)	14.1 (351)	17.0 (788)	29.4 (766)	24.1 (607)	15.7 (227)	24.8 (1600)
Surgery and Hormone therapy	3.2 (18)	1.0 (17)	0.8 (21)	1.3 (56)	2.1 (54)	1.1 (27)	0.7 (11)	1.4 (92)
Surgery and radiotherapy	0.4 (2)	0.3 (5)	0.6 (15)	0.4 (22)	0.3 (8)	0.2 (5)	0.0 (0)	0.2 (13)
Surgery alone	30.8 (172)	29.8 (518)	24.9 (618)	27.9 (1309)	42.3 (1101)	34.7 (875)	30.1 (435)	37.1 (2413)
Expectant management	10.8 (60)	12.1 (211)	19.3 (480)	15.0 (751)	14.2 (370)	23.1 (581)	33.1 (479)	21.2 (1431)
Other treatments	0.8 (5)	0.2 (4)	0.2 (5)	0.2 (13)	0.3 (8)	0.2 (5)	0.5 (5)	0.2 (18)
Total	100 (558)	100 (1737)	100 (2487)	100 (4782)	100 (2603)	100 (2519)	100 (1445)	100 (6567)
Mean age at diagnosis (range)	65.8 (50.8–78.1)	66.8 (54.4–82.8)	68.8 (54.3–86.0)		64.8 (50.9–78.2)	66.6 (53.1–82.5)	68.1 (56.5–83.2)	

Table 2a – Treatment broken down by stage for the control arm of ERSPC.

Treatment	Control arm								
	Organ confined disease			Advanced disease			Metastatic disease		
	1994–1998 % (No.)	1999–2002 % (No.)	2003–2006 (No.)	1994–1998 % (No.)	1999–2002 % (No.)	2003–2006 % (No.)	1994–1998 % (No.)	1999–2002 % (No.)	2003–2006 % (No.)
Hormone and radiotherapy	8.2 (31)	14.8 (174)	16.1 (218)	12.4 (17)	31.2 (106)	29.9 (79)	1.5 (1)	2.1 (3)	2.4 (3)
Hormone therapy alone	13.1 (49)	12.0 (142)	14.8 (200)	51.1 (71)	49.1 (168)	57.8 (153)	92.6 (64)	86.6 (131)	84.9 (115)
Radiotherapy alone	21.6 (81)	20.9 (246)	16.0 (216)	24.8 (34)	12.7 (43)	6.1 (16)	2.9 (2)	1.4 (2)	1.6 (2)
Surgery and hormone therapy	3.3 (12)	1.0 (11)	0.9 (12)	2.2 (3)	0.3 (1)	0.4 (1)	1.5 (1)	0.7 (1)	–
Surgery and radiotherapy	0.3 (1)	0.4 (4)	0.7 (10)	–	–	–	–	–	0.8 (1)
Surgery alone	37.7 (141)	35.1 (413)	28.8 (388)	8.0 (11)	4.8 (17)	2.5 (7)	1.5 (1)	6.3 (10)	6.3 (9)
Expectant management	14.8 (55)	15.5 (182)	22.6 (306)	1.5 (2)	1.8 (6)	3.3 (9)	–	2.8 (4)	4.0 (5)
Other treatments	1.0 (5)	0.4 (5)	0.2 (2)	–	–	–	–	–	–
Total	100.0 (375)	100.0 (1177)	100.0 (1352)	100.0 (138)	100.0 (341)	100.0 (265)	100.0 (69)	100.0 (151)	100.0 (135)

Table 2b – Treatment broken down by stage for the screening arm of ERSPC.

Treatment	Screening arm								
	Organ confined disease			Advanced disease			Metastatic disease		
	Initial round% (No.)	2nd round% (No.)	3rd round% (No.)	Initial round% (No.)	2nd round% (No.)	3rd round% (No.)	Initial round% (No.)	2nd round% (No.)	3rd round% (No.)
Hormone and radiotherapy	3.3 (65)	7.1 (150)	9.1 (96)	6.9 (23)	32.7 (33)	45.8 (24)	4.7 (4)	9.0 (8)	2.8 (1)
Hormone therapy alone	3.8 (76)	5.5 (116)	6.1 (64)	15.9 (53)	25.5 (25)	22.9 (12)	81.2 (70)	70.5 (58)	80.6 (32)
Radiotherapy alone	26.0 (518)	24.9 (524)	17.2 (180)	56.2 (188)	26.5 (26)	8.3 (4)	4.7 (4)	5.1 (4)	–
Surgery and hormone therapy	1.9 (38)	0.9 (20)	0.3 (3)	0.6 (2)	1.0 (1)	6.3 (3)	–	1.3 (1)	5.6 (2)
Surgery and radiotherapy	0.1 (1)	0.1 (3)	–	0.3 (1)	–	–	–	1.3 (1)	–
Surgery alone	47.6 (947)	36.1 (757)	31.1 (326)	18.3 (61)	12.2 (12)	8.3 (4)	4.7 (4)	7.7 (6)	5.6 (2)
Expectant management	17.0 (337)	25.0 (526)	35.9 (376)	1.8 (6)	2.0 (2)	8.3 (4)	4.7 (4)	5.1 (4)	2.8 (1)
Other treatments	0.3 (7)	0.3 (5)	0.3 (3)	–	–	–	–	–	2.8 (2)
Total	100.0 (1989)	100.0 (2101)	100.0 (1048)	100.0 (334)	100.0 (99)	100.0 (51)	100.0 (86)	100.0 (82)	100.0 (40)

favourable distribution over time. This is most likely a direct consequence of the increasing rate of opportunistic PSA screening in the control arm of ERSPC. Beemsterboer et al. found an opportunistic testing rate in the control arm of 7.6% per year in the first 1.5 years after randomisation (ERSPC, Rotterdam section).[12] Otto et al., also using ERSPC Rotterdam data, found that after 3 years of follow-up, 20.2% of men in the control arm had had at least 1 PSA test as compared to 14.1% opportunistic PSA testing in the screening arm.[10] In other ERSPC centres the rate of opportunistic screening in men randomised to the control arm varied from 6.7% up to 36%.[13]

At the beginning of the study period surgery and endocrine therapy were most frequently applied in prostate cancers detected in the control arm. At the end of the study period the combination of endocrine therapy and radiotherapy and expectant management were seen relatively more, but surgery and endocrine therapy remained the most common treatments. These changes in treatment are most likely due to (a) the observed change in tumour characteristics, (b) ageing of the cohort (more expectant management), mean age at diagnosis (Table 2) and (c) positive results for adjuvant or neoadjuvant hormone therapy in addition to radiotherapy in locally advanced prostate cancer.[14] Cooperberg et al. found that in the US the majority of patients younger than 60 years with low-risk cancers (i.e. PSA at diagnosis $\leqslant$10 ng/ml, biopsy Gleason <7 and clinical stage T1 or T2A) received radical prostatectomy. With increasing age, like in our study cohort, this proportion dropped rapidly, whilst endocrine therapy and expectant management increased with advancing age.[15] In older patients (>65 years) diagnosed with these low-risk tumours diagnosed in the years 1989–2001, expectant management was relatively uncommon. Most patients received radiotherapy or endocrine therapy.[16] Wolters et al. compared all treatments applied in both arms of the ERSPC during the median follow-up period of 9 years and found that PSA at diagnosis, age and clinical T stage are the most important factors in treatment choice.[9] But whereas that study focussed on differences in treatment in screening and control arm, our aim was to describe change of treatment over time taking into account stage at time of diagnosis.

Men diagnosed with prostate cancer in the screening arm had more favourable prognostic factors than those cases in the control arm when comparing time periods side by side. During the total observation period, mean age at diagnosis was 66.2 years for those men randomised to the screening arm versus 67.7 years for men in the control arm. In the screening arm organ confined disease was more frequent (92% versus 80% in the control arm) and also a larger proportion of low-grade tumours (72% versus 54% in the control arm) were observed. Endocrine therapy was offered much more often in the control arm (22% versus 8% in the screening arm) and surgery and expectant management more often in the screening arm, 37% versus 28% in the control arm for surgery and 21% versus 15% in the control arm for expectant management. These observations are in line with other studies comparing the tumour features and applied treatments of screen detected and clinically diagnosed prostate cancers.[4,5,17–19]

However, when comparing tumour characteristics of the last period (2003–2006) in the control arm with tumour

characteristics of cancers detected at the initial screening round we observed similarities. The proportion of T1C tumours in the control arm was 50% in the last period whilst 48% of the cancers detected at the initial screening round were staged as T1C, pointing to more screening activities in the control arm over time.

Despite the fact that the ERSPC cohort is a closed and thus ageing cohort, prostate cancer was detected more often in an early stage in the control arm. Our data showed that the proportions of organ confined disease in the control arm were 73.1% in 1994–1998 and 83.7% in 2003–2006. Advanced disease reduced from 26.9% to 16.4%. This is in line with the study of Cremer et al.[20] describing the situation in the Dutch population, using incidence data. They also report an increase in detection of early stage disease, leading to a decrease of metastatic prostate cancer and a lower mortality rate and increased survival.[20]

The decrease of Gleason >7 prostate cancers in the control arm (from 21.3% towards 16.8%) should be interpreted with caution due to the so-called Will Rogers Phenomenon. However, this statistical artefact of Gleason score reclassification results in higher Gleason score readings between 1992 and 2002; strengthening our observation of decreasing high grade tumours in the control arm over time.[21]

The comparison of prostate cancers detected at the initial screening round with those cases detected at repeat screening rounds showed a remarkable stage and grade shift in favour of the repeat screening rounds. These observations were reported earlier. In two subsequent screening rounds, advanced disease reduced from 19% to 4% and tumours with Gleason scores >7 decreased from 8% to 3% in the Dutch centre.[8] Sweden also reported that PSA screening rapidly cause a stage shift, which leads to only detecting low-stage and also low-grade malignancies.[19]

In conclusion, the earlier reported favourable stage and grade shift as a result of screening is confirmed with longer follow-up data. Also, the tumour characteristics of prostate cancers found in the control arm of the ERSPC showed a favourable shift over time. The stage and grade shift coincided with a change of treatment reflected in an increasing occurrence of expectant management as initial treatment. The tumour characteristics of prostate cancers detected in men in the control arm become, with advancing time, more comparable to prostate cancers detected in the initial screening round. These observations point towards an increasing rate of opportunistic testing in men randomised to the control arm. We propose that future studies perform a survival analysis in different time periods after randomisation in the control arm of the ERSPC.

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Conflict of interest statement

None declared.

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